

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-268**

**SUMMARY REVIEW**

### Division Director Review

**APPLICANT:** Novartis  
**DRUG:** artemether/lumefantrine  
**TRADE NAME:** Coartem  
**NDA:** 22-268  
**Date of Submission:** June 27, 2008  
**PDUFA goal date:** December 27, 2008  
**Formulation:** 20 mg artemether/ 120 mg lumefantrine  
**Indication:** Treatment of acute uncomplicated malaria due to *Plasmodium falciparum*  
**(b) (4)**  
**Related IND:** pre-IND 75,287 (no IND opened)

### Material Reviewed:

Administrative Action Package (4 volumes) including:

- Project Management Documents (regulatory documents, minutes, faxes): Gregory DiBernardo, Diana Willard, Judit Milstein
- Clinical Reviews: Elizabeth O'Shaughnessey, Sue Lim, Ozlem Belen,
- Cross-Discipline Team Leader Review: Joette Meyer
- Microbiology Reviews: Aaron Ruhland, Simone Shurland, Shukal Bala
- Clinical Pharmacology Reviews: Dakshina Chilakuri, Gerlie Gieser, Phil Colangelo
- Interdisciplinary Review Team (thorough QT study) Review: Christine Garnett, Joanne Zhang, Moh-Jee Ng, Suchitra Balakrishnan, Christoffer Tornoe, Norman Stockbridge
- Statistics Reviews: Lan Zeng, Xianbian Li, Karen Higgins, Daphne Lin
- Pharmacology/Toxicology Reviews: Owen McMaster, Terry Williams, Rama Dwivedi, Ying Mu, William Taylor, Abby Jacobs.
- Chemistry Reviews: Dorota Matecka, Shrikant Pagay, Rapti Maduware, Norman Schmuft, Elaine Morefield
- Pediatric and Maternal Health Staff/ Maternal Health Team (MHT) Review: Leyla Sahin, Karen Feibus, Lisa Mathis.
- Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis (OSE/DMEPA) Reviews: Denise Baugh, Todd Bridges, Linda Y. Kim-Jung, Denine Toyer, Carol Holquist
- Office of Surveillance and Epidemiology/Division of Risk Evaluation (OSE/DRISK), Patient Package Insert Review: LaShawn Griffiths, Jodi Duckhorn
- Division of Scientific Investigations (DSI) Reviews: Susan Thompson, Tejashri Purohit-Sheth, Joseph Salewski,
- Office of Medical Policy / Division of Drug Advertising and Marketing (DDMAC) Review: Carrie Newcomer, Kathleen Klemm
- Safety Evaluation and Labeling Development (SEALD) Review: Jeanne Delasko, Laurie Burke
- Division of Neurology Products/OND Consult Reviews: Kenneth Bergmann, Dav Hawver, Eric Bastings
- Advisors and Consultant Staff: (quick minutes) Jamie Kim, Igor Cerny,
- Advisory Committee Background Material: Division of Anti-Infective and Ophthalmic Products Advisory Committee meeting held December 3, 2008, Silver Spring, Maryland

**TABLE OF CONTENTS:**

RECOMMENDATIONS:	3
2.1 Administration Instructions	3
2.2 Dosage in Adult Patients (> 16 years of age)	3
2.3 Dosage in Pediatric Patients	3
2.4 Dosage in Patients with Hepatic or Renal Impairment	4
Post Marketing Requirements and Commitments:	4
Post-Marketing Commitment:	6
BACKGROUND:	7
Coartem:	7
Malaria:	7
NDA Submission:	8
Artemether/lumefantrine studies in China:	9
REVIEW SUMMARY:	11
Efficacy - Uncomplicated <i>Plasmodium falciparum</i> malaria:	14
1) Factorial Design Studies AB/M02 and A023:	14
2) Number of Doses – Study A012:	14
3) Studies comparing Coartem (4-dose) to chloroquine - Studies A007, A011, AIC04:	15
4) Studies comparing Coartem (4-dose) to Fansidar - Studies AICO4, A005, A010:	15
5) 4-dose Studies conducted in Thailand – Studies A003, A004, A008:	16
6) Comparing 4-dose to 6-dose regimen in Thailand – Study A025:	16
7) 6-dose Studies in Thailand – A026 and A028:	18
8) 6-dose study in Non-Immune travelers in Europe and Colombia - Study 2401:	19
9) Pediatric Studies testing 6-dose regimen in Africa – Studies A2403 and B2303:	20
Discussion:	20
Acceptability of Foreign Studies:	22
Text of 21 CFR 314.106, Foreign data:	22
Excerpts of Text from 21 CFR 312.120, Foreign clinical studies not conducted under an IND:	22
Statistical Summary:	23
Mixed infections: Uncomplicated <i>Plasmodium vivax</i> malaria:	25
Safety Summary:	25
QT prolongation:	26
CNS Events:	26
Neurology Consult:	27
Drug-Drug Interactions:	27
Hepatic or Renal Impairment:	27
Geriatric Patients:	27
Pregnancy:	28
Nursing mothers:	29
Primaquine:	29
Clinical Pharmacology:	30
Microbiology:	32
Pharmacology /Toxicology:	33
Chemistry and Inspections:	33
OSE/DMEPA (previously DMETS) recommendations:	34
Orphan Designation/Pediatrics:	34
Advisory Committee Meeting:	35
Financial Disclosure:	35
Division of Scientific Investigation:	35
Labeling:	35
Proprietary Name:	36
CONCLUSIONS:	36
RECOMMENDED ACTION:	36

## RECOMMENDATIONS:

The Coartem application should be approved for the treatment of uncomplicated malaria. The text that should be included in the approved labeling regarding the indication and the dosage and administration instructions is provided below:

### 1. INDICATIONS AND USAGE

Coartem (artemether/lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported. [see *Clinical Studies (14.1)*]

#### Limitations of Use:

- Coartem Tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Coartem Tablets are not approved for the prevention of malaria.

### 2. DOSAGE AND ADMINISTRATION

#### **2.1 Administration Instructions**

Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine. [see *Warnings and Precautions (5.6)*]

For patients who are unable to swallow the tablets, such as infants and children, Coartem Tablets may be crushed and mixed with a small amount of water (one to two teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

#### **2.2 Dosage in Adult Patients (> 16 years of age)**

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

For patients weighing less than 35 kg, see Dosage in Pediatric Patients (2.3).

#### **2.3 Dosage in Pediatric Patients**

A 3-day treatment schedule with a total of 6 doses is recommended as below:

**5 kg to less than 15 kg bodyweight:** One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days (total course of 6 tablets).

**15 kg to less than 25 kg bodyweight:** Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days (total course of 12 tablets).

**25 kg to less than 35 kg bodyweight:** Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) for the following two days (total course of 18 tablets).

**35 kg bodyweight and above:** Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

#### **2.4 Dosage in Patients with Hepatic or Renal Impairment**

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. 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. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe hepatic or renal impairment.[see *Warnings and Precautions* (5.7)]

### **Post Marketing Requirements and Commitments:**

Novartis agreed to the following post-marketing requirements (PMRs) and post-marketing commitments (PMC) in their letter dated March 26, 2009. These PMRs/PMC include 2 clinical, 2 pharmacology toxicology, 1 micro, 2 chemistry and 8 clinical pharmacology studies or clinical trials as listed below:

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

For a period of five years following approval, 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 outcomes. You should include representation of adults > 65 years, children ≤ 16 years, and overweight patients (BMI ≥ 25 kg/m<sup>2</sup>). Submit yearly reports summarizing data on patients treated with Coartem Tablets within the previous year and the final report integrating information on all patients in the Final Report Submission.

**2. Submit surveillance reports to evaluate the potential development of resistance to Coartem Tablets.**

For a period of five years following approval, 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. Perform spectral characterization of all specified impurities for lumefantrine impurities (b) (4) and artemether impurities (b) (4)**

The structure of lumefantrine impurities (b) (4) and artemether impurities (b) (4) should be characterized using spectral procedures such as <sup>1</sup>H- and <sup>13</sup>C-NMR (nuclear magnetic resonance), infrared (IR), ultraviolet and mass spectroscopy. Tabulated, interpreted data for all spectra, and copies of IR and <sup>1</sup>H-NMR spectra should be submitted.

**6. Conduct an *in vitro* study to characterize the induction potential of artemether, dihydroartemisinin (DHA), and lumefantrine on the metabolism of substrates of CYP3A4.**

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 Labeling* (<http://www.fda.gov/cder/guidance/6695dft.pdf>) for details on the conduct of the *in vitro* study.

If the results of this *in vitro* study are positive, a clinical trial will be needed to further assess this risk (see Item 14, below).

**7. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and rifampin.**

If, upon review, it is determined that the clinical trial discussed in Item 11 below adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* 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, the components of Coartem Tablets, and protease inhibitors (PIs).**

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

**9. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and non-nucleoside reverse transcriptase inhibitors (NNRTIs).**

If, upon review, it is determined that the clinical trial discussed in Item 13 below adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

- 10. Complete 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.”**

- 11. Complete a clinical drug interaction trial to evaluate the effect of a co-administered CYP3A4 inducer on the pharmacokinetics of artemether and lumefantrine, the components of Coartem Tablets.**

Complete 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 artemether and lumefantrine. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin will not be needed (see Item 7 above).

- 12. Complete a clinical drug interaction trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a protease inhibitor (PI).**

Complete a clinical drug interaction trial using a representative PI, such as lopinavir/ritonavir or ritonavir, to evaluate the two-way interaction between artemether and lumefantrine and a PI. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and PIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and a PI will not be needed (see Item 8 above).

- 13. Complete a clinical trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a non-nucleoside reverse transcriptase inhibitor (NNRTI).**

Complete a clinical drug interaction trial using a representative NNRTI, such as efavirenz or nevirapine, to evaluate the two-way interaction between artemether and lumefantrine and a NNRTI. If, upon review, it is determined the trial adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and an NNRTI will not be needed (see Item 9 above).

- 14. Conduct a clinical interaction trial to evaluate the induction potential of artemether and lumefantrine, the components of Coartem Tablets, on CYP3A4 substrates.**

If the results of the *in vitro* study (see Item 6 above) are positive, a clinical trial will be needed to further characterize the effect of artemether and lumefantrine on the pharmacokinetics of co-administered drugs that are metabolized by the CYP3A4 enzyme system, such as oral contraceptives.

### ***Post-Marketing Commitment:***

- 15. Develop a dissolution test method for Coartem Tablets to achieve a minimum (b) dissolution of each component, artemether and lumefantrine.**

Develop a test method to achieve (b) dissolution of each component in Coartem Tablets, artemether and lumefantrine, through the proposed shelf life. If possible, one dissolution test method should be developed for both components. Two yearly interim reports should also be submitted.

## BACKGROUND:

### **Coartem:**

Coartem is a combination product containing two antimalarial drugs: artemether and lumefantrine. Each Coartem Tablet contains 20 mg of artemether and 120 mg of lumefantrine, in a 1:6 ratio. The tablets are yellow, round, and flattened with beveled edges and scored on one side. They are imprinted with N/C on one side and CG on the other side.

Novartis developed Coartem outside the United States, therefore the development program did not include an IND and the development program and protocols were not reviewed by the FDA. Coartem was first marketed by Novartis in Gabon and Europe in 1998 for the treatment of uncomplicated falciparum malaria, the same indication being sought in the US. The drug is currently marketed in 87 countries; in Europe it is marketed under the name Riamet and in the rest of the world it is marketed under the name Coartem. Coartem is the first artemisinin combination product submitted for review to FDA. The World Health Organization (WHO) recommends artemisinin-containing combination therapy (ACT) for *Plasmodium falciparum* treatment to prevent failure due to drug resistance.

(b) (4)



### **Malaria:**

Malaria is a serious infection that affects millions of people worldwide, particularly in Sub-Saharan Africa, but also in South East Asia, the Papua/New Guinea Region, and South America. There are an estimated 300-600 million patients infected annually, and 1 to 3 million deaths.<sup>1</sup> Mortality is particularly high among children under the age of 5, accounting for over 75% of malaria deaths.<sup>2</sup>

Malaria parasites are carried by the *Anopheles* mosquito, and introduced into the human as sporozoites via the bite from the mosquito. The sporozoites leave the bloodstream, enter the liver, and mature within 5-15 days to schizonts. The mature schizont ruptures, releasing merozoites into the blood stream. Merozoites invade red blood cells (RBC), mediated by receptor-ligand activity between the parasite and erythrocyte (e.g., merozoites surface protein, MSP-1; circumsporozoite protein, CSP; apical membrane antigen-1, AMA-1; erythrocyte binding antigen 175, EBA-175; and sporozoite surface protein-2, SSP2).<sup>3</sup> In the RBC, they mature to trophozoites which rupture to release more merozoites and continue the infection. (There is no dormant hypnozoites stage associated with *P. falciparum*, in contrast to *P. vivax* and *P. ovale*.) As the parasite matures, it induces knob formation on the RBC surface, increasing RBC cytoadherence to endothelium in capillaries and postcapillary venules in the liver, brain, kidneys and other organs.<sup>4</sup> This sequestration of RBCs in capillaries, leads to microcirculatory problems and metabolic dysfunctions characteristic of the malaria infection.

<sup>1</sup>Hommel M. Towards a research agenda for global malaria elimination. *Malaria Journal* 2008; 7(S1):S1. <http://www.malariajournal.com/content/7/S1/S1>

<sup>2</sup> Children and Malaria. Roll Back Malaria. [http://www.rbm.who.int/cmc\\_upload/0/000/015/367/RBMInfosheet\\_6.htm](http://www.rbm.who.int/cmc_upload/0/000/015/367/RBMInfosheet_6.htm)

<sup>3</sup> Cellular and Molecular Biology of *Plasmodium*. <http://www.tulane.edu/~wiser/malaria/cmb.html#msp>

<sup>4</sup> Krogstad DJ. *Plasmodium* Species (Malaria). Principles and Practice of Infectious Diseases. ed. Mandell, Douglas, and Bennett. Churchill Livingstone c. 2000.

Malaria symptoms usually appear 1-2 weeks after the mosquito bite, initially flu-like symptoms including headache, fever, muscle pain, lassitude, nausea, and anorexia. The release of parasites in the bloodstream is associated with the acute febrile illness. Fever may occur at 2-3 day intervals or continuously, depending on the synchronization of maturation and release of the merozoites. Continued multiplication and release of the parasites is associated with clinical fevers and chills; the repeat cycles result in damage to red cells and red cell sequestration in various organs, leading to anemia, hypoglycemia, lactic acidosis, renal compromise, hepatomegaly, splenomegaly, gastroenteritis, pulmonary edema, and may include cerebral malaria (including seizures, impaired consciousness, and coma). Inflammatory cytokines such as TNF- $\alpha$  are increased in patients with malaria.

Untreated malaria particularly in young children and travelers to endemic regions is progressive, severe and often fatal if untreated. Persons living in endemic areas may have partial immunity, but can also develop severe and fatal disease. Therefore, prompt treatment is warranted, and placebo controlled studies are not considered ethical. A number of drugs are available for the treatment of malaria (Lariam, Malarone, chloroquine, Fansidar) however, because the malaria parasite develops resistance to some of these, new therapies are important. Extensive chloroquine resistance has been documented in Africa, Asia and Indonesia; also Fansidar is ineffective in some regions.

Malaria in the US is rare; approximately 1500 cases of malaria are reported to CDC annually. In 2006, there were 1564 cases reported, six of which were fatal.<sup>5</sup> Other US groups that may become infected with the parasite include Peace Corps workers, embassy workers, and military staff who work in or visit the endemic areas. Therefore, availability of new products evaluated and used in these endemic regions is valuable.

### **NDA Submission:**

The Coartem development program was conducted completely outside the US, and the clinical trials that supported the safety and efficacy of Coartem had already been completed before Novartis met with the Agency to discuss submitting a New Drug Application for Coartem. The Division and company met for two pre-NDA meetings, held October 30, 2006, and November 9, 2007. During these meetings, Novartis listed the studies they had conducted and discussed with FDA their submission plans, including which study reports would need to include electronic datasets for review and the level of detail that would need to be included in the NDA. In addition, the Division noted that the study sites should be available for inspection.

Novartis submitted study reports for the 24 clinical trials they conducted between 1993 and 2007, including 8 clinical trials for which patient line listings and datasets were submitted to enable the Division to conduct a comprehensive review. These 8 trials included (a) two studies evaluating the contribution of the artemether and lumefantrine components to the Coartem treatment effect using factorial design studies and (a) six studies evaluating the safety and efficacy of the 6-dose regimen. For the other 16 studies, Novartis provided study reports and case report tabulations.

Also included in the NDA were study reports and brief patient listings for 4 studies that were conducted by the Academy of Military Medical Sciences (AMMS) in China from 1987 to 1989.<sup>6</sup> These studies were not sponsored by Novartis, but are included in the NDA and summarized in this review as background information. These studies led to the licensing of artemether/lumefantrine in China In 1992.

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<sup>5</sup> Mali S et al Malaria surveillance-United States, 2006. *MMWR Surveill Summ* 2008; 57(5):24-39.

<sup>6</sup> EDR link \\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Subsequently, Ciba (became Novartis) began collaboration with AMMS to develop artemether/lumefantrine and conducted studies in other parts of the world starting in 1993.

**Artemether/lumefantrine studies in China:**

Study reports for the AMMS studies were included in the NDA. These studies were not inspected, and the DSI review noted that these studies were not done in complete compliance with GCP. These results are presented, because they provide background information on early work with these two drugs, and the results reported for these studies are comparable to the results reported in the Novartis trials.

**(1) AMMS1 - Study conducted in 1987 to evaluate the efficacy of different ratios of artemether and lumefantrine.**

Forty male or female patients 14-51 years of age were randomized to artemether/ lumefantrine at a 1:5 ratio (group 1) or artemether lumefantrine at a 1:6 ratio (group 2).

- Subjects in group 1 received 4 tablets (each tablet contained 20 mg artemether/100 mg lumefantrine) at 0, 8, 24 and 48 hours.
- Subjects in group 2 received 4 tablets (each tablet contained 20 mg artemether/120 mg lumefantrine) at 0, 8, 24, and 48 hours.

Parasite clearance time (mean=34-36 hours) and, fever clearance time (mean=22-23 hours) were similar for the two groups. The 28 day cure rate was 16/20 (80%) in the 1:5 ratio arm compared to 20/20 (100%) in the 1:6 ratio arm. Four patients recrudesced before day 28 in the 1:5 arm and 0 patients recrudesced before day 28 in the 1:6 arm. The results are shown in the table below and support that the product with the 1:6 ratio, containing a higher amount of lumefantrine, had a better outcome (28-day cure rate), and a lower recrudescence rate.

	group 1	group2
ratio of artemether : benflumetol	1:5	1:6
number of patients	20	20
mean 24 hr parasite reduction rate (%) ± SD	94.2 ± 6.6	96.3 ± 8.1
mean parasite clearance time (h) ± SD	36.0 ± 6.6	34.8 ± 5.4
mean fever clearance time (h) ± SD	22.4 ± 9.8	23.2. ± 8.1
recrudescence before day 28	4	0
28 day cure rate (%)	80.0	100.0

**(2) AMMS2- Study conducted in 1988 to demonstrate the contribution of each component to the treatment effect.**

Sixty male or female patients 14-46 years were randomized into one of 3 groups.

- Group 1 received 20 mg artemether/120 mg lumefantrine tablets, 4 tablets per dose given at 0, 8, 24, 48 hours,
- Group 2 received 80 mg of artemether only at 0, 8, 24 and 48 hours and
- Group 3 received 480 mg of lumefantrine (benflumetol) only at 0, 8, 24, and 48 hours.

Parasite clearance, fever clearance, and 28-day cure rates are presented in the table below, showing that the combination had a better 28-day cure rate (90%) than either drug alone (45% artemether, 75% lumefantrine). The combination also resulted in faster fever and parasite clearance than lumefantrine alone.

	group 1 compound artemether	group2 artemether only	group 3 benflumetol only
No. of cases	20	20	20
mean 24 hr parasite reduction rate (%) $\pm$ SD	97.3 $\pm$ 3.8	95.1 $\pm$ 5.2	74.5 $\pm$ 15.7
mean parasite clearance time (h) $\pm$ SD	35.6 $\pm$ 7.8	38.7 $\pm$ 8.2	68.4 $\pm$ 14.7
mean fever clearance time (h) $\pm$ SD	23.8 $\pm$ 5.4	19.7 $\pm$ 8.4	40.2 $\pm$ 13.9
recrudescence before day 28	2	11	5
28 day cure rate (%)	90	45	75

**(3) AMMS3- Study conducted in 1988 to evaluate three different regimens (timing and number of doses).**

Sixty-six male or female patients 14-45 years were randomized into one of 3 groups, and received one of the following regimens. Each dose consisted of 4 tablets of 20mg artemether/120 mg lumefantrine per tablet.

Three different regimens were tested:

- 4 doses over 3 days, given at 0, 8, 24 and 48 hours
- 3 doses over 3 days, given at 0, 24 and 48 hours
- 4 doses over 2 days, given at 0, 8, 24 and 32 hours

Results are presented below, showing similar fever and parasite clearance time among the three arms; however, the 28 day cure was highest in Group 1 with the 4 dose regimen given over 48 hours (87.5%), lowest in Group 2 with the 3-dose regimen (72.7%) and intermediate in Group 3 with the 4 dose regimen over 32 hours (80%). The results are shown below:

	group 1	group 2	group 3
regimen	4 doses over 3 days	3 doses over 3 days	4 doses over 2 days
No. of patients	24	22	20
24 h parasite reduction rate (%)	96.5 $\pm$ 8.0	93.6 $\pm$ 10.1	97.8 $\pm$ 8.4
mean parasite clearance time (h)	40.7 $\pm$ 6.8	40.9 $\pm$ 7.3	38.8 $\pm$ 6.5
mean fever clearance time (h)	22.2 $\pm$ 5.5	26.9 $\pm$ 7.0	21.8 $\pm$ 6.7
recrudescence before day 28	3	6	4
28 day cure rate (%)	87.5	72.7	80

**(4) AMMS4- Study conducted in 1989 to evaluate artemether/lumefantrine in pediatric patients.**

One hundred male or female patients 5-14 years of age were treated with 2 tablets, 2.5 tablets, 3 tablets, or 3.5 tablets depending on age, and received drug at 0, 8, 24, and 48 hours. Each tablet contained 20 mg artemether/120 mg lumefantrine. Results of parasite and fever clearance were comparable to that seen in adults. The 28 cure rate was 93% as shown in the table below.

Fever clearance time (mean $\pm$ SD) (h)	parasite decrement (mean $\pm$ SD) by 24 h (%)	Asexual parasite clearance time (mean $\pm$ SD) (h)	Recrudescence	28 day cure rate (%)
23.0 $\pm$ 8.4	96.3 $\pm$ 11.5	40.6 $\pm$ 6.9	7	93

In this AMMS study report, the following background information is presented:

In this region of China chloroquine-resistant falciparum malaria is prevalent. In 1989, the WHO 28-day in vivo observation method (Lit. 1) for chloroquine sensitivity was used and 22 cases of falciparum malaria were treated with the chloroquine as part of another study (1, appx. VI). As a result 9 cases were cured (41 %), the remainder were resistant, respectively 5 (R I), 6 (R II) and 2 (R III).

Also in 1989, 37 cases treated with chloroquine were observed with the same method, among them 21 cases were cured (57 %), whilst 7, 8, and 1 cases were R I-III resistant respectively (unpublished data on file AMMS).

**Comment:** *These studies demonstrate the following:*

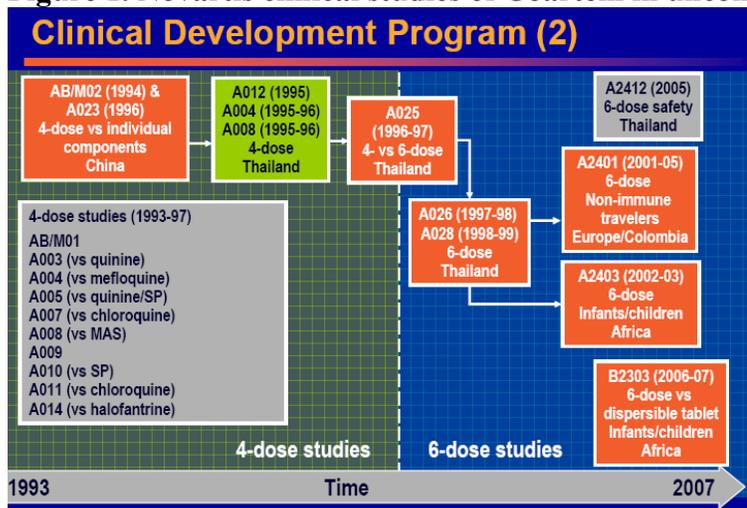
- each component of the combination makes a contribution to the treatment effect (AMMS2)
- the 1:6 tablet containing the higher lumefantrine content achieved a higher 28-day cure rate than the 1:5 tablet containing a lower amount of lumefantrine (AMMS1)
- that 4 doses given over 48 hours have a better 28-day cure rate than 3 or 4 doses given over a shorter period of time (AMMS3).
- the 20 mg artemether/120 mg lumefantrine tablets worked in curing malaria in children in a chloroquine-resistant area, with a 28-day cure rate of 93%, which exceeded the local historical cure rate of 41-57% in patients treated with chloroquine (AMMS4).

*These studies were done two decades ago, they were not inspected, and they may have been not in complete compliance with GCP; these limitations are noted. These studies led Ciba to collaborate with the Chinese AMMS to develop Coartem in other parts of the world*

## REVIEW SUMMARY:

Figure 1 below was shown during the Novartis presentation at the December 3, 2008 Advisory Committee meeting, and provides an overview of the time frame and locations where these 24 Coartem clinical studies were conducted. The 4-dose studies listed in the gray-shaded area were conducted between 1993 and 1997 and provided initial data on Coartem. The two factorial studies, AB/MO2 and A023, were conducted in 1994 and 1996 in China and evaluated artemether or lumefantrine alone and in combination. During 1995-1996, the 4-dose studies conducted in Thailand (in green-shaded area) showed the efficacy of a 4-dose regimen was too low in this region with a high rate of resistant malaria. This led to conduct of studies that evaluated the 6-dose regimen in Thailand from 1996 to 1999, and in Europe, Columbia and Africa in from 2001 to 2007.

**Figure 1. Novartis clinical studies of Coartem in uncomplicated malaria**



The table below provides more detail regarding these studies including the study numbers, study locations, populations studied, control regimens evaluated, and number of patients enrolled. Results from these studies support the efficacy of Coartem, as listed below. The quantitative results are then briefly summarized in subsequent text and tables:

- Studies AB/MO2 and A023 showed the contribution of each component to the efficacy of the combination.
- Study A012 evaluated different numbers of Coartem tablets per dose, and showed that the 4-tablet per dose regimen was better than regimens with fewer tablets per dose or fewer doses.
- Studies A07, A011, and AIC04 showed the 4-dose regimen of Coartem to be statistically superior at  $p < 0.001$  to chloroquine.
- Studies A003, A004, A008 were conducted in Thailand and showed that the 4-dose regimen was not effective in Thailand compared to quinine, mefloquine, or mefloquine/ artesunate. This prompted study of the 6-dose regimen.
- Study A025 was conducted in Thailand and showed that the 6-dose regimen was superior to the 4-dose regimen in evaluable patients.
- Studies A026, A028, were conducted in Thailand and compared the Coartem 6-dose regimen to mefloquine/artesunate.
- Study A2401 evaluated the 6-dose regimen in travelers from Europe and Columbia,
- Studies A2403 and B2303 evaluated the 6-dose regimen in pediatric patients in Africa.

**Table of Completed Clinical Studies of Coartem**

Study No.	Region/year/study design/ AL regimen	Population	Patients (n)	
			AL	Comparator
Studies included in original registration dossier				
AB/M1	China/1993/OL/4-dose	Adults	102	None
AB/MO2	China/1994/OL/4-dose	Adults	53	Artemether (52); Lumefantrine (52)
A009	Gambia/1995-6/OL/4-dose	Children (5-25 kg)	60	None
A010	Gambia/1996-7/DB, MC/4-dose	Children (6-25 kg)	144	Fansidar® (143)
A011	Tanzania/1996/OL/4-dose	Children ( $\geq 5$ kg)	130	Chloroquine (130)
A003	Thailand/1995-6/OL, MC/4-dose	Children (5-12 years)	111	Quinine (108)
A008	Thailand/1995-6/OL, MC/4-dose	Children (> 5 years) & adults	309	MAS (308)
A004	Thailand/1995-96/DB/4-dose	Adults	126	Mefloquine (126)
A005	UK/1996-97/OL,MC/4-dose	Adults	12	Quinine/Fansidar (11)
A007	India/1996-97/DB/4-dose	Adults	89	Chloroquine (90)
A012	Thailand/1995/DB,MC/4-dose	Adults	87	None
A014	Europe/1996-97/DB, MC/4-dose	Adults	51	Halofantrine (52)

Study No.	Region/year/study design/ AL regimen	Population	Patients (n)	
			AL	Comparator
Studies included in original registration dossier				
A023	China/1996/DB/4-dose	Adults	52	Lumefantrine
A025*	Thailand/1996-97/DB/4- & 6-dose	Adults	108 & 208	None
A026	Thailand/1997-98/OL,MC/6-dose	Adults	125	MAS (41)
Extension of 6-dose regimen to patients < 10 - > 5 kg				
A2403	Kenya,Nigeria,Tanzania/ 2002-2003/OL/MC/6-dose	Children (5-25 kg)	310	None
Additional studies supporting the 6-dose regimen				
A2401	Europe, Colombia/6-dose	Adults	165	None
A028	Thailand/1998-99/OL,MC/6-dose	Adults	162	MAS (50)
A030	Vietnam/2001/OL/6-dose	Adults	45	MAS (38)
ABD01	Bangladesh/2002-03/OL/6-dose	Adults	103	Quinine/Fansidar (103)
ABR01	Brazil/2000-02/OL/6-dose	Adults	28	Quinine/doxycycline (31)
AIC04	Senegal/2000/OL/4-dose	Adults	36	Chloroquine (36)
AIC04	Cameroon/2000/OL/4-dose	Adults	30	Fansidar (30)
Additional supportive data for the NDA submission				
B 2303	Kenya, Mali, Tanzania, Zanzibar, Benin, Mozambique/MC/6 dose	Children (5-35 kgs)	447	Coartem dispersible (434)

AL = Artemether-lumefantrine; DB = double-blind, MC = multicenter, OL = open-label, MAS = mefloquine/artesunate.

\*In study 025 two 6-dose regimens were used, with doses given over 60 hours or 96 hours

Source: Applicant's preNDA background document, October 2006.

The Division reviewed the two factorial studies (**AB/MO2** and **A023**) and the six recently-conducted studies (**A025**, **A026**, **A028**, **A2401**, **A2403**, and **B2303**) in detail to evaluate the safety and efficacy of the 6-dose regimen in adult and pediatric patients, as well as non-immune travelers. In addition, other studies that were included in the Coartem NDA were examined. Overall, these study results provided substantial evidence from adequate and well-controlled trials of the safety and efficacy of Coartem in adult as well as pediatric patients >5 kg (essentially pediatric patients 2 months or older) for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*.

In general, the design of these studies is consistent with the draft guidance for industry "*Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis*" posted in 2007;<sup>7</sup> the Novartis studies were conducted before the guidance was published. Patients in the studies were evaluated for parasitemia at baseline, daily until parasite clearance, and at day 28 to determine

<sup>7</sup> Draft Guidance for Industry Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis, available at <http://www.fda.gov/cder/guidance/index.htm>

parasitological cure. Main secondary endpoints were fever clearance time and parasite clearance time. Clinical outcome was reviewed.

## **Efficacy - Uncomplicated *Plasmodium falciparum* malaria:**

### **1) Factorial Design Studies AB/M02 and A023:**

The Code of Federal Regulations (21 CFR 300.50) specifies that when a fixed-combination drug is developed, the following terms are met:

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

This requirement was addressed in two of the studies submitted, **AB/MO2** and **A023**, both conducted in China. In these trials, Coartem achieved faster parasite clearance and fever clearance times than lumefantrine, and the combination yielded higher 28-day cure rates than artemether alone, as shown in the Table 1 below. These differences were statistically significant.

**Table 1. Outcome in Study AB/M02 and A023**

<b>Population<sup>1</sup>Study No. Region/patient ages</b>	<b>28-day cure rate<sup>2</sup> n/N (%) patients</b>	<b>Median PCT [25<sup>th</sup>,75<sup>th</sup> percentile]</b>	<b>Median FCT<sup>3</sup> [25<sup>th</sup>,75<sup>th</sup> percentile]</b>
<b>Study AB/MO2</b> China, ages 13 - 57 years			
Coartem Tablets	50/51 (98.0)	30 hours [24, 36]	24 hours [12, 48]
Artemether <sup>4</sup>	24/52 (46.2)	30 hours [24, 33]	21 hours [12, 30]
Lumefantrine tablets <sup>5</sup>	47/52 (90.4)	54 hours [45, 66]	60 hours [36, 78]
<b>Study A023</b> China, ages 12 - 65 years			
Coartem Tablets	50/52 (96.2)	30 hours [24, 36]	21 hours [24, 36]
Lumefantrine tablets <sup>6</sup>	45/51 (88.2)	48 hours [42, 60]	36 hours [42, 60]
<sup>1</sup> In mITT analysis, patients whose status was uncertain were classified as treatment failures. <sup>2</sup> Efficacy cure rate based on blood smear microscopy. <sup>3</sup> For patients who had a body temperature >37.5°C at baseline only <sup>4</sup> 95% CI (Coartem tablets – artemether) on 28-day cure rate: 37.8%, 66.0% <sup>5</sup> P-value comparing Coartem Tablets to lumefantrine tablets on parasite clearance time (PCT) and fever clearance time (FCT): < 0.001 <sup>6</sup> P-value comparing Coartem Tablets to lumefantrine tablets on parasite clearance time (PCT): <0.001 and on fever clearance time (FCT): <0.05			

### **2) Number of Doses – Study A012:**

Study A012 conducted at Mahidol University in Thailand evaluated different numbers of Coartem tablets per dose and different numbers of doses per regimen for the treatment of uncomplicated malaria. Each Coartem tablet contained 20 mg artemether/120 mg lumefantrine. Three regimens were tested:

- 4-tablet per dose, 4-dose regimen given at 0, 8, 24, and 48 hours,
- 2-tablet per dose, 4 dose regimen given at 0, 8, 24, and 48 hours, and
- 4-tablet per dose, 3-dose regimen given at 0, 8, and 24 hours.

There were about 87 patients per arm; they ranged in age from 15 to 60 years. In the table below, the differences in the 28 day cure outcome between the 4x4 dose regimen vs. the 4x2 tablets arm and the 3x4 tablets arm were statistically significant. Hence, subsequent studies evaluated a regimen of Coartem 20/120 tablets, 4 tablets at 0, 8, 24, and 48 hours (4x4 regimen).

**Table 2. Study A012 Dose Comparison**

**Exhibit 8.1.-1: 28 day cure rate (ITT)**

	4x4 tablets n=87	4x2 tablets n=87	3x4 tablets n=86
28 day cure rate	71.3%	47.1%	48.8%
95% confidence interval *	[60.6, 80.5] %	[36.3, 58.1] %	[37.9, 59.9] %

**Exhibit 8.1.-2: 28 day cure rate (evaluable patients)**

	4x4 tablets n=81	4x2 tablets n=76	3x4 tablets n=79
28 day cure rate	76.5%	53.9%	53.2%
95% confidence interval *	[65.8, 85.2] %	[42.1, 65.5] %	[41.6, 64.5] %

**3) Studies comparing Coartem (4-dose) to chloroquine - Studies A007, A011, AIC04:**

Studies A007, A011, and AIC04 (conducted in India, Tanzania, and Senegal, respectively) compared Coartem to chloroquine, and in each of these three studies, the cure rate of the Coartem 4-dose regimen was statistically superior to chloroquine ( $p < 0.001$  in each study) at either 14-days or 28-days after treatment. These three studies demonstrate the efficacy of Coartem and corroborate the results of study AMMS4 done in China in 1989 (above).

**Table 3. Efficacy of Active-Controlled Studies with 4-Dose Coartem Regimen**

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
A007	Coartem	89	-	-	95.4%	36 hr	98.8%	18 hr
	Chloroquine	90	-	-	19.7%*	60 hr	70.7%	27 hr
A011	Coartem	130	92.4%	84.1%	-	-	97.8%	-
	Chloroquine	130	29.6%	8.6%*	-	-	59%	-
AIC04 Senegal	Coartem	36	-	100%	-	1 day	94.3%	-
	Chloroquine	36	-	63.9%*	-	2 days	54.7%	-

**4) Studies comparing Coartem (4-dose) to Fansidar - Studies AICO4, A005, A010:**

Coartem has a higher cure rate in compared to Fansidar in 28-day cure rate in one study (AICO4), and was comparable to Fansidar in a second study (A010). In UK patients, Coartem resulted in faster parasite clearance compared to quinine and Fansidar.

**Table 4. Efficacy of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen**

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
AIC04 Cameroon	Coartem	30	-	93.3%	-	2 days	76.8%	-
	Fansidar	30	-	53.3%	-	7 days	49.2%	-
A005 UK	Coartem	12	-	-	100%	36 hr	99.2%	-
	Quinine/ Fansidar	11	-	-	100%	69 hr	87.6%	-
A010 Gambia	Coartem	144	-	93.3%	-	-	99.2%	-
	Fansidar	143	-	97.7%	-	-	92.5%	-

Fansidar = sulfadoxine/pyramethamine

*Comments: The early 4-dose studies summarized above showed that the 4-tablet per dose, 4 dose regimen was superior to regimens with fewer tablets and fewer doses. The combination was superior to either of the components. The 4-dose regimen was superior to chloroquine in three studies done in different parts of the world (India, Tanzania, and Senegal). Coartem activity compared to Fansidar varied depending on the country where the studies were conducted. Additional 4-dose studies were then undertaken in Thailand.*

#### **5) 4-dose Studies conducted in Thailand – Studies A003, A004, A008:**

The efficacy of the 4-dose regimen in Thailand (A003, A004, A008) was compared to quinine, mefloquine, or mefloquine/ artesunate, and was lower than in other parts of the world and lower than the control drugs. As shown in the Table 5 and 6 below, the 28-day rates for Coartem ranged from 60-82%, for the control drugs from 71-97%. Even though the 28-day cure rate was lower for Coartem, the parasite and fever clearance time was faster in the artemisinin-containing treatments (Coartem, MAS). The low 28-day cure rate of the 4-dose regimen in Thailand led to the evaluation of the 6-dose regimen in Thailand.

**Table 5. Efficacy of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen**

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
A003	Coartem	111	-	-	60.8%	40 hr	98.6%	52 hr
	Quinine	108	-	-	71.8%	77 hr	67.3%	88 hr
A004	Coartem	126	-	-	69.3%	43 hr	98.6%	32 hr
	Mefloquine	126	-	-	82.4%	66 hr	76.1%	54 hr
A008	Coartem	309	-	-	82.1%	-	100%	-
	MAS	308	-	-	97.3%	-	100%	-

#### **6) Comparing 4-dose to 6-dose regimen in Thailand – Study A025:**

As a result of the poor outcome of the 4-dose regimen in the Thai studies (A003, A004, A008), a 6-dose regimen was evaluated and compared to the 4-dose regimen in Study A025 conducted in Thailand. (x=active treatment, p=placebo) The dosing schedule is shown in Figure 2.

**Figure 2. Dosing in Study A025**

<b>Dosing in Study A025</b>	1	2	3	4	5	6	7	8
Time (hr.)	0	8	24	36	48	60	72	96
4 doses over 48 hours	x	x	x	p	x	P	p	p
6 doses over 60 hours	x	x	x	x	x	X	p	p
6 doses over 96 hours	x	x	x	p	x	P	x	x

Study A025 showed that the 6 dose-regimen was more effective than the 4-dose regimen; this difference was statistically significant in the evaluable population, as shown in Tables 6 and 7 adapted from Dr. Li’s review. The finding of statistical superiority in the evaluable population and the differences in outcome in the ITT population support the effectiveness of the 6-dose regimens. In addition, given that the 4-dose regimen is an active regimen, the results provide evidence of the effectiveness of the 6-dose regimen of Coartem. As seen in Table 6, in the 4-dose arm, 16.7% of patients discontinued from the study for lack of efficacy compared to 1.7 and 3.4% in the 6-dose regimens. Between 9-16% of patients were lost to follow up in these arms; these losses (patients) were classified as failures in the ITT population, and excluded from the denominator in the evaluable population.

**Table 6. Study A025 - comparing 4-dose and 6-dose regimens in Thailand – Reasons for Premature Discontinuation**

Study 25	4 doses 48 hours	6 doses 60 hours	6 doses 96 hours
Enrolled/Randomized	120	118	121
Premature discontinuation	35(29.2%)	23(19.5%)	18(14.9%)
<b>Unsatisfactory therapeutic response</b>	<b>20(16.7%)</b>	<b>4(3.4%)</b>	<b>2(1.7%)</b>
Lost to follow-up	11(9.2%)	19(16.1%)	15(12.4%)
Other	5	3	1
Evaluable patient population	104 (86.7%)	96 (81.4%)	106 (87.6%)

**Table 7. Study A025 - 28-day cure rate rates in ITT and Evaluable populations**

Population parameter	28-day Cure Rate		
	4 doses (48 hours)	6 doses (60 hours)	6 doses (96 hours)
<b>ITT</b>	85/120 (70.8%)	96/118 (81.4%)	104/121 (86.0%)
95%CI	[61.8%, 78.8%]	[73.1%, 87.9%]	[78.5%, 91.6%]
Diff [97.5%CI]		10.5% [-1.9%,22.8%]	15.1% [2.8%, 27.3%]
p-value		0.069	0.0048
<b>Evaluable</b>	84/104 (80.8%)	93/96 (96.9%)	104/106 (98.1%)
95%CI	[71.9%, 87.8%]	[91.1%, 99.4%]	[93.4%, 99.8%]
Diff [95%CI]		16.1% [7.8%, 24.4%]	17.3%[9.3%, 25.3%]
Diff [97.5%CI]		16.1% [6.0%, 26.7%]	17.3% [7.6%, 27.7%]
p-value		<b>&lt; 0.001</b>	<b>&lt; 0.001</b>

Table by Dr. Li - Adopted from sponsor’s Exhibit 8.1.-1 and 8.1.-2, study report (page 37).  
97.5% CIs were calculated by the reviewer using the exact method.

Although the 6-dose 60-hour regimen has a numerically lower outcome than the 6-dose 96 hour regimen, this difference was not significant. Coupled with the greater simplicity of the 6-dose regimen over 60 hours, this regimen was chosen as the regimen to further evaluate in subsequent studies.

**7) 6-dose Studies in Thailand – A026 and A028:**

In addition to study A025, two studies evaluating treatment of malaria in Thailand in pediatric and adult patients were submitted, A026 and A028. In these studies, patients were randomized to Coartem or mefloquine plus artesunate tablets (MAS). MAS is not approved in the US, however mefloquine (Lariam) is approved for treatment as a 1250 mg single dose.

In studies 026 and 028, randomization was 3:1, thus fewer patients were enrolled in the MAS arms, and the studies were not designed to test for statistical significance. As noted in the statistical review, “MAS was included [in 026 and 028] for comparison with historical data rather than a formal statistical comparison. Since MAS could not be blinded, the study was designed as an open label study”.<sup>8</sup> The outcome of 28-day cure rate is numerically higher in the MAS arm compared to the Coartem 6-dose arm. Of note is that the cure rate observed for the Coartem 6-dose arm exceeds what was observed in studies of patients treated with chloroquine in areas where chloroquine resistant malaria is prevalent, Studies A007, A011, and AIC04, and the 28-day sure rates are higher than the cure rates observed in the Coartem 4-dose regimen studies from Thailand that led to the investigation of a 6-dose regimen. Considering data on the progression of malaria in the absence of effective therapy, the clinical trials support the effectiveness of Coartem in treatment of uncomplicated malaria.

**Table 8. Study 026 evaluation 6-dose regimen of Coartem**

<b>Study A026, Thailand</b>		Coartem	MAS
Enrolled/Randomized		150	50
Study Center 1 / Study Center 2		21/129	7/43
Premature discontinuation		23(15.3%)	5(10.0%)
<b>Unsatisfactory therapeutic response</b>		<b>4(2.7%)</b>	<b>0</b>
Lost to follow-up		17(11.3%)	5(10.0%)
Other		2	0
<b>Study A026 Thailand</b>		Coartem	MAS
ITT		130/150 (86.7%)	47/50 (94.0%)
95%CI		[80.2%, 91.7%]	[83.5%, 98.7%]
Diff(Coartem-MAS) [95%CI]		-7.3% [-15.9%, 1.2%]	
Evaluable		130/134 (97.0%)	47/47 (100%)
95%CI		[92.5%, 99.2%]	[92.5%, 100%]
Diff(Coartem-MAS) [95%CI]		-3.0% [-7.9%, 4.4%]	

Adapted from Statistical Review, Dr. Li.

**Table 9. Study A028 evaluating 6-dose regimen of Coartem**

<b>Study A028, Thailand</b>		Coartem	MAS
Enrolled/Randomized		164	55
Premature discontinuation		16(9.8%)	2(3.6%)
<b>Unsatisfactory therapeutic response</b>		<b>7(4.3%)</b>	<b>0</b>
Lost to follow-up		9(5.5%)	2(3.6%)
<b>Study A028 Thailand</b>		Coartem	MAS
ITT		148/164 (90.2%)	53/55 (96.4%)
95%CI		84.6%, 94.3%	87.5%, 99.6%
Diff(Coartem-MAS) [95%CI]		-6.1%[-12.8%, 0.6%]	
Evaluable		148/155 (95.5%)	53/53 (100%)
95%CI		90.9%, 98.2%	93.3%, 100%

<sup>8</sup> Statistical Review Dr. Xianbin Li, November 24, 2008, page 15

Diff(Coartem-MAS) [95%CI]	-4.5%[-9.3%, 2.1%]
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Adopted from Exhibit 8.1.-1 & 2 in sponsor's study report (page 31)

Adapted from Statistical Review by Dr. Li

*Comments: The lower efficacy seen in the 4-dose studies done in Thailand increased when a 6-dose regimen was used. The 6-dose regimen was superior to the 4-dose regimen in a study where the two were compared directly, and the 28-day cure rates of the 6-dose regimen were also similar to the 28-day cure rates seen with the mefloquine/artesunate control arms. The 6-dose regimen was effective in Thailand.*

### **8) 6-dose study in Non-Immune travelers in Europe and Colombia - Study 2401:**

Study 2401 enrolled patients from Switzerland, Germany, France and Colombia, South America. Patients ranged in age from 16-66 years, and received the 6-dose regimen over 60 hours. The data from Study 2401 assesses safety and efficacy from a population of patients from regions of the world where malaria is not endemic; in general, persons infected with malaria in this study would not have pre-existing immunity (analogous to US travelers). The 28-day cure rate was 74% in the ITT population and 96% in the evaluable population. A more detailed analysis showed that the major reason for being considered a failure in the ITT population was loss to follow-up (10%), although early and late failures were also seen.

**Table 11. Outcome in Study 2401, Non-Immune Travelers**

Study 2401 in Europe/Columbia, ages 16 – 66 years	ITT 120/162 (74.1)	Evaluable 119/124 (96.0)	Median PCT [25 <sup>th</sup> , 75 <sup>th</sup> percentile]	Median FCT <sup>2</sup> [25 <sup>th</sup> , 75 <sup>th</sup> percentile]
Early failure	6 (3.7)	1 (0.8)	-----	-----
Late failure	3 (1.9)	3 (2.4)	42 hours	37 hours
Lost to follow up	17 (10.5)		[34, 63]	[18, 44]
Other	16 (9.9)	1 (0.8)		

The data were analyzed based on the weight of the patient (< 70 kg, or ≥ 70 kg). As shown in Table 12, a difference in outcome was seen but the main reason for the lower 28-day cure rate the patients >70 kg (67%) is accounted for by missing data, not documented treatment failure.

**Table 12. Outcome in Study 2401, by patient weight**

	< 70 kg N = 61	≥ 70 kg N = 98
<b>Cure</b>	<b>53 (87%)</b>	<b>66 (67%)</b>
<b>Failure</b>	<b>3 (5%)</b>	<b>8 (8%)</b>
Parasite clearance not achieved by day 7	1	2
Reappearance of parasites	0	3
Anti-malaria rescue medication taken	2	2
Patient withdrawn due to lack of efficacy	0	1
<b>Missing</b>	<b>5 (8%)</b>	<b>24 (24%)</b>
Lost to follow-up/Patient withdrew	4	20
Count not done or too early	1	4

**9) Pediatric Studies testing 6-dose regimen in Africa – Studies A2403 and B2303:**

Studies A2403 (Nigeria, Kenya, Tanzania) and B2303 (Tanzania) enrolled pediatric patients 2 months to 12 years of age. Children received whole tablets or crushed tablets (20 mg artemether/ 120 mg lumefantrine). The number of tablets per dose was determined by the patient’s weight (1 tablet if < 15 kg, 2 tablets if <25 kg, 3 tablets if <35 kg). Results are shown below for the ITT populations. Because these studies were conducted in endemic areas, reappearance of parasitemia may represent either re-infection or recrudescence. The company-presented PCR-corrected rates were approximately 10% higher, but the microbiology team did not consider PCR-corrected rates acceptable because the assay could not be verified because performance characteristic for the PCR assay were not submitted for review.

**Table 10. Studies in Pediatric Patients in Africa**

Studies in Africa Weight Category	Coartem 6-Dose Regimen	
	28-day Cure Rate n/N (%) patients	Median PCT [25th - 75th percentile]
<b>Study A2403</b>		
5 - < 10 kg	133/154 (86)	24 [24 - 36]
10 - < 15 kg	94/110 (86)	35 [24 - 36]
15 - < 25 kg	41/46 (89)	24 [24 - 36]
<b>Study B2303</b>		
5 - < 10 kg	61/83 (74)	36 [24 - 36]
10 - < 15 kg	160/190 (84)	35 [24 - 36]
15 - < 25 kg	123/145 (85)	35 [24 - 36]
25 - < 35 kg	30/34 (88)	26 [24 - 36]

Source: slide 26 from FDA efficacy presentation at December 3, 2008 Anti-Infective Drugs Advisory Committee meeting.

**Discussion:**

Novartis submitted results of 24 clinical studies. Although none of the studies included a placebo control arm, efficacy of Coartem has been shown in a number of ways, including studies in Asia and Africa where Coartem was shown to be superior to chloroquine (A007, A011, AIC04).

Chloroquine resistance is wide spread in the regions where these studies were conducted, and the low 28-day cure rates reported with chloroquine can be considered as an indirect estimate (likely an overestimate) of the response rates in untreated patients. According to the WHO, chloroquine resistance has been documented in all falciparum-endemic areas except Central America and the Caribbean.<sup>9</sup> In Kenya, in vitro tests showed chloroquine resistance of 60% compared to no resistance to amodiaquine, pyrimethamine/sulfadoxine, pyrimethamine /sulfalene.<sup>10</sup> Zucker reported that chloroquine-resistance accounted for 69% attributable mortality in Kenyan children based on data from a study showing case fatality of 13% among 296 children treated with chloroquine and 4.1% in 171 treated with Fansidar, quinine or TMP/SMX, relative risk = 3.22 (95% CI: 1.47, 7.04).<sup>11</sup> Chloroquine

<sup>9</sup> WHO Guidelines for the treatment of malaria. WHO/HTM/MAL/2006.1108. p 167.

<sup>10</sup> Hagos B, Khan B, Ofulla AV, Kariuki D, Martin SK. Response of falciparum malaria to chloroquine and three second line antimalarial drugs in a Kenyan coastal school age population. *East Afr Med J.* 1993 Oct;70(10):620-625.

<sup>11</sup> Zucker JR, TK Ruebush, C Obonyo, et al. The Mortality consequences of the continued use of chloroquine in Africa: Experience in Siaya, Western Kenya. *Am J Trop Med Hyg* 68(4),2003:386-390.

failure rates as high as 50% to 95% have been reported in some parts of Nigeria.<sup>12</sup> Children in Ghana randomized to four different drug regimens had the following PCR-corrected 28 day cure rates: 100% for amodiaquine/artesunate, 97.5% for Coartem, 60% for sulfadoxine/pyrimethamine, and 25% for chloroquine.<sup>13</sup>

In some studies, Coartem performed better compared to other antimalarials. In Uganda patients on Coartem had 28-day failure rates of 6.7% (95% CI 3.9-11.2%) compared to 17.4% (95% CI 13.1-23.1%) for amodiaquine plus artesunate and 26.1% (95%CI 21.2-32.1%) for amodiaquine plus sulfadoxine-pyrimethamine ( $p < .05$ ).<sup>14</sup> In Rwanda, artesunate/lumefantrine 28-day cure rates were 96% (233/241) vs. 79% (196/247) for amodiaquine with sulfadoxine/pyrimethamine ( $p < 0.0001$ ).<sup>15</sup>

The estimated burden of malaria is highest in Africa where more than 80% of malaria cases (estimated 212 million) occur, and 90% of the fatal cases (estimated 800,000 persons) also occur in Africa, 85% in children under 5 years of age, based on examination of data in 2006.<sup>16</sup> Within Africa, the burden is greatest in Nigeria, Congo, Ethiopia, Tanzania, and Kenya, respectively, and the pediatric studies A2402 and B2303 were conducted in three of these countries. Outside Africa, the burden is high in India, Sudan, Myanmar, Bangladesh, and Indonesia. The comparative Coartem vs. chloroquine studies were done in two of these countries, Tanzania and India. Study A007 was done in India and the 28-day cure rate was 95% for Coartem and 20% for chloroquine ( $p < 0.001$ ). Study A011 was done in Tanzania and showed that Coartem was superior to chloroquine, with 28-day cure rates of 84% for Coartem and 6% for chloroquine ( $p < 0.001$ ). And finally Study AIC04 done in Senegal also showed a significant difference in outcome: 100% for Coartem and 64% for chloroquine. In this context, Coartem is effective. Evidence that Coartem is superior to an ineffective therapy in these studies also provides assay sensitivity in studies where Coartem was compared to MAS, and both regimens had high 28-day cure rates showing efficacy.

Other studies that demonstrate that Coartem is effective in the treatment of uncomplicated malaria include:

- Studies AB/MO2 and A023 used a factorial (or partial factorial) design and showed that the combination is superior to each of the components, and each contributed to the treatment effect.
- Study A012 showed that the 4-dose regimen was superior to regimens using a smaller number of tablets per dose or fewer than 4 doses.
- Study A025 showed that the 6-dose regimen was superior to the 4-dose regimen in the evaluable population and performed better in the ITT population.
- Studies A2401 in non-immune travelers and Studies A2403 and B2303 in African pediatric patients demonstrated that the 6-dose regimen was effective in treating malaria, taking into account the low efficacy rates achieved with chloroquine in studies A007, A011 and AIC04 and in published studies.

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<sup>12</sup> Palade CO, AO Ogundele, BO Yusuf, et al. High efficacy of two artemisinin-based combinations (artemether-lumefantrine and artesunate plus amodiaquine) for acute uncomplicated malaria in Ibadan, Nigeria. *Tropical Medicine and International Health* May 2008. Vol 13. No 5 p 635-643.

<sup>13</sup> KA Komam, B Abuaku, N Duah, N Quashie. Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana. *Acta Tropica* 2005;95:194-203.

<sup>14</sup> Dorsey G, S Staedke, TD Clark, et al, PJ Rosenthal. Combination Therapy for Uncomplicated Malaria in Ugandan Children. *JAMA* 2007;297:2210-2219.

<sup>15</sup> CI Fanello, C Karema, W van Doren et al. A randomized trial to assess the safety and efficacy of artemether-lumefantrine (Coartem) for the treatment of uncomplicated *Plasmodium falciparum* malaria in Rwanda. *Trans Royal Soc Trop Med Hyg* 2007;101:344-350.

<sup>16</sup> World Malaria Report 2008, WHO/HTM/GMP/2008.1

### **Acceptability of Foreign Studies:**

As noted previously, Coartem was submitted as a complete NDA without any IND development in the US and included only foreign studies. The Code of Federal Regulations allows foreign data (21 CFR 314.106 and 21 CFR 312.120) to be submitted in support of a US application if various criteria are met:

#### **Text of 21 CFR 314.106, Foreign data:**

- (a) General. The acceptance of foreign data in an application generally is governed by [§ 312.120](#) of this chapter.
- (b) As sole basis for marketing approval. An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.
- (c) Consultation between FDA and applicants. Applicants are encouraged to meet with agency officials in a "presubmission" meeting when approval based solely on foreign data will be sought.

#### **Excerpts of Text from 21 CFR 312.120, Foreign clinical studies not conducted under an IND:**

##### **§ 312.120 Foreign clinical studies not conducted under an IND.**

- (a) *Introduction.* This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug based solely on foreign clinical data is governed by §314.106.
- (b) *Data submissions.* A sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval shall submit to FDA the following information:
- (1) A description of the investigator's qualifications;
  - (2) A description of the research facilities;
  - (3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;
  - (4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and
  - (5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under §314.126.
- (c) *Conformance with ethical principles.* (1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" (see

paragraph (c)(4) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the “Declaration of Helsinki” or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the “Declaration of Helsinki” and how they offer greater protection.

(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a “review committee” means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

(4) The “Declaration of Helsinki” states as follows: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects (*see CFR for complete text which provides background and principles of studies involving human subjects*)

The studies submitted in the Coartem NDA met the above criteria. The complete protocols, audited study reports, patient level data and electronic datasets for the eight clinical studies were submitted for complete review, study reports and case report tabulations for the other studies were submitted. The study sites in China, Thailand and Africa (Kenya, Tanzania) were inspected. These inspections included review of records from studies A023 and AB/MO2 in China; Studies A025, A026 and A028 in Thailand; and Studies A2403 and B2303 in Kenya and Tanzania. The sites inspected were found to be acceptable by the Division of Scientific Investigation. Dr. Thompson notes that “All studies performed since the collaboration between Ciba/Novartis and the Chinese partners (from 1992) were conducted to international GCP guidance and Ciba/Novartis SOPs, and comply with the Declaration of Helsinki and its revisions. Studies performed by the AMMS, Beijing China, were not totally compliant with GCP.”

*Comment: The deviations from GCP in the AMMS China studies are not stated in the consult, and the AMMS studies are not relied on as part of the demonstration of efficacy.*

Malaria is not endemic in the US, and patients with malaria in the US acquired it abroad, by travel or work in the same regions that the studies were conducted. The studies included European non-immune travelers and African pediatric patients who generally have either very low or no immunity; US patients also lack immunity. The Novartis Coartem clinical trials were conducted in China, Thailand, Africa (Kenya, Nigeria, Tanzania) Europe (Switzerland, Germany, France) and South America (Colombia), thereby including patients of many nationalities. In summary, it can be concluded that these foreign studies can be relied on for approval and the results are applicable to the US population.

### **Statistical Summary:**

Both the ITT and the evaluable populations were reviewed. The draft guidance to industry document on malaria cited above recommends the MITT population should be evaluated, but the ITT population was evaluated because essentially all but a few patients in that population had documented parasitemia at baseline, and the overall conclusions and interpretations did not differ. As would be expected, the 28-day cure rates in the ITT populations of studies AB/MO2, A023, A025, A026, A028, A2401, A2403 and B2303, were lower than in the evaluable populations, because losses to follow-up were classified as

failures. In the evaluable population, failure was due to documented parasitemia by the 28-day visit. These failures were primarily late failures, although some early failures were seen in the two pediatric African studies. The early failures, however, may be due to re-infection, because these studies were conducted in high transmission areas and they were not PCR-corrected as noted earlier. Results of these analyses will be included in the CLINICAL STUDIES section of the labeling (see Table 14).

**Table 14 . Clinical Efficacy of 6-dose Regimen of Coartem Tablets**

Study No. Region/ages	28-day cure rate <sup>1</sup> n/N (%) patients		Median PCT [25 <sup>th</sup> , 75 <sup>th</sup> percentile]	Median FCT <sup>2</sup> [25 <sup>th</sup> , 75 <sup>th</sup> percentile]
	mITT <sup>3</sup>	Evaluable		
<b>Study A025</b> Thailand, ages 3 – 62 years	96/118 (81.4)	93/96 (96.9)	44 hours [22, 47]	35 hours [20, 46]
Early failure <sup>4</sup>	0	0		
Late failure <sup>5</sup>	4 (3.4)	3 (3.1)		
Lost to follow up	18 (15.3)			
<b>Study A026</b> Thailand, ages 2 – 63 years	130/149 (87.2)	130/134 (97.0)	NA	22 hours [21, 42]
Early failure <sup>4</sup>	0	0		
Late failure <sup>5</sup>	4 (2.7)	4 (3.0)		
Lost to follow up	13 (8.7)			
<b>Study A028</b> Thailand, ages 12 – 71 years	148/164 (90.2)	148/155 (95.5)	29 hours [18, 40]	29 hours [8, 51]
Early failure <sup>4</sup>	0	0		
Late failure <sup>5</sup>	7 (4.3)	7 (4.5)		
Lost to follow up	9 (5.5)			
<b>Study A2401</b> Europe/Columbia, ages 16 – 66 years	120/162 (74.1)	119/124 (96.0)	42 hours [34, 63]	37 hours [18, 44]
Early failure <sup>4</sup>	6 (3.7)	1 (0.8)		
Late failure <sup>5</sup>	3 (1.9)	3 (2.4)		
Lost to follow up	17 (10.5)			
Other <sup>6</sup>	16 (9.9)	1 (0.8)		
<b>Study A2403</b> Africa, ages 2 months – 9 years	268/310 (86.5)	267/300 (89.0)	24 hours [24, 36]	8 hours [8, 24]
Early failure <sup>4</sup>	2 (0.6)	0		
Late failure <sup>5</sup>	34 (11.0)	33 (11.0)		
Lost to follow up	2 (0.6)			
Other <sup>6</sup>	4 (1.3)			
<b>Study B2303</b> Africa, ages 3 months – 12 years	374/452 (82.7)	370/419 (88.3)	35 hours [24, 36]	8 hours [8, 23]
Early failure <sup>4</sup>	13 (2.9)	0		
Late failure <sup>5</sup>	49 (10.8)	49 (11.7)		
Lost to follow up	6 (1.3)			
Other <sup>6</sup>	10 (2.2)			

<sup>1</sup> Efficacy cure rate based on blood smear microscopy

<sup>2</sup> For patients who had a body temperature >37.5°C at baseline only

<sup>3</sup>In mITT analysis, patients whose status was uncertain were classified as treatment failures.

<sup>4</sup>Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days

<sup>5</sup>Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28 day follow-up period

<sup>6</sup>Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment

### **Mixed infections: Uncomplicated *Plasmodium vivax* malaria**

Novartis requested that Coartem be labeled for uncomplicated malaria due to *P. falciparum* including mixed infections, and their application included 43 patients with mixed infections, all of whom had clearance of parasites at the end of 7 days, but 33% of whom relapsed on follow-up. In addition there were no cases of infections due to *P. vivax* alone to evaluate the efficacy of Coartem, and such information would be expected before including the indication in labeling.

Two published articles were identified that reported on patients with *P. vivax* infections treated with Coartem. In one study, 774 mostly pediatric patients were randomized to Coartem vs. dihydroartemesinin-piperaquine (D-P), of whom 175 had *P. vivax* infection and 113 had mixed falciparum and vivax infection.<sup>17</sup> By day 3, 99% of these patients cleared parasitemia, but by day 42, 57% (n=141) of the Coartem and 14% (n=147) of the D-P patients, respectively, relapsed. 91 patients with recurrent *P. vivax* alone were retreated with either quinine plus primaquine with or without doxycycline (n=26) or with amodiaquine plus primaquine (n=65) and followed an additional 28 days. The cumulative risk of recurrence in these patients was reported to be 26%. In a second study,<sup>18</sup> 98 patients were randomized to chloroquine or Coartem, and then received 15 mg primaquine over 14 days. At 28 day follow up, 9 patients in each arm were lost-to follow up, and the cure rates were 42/42 (100%) and 37/38 (97.4%), respectively.

The above results indicate that Coartem is effective in clearing the erythrocytic stage of parasitemia, but does not work against the hypnozoite liver stage and treatment with an agent such as primaquine is needed to eliminate hypnozoites and prevent relapses of vivax malaria. Before the indication could be granted, patient level data from the two published studies need to be submitted and reviewed.

At present, the following information is to be included in the Coartem labeling in the WARNING AND PRECAUTIONS section:

#### **5.7 *Plasmodium vivax* Infection**

Coartem Tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of *P. vivax* infection. However, relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

### **Safety Summary:**

Coartem was evaluated in clinical trials involving 1434 adult and 1991 pediatric patients (2 months to 16 years of age) who received 4-dose or 6-dose regimens. There were 1979 patients treated with a 6-dose regimen of Coartem Tablets, including 647 adults (older than 16 years) and 1332 children (16 years and

<sup>17</sup> Ratcliff A et al. Two fixed-dose artemisinin combinations for drug-resistance falciparum and vivax malaria in Papua, Indonesia: an open label randomized comparison. [www.thelancet.com](http://www.thelancet.com) Vol 369 March 3, 2007, p757-65.

<sup>18</sup> Krudsood S et al. Clinical efficacy of chloroquine versus artemether-lumefantrine for *Plasmodium vivax* treatment in Thailand. *Korean J Parasit* 2007;45(2):111-4.

younger). The 6-dose regimen of Coartem Tablets was studied in active-controlled (366 patients) and non-controlled trials (1613 patients). The patients that received the 6-dose regimen ranged from 2 months to 71 years: 1332 (67%) were 16 years and younger, and 647 (33%) were older than 16 years; only 7 patients were older than 65 years. Males represented 73% of the adult and 53% of the pediatric populations. Most of the adult patients were enrolled in studies in Thailand, while the majority of pediatric patients were enrolled in studies in Africa. Travelers from Europe and South America were also included in a non-comparative study.

In adults, the most frequently reported adverse reactions were headache, anorexia, dizziness and asthenia. In children, the adverse reactions were pyrexia, cough, vomiting, anorexia and headache. Most adverse reactions were mild, did not lead to discontinuation of study medication, and resolved.

Discontinuation of Coartem Tablets due to adverse drug reactions occurred in 1.1% of patients treated with the 6-dose regimen overall: 1/647 (0.2%) of adults and 21/1332 (1.6%) of children. Of the few reported deaths (3 adult, 4 pediatric), none were considered treatment-related, but were due to underlying disease, trauma or accident.

In limited comparative studies, the adverse reaction profile of Coartem Tablets appeared similar to a regimen of mefloquine plus artesunate.

The areas of special interest that were evaluated closely included the following:

**QT prolongation:**

A thorough QT study (A2101) was conducted and reviewed by the Interdisciplinary Review Team. It showed that the QTcF was 7.5 msec (5.5, 8.5), and 5% of patients had QTcF values over 60 msec, while 0.3% had QTcF>500 msec measured. The IRT recommended that information on QT prolongation be (b) (4) a warning/precaution, given the short duration of treatment and small size of QT prolongation. The IRT recommended labeling revisions to the text of the package insert (PI) for section 12.5, Effects on the Electrocardiogram, which have been incorporated in the PI.

No clinically-significant QT prolongations and specifically no torsades de pointes were reported in clinical trials or in post-marketing. Nevertheless, labeling warns about the use of Coartem in populations at risk including congenital QT prolongation, electrolyte imbalance (low potassium, magnesium), those receiving other QT prolonging drugs (e.g., cardiac, antimalarial), or those receiving drugs that are metabolized by CYP2D6 and have cardiac effect (e.g., flecainide, imipramine, amitriptyline, clomipramine). Notably, various antimalarial products (halofantrine, quinine) prolong the QT interval and may increase the risk of arrhythmia. The QT concern arose because lumefantrine is related to halofantrine, an antimalarial drug with known QT prolongation, thus these two drugs should not be given within one month of each other.

**CNS Events:**

The artemisinin drugs have been shown to cause neurotoxicity in animals, and toxicity related to various nuclei that control hearing and balance were affected in dogs when Coartem was given IM, but not when given PO. Tinnitus, hearing loss, vertigo, or loss of balance was not reported in clinical trials. The majority of events seen in clinical trials such as headache and dizziness were considered to be related to the underlying malaria infection and exacerbated at the start of treatment, but these were not considered drug-related. Nevertheless, an audiometry study is currently under way (A2417) and will be submitted

as a post-marketing requirement. A juvenile rat study will be repeated as a PMR to evaluate CNS toxicity because the initial study was considered flawed by the pharmacology/toxicology reviewers.

### **Neurology Consult:**

Because of the concern that artemisinins may cause CNS toxicity, and to obtain comments about the toxicology and clinical studies evaluating neurological events, a consult was requested from the Division of Neurology Products (DNP) and received December 19, 2008. The DNP preclinical reviewer did not consider that preclinical testing had adequately characterized the neurotoxicity and recommended some comparative IM and PO studies. Clinical recommendations included labeling the existing findings from animals, and potentially considering a clinical study with detailed neurologic evaluation. The DNP clinical reviewer commented that if the risk/benefit of the product is robust, the additional study may not be needed.

*Comment: Although thoughtful recommendations were provided in the consult, there were various practical reasons why these could not be adopted. For example the suggestions of additional animal studies to compare IM and PO routes did not consider the difference in metabolism of artemether when given by these 2 different routes. However, Novartis will be asked to repeat a juvenile rat study to more evaluate the neurotoxicity in a young animal.*

*A prospective clinical study in young children was proposed, and while useful in principle, it did not consider that (a) malaria patients have neurologic symptoms at baseline and a detailed neurologic examination in the acute setting may not be feasible, and (b) picking up a serious event in such a study would be unlikely given that the product has been used for 10 years and serious neurotoxicity has not been reported.. However, Novartis is being asked to collect data, working in collaboration with the CDC, on patients in the US who receive Coartem over the next 5 years, and information on adverse events is among the information being requested.*

### **Drug-Drug Interactions:**

Both artemether and lumefantrine are substrates of CYP3A4, and therefore it's important to take this into consideration if prescribing Coartem to patients receiving drugs that are substrates, inhibitors or inducers of CYP 3A4, such as antiretroviral drugs (ART). Although no HIV patients were enrolled in the clinical trials, if patients were to receive ARTs and Coartem, there may be reduction in levels and effect on efficacy. Inhibitors may increase levels of Coartem, but conversely, Coartem may reduce the effectiveness of oral contraceptives. Lumefantrine inhibits CYP2D6 in vitro, so Coartem may increase levels of drugs metabolized by CYP2D6.

Ketoconazole, a potent CYP3A4 inhibitor only increased Coartem levels moderately and no dosage adjustment is needed. Mefloquine reduced lumefantrine levels, possibly due to mefloquine-related decrease in bile production. Quinine slightly decreased artemether exposure.

This information will be reflected in product labeling.

### **Hepatic or Renal Impairment:**

Clinical studies included patients with mild to moderate renal or hepatic impairment and there was no difference in safety. However, patients with severe impairment were not studied.

### **Geriatric Patients:**

There were only 7 patients over the age of 65 in these studies, therefore labeling will indicate that insufficient number of geriatric patients were studied to characterize Coartem in this population.

**Pregnancy:**

The Maternal Health Team (MHT) reviewed results of an observational study in Zambia, the literature on pregnancy and the artemisinin class, and product labeling. In the observational study, 495 pregnant women received Coartem and 501 received Fansidar. No adverse pregnancy outcomes or malformations (above background) were reported, noting that umbilical hernias are seen in 3.7% of births but this is less than the background rate of 8-23% range seen in the population in Zambia. In published studies reporting on pregnancy outcomes in over a 1000 pregnant patients exposed to artemisinin derivatives (e.g., artemether, artesunate), there was no observed increase in adverse pregnancy outcome (e.g., teratogenic effect, spontaneous abortion, mortality) over background rates. Therefore, the MHT recommended a Pregnancy category C (b) (4)

The MHT suggested Novartis be encouraged to conduct a pregnancy surveillance registry, sponsor a pharmacokinetic study in pregnant women, and conduct a lactation study. MHT also made specific labeling revisions that were incorporated in the PI.

The MHT review discusses that the possible mechanism of embryotoxicity with Coartem drug is through depletion of erythroblasts (primitive erythrocytes), causing anemia and cell death due to hypoxia, and this takes place during gestational age 4-10 weeks. In monkeys exposed to 3 days of Coartem, embryotoxicity was not seen, suggesting that short-term exposure may not cause the same damage as long term exposure evaluated in animal toxicology studies. WHO currently recommends ACTs in the second and third trimester, and in first trimester when other drugs are not available.

No efficacy studies of Coartem in pregnancy were submitted in the NDA. In December 2008, a publication appeared reporting on outcome in pregnant women treated with Coartem vs. artesunate in Thailand.<sup>19</sup> The publication was reviewed and discussed with the MHT. The reported efficacy of Coartem was statistically lower in the ITT and per protocol populations vs. 7 days of artesunate, as shown in Table 15 below.

**Table 15. Outcome in Pregnant Patients**

Cure rates in pregnant women at 42 days evaluation	Coartem	Artesunate x 7 days	P value
ITT population (n = 125/128)	87.2% (n=125)	95.2% (n=128)	0.026
Per protocol population	86.8% (n=124)	94.9%	0.029

Adapted from Table 4 p 1707 of McGready publication

Although the clinical pharmacology reviewers did not find an exposure response relationship in the studies reviewed (which included 4-dose studies and some 6-dose studies), a dose-response relationship has been observed. A number of studies found that efficacy increased when:

- the content of the lumefantrine in the tablet increased;
- the number of 20 mg artemether/120 mg lumefantrine tablets was increased from 2 tablets per dose to 4 tablets per dose
- the number of doses increased from 3 doses to 4 doses to 6 doses

Furthermore, given that in the Thai Studies 026 and 028, there were numerically more failures in the Coartem arm than the MAS arm, the question arises whether in this high-drug-resistance region, a different product (perhaps a 1:7 ratio tablet) might achieve 28-day cure rates in the Coartem arm like in the MAS arm. Alternatively, an 8-dose regimen may be needed in some pregnant patients to affect cure.

<sup>19</sup> McGready R et al. A Randomized Controlled Trial of Artemether-Lumefantrine Versus Artesunate for Uncomplicated *Plasmodium falciparum* Treatment in Pregnancy. PLOS Medicine December 2008; 5(12)1699-1715. [www.plosmedicine.org](http://www.plosmedicine.org)

There were no deaths reported and infant outcomes at 1 year did not differ. The low efficacy was attributed by the authors to probable low lumefantrine levels. As discussed in Dr. O'Shaughnessy's addendum, the PK data for this study are not published, and detailed information is not provided.

Until further information is available, the labeling will indicate that the efficacy of Coartem in pregnant women has not been established. MHT confirmed that FDA does not have the authority to require efficacy studies in pregnant women, however, Novartis will be encouraged to undertake a study in pregnant women to evaluate both PK and efficacy – for example, it should be noted that based on studies in adults and pediatric patients in Thailand, it was determined that a 3 day (6 dose) regimen was needed and a 2 day (4-dose) regimen was inferior. It is possible that in pregnancy, some patients may need even longer treatment or alternative dosing. The PK data from the McGready study, when available, should help inform the next study.

### **Nursing mothers:**

There is no information on excretion of drug into human milk although animal data suggest both drugs are excreted. MHT recommended a lactation study to test the amount of drug excreted into milk. However, pediatric studies enrolled patients down to the age of 2 months, and toxicity was not reported. As noted previously, levels of drugs in other populations have been variable, and no exposure-response relationship for efficacy or adverse events was demonstrated in the clinical pharmacology review of the data. Given the seriousness of the infection, the labeling reflects that the benefit of treatment should be weighed against potential risks.

*Comment: Information on these safety issues is reflected in product labeling, and patient product information labeling.*

### **Primaquine:**

As noted above, Novartis initially requested approval for Coartem in treatment of patients with mixed falciparum and vivax infection, but Coartem does not appear effective against the liver (hypnozoites) stage of infection, thus patients would need to receive a product effective against hypnozoites, e.g., primaquine. The question whether the use of Coartem and primaquine might increase the QT interval (Coartem includes lumefantrine, a compound related to halofantrine) was raised. On February 6, 2008, Novartis was asked to provide any information on current or ongoing studies, including literature data, 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. Their results were sent on February 19, 2009, and concluded that available data do not support a QT effect of primaquine. The following is a summary from the applicant's submission.

Primaquine was evaluated *in vitro* for its effects on sodium and potassium currents in isolated rat ventricular muscle and myocytes.<sup>20</sup> The results suggest that primaquine blocks cardiac sodium channels, but not potassium channels (chloroquine in contrast does block K<sup>+</sup> 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.

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<sup>20</sup> Orta-Salazar G et al. Inhibition of cardiac Na<sup>+</sup> current by primaquine. *Br J Pharmacol* 2002;135:751-63.

The C<sub>max</sub> for a 45 mg dose of primaquine is 153 ± 24 ng/mL.<sup>21</sup> However, the usual clinical dose is 15 to 30 mg. At these doses, the primaquine exposure at C<sub>max</sub> is approximately 220 nM. This concentration is about 45 fold below the IC<sub>50</sub> 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 affect the potassium channel *in vitro*, no cardiac related adverse events were reported.<sup>22</sup> This included a trial where 123 patients with *P. vivax* malaria in Indonesia were randomized to halofantrine or chloroquine, and primaquine was given to all subjects concurrently and continued 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. However, in these studies, there is no specific mention of ECGs and therefore it cannot be assumed they were performed.

Therefore, the clinical review team recommended that based on the fact that primaquine does not appear to affect the potassium channel in cardiac cells, the Coartem labeling does not need to include a precaution or ECGs monitoring if primaquine is given after Coartem.

The QT-IRT advised the team that recommending ECG monitoring in labeling is generally reserved for drugs when clinical events associated with QT prolongation such as sudden death or torsade de pointes are observed during clinical trials or post-marketing. Based on this advice, therefore, the Coartem labeling does not include any recommendations regarding ECG monitoring, but does include precautionary statements about the possibility of QT prolongation with Coartem and other QT prolonging drugs.

### **Clinical Pharmacology:**

Artemether and lumefantrine are both lipophilic products (neither is soluble in water). They are metabolized by cytochrome p450, mainly CYP 3A4. Artemether is metabolized to dihydroartemisinin (DHA), and auto induction of the enzyme leads to lower artemether levels and higher DHA levels. The half life is approximately 2 hours. However, because DHA is active against the malaria parasite,<sup>23</sup> this metabolism does not reduce the antimalarial activity. Lumefantrine (also known as beflumetol) is metabolized by CYP 3A4/5 to desbutyl-lumefantrine. Lumefantrine has a half life lasting 3-6 days, and inhibits CYP2D6; therefore it may lead to drug-drug interactions for drugs that are handled by this enzyme.

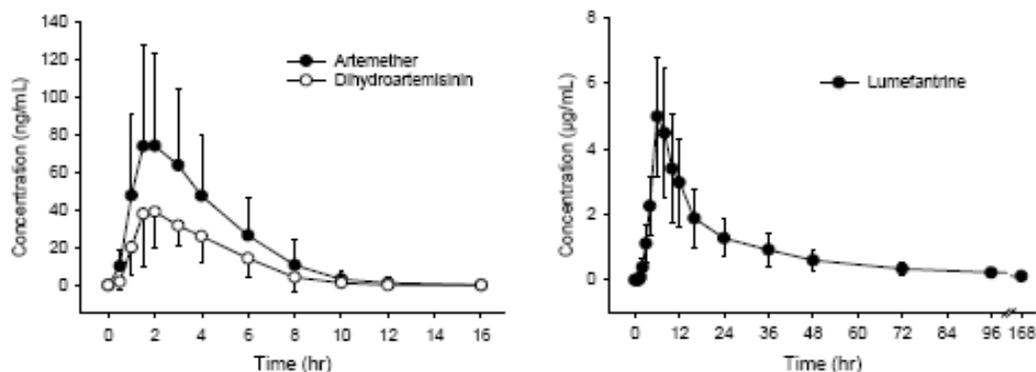
The pharmacokinetic properties of these two drugs correlate with the antiparasitic activity of each component of the combination. The artemether is able to effect early parasite reduction, while lumefantrine, with the longer half life, is effective in preventing recrudescence. The plasma profiles of artemether, DHA (on left) and lumefantrine (on right) is displayed in the figure below, showing that after one dose, artemether and DHA levels rise quickly and peak at about 2 hours, while lumefantrine levels rise slower and lumefantrine elimination is slower so that drug is measurable up to 168 hours. The lumefantrine levels are responsible for the effect on the 28 day cure rates.

<sup>21</sup> Hill DR et al. Primaquine: Report from CDC expert meeting on malaria chemoprophylaxis. *Ann Trop Med Hyg* 2006; 75(3):401-15.

<sup>22</sup> Krudsood S et al. Clinical efficacy of chloroquine versus artemether-lumefantrine for *Plasmodium vivax* treatment in Thailand. *Korean J Parasit* 2007;45(2):111-4. Fryanuff et al. Halofantrine and primaquine for radical cure of malaria in Irian Jaya, Indonesia *Ann Trop Med Parasitol* 1997; 91(1):7-16.

<sup>23</sup> DHA has comparable activity to artesunate <http://www.ncbi.nlm.nih.gov/pubmed/11897605>

**Figure 4-1** Artemether, DHA and lumefantrine plasma profiles (mean  $\pm$  SD) in fed healthy volunteers after a single dose of Coartem (80/480 mg)



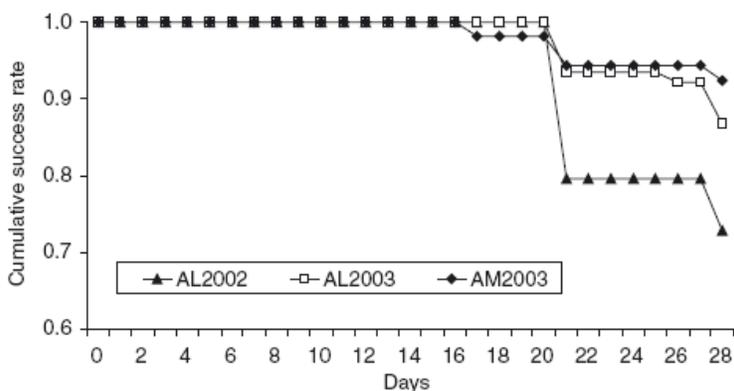
In the clinical pharmacology review, it is noted that lumefantrine is the key pharmacokinetic parameter that influences the 28 day outcome, “The extent of systemic exposure to lumefantrine is thus clearly associated with cure, and its long lasting exposure/effect when co-administered with artemether 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.”<sup>24</sup> Regarding artesunate, “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.” Furthermore, “Based on 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.” According to the clinical pharmacology group, an exposure-response analysis involving 4-dose and 6-dose studies failed to show an exposure-response relationship, suggesting the levels achieved are on the plateau of the exposure response curve. The levels for given doses are variable, and in the analyses, no exposure-response relationship was demonstrated.

In a food effect study, normal volunteers ingested a high-fat meal, resulting in a two-fold increase in artemether levels and 16-fold increase in lumefantrine levels. In clinical studies, it was recommended that patients receive Coartem with food, although no specific diaries were kept to document food consumption. It is noted that patients who develop malaria may feel sick and averse to eating early in the course of infections; but can resume regular intake as the infection is brought under control. The labeling will recommend Coartem be taken with food.

Although not reported in these clinical studies, some publications note that low lumefantrine levels were considered the reason for failure of treatment. Denis et al studied artemether-lumefantrine in northwest Cambodia in two seasons, and found that efficacy correlated with lumefantrine levels. The figure below shows the outcome in the three treatment arms, artemether/lumefantrine in 2002 (AL2002), artemether/lumefantrine in 2003 (AL2003) and artesunate-mefloquine (AM2003). The AL2002 patients had a 28-day response rate of 71% compared to 86% for AL2003 and 92% for AM2003 (see figure below from page 1804 of the publication).<sup>25</sup> Lumefantrine levels in the AL2003 cures was significantly higher than in AL2003 failures ( $p=0.02$ ).

<sup>24</sup> Clinical Pharmacology review by Dr Dakshina Chilukuri, p 10-11.

<sup>25</sup> Denis MB et al. Efficacy of artemether–lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia. *Tropical Medicine and International Health* 2006; 11(12)1800-7.



**Figure 1** Cumulative success rate of patients treated with artemether-lumefantrine in 2002 (AL2002), 2003 (AL2003) or with mefloquine + artesunate (AM2003).

Pharmacokinetic data are available in adult patients, including some patients over 70 kg of weight. No PK data were provided for pediatric patients, patients with renal and hepatic patients, or pregnant patients. However, clinical data were available for these populations and examined to determine whether there were any differences in safety and efficacy of Coartem. As a result of these analyses, the labeling will include a summary of findings in pediatric and adults patients, and state that there is insufficient data on geriatric patients (only 7 patients were in the clinical trials). Coartem was safe and effective in the subsets of patients with mild or moderate renal or hepatic impairment, so no dosage adjustment will be recommended for these patients. However, the labeling will state that no patients with severe renal or hepatic failure were studied. Safety derived from an observational study in pregnant women is summarized in the Pregnancy section; however, the section also states that the efficacy in pregnant women has not been established.

The F4 (to be marketed) formulation was used in 7 of the pivotal studies (A023, A025, A026, A028, A2401, A2403, B2303), the F81 formulation was used in AB/MO2. Although no formal bioequivalence (BE) study between these formulations was conducted, the clinical pharmacology team determined that the level of efficacy seen in this trial obviated the need for a formal BE study.

*Comment: The pharmacokinetic properties of the two individual drugs provide the rationale and justification for combining them into a fixed combination product. Artemether has a short half-life of 2 hours and is rapidly metabolized to dihydroartemisinin (DHA), a metabolite with antiparasitic activity. The levels of these compounds correlate with parasite reduction, as well as fever reduction. The lumefantrine has a longer half-life of 3-6 days, and while the drug alone has slow parasite and fever clearance time, lumefantrine levels are associated with the long-term outcome of treatment, the 28-day cure. Thus, from a pharmacokinetic perspective, each product plays a role in the combination. Although the clinical pharmacology review concluded that there was no exposure-response relationship, 28-day outcome depends on the presence of lumefantrine in the combination, and there is a correlation between response and total drug (doses and duration) administered, as seen in the Clinical Studies submitted with this application.*

*Although a number of drug interaction studies were submitted, additional studies are warranted and have been requested as PMRs.*

### **Microbiology:**

Both artemether and lumefantrine are blood schizonticidal agents, active against the erythrocytic stage of *Plasmodium* infection. An exdoperoxidase moiety is thought to mediate the activity of the artemether, but the lumefantrine mechanism of action is unknown. Artemether is derived from the

wormwood plant, *Artemisia annua*. Other agents in the class are artesunate and artemether. The artemisinin class has been developed and used in China before being introduced and evaluated in other parts of the world. Lumefantrine is related to the drug halofantrine. Halofantrine was approved for treatment in the US but the NDA has recently been withdrawn by the company (NDA 20-250) because the product is no longer marketed.

In clinical trials, reappearance of malaria parasites particularly from endemic, high transmission areas is evaluated by PCR, and PCR-corrected cure rates are reported. This assay is intended to distinguish patients who have true recrudescence of the malaria parasite responsible for the original infection from patients who develop a new malaria infection due to a PCR-confirmed new strain. Although Novartis presented PCR-corrected rates, and requested to include these in labeling, they were unable to provide the data needed by the microbiology reviewer to verify the performance characteristics and methodology of the PCR assay. Therefore the uncorrected parasite recrudescence rates as determined by slide examination are reported.

#### Gametocytes

Gametocyte clearance was requested in labeling, given that the gametocyte is the source of transmission of the disease from person to person via the mosquito vector. Although gametocyte clearance was noted in some of the study, the decision not to include this in labeling was because (a) a study to correlate clearance of gametocytes with actual reduced transmission was not done, (b) and specific anti-gametocyte activity of Coartem was not studied. The gametocyte clearance could have been the consequence of eliminating asexual parasites thus preventing further gametocyte generation, and not due to direct anti-gametocyte activity. In some patients, gametocytes persisted past the 28 day visit. Thus this claim will not be included in labeling.

#### **Pharmacology /Toxicology:**

Major organs of toxicity are the nervous system and cardiac system. Rat and dog studies were conducted to look at these issues. The dog studies identified toxicity to the hearing and balance centers at high doses. When artemether was given IM to dogs, lesions in the pontine and cerebellar nuclei, and nucleus vestibularis, nucleus hypoglossus and nucleus cuneatus were seen. Dogs and rats that received artemether orally for three months did not show these changes. A juvenile rat study was considered inadequate and will need to be repeated (see Addendum to Pharm Tox review dated March 6, 2009) to evaluate toxicity in a young animal.

Reproductive studies showed fetal loss and resorption, but no teratogenicity. Cardiac and skeletal malformations have apparently been seen with other artemisinin compounds (e.g., artesunate) and Novartis has included this information in labeling.

Carcinogenicity studies are not warranted given the treatment regimen is short (3 days).

A number of degradation products/impurities were identified in Coartem, and discussed by the pharmacology/toxicology and chemistry reviewers. As a result, Ames assay testing for genotoxic potential was requested for certain of these moieties (b) (4) and will be completed as Post-Marketing Requirements.

#### **Chemistry and Inspections:**

Artemether is a methoxy derivative of artemisinin manufactured (b) (4) It is synthesized in a (b) (4) process

from plant extract of *Artemisia annua*. Artemisinin is reduced to get the intermediate dihydroartemisinin (DHA), which is then methylated to artemether.

Lumefantrine is structurally related to quinine, mefloquine, and halofantrine. Manufacture involves (b) (4) and the following facilities: (b) (4)

The issue of qualification of acceptance criteria for impurities was discussed between chemistry and pharmacology/toxicology. Various impurities (intermediates and degradation products) found in the drug needed to be discussed and resolved before the product could be approved. As noted above, Novartis will conduct bacterial reverse mutation studies (Ames assays) on four impurities as post-approval studies. Specifications for the (b) (4) will be set at NMT (b) (4) and (b) (4) for The (b) (4) impurity.

According to chemistry reviewers, the application provided sufficient information to assure identity, strength, purity, and quality of both drug substances and the drug product, and any issues identified during the review of the applications were resolved satisfactorily. Stability data were available for (b) (4) production batches and support a 2 year shelf-life when stored at 25°C, USP controlled room temperature. (Dr Matecka's review).

The final product is made in two facilities in the US and these were considered acceptable. There are 11 facilities involved in the manufacture of the drug substances. In December 2008, three of the facilities were issued 483 inspection reports that were considered to be OAI (official action indicated), and an initial recommendation of withhold approval was made. This prompted meetings and discussions between the clinical, chemistry and compliance staff, as well as the company, to work to resolve the issues. Two of these OAI issues were resolved promptly, however, the third issue did not get resolved until March 2009. Specifically, the (b) (4) facility had an impurity that was reported in a column and Novartis had to investigate this finding and provide additional information to Compliance to resolve the issue. Also, as of December 2009, two other facilities, (b) (4) had not been inspected. The inspections of the two (b) (4) facilities were completed in March 2009 and found to be acceptable, no FDA 483 was issued. As a result, according to the chemistry review of March 30, 2009, "all manufacturing facilities involved in the manufacturing, packaging and testing of both drug substances and product are now acceptable; and overall acceptable recommendation was made by the Office of Compliance on 27-Mar-2009."

### **OSE/DMEPA (previously DMETS) recommendations:**

**Trade Name:** see under Labeling

**Patient Package Insert:** see under Labeling

### **Orphan Designation/Pediatrics:**

This product was granted orphan designation for the *treatment of infections due to Plasmodium falciparum or mixed infections including Plasmodium falciparum* on August 31, 2007. Therefore, the applicant is not required to conduct further pediatric studies of Coartem. However, studies with the crushed Coartem Tablet were done in patients as low as 5 kg (2 months of age). (b) (4)

### **Advisory Committee Meeting:**

The application was presented before the Anti-Infective Advisory committee on December 3, 2008. The committee voted 17:1 that Coartem was safe and 18:0 that the product was effective in the treatment of uncomplicated falciparum malaria. The vote on the co-infections with *P. vivax* was split, with most of the comments dealing with the issue of liver stage of the infection and relapse. Additional comments dealt with recommending that drug-drug interactions studies be done, and that data be obtained on patients in the US, given that their immune status may differ from patients in endemic regions. These recommendations have all be taken into consideration and addressed either in labeling and/or in requests for post-marketing studies.

### **Financial Disclosure:**

OMB Form 0910-0396 was submitted and reviewed. The applicant obtained certifications from investigators and sub-investigators of the 8 clinical studies. No investigator had any disclosable information to reveal.

### **Division of Scientific Investigation:**

DSPDP worked closely with DSI, and spoke with Novartis to ensure that inspections were conducted in a timely manner. Overall, the inspections found that the studies were conducted in compliance with Good Clinical Practice (GCP), the data in the application were acceptable. See further comments under **Foreign Studies**.

### **Labeling:**

The labeling was submitted in PLR format, and was edited substantially by the Division and other reviewers. The following groups reviewed and made changes to the labeling including the Package Insert, the Patient Package Insert, and Container and Carton labels:

- OND/Clinical reviewers
- OND/Maternal Health Team
- OND/Pediatric Team
- OTS/Statistical reviewers
- OND/Microbiology reviewers
- ONDQA/Chemistry reviewers
- OND/Pharmacology/Toxicology reviewers
- OTC/Clinical Pharmacology reviewers
- OND/SEALD
- OSE/DRISK
- OND/DDMAC
- OND/IRT
- OND/DMEPA
- OND/Neurology

Recommendations from SEALD, IRT, DRISK, DMEPA, Neurology, Maternal Health Team, Pediatrics were relayed to Novartis for inclusion in the labeling, In addition the reviewers held labeling teleconferences to discuss any areas where factual information and clarity of communicating information needed to be resolved. The final labeling was agreed upon **March 11, 2009**.

**Proprietary Name:**

DMEPA initially turned down the trade name “Coartem” because of concerns regarding confusion with Comtan (ecotocapone) used for the treatment of Parkinson disease [21 CFR 201.10(c)(5)]. However, Novartis provided a rebuttal, justifying why there should be no confusion with the product and the name. They stated that because (a) there are approximately 1500 patients yearly with malaria diagnosed in the US, (b) retail pharmacies will not stock Coartem because of the limited patient population, and (c) patients would use the product in a healthcare environment. Novartis indicated that Coartem would be available through 3 major wholesalers nationwide. Novartis intends to have <sup>(b) (4)</sup> of Coartem available initially. Taking this new information into consideration, DMEPA agreed to the trade name.

**CONCLUSIONS:**

Coartem is a new antimalarial product, consisting of a fixed-combination drug. The product contains artemether and lumefantrine, an artemisinin-containing treatment, for treatment of malaria. Early studies showed that a 4-tablet, 4-dose regimen was superior to doses of 2 tablets or 3 doses. Two factorial design studies demonstrated that each component contributed to the treatment effect. The 4-dose studies showed that Coartem was superior to chloroquine, and similar to other antimalarials in Africa and parts of Asia. However, studies in Thailand where malaria resistance is high yielded low efficacy in evaluable patients, therefore the 6-dose regimen was developed, and shown to be superior to the 4-dose regimen in the evaluable population. The 6-dose regimen was effective in treating patients from 5kg and greater in various parts of the world (South East Asia, Africa, South America, Europe).

As summarized above, these studies were conducted on many continents, but none were conducted in the US. The CFR allows the agency to rely on foreign data for approval if those data meet certain criteria. Review of this application confirms that the criteria were met, as documented by a review of clinical study reports and detailed review the 8 main studies, and by DSI inspections of study sites in China, Thailand and Africa to confirm their compliance with GCP. Also, given that the US population is diverse, data obtained from patients in other parts of the world are applicable. Patients who contract malaria do so by traveling to endemic countries, including travelers visiting friends and family in those countries. The clinical studies were conducted in endemic areas as well as in travelers from Europe (Germany, Switzerland) and Colombia who were presumed to be non-immune, and in young pediatric patients who would also be presumed to be non-immune.

Finally, as recommended by the Anti Infective Advisory Committee members and the review team, Novartis will conduct a number of PMRs/PMC, including collaborate with CDC to conduct an observational study of patients in the US treated for malaria with Coartem.

**RECOMMENDED ACTION:**

An approval letter should be issued and include the 14 PMRs and 1 PMC listed above. In addition, Novartis qualifies for a priority review voucher.

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/s/

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Renata Albrecht  
4/3/2009 04:20:56 PM  
MEDICAL OFFICER

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