NOVARTIS

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

Coartem® (artemether-lumefantrine) Tablets for the treatment of malaria in patients with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*

NDA 22-268

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List of Abbreviations

ABR	auditory brainstem response
ACPR	adequate clinical and parasitological response
ACT	artemisinin combination therapy
AE	adverse event
ALT	alanine aminotransferase
AMMS	Academy of Military Medical Sciences
AQ	amodiaquine
AQSP	amodiaquine, sulfadoxine-pyrimethamine
AS	artesunate
ASAQ	artesunate plus amodiaquine
ASCD	artesunate plus chloroproguanil-dapsone
AST	aspartate aminotransferase
ASSP	artesunate, sulfadoxine-pyrimethamine
AUC	area under the curve of blood/plasma concentration versus time
AUC∞	area under the curve (extrapolated to infinity)
AUC_{last}	area under the plasma concentration time curve from time 0 to the last measurable time point
BAV	bioavailability
CAR	nuclear constitutive androstane receptor
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum blood/plasma concentration
CQ	chloroquine
CQSP	chloroquine, sulfadoxine- pyrimethamine
CRFs	Case Report Forms
CRO	contract research organization
CYP	cytochrome P450
dB	decibel
DHA	dihydroartemisinin
DNP	dihydroartemisinin, naphtoquine and trimetoprim
DP	dihydroartemisinin, piperaquine

EC	effective concentration
ECG	electrocardiogram
ETF	early treatment failure
f	female (sex/gender)
FCT	fever clearance time
FDA	Food and Drug Administration
GCT	gametocyte clearance time
HCl	hydrochloride
HEK293	human embryonic kidney cells
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HS	healthy subjects
IC_{50}	concentration of a drug required for 50% inhibition in vitro
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ITT	intent-to treat
LCF	late clinical failure
LLOQ	lower limit of quantification
LPF	late parasitological failure
m	male (sex/gender)
M	total number of evaluable patients
MAP	Malaria Atlas Project
MAS	artesunate-mefloquine
MRI	magnetic resonance nuclear
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to treat
n	number of patients in study/treatment group
N	Total number of patients
NDA	New Drug Application
PA	primary analysis
PCR	polymerase chain reaction
PCT	parasite clearance time

PK	pharmacokinetics
PD	pharmacodynamics
PMNS	Post-malaria neurological syndrome
PP	per protocol
QT	measure of time between start of Q wave and end of T wave in heart's electrical cycle
QT_C	QT interval corrected for rate
QTc(F)	QTc Fridericia
RBC	red blood cell count
RBM	Roll Back Malaria
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Class (for MedDRA)
SM	Sulfamethoxypyrazine
SP	sulphadoxine pyrimethamine, Fansidar®
UNICEF	United Nation Children's Fund
USA	United States of America
WHO	World Health Organization

1 Executive Summary

Coartem® (artemether-lumefantrine) Tablets is a highly effective artemisinin-based combination therapy (ACT) that is registered in 83 countries worldwide, including Europe and Switzerland, and is recommended by the World Health Organization (WHO) for the treatment of acute, uncomplicated *P falciparum* malaria.

Coartem is a fixed-dose combination tablet of 20 mg artemether (an artemisinin derivative) and 120 mg lumefantrine. Coartem is a fixed-dose combination tablet of 20 mg artemether (an artemisinin derivative) and 120 mg lumefantrine in a 1:6 ratio. Both components are blood schizonticides, and they have complementary pharmacokinetics and dissimilar modes of action, thus providing synergistic antimalarial activity. Artemether is rapidly eliminated from plasma with a half-life of 2-3 hours, whereas lumefantrine is eliminated more slowly with a half-life of 3-6 days.

Proposed Indication

Coartem is indicated for treatment of malaria in patients of 5 kg bodyweight and above with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P falciparum*. Coartem is effective against both drug-sensitive and drug-resistant *P falciparum* and is recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Background Information

Malaria is a global life-threatening disease caused by four species of *Plasmodia* parasite, and among these, *P falciparum* is the most deadly form. *P falciparum* malaria affects around 240 million people worldwide every year, and causes around 1 million deaths annually, 85% occurring in children below 5 years of age (WHO 2008). Historically, chloroquine was used to treat malaria, but increasingly, resistance to chloroquine and many other antimalarial drugs has become a major impediment to the effective treatment of *P falciparum* malaria.

Because of the rising threat of resistance to available antimalarial drugs, the WHO recommends use of combination therapy, specifically ACTs for the treatment of uncomplicated *P falciparum* malaria. Coartem is the first fixed-dose ACT prequalified by the WHO for the treatment of uncomplicated *P falciparum* malaria and is recommended in the WHO treatment guidelines.

In the US, approximately 1,500 cases of malaria are reported to the Centers for Disease Control and Prevention (CDC) annually, of which approximately 50% are known to be *P falciparum* (Mali et al 2008). Currently, there are no ACTs approved for use in the United States, and the only approved combination therapy is Malarone® (atovaquone-proquanil HCl). However, resistance to Malarone has recently been reported in some regions of the world (Boggild et al 2007). Therefore, in line with WHO recommendations, an alternative treatment such as an ACT should be made available to US patients.

Development program

The clinical development program for Coartem included a total of 4,911 patients who have participated in 20 Novartis-sponsored studies conducted between 1993 and 2007. A total of 3,599 patients have been treated with Coartem, including 1,572 adults (>16 years of age) and 2,027 pediatric patients (≤16 years of age). These studies were conducted in a range of geographic areas (mainly Asia and Africa) with varying levels of multi-drug resistant *P falciparum* and in travelers from non-endemic regions (Europe and Colombia) suffering from *P falciparum* malaria.

All studies investigated the efficacy and safety of either a 4-dose regimen (consisting of 1 dose at diagnosis followed by a dose at 8, 24, and 48 hours) or a 6-dose regimen (consisting of 1 dose at diagnosis followed by a dose at 8, 24, 36, 48, and 60 hours) of Coartem with dose adjustment according to body weight ranges (i.e. 5-<15, 15-<25, 25-<35, ≥ 35 kg). The 6-dose regimen was selected for further development based on evidence that it provided superior efficacy.

Of the 20 Novartis-sponsored studies, 8 were considered as key to support registration of the 6-dose regimen:

- Two randomized double-blind studies (AB/MO2 and A023) designed to compare the efficacy of the 4-dose Coartem regimen with artemether or lumefantrine monotherapy.
- One randomized double-blind study (A025) which compared the efficacy of the Coartem 4-dose versus 6-dose regimen.
- Two randomized, open-label studies (A026 and A028) designed to confirm the efficacy and safety of the Coartem 6-dose regimen in Thailand. Both studies included mefloquine plus artesunate as an active control.
- Two studies (A2403 and B2303) designed to confirm the efficacy and safety of the Coartem 6-dose regimen in infants and children with body weight as low as 5 kg.
- One single-arm study (A2401) designed to confirm the efficacy of the Coartem 6-dose regimen in non-immune travelers.

The primary efficacy endpoint in these studies was the 28-day parasitological cure rate, which was either uncorrected or corrected for re-infection by PCR (polymerase chain reaction) analysis, which is key in highly endemic regions in order to distinguish a new infection (via another mosquito bite) from a recrudescence (of the original infection). Secondary endpoints included time to clearance of fever, parasites,and gametocytes.

Dose selection

Studies AB/MO2 and A023 conducted in China demonstrated that the combination of artemether and lumefantrine (4-dose regimen) was more effective than either drug used alone. Coartem improved the 28-day cure rate compared with artemether alone, and Coartem cleared parasites approximately 20 hours faster and fever approximately 10 hours faster than lumefantrine alone. However, subsequent studies (A004, A008, and A012) conducted in Thailand, where multi-drug resistant *P falciparum* malaria is common, did not confirm the

efficacy of the 4-dose regimen (28-day cure rate around 80% or below). Therefore, further clinical development of a 6-dose regimen was pursued.

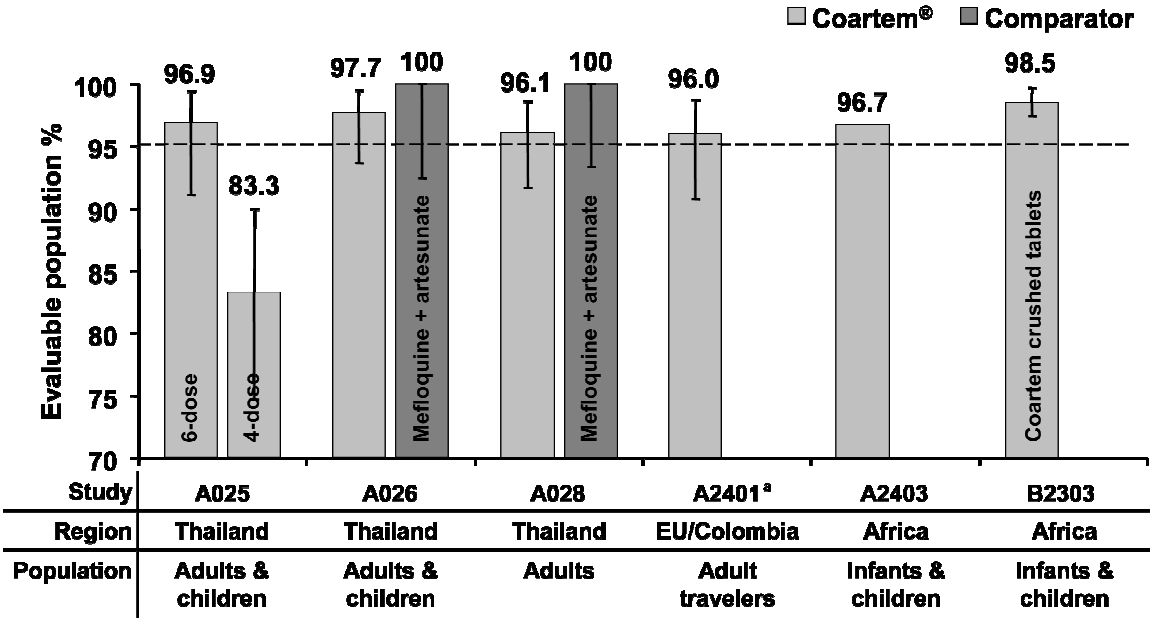
Study A025 demonstrated that the 6-dose regimen was significantly more effective than the 4-dose regimen with respect to the 28-day PCR corrected cure rate in the evaluable population (97% versus 83% ; $p < 0.001$).

Efficacy of the Coartem 6-dose regimen

The efficacy and safety of the 6-dose regimen was subsequently confirmed in different patient population comprising adults and pediatric patients non-immune or semi-immune to malaria.

- The Coartem 6-dose regimen consistently achieved a >95% 28-day PCR-corrected cure rate among evaluable patients in multiple studies conducted in a variety of geographic regions and in diverse patient populations with respect to age, body weight, and immunity, including non-immune travelers (Figure 1-1).
- Coartem also consistently achieved rapid clearance of fever, parasitemia, and gametocytes
- Although only few patients with mixed infections were enrolled in clinical trials, the available data indicate that other *Plasmodium* species are also rapidly cleared from the blood.

Figure 1-1 28-day PCR-corrected parasitological cure rate among evaluable patients treated with the 6-dose Coartem regimen



[a] PCR uncorrected.

Safety

The clinical trial safety database includes 20 Novartis-sponsored studies, comprising 1572 adults patients (> 16 years of age) and 2027 pediatric patients (≤16 years of age). The overall safety analysis showed the following:

- The most frequently reported AEs were unspecific, likely to be related to the signs and symptoms of malaria or fever related disorders
- The vast majority of nervous system and ear/labyrinth disorders were transient and reversible
- There were few deaths or serious adverse events, and most of those that did occur were not related to Coartem treatment.
- There were no death or AEs related to QTc prolongation
- Coartem was not associated with any increased risk of hematologic or hemolytic-related adverse events.
- There were few deaths or serious adverse events, and most of those that did occur were not related to Coartem treatment.
- Beside some cases of skin reactions and hypersensitivity, the post-marketing experience did not highlight any new safety signal, in particular following repeated administration.

Overall Benefit/Risk

Coartem is the first fixed-dose oral ACT for acute uncomplicated *P. falciparum* malaria pre-qualified by the WHO, and the combination of artemether and lumefantrine should limit the development of resistance. Numerous Novartis-sponsored and around 40 non-Novartis–sponsored studies have demonstrated that the recommended Coartem 6-dose regimen consistently provides high efficacy in a range of patient populations with different levels of immunity (including non-immune patients) and is well tolerated in adults and children as young as 2 months of age (≥ 5 kg).

P. falciparum malaria can rapidly progress into a severe life-threatening form if not effectively treated. In the United States, malaria is primarily a problem for travelers to endemic areas. With increasing international travel, the numbers of patients with malaria returning to the United States from endemic countries is set to increase; particularly as increasing drug resistance to *P. falciparum* makes effective chemoprophylaxis more difficult.

No ACT is currently registered in the United States despite a clear therapeutic benefit and the fact that it is recommended by the WHO. Only one oral fixed combination therapy (i.e. Malarone ®) is available in the United States, and resistance to this therapy has recently been described. Additionally, as Malarone is also used for prophylaxis, it would be beneficial to have an additional approved treatment available. Coartem would provide patients in the United States with an effective, easily-administered oral treatment for acute uncomplicated *P. falciparum* malaria, with minimal risk, particularly when compared with the risks of untreated malaria.

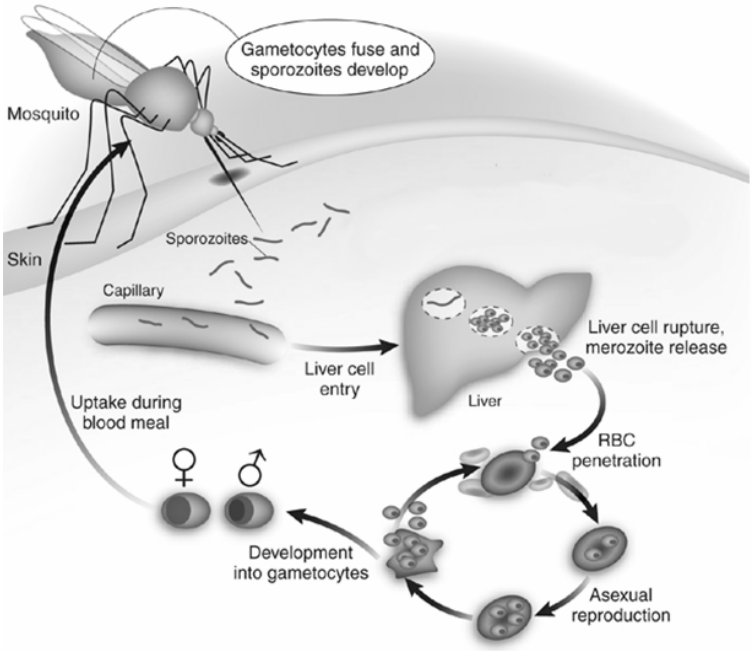
2 Background Information

2.1 Malaria: a Global Life-Threatening Disease

An estimated 3.3 billion people, approximately 50% of the world's population, are at risk for malaria. Of the 4 species of *Plasmodia* that cause malaria in humans, *P falciparum* has the highest potential to rapidly progress to severe illness or death. *P falciparum* malaria affects around 240 million people worldwide every year, and causes more than 1 million deaths annually, 85% being children under 5 (WHO 2008).

When an infected mosquito bites a human, sporozoites enter the human circulation and penetrate the liver cells, where they reproduce asexually (Figure 2-1). This intracellular form of the parasite is known as a schizont. When the hepatocytes burst, schizonts release merozoites into the blood, which are capable of infecting erythrocytes. Inside the erythrocytes, the merozoites reproduce asexually and either rapidly infect new red blood cells to complete the erythrocytic cycle, or die. In addition, when infection of new blood cells occurs, the parasites may also grow into immature gametocytes, which can be taken up in the blood meal of another feeding mosquito. The male gametocyte undergoes rapid nuclear division and produces a flagellated microgamete, which fuses with and fertilizes the female gametocyte forming a zygote. The zygote develops into an ookinete, which then sticks to the gut wall of the mosquito and moves to the outermost layer of the stomach to form an oocyst. When it breaks, it releases sporozoites, which migrate to the salivary glands of the mosquito to restart the parasite's life cycle (Jones and Good 2006).

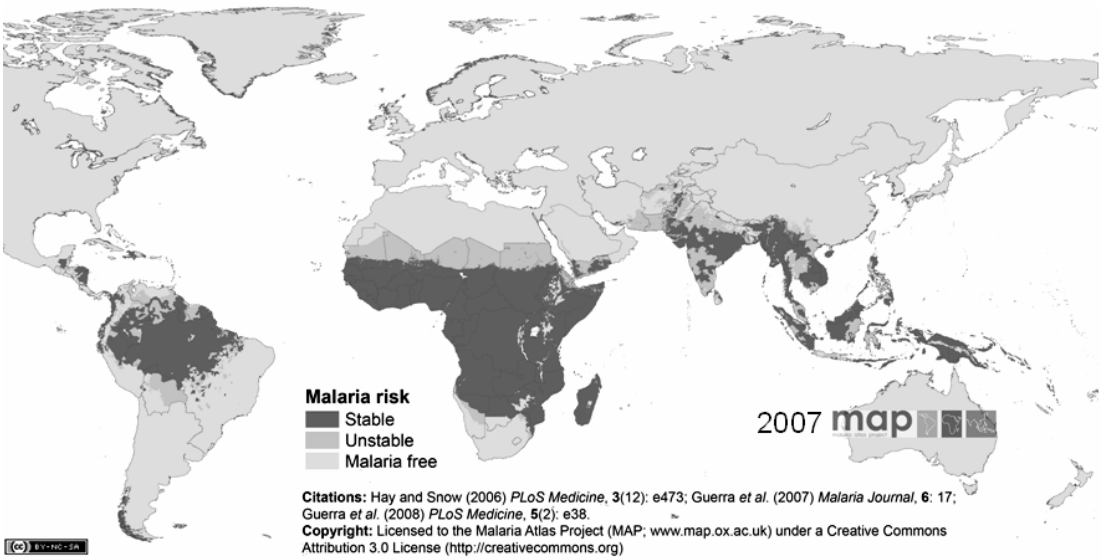
Figure 2-1 Life cycle of *P falciparum*.



Global prevalence and estimated drug resistance

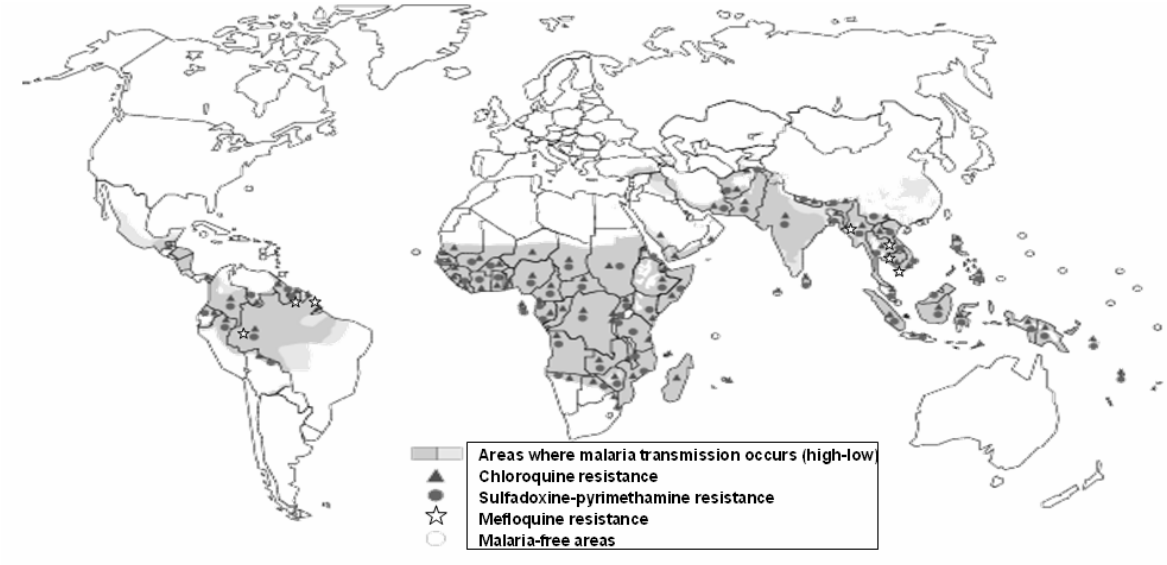
An estimated 2.37 billion people live in areas at risk for transmission of *P falciparum* malaria, primarily in sub-Saharan Africa, Central and South America, Southern Asia, and Papua New Guinea (Figure 2-2) (MAP 2007). Drug resistance is a major impediment to treatment of *P falciparum* malaria. In the majority of regions where *P falciparum* predominates, the parasites are resistant to common antimalarial drugs such as chloroquine and sulphadoxine-pyrimethamine (SP), and resistance to more recent treatment options such as mefloquine and atovaquone-proguanil HCl is emerging (Figure 2-3) (WHO 2008, Boggild et al 2007). Therefore, new treatment options for malaria are necessary.

Figure 2-2 Geographic regions at risk for transmission of *P falciparum* malaria.



Stable: > 0.1 confirmed *P falciparum* malaria cases per 1000 resident population
Unstable: < 0.1 confirmed *P falciparum* malaria cases per 1000 resident population

Figure 2-3 Estimated areas with drug resistant *P falciparum*.



2.2 Current WHO Recommendations for Treatment of Malaria

Because of the rising threat of resistance to available antimalarial drugs, the WHO recommends use of an artemisinin based combination therapy (ACT) for the treatment of uncomplicated *P. falciparum* malaria (WHO 2006).

Artemisinin-Based Combination Therapies

Artemisinin-based combination therapies have been widely adopted worldwide. The combination of an artemisinin derivative with another effective antimalarial drug that has a complementary mechanism of action and pharmacologic profile can overcome the emergence of drug resistance.

Artemisinin derivatives have the most potent and rapid onset of anti-parasitic activity of any antimalarial drug available today and are active active against all *Plasmodium* species that infect humans. They allow more parasite clearance than any other antimalarial drug (parasite numbers can be reduced by a factor of 10^5 per asexual cycle, compared with 10^2 – 10^3 with other antimalarial drugs).

When combined with antimalarial drugs with slower elimination rates (eg, lumefantrine), shorter courses of treatment (3 days) are effective. Combinations of antimalarial drugs are now recommended by the WHO, because combination therapy is usually more effective than monotherapy and minimizes the risk of treatment failure due to the development of drug resistance during treatment. If a parasite resistant to one component of a combination emerges during treatment, it should be killed by the other component (WHO 2006).

Coartem is Widely Used Worldwide for *P. falciparum* Malaria

Coartem (artemether-lumefantrine) is the first fixed-dose ACT prequalified by the WHO since April 26, 2004 and is widely available internationally. Artemether and lumefantrine have both

been included on the WHO model list of Essential Medicines since March 2002 and on the first WHO model List of Essential Medicines for Children since October 2007 (WHO 2007).

Artemether has a rapid onset of action and is rapidly eliminated, whereas lumefantrine is eliminated more slowly and provides a high long-term cure rate after a short treatment course. The combination thus provides rapid clearance of parasitemia and most malaria-related symptoms, coupled with prevention of recrudescence. In addition, Coartem is a fixed-dose ACT with a fixed ratio of components in a single tablet. This allows better compliance to treatment than free combinations of loose tablets.

Following the original approval of Coartem in 1998, resistance to older antimalarial drugs continued to increase. By 2002, 15 of 31 countries surveyed by the WHO had median clinical failure rates for chloroquine greater than 25% (WHO/UNICEF 2003), which was the threshold for a change in antimalarial policy as defined by the WHO (WHO 1999). As a replacement for chloroquine, a fixed combination of sulfadoxine and pyrimethamine (SP) was adopted in many countries. Unfortunately, the rapid development of acquired drug resistance is already limiting the effectiveness of SP, particularly in Eastern and Southern Africa with failure rates in excess of 20% (WHO/UNICEF 2003).

Against this background, and with an increasing focus on ACTs as the antimalarial drugs with the best potential for treatment of acute multi-drug resistant *P falciparum* malaria, further studies were performed using the Coartem 6-dose regimen. It is now the approved treatment regimen for acute, uncomplicated *P falciparum* malaria in adults and pediatric patients with a body weight ≥ 5 kg, irrespective of the immune status of the patients and of the local multi-drug resistance situation, in the majority of the 83 countries in Africa, Asia, Europe and Latin America where the drug is registered..

2.3 Malaria in the United States

The number of cases of malaria reported to the CDC has risen steadily since the late 1970s and is now at approximately 1,500 cases per year. Of the reported cases, nearly 50% are known to be due *P. falciparum* (Table 2-1) (Mali et al 2008).

Table 2-1 Malaria Cases Reported to the Centers for Disease Control and Prevention (2004-2006)

	Malaria cases, n (%)		
Plasmodium species	**2004**	**2005**	**2006**
P. falciparum	656 (49.5)	742 (48.6)	613 (39.2)
P. vivax	315 (23.8)	337 (22.1)	275 (17.6)
P. malariae	47 (3.5)	54 (3.5)	46 (2.9)
P. ovale	27 (2.0)	38 (2.5)	47 (3.0)
Mixed	17 (1.3)	12 (0.8)	10 (0.6)
Unreported/undetermined	262 (19.8)	345 (22.6)	573 (36.6)
Total	**1,324**	**1,528**	**1,564**

Several factors contribute to the potential risk of malaria in the United States, including extensive travel by US citizens to endemic regions, US citizens living in endemic regions, and people from endemic regions traveling to the United States. Lack of compliance to available

prophylactic regimens is also common and can increase the risk of malaria among US citizens (Mali et al 2008).

Current Treatments Available in the United States

The CDC has developed guidelines for the treatment of malaria based on drugs currently available for use in the United States (CDC 2007a). The treatment guidelines for *P falciparum* malaria are outlined in Table 2-2. Atovaquone-proguanil HCl (Malarone®) is the only fixed combination therapy available. Since June 21, 2007 an artemisinin derivative (inravenous artesunate) became available for treatment of Severe Malaria in the United States under an IND treatment protocol (IND protocol # 76,725. The treatment is available by contacting the CDC malaria hotline (CDC 2007b).

Table 2-2 The Centers for Disease Control and Prevention guidelines for treatment of *P falciparum* malaria in the United States

Clinical diagnosis	Region	Recommended drug
Uncomplicated malaria/ *P falciparum*	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	Chloroquine phosphate (Aralen®) Hydroxychloroquine (Plaquenil®)
	Chloroquine-resistant (All malarious regions except those specified as chloroquine-sensitive listed in the box above)	Quinine sulfate plus one of the following: Doxycycline, tetracycline, clindamycin Atovaquone-proguanil HCl (Malarone®) Mefloquine (Lariam®)

3 Preclinical Background Information

3.1 Mechanism of Action

Coartem is a fixed-dose combination tablet of 20 mg artemether (an artemisinin derivative) and 120 mg lumefantrine (a racemic mixture of a synthetic racemic fluorene derivative formerly known as benflumetol) in a 1:6 ratio. Both components are blood schizonticides, with complementary pharmacokinetics and dissimilar modes of action, thus providing synergistic antimalarial activity.

The mechanisms of action of artemisinins and lumefantrine are uncertain. The antimalarial activity of artemisinins may result from the production of free radicals that follows the iron-catalyzed cleavage of the artemisinin endoperoxide bridge in the parasite food vacuole or from inhibition of a parasite calcium ATPase. The antimalarial mechanism of action of lumefantrine is not well defined.

Artemether is largely converted to an active metabolite, DHA, which is more effective as a schizontocide than the parent drug. In studies using fresh isolates from field samples from Tanzania, China and Thailand, tests to determine parasite sensitivity to artemether, artemisinin and DHA were conducted. Freshly prepared plates used in the *in vitro* sensitivity field test procedures for inhibition of schizont maturation showed a close correlation between individual EC_{50}, EC_{90} and EC_{99} values comparing the ratio of artemisinin/artemether values against the ratio of artemisinin/DHA values. The blood schizontocidal activities of artemisinin

and DHA show a highly significant correlation, DHA being approximately 10-times as effective as the parent drug at the median effective concentration (EC_{50}) and more marked at the EC_{90} and EC_{99} values. Therefore artemisinin was used as a marker for artemether activity in the field studies following rigorous laboratory comparison which demonstrated excellent correlation between EC_{50}, EC_{90}, EC_{99} values determined for both artemether and artemisinin.

Resistance

Resistance has arisen to all classes of antimalarials except, as yet, to the artemisinin derivatives (WHO 2006). However. resistance can be prevented, or its onset slowed considerably, by ensuring very high cure rates through full adherence to correct dose regimens.

One publication (Denis et al 2006) reported a series of three open-label studies in Cambodia, in one of which the cure rate with Coartem was unexpectedly low. Although White (2008) hypothesized that sensitivity to artemisinins may have declined particularly in western Cambodia (following approximately 30 years use in various formulations and doses), the authors concluded that the rate of treatment failure was likely to be rather due to low lumefantrine blood concentrations rather than to drug resistance. Indeed, there was no difference in the *in vitro* susceptibility in isolates sampled from patients who were successfully treated and those who were treatment failures.

Further *in vitro* suceptibility studies showed no resistance to lumefantrine in isolates from Congo (Pradines et al 2006) or from the Comoros (Parola et al 2007). Only Legrand et al (2007) reported an elevated IC_{50} *in vitro* for lumefantrine in French Guiana. and decreased susceptibility to lumefantrine had been observed previously in Senegalese isolates (Pradines et al 1999). However Legrand et al 2007 stated that the significance of their observation in terms of therapeutic efficacy was unclear, since it might result from counterfeit, underdosed drugs.

Sisowath et al 2007 could not explain the two recrudescent infections observed in Zanzibar by enhanced pfmdr1 copy numbers, although their results confirm the involvement of different pfmdr1 alleles in lumefantrine tolerance in vivo (Sisowath et al 2005). The study used the standard six dose regimen, the two treatment failures might have been caused by insufficient drug bioavailability (lumefantrine plasma concentrations were not available).

Ménard et al 2005 in the Central African Republic found an IC_{50} for dihydroartemisinin similar to that obtained for isolates from other African countries, but lower than that observed for Asian isolates.

However the inconsistent relationship between *in vitro* and *in vivo* findings has been emphasized, e.g. in. Cambodia (White 2008).

On the other hand, 12 published cases of resistance to atovaquone-proguanil have been summarized by Boggild et al 2007 in *Plasmodium falciparum* malaria: Seven cases of atovaquone-proguanil treatment failure in non-immune travelers, with the remaining five occurring in semi-immune individuals. All published failures have occurred in patients whose malaria was acquired in Africa., Only 7 of 12 have had isolates with genetically confirmed markers of resistance, notably mutations in the cytochrome b gene.

Conversely, resistance to Coartem has not emerged so far as a significant clinical problem.

3.2 Toxicology

Coartem and its components have been tested *in vitro* and *in vivo* in a complete range of acute and subchronic animal toxicology studies, including reproductive toxicology, genotoxicity, and juvenile animal studies. Mechanistic neurotoxicity studies were performed in both rats and dogs to evaluate functional and histopathologic changes.

Repeat Exposure

Toxicity studies of up to 13-week duration in the rat and dog showed that continuous exposure to doses ranging from 20 to 1000 mg/kg/day for one to three months was associated with anemia, inflammation of the lymph nodes, and mild decreases in liver enzymes (ALT and AST). The effects on erythropoiesis resulted in sideroblastic, microcytic, hypochromic anemia, reticulocytis and thrombocytosis at higher dose levels, and a reduced myeloid:erythroid ratio with early, intermediate and late normoblastic hyperplasia. The erthroid effects were related to the artemether component, whereas the lymph node inflammation was associated with lumefantrine, based on independent studies with each component. Endocrine effects were observed after 3 months of dosing, and then only in one species. The changes included pituitary effects in rats but not dogs, especially in males, which did not include functional changes. Thyroid stimulation and hyperplasia were observed after 3 months of treatment in the rat. All of these changes were partially or fully reversible and were not considered limiting for the intended 3-day treatment duration in humans.

Nervous system

In animal models, intramuscular injection of artemisinin derivatives, including artemether, have been associated with neurotoxicity focused on pathways involved in hearing and balance, which manifests as lesions in specific brain nuclei involving the auditory and vestibular pathways. Details are provided in Section 7.4.1.

hERG K+ chanel

QTc prolongation is a known class effect of many antimalarial drugs. Therefore, the effects of lumefantrine and its major metabolite desbutyl-lumefantrine on wild type hERG K+ channels was investigated in stably transfected human embryonic kidney cells (HEK293) using the whole cell patch-clamp technique. These *In vitro* electrophysiology studies showed that lumefantrine and desbutyl-lumefantrine inhibited the hERG tail current with a higher IC_{50} value than mefloquine, chloroquine or halofantrine (Table 3-1). Notably, the IC_{50} for lumefantrine was 200-fold higher than that of halofantrine. All of the tested antimalarial drugs inhibited the hERG K+ channels in a concentration- and time-dependent manner. Only halofantrine blocked hERG tail currents voltage-dependently. Lumefantrine and desbutyl-lumefantrine also showed a slower inhibition of IKr than the other tested antimalarials. These data, together with calculated cardiac safety indices, suggested that lumefantrine and desbutyl-lumefantrine have a much weaker proarrhythmic potential than other anti malarials.

Table 3-1 In vitro 50% inhibitor concentration hERG tail current in HEK 293 cells and cardiac safety index of antimalaria drugs

Agent	IC_{50}- IKr in uM	IC_{50}/therapeutic free plasma concentration[1]
Halofantrine	0.04	0.07
Chloroquine	2.5	6.3
Mefloquine	2.6	50
Desbutyl-lumefantrine	5.5	~2900
Lumefantrine	8.1	48

[1]Cardiac safety index > 30 means cardiac toxicity is unlikely

Carcinogenicity and mutagenesis

Given that Coartem treatment is only 3 days (6 doses) in duration and genotoxicity studies did not identify a clastogenic, aneugenic, or mutagenic risk, carcinogenicity studies were deemed unnecessary and were not performed. No evidence of mutagenicity was detected *in vitro* or *in vivo* with an artemether/lumefantrine combination. In the micronucleus test, myelotoxicity was seen at all dose levels (500, 1,000, and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Teratogenicity

Reproductive and development studies have been completed to evaluate the teratogenic potential of Coartem in the rat and rabbit, effects on fertility and early embryonic development in rats, and pre- and post-natal development in the rat. While embryotoxicity was demonstrated in the rat and the rabbit for both Coartem and artemether, studies performed by Novartis in these species have found no evidence to suggest that Coartem, artemether, or lumefantrine is teratogenic. Nevertheless, artemisinin derivatives as a class are known to be embryotoxic and teratogenic based on recent published literature. Fetal malformations (cardiovascular and skeletal malformations) in rats, rabbits, and fetal death in monkeys have been reported when other artemisinin derivatives were administered to pregnant animals during the organogenesis period, suggesting that artemisinin derivatives as a class have a potential risk of teratogenicity in humans (Clark et al 2004, Longo et al 2006).

4 Clinical Pharmacology

The pharmacologic profile of artemether, lumefantrine, and their respective metabolites (dihydroartemisinin [DHA] and desbutyl-lumefantrine, respectively) was investigated in 22 studies (see Appendix Table 1), including 10 studies in healthy volunteers and 12 studies in patients (including pediatric patients) with malaria. Desbutyl-lumefantrine was measured in only two studies, one in healthy volunteers and one in patients with malaria.

4.1 Absorption, Distribution, Metabolism, and Excretion

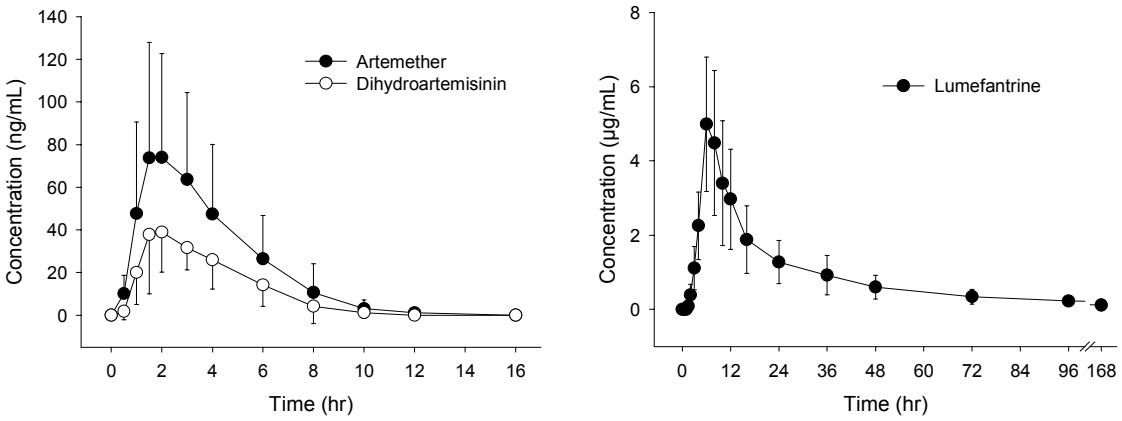
Absorption and distribution

After oral administration of Coartem, artemether is fairly rapidly absorbed and the peak plasma concentration (C_{max}) is reached approximately 2 hours after dosing (Figure 4-1). The active metabolite, DHA, also appears rapidly in plasma with a C_{max} reached approximately 2 hours post-dose. Absorption of lumefantrine (Figure 4-1), a highly lipophilic compound, is slower and starts after a lag-time of up to 2 hours. Peak plasma concentrations are reached approximately 6-8 hours after administration.

Artemether is rapidly eliminated from plasma with a half-life of 2-3 hours, whereas lumefantrine is eliminated more slowly with a half-life of 3-6 days. In accordance with its long elimination half-life, lumefantrine exposure increases after each dose of Coartem and reaches a peak on day 3 (i.e. last day of dosing).

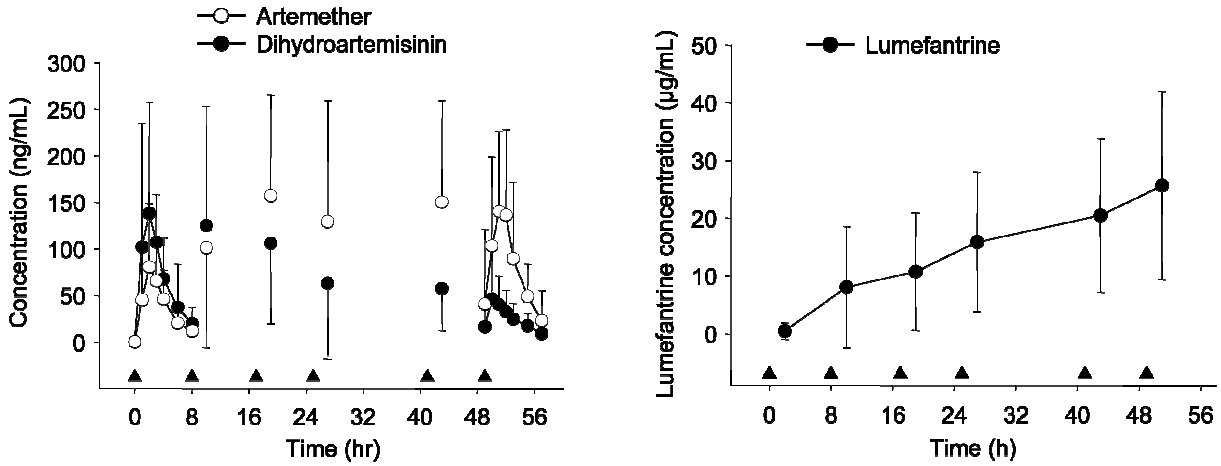
Demographic characteristics such as sex and bodyweight appeared to have no clinically relevant effects on the pharmacokinetics of Coartem (regression approach).

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



Repeated administration of Coartem over three days resulted in a progressive decrease in artemether exposure, with an increase in DHA (Figure 4-2). After last dose of Coartem, C_{max} or AUC_{last} of artemether was approximately 30-40% of that after first dose in healthy volunteers or patients. Despite the change in the metabolite-to-parent ratio, the sum of the exposure to artemether and DHA was similar after the first dose and the last dose in patients treated with the 6-dose regimen over three days (Study A028). *In vitro*, antimalarial activity of DHA was approximately three times that of artemether (Teja-Isavadharm et al 1996). Thus, the change in metabolite-to-parent ratio is not expected to have an impact on efficacy. Lumefantrine exposure increases after each dose of Coartem as expected from natural accumulation to reach its peak on last day/dose of administration (Figure 4-2). In accordance with its long elimination half-life of several days, steady state for lumefantrine pharmacokinetic parameters is not reached after three days of administration.

Figure 4-2 Mean ± SD plasma concentrations of artemether and DHA (left panel) and lumefantrine (right panel) after Coartem 6-dose regimen in malaria patients



Note: black triangles on the X axis show Coartem dose administration

Metabolism

Metabolism in animals and humans occurs primarily in the liver via the cytochrome P450 (CYP) isoenzyme CYP3A4, which generates active metabolites of artemether (i.e. DHA) and lumefantrine (i.e. desbutyl-lumefantrine). Human liver microsomes metabolize artemether to the primary biologically active metabolite (DHA) predominantly through CYP3A4/5, with more modest contributions from CYP1A1, 1A2, 2B6, 2C9 and 2C19. Lumefantrine is N-debutylated when incubated in human liver microsomes, which was catalyzed mainly by CYP3A4. Glucuronidation of lumefantrine takes place directly and after oxidative biotransformation *in vivo* in animals (dogs and rats).

Excretion

No urinary excretion data are available for humans, but there is no evidence of renal excretion in animals. In rats and dogs, no unchanged artemether was excreted in feces or urine as a result of its rapid and extensive metabolism, but a large number of metabolites has been detected, of which only a few could be identified. A major dose part of lumefantrine representing unabsorbed drug was excreted in the feces, while metabolites represented a minor dose fraction. Lumefantrine O- or N-glucuronides were shown to be excreted with the bile though appeared to be hydrolyzed in the gut releasing lumefantrine.

Effect of Food on Bioavailability

The effect of food on the absorption and bioavailability of Coartem has been investigated in a single dose (80/480 mg), crossover study in 16 Chinese healthy volunteers (Study A020). Food enhanced the absorption and bioavailability of artemether more than 2-fold and that of lumefantrine 16-fold compared with fasted conditions when Coartem was taken after a FDA standard high-fat breakfast. Therefore all subsequent safety/tolerability and PK studies in healthy volunteers have been conducted under fed conditions to maximize drug exposure.

In malaria patients, food was shown to increase lumefantrine exposure but to a lesser extent (approximately 2-fold), possibly because of the lower amount of food and/or lower amount of fat ingested by acutely ill patients (Ezzet et al 2000). Most of the clinical trials in adult/adolescent and pediatric patients were conducted with the recommendation to take Coartem with food as far as possible.

4.2 Drug-Drug Interactions

At clinically relevant concentrations, artemether has little or no capacity as an inhibitor of the major cytochrome P450 enzymes, and lumefantrine has little or no capacity to inhibit the major P450 enzymes except for CYP2D6 as observed *in vitro* at therapeutic plasma concentrations. Co-administration of Coartem with drugs that are metabolized by this isoenzyme with a narrow therapeutic index (e.g., neuroleptics and tricyclic antidepressants) is therefore contraindicated. *In vitro*, the anti-malaria compounds quinine and halofantrine (substrates of CYP3A4) were shown to inhibit lumefantrine metabolism at therapeutically relevant concentrations (Halliday et al 1995, Zhao et al 1996). However, the drug-drug interaction study of Coartem with quinine in healthy volunteers did not confirm the *in vitro* finding, and no change in lumefantrine exposure was observed when Coartem was co-administered with quinine (see below). The PK profile of artemether (and DHA) was not altered by lumefantrine co-administration (van Agtmael et al 1999), and likewise the PK of lumefantrine was not altered by co-administration of artemether.

Effect of CYP3A4 inhibitors: The concurrent oral administration of ketoconazole (400 mg on day 1 followed by 200 mg o.d. for 4 additional days) with Coartem (single dose on day 1) led to a modest increase ($\leq$ 2 fold) in artemether, DHA, and lumefantrine exposure in healthy subjects (Table 4-1). This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in ECG parameters. Based on this study, dose adjustment of Coartem is considered unnecessary in patients with *P falciparum* malaria when administered in association with ketoconazole or other potent CYP3A4 inhibitors (Study A2301). Furthermore, any change in the metabolism extent of artemether or in the metabolite-to-parent (DHA/artemether) ratio is of no concern for the clinical outcome since both compounds are active.

Interactions with other antimalarials: The sequential oral administration of mefloquine in healthy volunteers (1,000 mg divided into three doses over 12 hours) prior to Coartem 6-dose regimen had no statistically significant effect on plasma concentrations of artemether or the artemether/DHA ratio, but there was a significant (approximately 30% to 40%) reduction in plasma levels (C_{max} and AUC) of lumefantrine (Table 4-1). This reduction in exposure, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production, was not considered to be clinically relevant (Lefèvre et al 2000). The pharmacokinetics of mefloquine was not affected by co-administration with Coartem.

Table 4-1 Summary of exposure (AUC) changes following drug-drug interactions

	Change in exposure (AUC)		
	Artemether	**Lumefantrine**	**Co-medication[1]**
Coartem + mefloquine	Unchanged	↓ 32%	Unchanged
Coartem + ketoconazole	↑ 2.5 fold	↑ 1.7 fold	Not measured
Coartem + quinine	↓ 46%	Unchanged	Unchanged

[1]mefloquine or ketoconazole or quinine

Interactions with other anti-infectives: Limited data exist on PK interactions between antiretroviral drugs and antimalarials, with both classes potentially being metabolized through cytochrome P450 pathways. To date, no data exist with respect to co-administration of Coartem with antiretroviral drugs in either healthy volunteers or patients infected with HIV. Due to variable patterns of inhibition, induction, or competition for CYP3A4 with protease inhibitor antiretroviral drugs, use of such drugs, especially combinations of them, concomitantly with Coartem requires caution.

4.3 Pharmacokinetics in Special Populations

Ethnic origin: There was no formal investigation of the effect of ethnic origin on the PK of artemether or lumefantrine. However, studies have been conducted in ethnically diverse areas of the world (eg, Africa and Southeast Asia). Descriptively, there was no evidence to suggest any relevant differences in the exposure between different ethnicities such as African, Asian, or Caucasian populations.

Hepatic and renal insufficiency: No specific PK studies have been performed in individuals with hepatic or renal insufficiency. However, as is frequently seen in acute malaria, many patients included in the clinical studies showed a certain degree of hepatic impairment, as indicated by increased liver enzymes and/or hepatomegaly. Furthermore, in a limited number of patients, increased values of serum creatinine were observed, possibly indicating a certain degree of renal impairment. A retrospective descriptive analysis of safety performed in those patients did not reveal any difference from the general study population (Bakshi et al 2000).

Elderly: No specific PK studies have been performed in elderly subjects. Elderly patients rarely present with symptoms of malaria in endemic countries. Consequently, only very few safety data could be collected in this population during the clinical program, which did not allow firm conclusions to be drawn.

Pediatrics: Coartem has been extensively studied in pediatric patients with malaria with bodyweight as low as 5 kg (i.e. approximately 2 months old), and the tablets are usually crushed prior to administration. The PK of artemether and lumefantrine have been investigated in two clinical trials in pediatric patients with malaria in Africa given crushed tablets. Overall, the data show that systemic exposure to artemether, DHA, and lumefantrine in pediatric patients (5 to < 35 kg body weight) was comparable to that in adult patients with malaria when dosed on a mg/kg body weight basis. Lumefantrine mean C_{max} ranged between 4.71 and 9.37 µg/mL in pediatric patients (Study A2403 and Study B2303) and between 5.60 and 9.0 µg/mL in adult patients (Ezzet et al 2000, Piola et al 2005, Ashley et al 2007). The respective AUC_{last} values ranged between 372 and 699 µg·h/mL in pediatric patients, and between 410 and 561 µg·h/mL in adults. Moreover, no relevant differences in artemether (and

DHA) exposure were observed between body weight groups 5 - < 15, 15 - < 25 and 25 - < 35 kg.

Pregnancy: Very limited data are available in pregnant women. Based on animal data, Coartem is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation. During the second and third trimesters, treatment is considered if the expected benefit to the mother outweighs the risk to the fetus. A study conducted in Thailand in 13 pregnant women (five in the second trimester and eight in the third trimester) with uncomplicated *P falciparum* malaria concluded that pregnancy is associated with reduced (approximately half) plasma concentrations of artemether, DHA, and lumefantrine compared to historical data in non-pregnant (1 female and 16 males) patients with malaria (McGready et al 2006a). A reduction in DHA concentrations in pregnancy following artesunate treatment was also reported previously (McGready et al 2006b). All patients treated with Coartem in this study were cured despite lower exposure to artemether and lumefantrine.

However, in a more recent trial conducted in 103 pregnant women with falciparum malaria in the 2nd and 3rd trimesters of pregnancy and treated with Coartem (McGready 2008, personal communication), plasma concentrations (mean [range] ng/mL) of lumefantrine (measured on day 7) were higher (483 [134-1454]) in pregnant women than those observed in non-pregnant adults (350 [204-869]) and previously reported (384 [62-835]) in study described above (McGready 2006a). There is no clear explanation for these inconsistent findings.

4.4 Pharmacodynamics

In population PK/PD modeling, lumefantrine AUC was identified as the key PK parameter influencing the 28-day cure rate. Higher lumefantrine AUC significantly increased the probability of cure at day 28. This was observed in a direct comparison of the 4- and 6-dose regimens in patients (Study A025) where cure rates increased with rising exposure to lumefantrine. Cure rates were 83%, 97%, and 99% for associated model-derived lumefantrine AUC values of 356, 561, and 712 µg·h/mL, respectively. In study A012 in patients with malaria, it was estimated that doubling the AUC increased the 28-day cure rate by approximately 80%, while halving the AUC decreased the cure rate by approximately 40%.

Analysis of data from study A2101 summarized in section 7.4.2 (ICH E14 definitive QTc study) demonstrated that the 95% confidence limits for the mean Cmax of lumefantrine do not cross the upper confidence band of the threshold of relevance for QTc change (10 msec vs placebo).

5 Overview of the Clinical Development Program

Coartem was originally developed by the Academy of Military Medical Sciences (AMMS) in Beijing, China. A different formulation of the combination was registered in China in 1992. Ciba-Geigy (subsequently Novartis) began further development in collaboration with Chinese partners in 1992. Subsequent studies, sponsored by Ciba/Novartis, evaluated Coartem in a broader range of clinical circumstances and geographic regions. The earlier of these studies evaluated the Coartem 4-dose regimen (see described). However, it became apparent that the

4-dose regimen did not provide optimal efficacy in some areas, such as Thailand, where multi-drug resistant *P. falciparum* malaria is prevalent, and further studies using two different 6-dose regimens were performed. On the basis of these studies, a regimen of 6 doses given over 60 hours was chosen for further clinical development and registration..

- The 4-dose regimen consists of 1 dose at diagnosis followed by a dose at 8, 24, and 48 hours. Each dose is adjusted for body weight as shown in Table 5-1 for a maximum total dose of 320 mg artemether and 1920 mg lumefantrine in patients ≥ 35 kg.
- The 6-dose regimen consists of 1 dose at diagnosis followed by a dose at 8, 24, 36, 48, and 60 hours. Each dose is adjusted for body weight as shown in Table 5-1 for a maximum total dose of 480 mg artemether and 2,880 mg lumefantrine in patients ≥ 35 kg.

Table 5-1 Dose per body weight

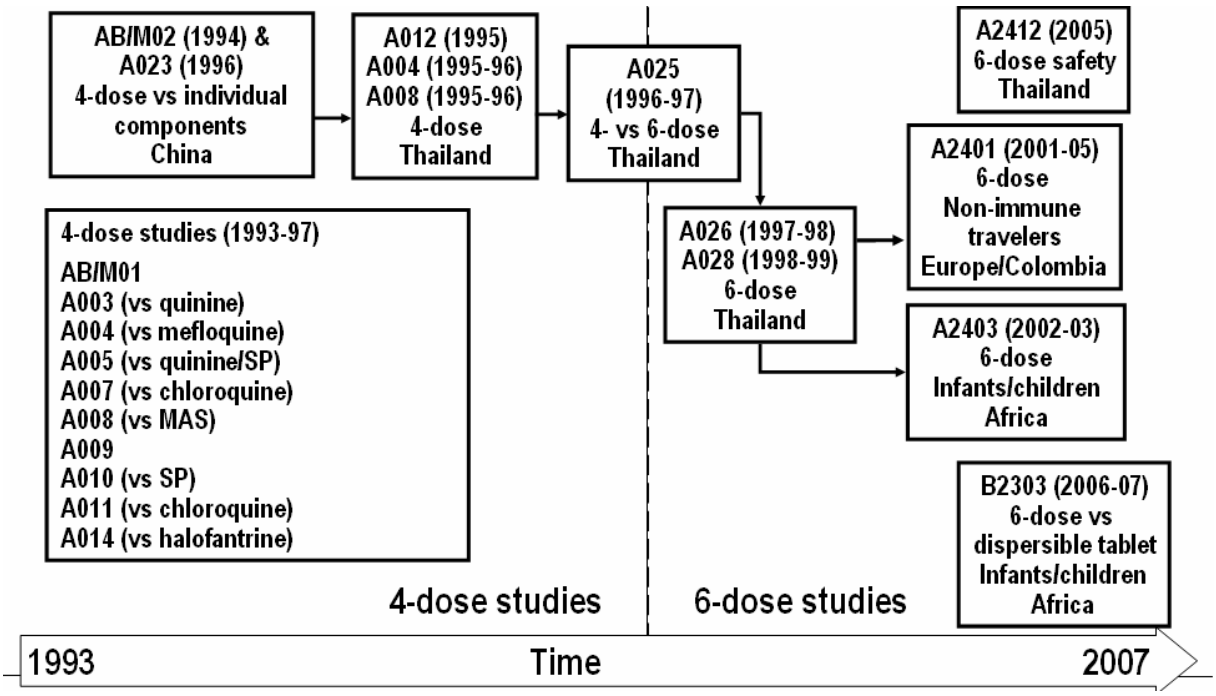
		Total mg per dose	
Body weight, kg	**Tablets per dose**	**Artemether**	**Lumefantrine**
5 < 15	1	20	120
15 < 25	2	40	240
25 < 35	3	60	360
≥ 35	4	80	480

Between 1993 and 2007, 20 studies were performed (Figure 5-1) that enrolled a total of 4911 patients with malaria, of whom 3599 were treated with Coartem, including 1572 adults (> 16 years of age) and 2027 pediatric patients (less or equal to 16 years of age. The studies were conducted in a range of geographic areas (Asia and Africa) with varying levels of drug resistant *P falciparum* and malaria endemicity and in travelers from non-endemic regions (Europe and Colombia) suffering from malaria. Patients included in the development program where either non-immune or semi-immune to *P falciparum*. Some of the studies performed, mainly those with the 4-dose regimen, included other antimalarial drugs or combinations as active comparators. Some studies allowed the inclusion of patients with mixed infections including *P falciparum* at baseline. No studies were performed in the United States.

Among the 20 Novartis sponsored-studies part of this NDA, 8 were identified as key in agreement with FDA as they provided substantial evidence in support of registration of the Coartem 6-dose regimen. These included:

- Two randomized, double-blind studies (ABMO2 and A023) that compared the efficacy of the Coartem 4-dose regimen with its individual components
- One randomized, double-blind study (A025) that compared the efficacy of the Coartem 4-dose versus 6-dose regimen
- Five studies providing substantial evidence of the efficacy and safety of the 6-dose regimen in a wide range of clinical settings (A026, A028, A2401, A2403, and B2303).

Figure 5-1 Overview of the clinical development program



5.1 Clinical Assessment of Efficacy

Study design considerations

- No placebo-controlled studies were performed for ethical reasons because untreated *P. falciparum* malaria may progress rapidly, with a potentially fatal outcome.
- Active comparators used in each controlled study were the standard therapies used in each country, in accordance with WHO recommendations at the time the studies were performed.
- All comparative studies were randomized, and double-blind designs were used where practical. Some of the 6 dose-regimen key studies used open-label, and in some cases non-comparative designs; the reasons for the use of such designs are discussed for each study, but in general relate either to the lack of suitable comparators at the time and in the region where the studies were conducted (e.g. Study A2403), or to practical considerations related to the time required for recruitment (e.g. studies in travelers from non-endemic countries such as Study A2401) or the excessive number of tablets patients would need to take if a double-blind/double-dummy design was used (e.g. Study A026 and Study A028).

Although the overall clinical program was conducted several years before the 2007 FDA draft guidance on clinical studies in the treatment of malaria was issued, the clinical development program for Coartem followed the principles outlined in that draft guidance (FDA 2007). Specifically:

- Studies were performed in a diverse range of geographical areas

- Studies were performed demonstrating the combination to have a measurable advantage over its components
- In most studies patients were evaluated in a controlled and monitored setting (in some cases patients were hospitalized for 28 days after starting treatment)
- Both patients likely to have partial immunity to malaria and those likely to be non-immune have been studied
- Patients of all ages have been studied, with large studies specifically performed in infants and children.
- A prospective observational study in pregnant women is ongoing
- Diverse racial groups were represented in the study populations (as a result of the diverse areas in which studies were conducted).
- The safety population included males and females spanning all ages
- Entry criteria for most studies were generally in line with those recommended in the guidance
- Efficacy, safety, and pharmacokinetics were evaluated in both adult and pediatric patients, and (as a result of studies being conducted in different geographical regions) patients of different ethnicity.
- Efficacy endpoints were in line with those recommended in the guidance.

Clinical Evaluations

Patients were followed for at least 28 days in all studies, except in study 010.

Giemsa-stained thick film blood smears were examined for asexual forms and gametocytes daily on days 1-8 and thereafter on days 15, 22, 29, and 42 (in some studies).

Polymerase Chain reaction (PCR) assessment was performed in 5 out of the 8 key studies. It was performed in two laboratories (one for studies A026, A028 and A025 and another for study A2403 and B2303). Correction for re-infection is important in endemic regions where it is likely that a patient may be re-infected. Genotyping of the parasite is therefore necessary to distinguish a new infection from recrudescence of the initial infection.

Body temperature was generally recorded at baseline, every 6-12 hours during Day 1, 2 and 3 of treatment, once or twice daily up to Day 8, and daily on Day 14 or 15 and 28 or 29. The precise timing, frequency, and duration of follow-up varied by study.

Efficacy Evaluations

Primary efficacy endpoint

- **28-day parasitological cure rate (PCR-corrected or uncorrected)**: Proportion of patients with clearance of asexual parasites within 7 days of initiating study treatment without recrudescence at day 28. The 28-day cure rate was either uncorrected or corrected for re-infection by polymerase chain reaction (PCR) assay.

Secondary efficacy endpoints

- **7-, 14-, and/or 42-day parasitological cure rate (PCR-corrected or uncorrected)**;
  Proportion of patients with clearance of asexual parasites within 7 days of initiating study treatment without recrudescence at day 7, 14, or 42 either uncorrected or corrected for re-infection by PCR assay
- **Parasite clearance** was evaluated by determining the following
  - **Time to parasite clearance (PCT)**: Time from first dose until first total and continued disappearance of asexual parasite forms which remains at least a further 48 hours as determined by examination of blood smears
  - **24-hour parasite reduction**: Percentage of parasites/µL at 24 hours compared to parasite density before the first dose of treatment (i.e. baseline) as determined by examination of blood smears; this endpoint was used as an alternative to PCT in some studies
  - **Asexual forms of *P falciparum* present by timepoint**: Number and percentage of patients with positive, negative, or missing slide by timepoint
- **Time to fever clearance (FCT)**: Time to fever clearance is defined as time from first dose until the first time the body temperature decreased below and remained below 37.5° C for at least a further 48 hours
- **Gametocyte clearance** was evaluated by determining either of the following
  - **Time to gametocyte clearance (GCT)**: Time from first dose until first total and continued disappearance of gametocytes which remains at least a further 48 hours
  - **Gametocytes present by timepoint**

Failure rate was assessed in each individual study based on either RI, RII, and RIII or ETF, LCF, and LPF, as defined below, depending on when the study was conducted.

- **RI, RII, RIII failure rate**:
  - **RI failure**: Clearance of asexual parasitemia within 7 days, followed by recrudescence
  - **RII failure**: Marked reduction of asexual parasitemia but no clearance asexual counts <25% of baseline within 48 hours of initiation of treatment but no or only temporary clearance of asexual parasitemia within 7 days.
  - **RIII failure**: No marked reduction of asexual parasitemia (asexual counts >25% of baseline at 48 hours or rise above baseline level at 48 hours without clearance of asexual parasitemia within 7 days
- **Early treatment failure; late clinical failure; late parasitological failure, and adequate clinical and parasitological response (WHO 2005):**
  - **Early treatment failure (ETF)** includes any of the following:

    Development of danger signs or severe malaria on Day 1, 2 or 3 in the presence of parasitemia

    Parasitemia on Day 2 higher than Day 0 count irrespective of axillary temperature

    Parasitemia on Day 3 with axillary temperature ≥ 37.5°C

Parasitemia on Day 3 ≥ 25% of the count on Day 0

- **Late clinical failure (LCF)** includes any of the following:

  Danger signs or severe malaria in the presence of parasitemia on any day between Day 4 and Day 28, without the patient previously meeting any of the criteria of ETF

  Axillary temperature ≥ 37.5°C in the presence of parasitemia on any day between Day 4 and Day 28, without the patient previously meeting any of the criteria of ETF

- **Late parasitological failure (LPF) and adequate clinical and parasitological response (ACPR)**

  LPF: Presence of parasitemia between Day 4 to Day 28 with temperature < 37.5°C, without the patient previously meeting any of the criteria of ETF or LCF

  ACPR: Absence of parasitemia on Day 28, irrespective of axillary temperature, without the patient previously meeting any of the criteria of ETF, LCF or LPF

Efficacy endpoints were determined both in the modified intent-to-treat (mITT) and the evaluable population. The mITT population (newly defined for this NDA) was defined as all randomized patients who received at least one dose of study drug. This definition matches the definition in the draft FDA guidance 'Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis' (FDA 2007). The definition of evaluable population was as it was in each single study report. In general, the evaluable population includes patients from the mITT who took no other drug with anti-malarial effect, and had parasite counts recorded up to Day 28 or who discontinued the study because of unsatisfactory therapeutic effect. The evaluable population is the most relevant population as the intent-to-treat analysis tends to underestimate the true efficacy of the drug considering as treatment failure patients who did not get a parasitological assessment at Day 28 and thus provides a "worst case scenario" (Stepniewska and White 2006).

5.2 Dose Selection Rationale

The dose selection was based on a series of studies described below demonstrating that:

1. The efficacy of the combination was superior to each individual component (Study ABM02 and Study A023)
2. The 6-dose regimen was the most effective with a 28-day cure rate > 95% in the evaluable population in areas with a high prevalence of multi-drug resistant *P. falciparum* malaria such as Thailand (Study A025).

5.2.1 Efficacy of Coartem versus Artemether or Lumefantrine Monotherapy

Studies AB/MO2 and A023 compared the efficacy of the Coartem 4-dose regimen with artemether and/or lumefantrine administered as monotherapy and were conducted in China.

AB/MO2

This single-center, randomized, double-blind study compared the 4-dose regimen of Coartem (80 mg artemether plus 480 mg lumefantrine) with the same regimen of each individual component in adult patients and pediatric patients (> 12 years of age) with uncomplicated *P. falciparum* malaria The demographic and baseline disease characteristics of the patient

population are shown in Table 5-2. The sample size in this study was determined in order to demonstrate that the combination would provide a cure rate of at least 90% as well as to be able to show a 10 hour clinically relevant difference for time to parasite clearance of Coartem versus lumefantrine.

Table 5-2 Study AB/MO2 – baseline demographic and disease characteristics

Characteristic	Coartem n = 53	Artemether n = 52	Lumefantrine n = 52
Sex, male/female, n (%)	43 (81)/10 (19)	45 (87)/7 (13)	44 (85)/8 (15)
Median age, years (range)	23 (13 - 57)	22 (13 - 54)	22 (13 - 53)
Median weight, kg (range)	50 (25 - 62)	50 (27 - 62)	50 (26 - 79)
Parasite density, asexual forms/µL			
Median	23,479	19,602	26,697
Geometric mean	19,431	20,386	22,415
Median temperature, °C	38.2	38.0	38.25

Tables 5-3, 5-4 and 5-5 summarize the key efficacy results for Study AB/MO2 for all patients, for adult and pediatric patients, respectively. The study demonstrated that the combination of artemether and lumefantrine was more effective than either of the constituent compounds used as monotherapy; In the overall patient population, the combination was associated with a more rapid clearance of parasites and fever than lumefantrine monotherapy ($p<0.001$, Wilcoxon test, Kaplan-Meier method), and a statistically higher 28-day parasitological cure rate than artemether monotherapy ($p<0.001$, Chi-Square test). No clinically relevant difference was observed between the adult and the pediatric population.

Table 5-3 Study AB/MO2 – efficacy in all patients

Evaluation		Coartem	Artemether	Lumefantrine
28-day uncorrected parasitological cure rate				
mITT population	n/N (%)	50/51 (98.0)	24/52(46.2	47/52 (90.4)
	(95% CI)	(89.6 - 100.0)	(32.2 - 60.5)	(79.0 - 96.8)
Evaluable patients	n/M (%)	50/50 (100.0)	24/44 (54.5)	47/51 (92.2)
	(95% CI)	(92.9 - 100.0)	(38.8 - 69.6)	(81.1- 98.8)
28-day PCR-corrected parasitological cure rate				
mITT population	n/N (%)	-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population	n/N (%)	51/51 (100.0)	50/52 (96.2)	52/52 (100.0)
	(95% CI)	(93.0 - 100.0)	(86.8 - 99.5)	(93.2 - 100.0)
Evaluable patients	n/M (%)	50/50 (100.0)	44/44 (100.0)	51/51 (100.0)
	(95% CI)	(92.9 - 100.0)	(92.0 - 100.0)	(93.0 - 100.0)
Median time to fever clearance (95% CI)[2], hours		36	30	38
mITT population		24.0 (12.0-36.0)	21.0 (12.0-30.0)	60.0 (48.0-66.0)
Median time to parasite clearance (95% CI)[2], hours		51	52	52
ITT population		30.0 (30.0-36.0)	30.0 (24.0-30.0)	54.0 (54.0-60.0)

Evaluation		Coartem	Artemether	Lumefantrine
Percent parasite reduction at 24 hours (mITT population)				
n		51	52	52
median		-99.3	-99.9	-78.2
25 – 75th percentiles		-100.0 -93.5	-100.0 -98.7	-91.8 -46.5
Patients with parasite reduction < 75% at 48 hrs				
mITT population	n/N (%)	0/51 (0.0)	0/52 (0.0)	5/52 (9.6)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population	n/N (%)	0/51 (0.0)	0/52 (0.0)	2/52 (3.8)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2	Negative slide	16/51 (31.4)	24/52 (46.2)	2/52 (3.8)
Day 3	Negative slide	46/51 (90.2)	50/52 (96.2)	19/52 (36.5)
Day 4	Negative slide	49/49 (100.0)	50/50 (100.0)	50/52 (96.2)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		-	-	-

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-4 Study AB/MO2 – efficacy in adults > 16 years of age

Evaluation		Coartem	Artemether	Lumefantrine
28-day uncorrected parasitological cure rate				
mITT population	n/N (%)	38/39 (97.4)	20/44 (45.5)	36/40 (90.0)
	(95% CI)	(86.5 - 99.9)	(30.4 - 61.2)	(76.3 - 97.2)
Evaluable patients	n/M (%)	38/38 (100.0)	20/37 (54.1)	36/39 (92.3)
	(95% CI)	(90.7 - 100.0)	(36.9 - 70.5)	(79.1 - 98.4)
28-day PCR-corrected parasitological cure rate				
mITT population	n/N (%)	-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population	n/N (%)	39/39 (100.0)	42/44 (95.5)	40/40 (100.0)
	(95% CI)	(91.0 - 100.0)	(84.5 - 99.4)	(91.2 - 100.0)
Evaluable patients	n/M (%)	38/38 (100.0)	37/37 (100.0)	39/39 (100.0)
	(95% CI)	(90.7 - 100.0)	(90.5 - 100.0)	(91.0 - 100.0)
Median time to fever clearance (95% CI)[2], hours		27	24	29
mITT population		24.0 (12.0-36.0)	24.0 (12.0-30.0)	54.0 (42.0-66.0)
Median time to parasite clearance (95% CI)[2], hours		39	44	40
mITT population		30.0 (30.0-36.0)	24.0 (24.0-30.0)	60.0 (48.0-60.0)

Evaluation		Coartem	Artemether	Lumefantrine
Percent parasite reduction at 24 hours (mITT population)				
n		39	44	40
median		-99.4	-100.0	-71.1
25 – 75th percentiles		-100.0 -97.7	-100.0 -98.8	-91.8 -40.0
Patients with parasite reduction < 75% at 48 hrs				
mITT population	n/N (%)	0/39 (0.0)	0/44 (0.0)	5/40 (12.5)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population	n/N (%)	0/39 (0.0)	0/44 (0.0)	2/40 (5.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2	Negative slide	13/39 (33.3)	23/44 (52.3)	2/40 (5.0)
Day 3	Negative slide	36/39 (92.3)	42/44 (95.5)	15/40 (37.5)
Day 4	Negative slide	37/37 (100.0)	42/42 (100.0)	38/40 (95.0)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		-	-	-

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-5 Study AB/MO2 – efficacy in pediatric patients ≤ 16 years of age

Evaluation		Coartem	Artemether	Lumefantrine
28-day uncorrected parasitological cure rate				
mITT population	n/N (%)	12/12 (100.0)	4/8 (50.0)	11/12 (91.7)
	(95% CI)	(73.5 - 100.0)	(15.7 - 84.3)	(61.5 - 99.8)
Evaluable patients	n/M (%)	12/12 (100.0)	4/7 (57.1)	11/12 (91.7)
	(95% CI)	(73.5 - 100.0)	(18.4 - 90.1)	(61.5 - 99.8)
28-day PCR-corrected parasitological cure rate				
mITT population	n/N (%)	-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population	n/N (%)	12/12 (100.0)	8/8 (100.0)	12/12 (100.0)
	(95% CI)	(73.5 - 100.0)	(63.1 - 100.0)	(73.5 - 100.0)
Evaluable patients	n/M (%)	12/12 (100.0)	7/7 (100.0)	12/12 (100.0)
	(95% CI)	(73.5 - 100.0)	(59.0 - 100.0)	(73.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		9	6	9
mITT population		12.0 (6.0-48.0)	12.0 (6.0-24.0)	66.0 (60.0-84.0)
Median time to parasite clearance (95% CI)[2], hours		12	8	12
mITT population		36.0 (NE - NE)	30.0 (30.0-36.0)	54.0 (48.0-60.0)

Evaluation	Coartem	Artemether	Lumefantrine
Percent parasite reduction at 24 hours (mITT population)			
n	12	8	12
median	-94.2	-98.8	-80.0
25 – 75th percentiles	-99.7 -90.4	-99.6 -96.7	-89.3 -58.9
Patients with parasite reduction < 75% at 48 hrs			
mITT population n/N (%)	0/12 (0.0)	0/8 (0.0)	0/12 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]			
mITT population n/N (%)	0/12 (0.0)	0/8 (0.0)	0/12 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)			
Day 2 Negative slide	3/12 (25.0)	1/8 (12.5)	0/12 (0.0)
Day 3 Negative slide	10/12 (83.3)	8/8 (100.0)	4/12 (33.3)
Day 4 Negative slide	12/12 (100.0)	8/8 (100.0)	12/12 (100.0)
Patients with recrudescence of *P falciparum* during the study, n/N (%)			
mITT population	-	-	-

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Study A023

Study A023 was a double-blind study in adult and pediatric (> 12 years of age) patients performed at a single center in China that compared a 4-dose regimen of Coartem with lumefantrine monotherapy, given either as a 4-dose regimen of tablets identical to that used for Coartem (total lumefantrine dose 1,920 mg) or as the registered schedule for lumefantrine in China at the time (eight 100 mg capsules at start, followed by 4 capsules each at hours 24, 48, and 72, to a total lumefantrine dose of 2,000 mg). The study was designed to have 80% power to show a 14-hour difference in parasite clearance time between coartem and lumefantrine tablets.

The demographic and baseline disease characteristics of the patient population are shown in Table 5-6 and were similar to the previous study.

Table 5-6 Study A023 – demographic and baseline disease characteristics

		Lumefantrine	
Characteristic	**Coartem 4-dose n = 52**	**Tablets n = 51**	**Capsules n = 50**
Sex, male/female, n (%)	45 (87)/7 (13)	42 (80)/9 (20)	39 (78)/11 (22)
Median age, years (range)	24 (13 - 56)	22 (13 - 65)	19 (12 - 47)
Median weight, kg (range)	50 (34 - 65)	50 (35 - 70)	50 (35 - 61)
Parasite density, asexual forms/µL			
Median	11,778	25,508	23,781
Geometric Mean	12,885	18,695	16,589
Range	1,288 - 95,374	1,026 - 148,626	1,103 - 127,281
Median temperature, °C (range)	37.45 (36.2 – 40.8)	37.9 (36.0 – 40.1)	38 (36.0 – 40.8)

Tables 5-7, 5-8 and 5-9 summarize the key efficacy results for Study A023 for all patients, for adult as well as for pediatric patients, respectively.

In the overall population, although the 28-day cure rate was similar between treatment groups, the median PCT was statistically significantly shorter in the Coartem group compared with either lumefantrine capsules or tablets ($p < 0.001$), and the median FCT was also significantly shorter in the Coartem group ($p = 0.017$ versus tablets; $p = 0.046$ versus capsules). No clinically relevant difference was observed between the adult and the pediatric population.

Table 5-7 Study A023 – Efficacy in all patients

			Lumefantrine	
Evaluation		**Coartem 4-dose**	**Tablets**	**Capsules**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		50/52 (96.2)	45/51 (88.2)	47/50 (94.0)
	(95% CI)	(86.8 - 99.5)	(76.1 - 95.6)	(83.5 - 98.7)
Evaluable patients	n/M (%)	50/51 (98.0)	45/49 (91.8)	47/49 (95.9)
	(95% CI)	(89.6 - 100.0)	(80.4 - 97.7)	(86.0 - 99.5)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population n/N (%)		51/52 (98.1)	50/51 (98.0)	49/50 (98.0)
	(95% CI)	(89.7 - 100.0)	(89.6 - 100.0)	(89.4 - 99.9)
Evaluable patients	n/M (%)	51/51 (100.0)	49/49 (100.0)	49/49 (100.0)
	(95% CI)	(93.0 - 100.0)	(92.7 - 100.0)	(92.7 - 100.0)
Median time to fever clearance (95% CI)[2], hours		24	31	35
mITT population		21.0 (11.9-24.2)	36.0 (29.8-54.0)	36.0 (18.1-54.0)
Median time to parasite clearance (95% CI)[2], hours		52	51	50
mITT population		30.0 (24.0-30.0)	48.0 (42.0-60.0)	54.0 (48.0-60.0)
Percent parasite reduction at 24 hours (mITT population)				
n		52	51	49
median		-99.9	-78.7	-86.7
25 – 75th percentiles		-100.0 -99.0	-95.9 -53.9	-95.3 -60.6
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/38 (0.0)	1/48 (2.1)	2/47 (4.3)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/38 (0.0)	0/48 (0.0)	1/47 (2.1)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2	Negative slide	21/52 (40.4)	1/51 (2.0)	2/49 (4.1)
Day 3	Negative slide	36/38 (94.7)	24/48 (50.0)	21/47 (44.7)
Day 4	Negative slide	51/51 (100.0)	47/49 (95.9)	46/49 (93.9)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		-	-	-

			Lumefantrine	
Evaluation		**Coartem 4-dose**	**Tablets**	**Capsules**

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-8 Study A023 – Efficacy in adults > 16 year of age

			Lumefantrine	
Evaluation		**Coartem 4-dose**	**Tablets**	**Capsules**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		40/42 (95.2)	37/42 (88.1)	36/38 (94.7)
	(95% CI)	(83.8 - 99.4)	(74.4 - 96.0)	(82.3 - 99.4)
Evaluable patients	n/M (%)	40/41 (97.6)	37/40 (92.5)	36/37 (97.3)
	(95% CI)	(87.1 - 99.9)	(79.6 - 98.4)	(85.8 - 99.9)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population n/N (%)		41/42 (97.6)	41/42 (97.6)	37/38 (97.4)
	(95% CI)	(87.4 - 99.9)	(87.4 - 99.9)	(86.2 - 99.9)
Evaluable patients	n/M (%)	41/41 (100.0)	40/40 (100.0)	37/37 (100.0)
	(95% CI)	(91.4 - 100.0)	(91.2 - 100.0)	(90.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		15	23	23
mITT population		17.9 (11.9-24.2)	42.0 (30.0-54.0)	30.0 (12.0-54.0)
Median time to parasite clearance (95% CI)[2], hours		42	42	38
mITT population		30.0 (24.0-30.0)	53.9 (42.0-60.0)	54.0 (48.0-60.0)
Percent parasite reduction at 24 hours (mITT population)				
n		42	42	37
median		-99.8	-80.8	-84.7
25 – 75th percentiles		-100.0 -99.0	-96.0 -53.9	-95.2 -60.6
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/31 (0.0)	0/39 (0.0)	2/36 (5.6)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/31 (0.0)	0/39 (0.0)	1/36 (2.8)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2 Negative slide		17/42 (40.5)	1/42 (2.4)	0/37 (0.0)
Day 3 Negative slide		29/31 (93.5)	18/39 (46.2)	16/36 (44.4)
Day 4 Negative slide		42/42 (100.0)	39/40 (97.5)	35/37 (94.6
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		-	-	-

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-9 Study A023 – Efficacy in pediatric patients ≤ 16 years of age

			Lumefantrine	
Evaluation		**Coartem 4-dose**	**Tablets**	**Capsules**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		10/10 (100.0)	8/9 (88.9)	11/12 (91.7)
	(95% CI)	(69.2 - 100.0)	(51.8 - 99.7)	(61.5 - 99.8)
Evaluable patients	n/M (%)	10/10 (100.0)	8/9 (88.9)	11/12 (91.7)
	(95% CI)	(69.2 - 100.0)	(51.8 - 99.7)	(61.5 - 99.8)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		-	-	-
	(95% CI)	-	-	-
Evaluable patients	n/M (%)	-	-	-
	(95% CI)	-	-	-
7-day uncorrected cure rate				
mITT population n/N (%)		10/10 (100.0)	9/9 (100.0)	12/12 (100.0)
	(95% CI)	(69.2 - 100.0)	(66.4 - 100.0)	(73.5 - 100.0)
Evaluable patients	n/M (%)	10/10 (100.0)	9/9 (100.0)	12/12 (100.0)
	(95% CI)	(69.2 - 100.0)	(66.4 - 100.0)	(73.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		9	8	12
mITT population		24.0 (6.0-24.4)	30.1 (6.1-120.0)	42.0 (36.0-54.0)
Median time to parasite clearance (95% CI)[2], hours		10	9	12
mITT population		29.9 (24.0-36.0)	48.0 (42.0-60.0)	48.0 (42.0-60.0)
Percent parasite reduction at 24 hours (mITT population)				
n		10	9	12
median		-99.9	-75.0	-90.7
25 – 75th percentiles		-100.0, -99.8	-84.4, -63.0	-97.3, -50.4
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/7 (0.0)	1/9 (11.1)	0/11 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/7 (0.0)	0/9 (0.0)	0/11 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2 Negative slide		4/10 (40.0)	0/9 (0.0)	2/12 (16.7)
Day 3 Negative slide		7/7 (100.0)	6/9 (66.7)	5/11 (45.5)
Day 4 Negative slide		9/9 (100.0)	8/9 (88.9)	11/12 (91.7)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		-	-	-

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Summary

These two studies clearly demonstrated that the combination of artemether with lumefantrine achieved a cure rate >90% and was more effective than either component used as monotherapy. Compared with artemether, Coartem dramatically improved the 28-day cure rate. Compared with lumefantrine, Coartem significantly reduced the median time to parasite

clearance by approximately 20 hours and reduced fever clearance time by approximately 10 hours, which are considered clinically relevant differences.

5.2.2 Selection of the 6-Dose Regimen

Based on the results of Study A004, A008 and A012 conducted with the 4-dose regimen in Thailand, a region with a high prevalence of multi-drug resistant *P. falciparum* malaria, it was decided to explore the efficacy of a 6-dose regimen.

Study A004

Study A008 was a randomized, double blind , parallel group, study comparing the efficacy and safety of the Coartem 4-dose regimen versus oral mefloquine in adults and children >12 years of age. Median parasite density at baseline was 17060 µl/ml. The 28-day cure rate achieved with the 4-dose regimen was 62.7% in the ITT population (versus 77.8% for mefloquine) and 69.3% (versus 82.4% for mefloquine) in the evaluable population.

Study A008

Study A008 was a randomized, open-label, parallel group, long-term (i.e. 9 week, 63 days) study comparing the efficacy and safety of the Coartem 4-dose regimen with mefloquine plus artesunate (MAS) in adults and children > 5 years of age. Median parasite density at baseline was 4057 µl/ml. The 28-day cure rate achieved with the 4-dose regimen was 73.1% in the ITT population (versus 84.1% with MAS) with and 82.1% in the evaluable population (versus 97.3% with MAS).

Study A012

Study A012 was a double-blind study that compared the 4-dose regimen with a similar regimen using half the total dose (2 tablets rather than 4 tablets per dose), and a shorter (24-hour) treatment schedule in adult and adolescent patients. Baseline parasite density ranged from approximately 1,100 to 198,000 asexual forms/µL (median 21,110/µL), with no major differences between treatment groups.

In contrast to the previous studies conducted in China, the 28-day uncorrected parasitological cure rate achieved with the 4-dose regimen was only 76.5% (evaluable patients), and lower 28-day parasitological cure rates were observed for the lower-dose and shorter treatment schedules (Table 5-10). There was a clear trend for better cure rates as total dose increased, but the 4-dose regimen was clearly not adequate in this setting in terms of 28-day parasitological cure rate. This suggested that higher doses might be more effective in regions with a high prevalence of multi-drug resistant *P. falciparum* malaria.

Table 5-10 Study 012 – 28-day parasitological cure rate

		Coartem dose regimen		
28 day parasitological cure rate		**4 x 4 tablets/ 48 h**	**4 x 2 tablets/ 48 h**	**3 x 4 tablets/ 24 h**
Uncorrected for re-infection	ITT population[1]	62/87 (71.3%)	41/87 (47.1%)	42/86 (48.8%)
	Evaluable patients[2]	62/81 (76.5%)	41/76 (53.9%)	42/79 (53.2%)
PCR-corrected for re-infection	Evaluable patients[3]	62/78 (79.5%)	41/75 (54.7%)	42/76 (55.3%)

[1]ITT population: all randomized patients
[2]Evaluable patients for 28-day cure rate: patients with parasite counts up to Day 29 or discontinued for 'unsatisfactory therapeutic effect' due to *P falciparum* recrudescence
[3]In this study, PCR-corrected cure rates were calculated by excluding patients shown to have re-infection from the denominator for the evaluable patients population

In view of the results of these studies, studies investigating a 6-dose regimen were subsequently performed, with the objective of identifying a treatment regimen that would allow for 28- day cure rate > 90% in the evaluable population.

5.2.3 Efficacy of 4- Versus 6-Dose Regimen

Study A025

Study A025 compared the 4-dose regimen with two different 6-dose regimens (6 doses given at 0, 8, 24, 36, 48, and 60 hours, or at 0, 8, 24, 48, 72, and 96 hours). This randomized, double-blind study was performed at two centers in Thailand, in adult and pediatric patients with uncomplicated *P. falciparum* malaria, and the observation period was up to 63 days. Doses were adjusted according to body weight ranges as described in Table 5-1. The study was designed to have 80% power to show a 15% difference in 28-day cure rate (95% vs 80%) between either of the 6-dose Coartem regimens and the 4-dose Coartem regimen, and used a Bonferroni multiplicity adjustment to account for for both comparisons.

The demographic and baseline disease characteristics of the patient population are shown in Table 5-11. Median parasite density in the 4-dose group was somewhat higher than in the two 6-dose groups, but mean parasite density was similar in all three treatment groups (approximately 10,000 asexual forms/µL).

Table 5-11 Study A025 - demographic and baseline disease characteristics

	Coartem treatment regimen		
Characteristic	**4-dose** n = 120	**6-dose/60 hours** n = 118	**6-dose/96 hours** n = 121
Sex, male/female, n (%)	83 (69) / 37 (31)	86 (73) / 45 (27)	81 (67) / 40 (33)
Median age, years (range)	24 (3 - 75)	23 (3 - 62)	21 (5 - 60)
Median weight, kg (range)	49.5 (12.5 - 92)	49.3 (10 - 90)	48.0 (12 - 76)
Parasite density, asexual forms/µL			
Median	11,891	6,276	7,480
Geometric mean	10,273	9,260	10.153
Range	381 – 199,980	415 – 195,735	290 – 464,880
Median temperature (range), °C	37.6 (36.0 – 40.8)	37.6 (36.0 – 40.8)	38.0 (36.0 – 41.5)

Tables 5-12 , 5-13 and 5-14 summarize the efficacy results from Study A025 for the overall adult and pediatric patients, respectively. In the overall study population, the 28-day cure rates were statistically significantly higher with both 6-dose regimens compared with the 4-dose regimen ($p < 0.001$, Cochran-Mantel-Haenszel test, controlling for center) in the evaluable population. The 28-day cure rate was also numerically better in the mITT population with the 6-dose regimens. The PCT or FCT were similar across the two treatment groups in pediatric patients (and for PCT in adults but not for FCT ; however the difference is not considered clinically relevant). Indeed these endpoints are reached rapidly, and as there is no difference in terms of total dose administered to the patients between the two dosing regimens in the first 36 hours of treatment, no difference should be expected between the two regimens. No clinically relevant difference for efficacy was observed between adult and pediatric patients.

Table 5-12 Study A025 – Efficacy in all patients

		Coartem treatment regimen		
Evaluation		**4-dose**	**6-dose/60 hours**	**6-dose/96 hours**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		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)
Evaluable patients	n/M (%)	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)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		86/118 (72.9)	97/118 (82.2)	105/121 (86.8)
	(95% CI)	(63.9 - 80.7)	(74.1 - 88.6)	(79.4 - 92.2)
Evaluable patients	n/M (%)	85/102 (83.3)	93/96 (96.9)	105/106 (99.1)
	(95% CI)	(74.7 - 90.0)	(91.1 - 99.4)	(94.9 - 100.0)
7-day uncorrected cure rate				
mITT population n/N (%)		120/120 (100.0)	115/118 (97.5)	118/121 (97.5)
	(95% CI)	(97.0 - 100.0)	(92.7 - 99.5)	(92.9 - 99.5)
Evaluable patients	n/M (%)	104/104 (100.0)	96/96 (100.0)	106/106 (100.0)
	(95% CI)	(96.5 - 100.0)	(96.2 - 100.0)	(96.6 - 100.0)
Median time to fever clearance (95% CI)[2], hours		61	59	80
mITT population		23.0 (20.9-36.0)	35.0 (21.7-43.4)	21.8 (21.0-34.0)
Median time to parasite clearance (95% CI)[2], hours		120	118	121
ITT population		43.8 (43.3-44.3)	43.6 (42.8-44.9)	43.6 (43.0-44.0)
Percent parasite reduction at 24 hours (mITT population)				
n		118	118	119
median		-99.1	-99.1	-98.3
25 – 75th percentiles		-99.9 -96.5	-100.0 -94.0	-99.9 -93.4
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/117 (0.0)	0/116 (0.0)	0/116 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/117 (0.0)	0/116 (0.0)	0/116 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2 Negative slide		27/118 (22.9)	31/118 (26.3)	27/119 (22.7)

Evaluation		Coartem treatment regimen		
		4-dose	**6-dose/60 hours**	**6-dose/96 hours**
Day 3	Negative slide	94/117 (80.3)	93/116 (80.2)	93/116 (80.2)
Day 4	Negative slide	116/116 (100.0)	109/111 (98.2)	114/117 (97.4)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population		16/120 (13.3)	3/118 (2.5)	2/121 (1.7)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-13 Study A025 – Efficacy in adults > 16 years of age

Evaluation		Coartem treatment regimen		
		4-dose	**6-dose/60 hours**	**6-dose/96 hours**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		67/99 (67.7)	71/88 (80.7)	78/92 (84.8)
	(95% CI)	(57.5 - 76.7)	(70.9 - 88.3)	(75.8 - 91.4)
Evaluable patients	n/M (%)	66/84 (78.6)	69/72 (95.8)	78/80 (97.5)
	(95% CI)	(68.3 - 86.8)	(88.3 - 99.1)	(91.3 - 99.7)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		68/97 (70.1)	72/88 (81.8)	79/92 (85.9)
	(95% CI)	(60.0 - 79.0)	(72.2 - 89.2)	(77.0 - 92.3)
Evaluable patients	n/M (%)	67/82 (81.7)	69/72 (95.8)	79/80 (98.8)
	(95% CI)	(71.6 - 89.4)	(88.3 - 99.1)	(93.2 - 100.0)
7-day uncorrected cure rate				
mITT population n/N (%)		99/99 (100.0)	86/88 (97.7)	89/92 (96.7)
	(95% CI)	(96.3 - 100.0)	(92.0 - 99.7)	(90.8 - 99.3)
Evaluable patients	n/M (%)	84/84 (100.0)	72/72 (100.0)	80/80 (100.0)
	(95% CI)	(95.7 - 100.0)	(95.0 - 100.0)	(95.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		48	41	60
mITT population		34.0 (20.9-41.0)	36.0 (22.3-43.8)	21.5 (20.9-34.0)
Median time to parasite clearance (95% CI)[2], hours		99	88	92
mITT population		43.8 (43.2-44.4)	43.9 (43.0-45.1)	43.6 (43.0-44.1)
Percent parasite reduction at 24 hours (mITT population)				
n		98	88	90
median		-99.0	-98.7	-98.6
25 – 75th percentiles		-99.9 -96.4	-100.0 -93.1	-99.9 -93.4
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/98 (0.0)	0/86 (0.0)	0/87 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/98 (0.0)	0/86 (0.0)	0/87 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2	Negative slide	20/98 (20.4)	21/88 (23.9)	21/90 (23.3)
Day 3	Negative slide	77/98 (78.6)	65/86 (75.6)	69/87 (79.3)

	Coartem treatment regimen		
Evaluation	**4-dose**	**6-dose/60 hours**	**6-dose/96 hours**
Day 4 Negative slide	96/96 (100.0)	82/84 (97.6)	85/88 (96.6)
Patients with recrudescence of *P falciparum* during the study, n/N (%)			
mITT population	14/99 (14.1)	3/88 (3.4)	2/92 (2.2)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Table 5-14 Study A025 – Efficacy in pediatric patients ≤ 16 years of age

		Coartem treatment regimen		
Evaluation		**4-dose**	**6-dose/60 hours**	**6-dose/96 hours**
28-day uncorrected parasitological cure rate				
mITT population n/N (%)		18/21 (85.7)	25/30 (83.3)	26/29 (89.7)
	(95% CI)	(63.7 - 97.0)	(65.3 - 94.4)	(72.6 - 97.8)
Evaluable patients	n/M (%)	18/20 (90.0)	24/24 (100.0)	26/26 (100.0)
	(95% CI)	(68.3 - 98.8)	(85.8 - 100.0)	(86.8 - 100.0)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)		18/21 (85.7)	25/30 (83.3)	26/29 (89.7)
	(95% CI)	(63.7 - 97.0)	(65.3 - 94.4)	(72.6 - 97.8)
Evaluable patients	n/M (%)	18/20 (90.0)	24/24 (100.0)	26/26 (100.0)
	(95% CI)	(68.3 - 98.8)	(85.8 - 100.0)	(86.8 - 100.0)
7-day uncorrected cure rate				
mITT population n/N (%)		21/21 (100.0)	29/30 (96.7)	29/29 (100.0)
	(95% CI)	(83.9 - 100.0)	(82.8 - 99.9)	(88.1 - 100.0)
Evaluable patients	n/M (%)	20/20 (100.0)	24/24 (100.0)	26/26 (100.0)
	(95% CI)	(83.2 - 100.0)	(85.8 - 100.0)	(86.8 - 100.0)
Median time to fever clearance (95% CI)[2], hours		13	18	20
mITT population		21.5 (19.2-43.1)	26.9 (20.3-45.3)	22.0 (20.0-43.6)
Median time to parasite clearance (95% CI)[2], hours		21	30	29
mITT population		44.0 (22.0-44.9)	43.0 (22.2-44.9)	43.6 (42.2-44.4)
Percent parasite reduction at 24 hours (mITT population)				
n		20	30	29
median		-99.8	-99.8	-97.5
25 – 75th percentiles		-100.0 -97.8	-100.0 -97.6	-99.9 -95.8
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)		0/19 (0.0)	0/30 (0.0)	0/29 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)		0/19 (0.0)	0/30 (0.0)	0/29 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2 Negative slide		7/20 (35.0)	10/30 (33.3)	6/29 (20.7)
Day 3 Negative slide		17/19 (89.5)	28/30 (93.3)	24/29 (82.8)
Day 4 Negative slide		20/20 (100.0)	27/27 (100.0)	29/29 (100.0)

Evaluation	Coartem treatment regimen		
	4-dose	6-dose/60 hours	6-dose/96 hours
Missing			
Patients with recrudescence of *P falciparum* during the study, n/N (%)			
mITT population	2/21 (9.5)	0/30 (0.0)	0/29 (0.0)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Summary

This study demonstrated that the 28-day cure rate achieved with the 6-dose regimen was significantly superior to that achieved with the 4-dose regimen in the evaluable population and numerically superior in the mITT population. Moreover, there were no obvious differences in tolerability between the 4-dose regimen and the two 6-dose regimens in this study (see Section 7.3.3). Therefore, because the 6-dose regimens were highly effective and well-tolerated (and this was confirmed in subsequent studies) no further studies of different dosing regimens were undertaken.

Of the two 6-dose regimens evaluated in Study A025, the 60-hour schedule was selected for further clinical development and registration. The overall efficacy of these alternative schedules was similar, and the shorter 60-hour schedule was chosen to optimize compliance, particularly in regions where treatment would be administered in an outpatient setting.

6 Efficacy of the 6-Dose Regimen

Several studies were conducted to confirm the efficacy of the Coartem 6-dose regimen in different geographic regions and populations (adult and pediatric patients).

6.1 Efficacy in Adult and Pediatric Patients

Subsequent to study A025 described above (Section 5.2.3), two large, randomized, open-label studies (A026 and A028) were conducted in Thailand to confirm the efficacy of the 6-dose regimen. These studies include artesunate, plus mefloquine (MAS) as an active control. In these studies artesunate, plus mefloquine (MAS) was also investigated for reference with historical control only, the trials were not designed to test for a difference or equivalence in efficacy or safety between Coartem and MAS.

Study A026

This study was performed at two centers in Thailand to confirm the efficacy, safety, and pharmacokinetics of the 6-dose/60-hour Coartem regimen in adults and children ≥ 2 years of age with uncomplicated *P falciparum* malaria. Patients in the Coartem group received the 6-dose regimen (1 to 4 tablets per dose, according to body weight), and patients in the MAS group received artesunate (4 mg/kg/day once daily for 3 days) plus mefloquine (25 mg/kg given as a split dose 15 mg/kg and 10 mg/kg on the 2nd and 3rd day). The study utilized an open-label design because the two treatments were clearly different in appearance and to

achieve blinding a double-dummy method would have required patients to take an unreasonably large number of tablets (i.e. up to 24 placebo tablets in addition to their active treatment). The study was designed to show that the lower limit of the the one-sided 95% confidence interval around the 28-day Coartem cure rate was above 90%. In addition, 50 patients were randomized to MAS to provide descriptive summary as a reference arm only.

Demographic and baseline disease characteristics were similar in the two treatment groups (Table 6-1).

Table 6-1 Study A026 – demographic and baseline disease characteristics

Characteristic	Coartem n = 150	MAS n = 50
Sex, male/female, n (%)	110 (73) / 40 (27)	37 (74) / 13 (26)
Median age, years (range)	22 (2 - 63)	25 (3 - 61)
Median weight, kg (range)	50 (8 - 81)	50 (11 - 66)
Parasite density, asexual forms/µL		
Median	9,374	5,285
Geometric mean	9,162	8,452
Range	264 - 254,490	625 - 177,840
Median temperature (range), °C	37.7 (35.6 – 40.2)	38.0 (36.0 – 39.9)

Efficacy results are summarized in Table 6-2 . Overall, the 28-day parasitological cure rates (with or without PCR correction) were high and similar in both treatment groups.. In both treatment groups, fever and parasites were cleared rapidly, with no major differences between treatments. No clinically relevant differences were observed between adults and children.

Table 6-2 Study A026 – Efficacy in adults > 16 years of age and in pediatric patients ≤ 16 years of age

	Adult		Pediatric		Total	
Evaluation	Coartem	MAS	Coartem	MAS	Coartem	MAS
28-day uncorrected parasitological cure rate						
mITT population n/N (%)	94/108 (87.0)	31/34 (91.2)	36/41 (87.8)	16/16 (100.0)	130/149 (87.2)	47/50 (94.0)
(95% CI)	(79.2 - 92.7)	(76.3 - 98.1)	(73.8 - 95.9)	(79.4 - 100.0)	(80.8 - 92.1)	(83.5 - 98.7)
Evaluable patients n/M (%)	94/95 (98.9)	31/31 (100.0)	36/39 (92.3)	16/16 (100.0)	130/134 (97.0)	47/47 (100.0)
(95% CI)	(94.3 - 100.0)	(88.8 - 100.0)	(79.1 - 98.4)	(79.4 - 100.0)	(92.5 - 99.2)	(92.5 - 100.0)
28-day PCR-corrected parasitological cure rate						
mITT population n/N (%)	94/108 (87.0)	31/34 (91.2)	36/40 (90.0)	16/16 (100.0)	130/148 (87.8)	47/50 (94.0)
(95% CI)	(79.2 - 92.7)	(76.3 - 98.1)	(76.3 - 97.2)	(79.4 - 100.0)	(81.5 - 92.6)	(83.5 - 98.7)
Evaluable patients n/M (%)	94/95 (98.9)	31/31 (100.0)	36/38 (94.7)	16/16 (100.0)	130/133 (97.7)	47/47 (100.0)

	Adult		Pediatric		Total	
Evaluation	**Coartem**	**MAS**	**Coartem**	**MAS**	**Coartem**	**MAS**
(95% CI)	(94.3 - 100.0)	(88.8 - 100.0)	(82.3 - 99.4)	(79.4 - 100.0)	(93.5 - 99.5)	(92.5 - 100.0)
7-day uncorrected cure rate						
mITT population n/N (%)	106/108 (98.1)	33/34 (97.1)	40/41 (97.6)	16/16 (100.0)	146/149 (98.0)	49/50 (98.0)
(95% CI)	(93.5 - 99.8)	(84.7 - 99.9)	(87.1 - 99.9)	(79.4 - 100.0)	(94.2 - 99.6)	(89.4 - 99.9)
Evaluable patients n/M (%)	95/95 (100.0)	31/31 (100.0)	39/39 (100.0)	16/16 (100.0)	134/134 (100.0)	47/47 (100.0)
(95% CI)	(96.2 - 100.0)	(88.8 - 100.0)	(91.0 - 100.0)	(79.4 - 100.0)	(97.3 - 100.0)	(92.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours						
mITT population	63 21.2 (19.9-24.0)	22 21.9 (20.0-26.0)	24 43.6 (22.3-45.0)	11 41.4 (20.7-66.0)	87 22.0 (20.8-41.9)	33 22.2 (21.1-41.4)
Median time to parasite clearance (95% CI)[2], hours						
mITT population	108 48.0 (NE - NE)	34 48.0 (NE - NE)	41 48.0 (NE - NE)	16 48.0 (NE - NE)	149 48.0 (NE - NE)	50 48.0 (NE - NE)
Percent parasite reduction at 24 hours (mITT population)						
n	108	34	41	16	149	50
median	-99.1	-99.8	-99.1	-99.7	-99.1	-99.7
25 – 75th percentiles	-100.0 - 97.1	-100.0 -98.0	-99.8 -95.3	-99.8 -99.3	-100.0 -96.5	-100.0 - 98.6
Patients with parasite reduction < 75% at 48 hrs						
mITT population n/N (%)	0/107 (0.0)	0/34 (0.0)	0/40 (0.0)	0/15 (0.0)	0/147 (0.0)	0/49 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]						
mITT population n/N (%)	0/107 (0.0)	0/34 (0.0)	0/40 (0.0)	0/15 (0.0)	0/147 (0.0)	0/49 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)						
Day 2 Negative slide	27/108 (25.0)	11/34 (32.4)	5/41 (12.2)	2/16 (12.5)	32/149 (21.5)	13/50 (26.0)
Day 3 Negative slide	98/107 (91.6)	32/34 (94.1)	36/40 (90.0)	12/15 (80.0)	134/147 (91.2)	44/49 (89.8)
Day 4 Negative slide	91/93 (97.8)	24/24 (100.0)	36/37 (97.3)	14/14 (100.0)	127/130 (97.7)	38/38 (100.0)

	Adult		Pediatric		Total	
Evaluation	**Coartem**	**MAS**	**Coartem**	**MAS**	**Coartem**	**MAS**
Patients with recrudescence of *P falciparum* during the study, n/N (%)						
mITT population	0/108 (0.0)	0/34 (0.0)	2/41 (4.9)	0/16 (0.0)	2/149 (1.3)	0/50 (0.0)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

Study A028

The primary objective of this study was to confirm the safety and efficacy of the Coartem 6-dose regimen in the formulation intended for marketing using the final manufacturing process (earlier development had used slightly different formulations and manufacturing processes). In contrast to Study A026, this study enrolled only patients > 12 years of age. The study was designed to show that the lower limit of the the one-sided 95% confidence interval around the 28-day Coartem cure rate was above 85%. In addition, 50 patients were randomized to MAS to provide descriptive summary as a reference arm only.

Baseline characteristics were similar in the two treatment groups (Table 6-3). Of note, 19% of patients had quinine detected in their blood at baseline (21% in the Coartem group, 15% in the MAS group), and 5% of the Coartem group and 9% of the MAS group had detectable levels of mefloquine in their blood at baseline. The entry criteria for this study specified that patients were permitted to have received recent treatment with other antimalarial drugs, provided that clear worsening of disease had been documented.

Table 6-3 Study A028 – demographic and baseline disease characteristics

Characteristic	**Coartem n = 164**	**MAS n = 55**
Sex, male/female, n (%)	115 (70) / 49 (30)	41 (75) / 14 (25)
Median age, years (range)	25 (12 - 71)	24 (12 - 60)
Median weight, kg (range)	50 (35 - 81)	52 (35 - 77)
Parasite density, asexual forms/µL		
Median	1,608	5,130
Geometric mean	2,063	3,329
Range	13 - 436,050	21 - 207,840
Median temperature (range), °C	37.5 (36.0 – 40.3)	37.6 (36.5 – 40.5)

Table 6-4 summarizes the efficacy results. The 6-dose Coartem regimen was associated with a high 28-day parasitological cure rate (with or without PCR correction). No clinically relevant differences were observed between adults and children. Notably, there was no difference in the cure rate among patients with detectable blood levels of quinine or mefloquine at baseline compared with patients who did not.

Table 6-4 Study A028 – Efficacy in adults > 16 years of age, in pediatric patients ≤ 16 years of age and in total

	Adult		Pediatric		Total	
Evaluation	**Coartem**	**MAS**	**Coartem**	**MAS**	**Coartem**	**MAS**
28-day uncorrected parasitological cure rate						
mITT population n/N (%)	134/149 (89.9)	41/43 (95.3)	14/15 (93.3)	12/12 (100.0)	148/164 (90.2)	53/55 (96.4)
(95% CI)	(83.9 - 94.3)	(84.2 - 99.4)	(68.1 - 99.8)	(73.5 - 100.0)	(84.6 - 94.3)	(87.5 - 99.6)
Evaluable patients n/M (%)	134/140 (95.7)	41/41 (100.0)	14/15 (93.3)	12/12 (100.0)	148/155 (95.5)	53/53 (100.0)
(95% CI)	(90.9 - 98.4)	(91.4 - 100.0)	(68.1 - 99.8)	(73.5 - 100.0)	(90.9 - 98.2)	(93.3 - 100.0)
28-day PCR-corrected parasitological cure rate						
mITT population n/N (%)	134/148 (90.5)	41/43 (95.3)	14/15 (93.3)	12/12 (100.0)	148/163 (90.8)	53/55 (96.4)
(95% CI)	(84.6 - 94.7)	(84.2 - 99.4)	(68.1 - 99.8)	(73.5 - 100.0)	(85.3 - 94.8)	(87.5 - 99.6)
Evaluable patients n/M (%)	134/139 (96.4)	41/41 (100.0)	14/15 (93.3)	12/12 (100.0)	148/154 (96.1)	53/53 (100.0)
(95% CI)	(91.8 - 98.8)	(91.4 - 100.0)	(68.1 - 99.8)	(73.5 - 100.0)	(91.7 - 98.6)	(93.3 - 100.0)
7-day uncorrected cure rate						
mITT population n/N (%)	148/149 (99.3)	43/43 (100.0)	15/15 (100.0)	12/12 (100.0)	163/164 (99.4)	55/55 (100.0)
(95% CI)	(96.3 - 100.0)	(91.8 - 100.0)	(78.2 - 100.0)	(73.5 - 100.0)	(96.6 - 100.0)	(93.5 - 100.0)
Evaluable patients n/M (%)	140/140 (100.0)	41/41 (100.0)	15/15 (100.0)	12/12 (100.0)	155/155 (100.0)	53/53 (100.0)
(95% CI)	(97.4 - 100.0)	(91.4 - 100.0)	(78.2 - 100.0)	(73.5 - 100.0)	(97.6 - 100.0)	(93.3 - 100.0)
Median time to fever clearance (95% CI)[2], hours	70	24	6	5	76	29
mITT population	29.0 (21.8-32.0)	27.5 (15.0-31.0)	38.3 (25.0-54.0)	20.5 (6.0-28.2)	29.0 (22.8-37.0)	23.0 (15.0-29.5)
Median time to parasite clearance (95% CI)[2], hours	149	43	15	12	164	55
mITT population	30.0 (25.8-32.3)	32.0 (26.0-32.3)	24.0 (24.0-39.7)	24.0 (16.0-31.5)	29.3 (25.8-32.0)	31.0 (25.5-32.0)
Percent parasite reduction at 24 hours (mITT population)						
n	148	43	15	12	163	55
median	-100.0	-100.0	-100.0	-100.0	-100.0	-100.0
25 – 75th percentiles	-100.0 - 99.0	-100.0 -99.7	-100.0 - 98.4	-100.0 - 100.0	-100.0 -99.0	-100.0 - 99.8

Evaluation	Adult		Pediatric		Total	
	Coartem	MAS	Coartem	MAS	Coartem	MAS
Patients with parasite reduction < 75% at 48 hrs						
mITT population n/N (%)	0/149 (0.0)	0/43 (0.0)	0/15 (0.0)	0/12 (0.0)	0/164 (0.0)	0/55 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]						
mITT population n/N (%)	0/149 (0.0)	0/43 (0.0)	0/15 (0.0)	0/12 (0.0)	0/164 (0.0)	0/55 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)						
Day 2 Negative slide	68/148 (45.9)	16/43 (37.2)	8/15 (53.3)	8/12 (66.7)	76/163 (46.6)	24/55 (43.6)
Day 3 Negative slide	139/149 (93.3)	40/43 (93.0)	15/15 (100.0)	12/12 (100.0)	154/164 (93.9)	52/55 (94.5)
Day 4 Negative slide	91/91 (100.0)	21/21 (100.0)	13/13 (100.0)	11/11 (100.0)	104/104 (100.0)	32/32 (100.0)
Patients with recrudescence of *P falciparum* during the study, n/N (%)						
mITT population	3/149 (2.0)	0/43 (0.0)	1/15 (6.7)	0/12 (0.0)	4/164 (2.4)	0/55 (0.0)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

6.2 Efficacy of the 6-Dose Regimen in Infants and Children

Two studies (A2403 and B2303) were conducted in Africa to confirm the efficacy and safety of the Coartem 6-dose regimen in infants and children with body weight between 5 and 35 kg.

Study A2403

Study A2403 was an open label, non-comparative trial conducted at 3 centers, one each in Kenya, Nigeria, and Tanzania in collaboration with the WHO. The primary objective of this study was to assess the safety of the 6-dose regimen in young children, particularly infants with a body weight of 5 - < 10 kg. Efficacy was a secondary objective. An open-label, non-comparative design was selected because the WHO could not identify a suitable comparator that it felt could be used ethically in patients with a body weight of 5- < 10 kg.

This study enrolled children and infants weighing 5 to 25 kg, with microscopically confirmed acute uncomplicated *P falciparum* malaria. Because these patients were likely to have little or no previous exposure to malaria and thus little immunity, an upper limit of 100,000/µL was specified for baseline parasite count.

Table 6-5 shows the patient population demographic and baseline disease characteristics. The dose given depended on body weight ranges as described previously (Table 5-1). Given the age of the patients it is likely that the tablets were crushed in most cases. Despite the upper

limit specified by the inclusion criteria, 2% of patients had a baseline parasite count > 100,000 asexual forms/µL.

Table 6-5 Study A2403 - demographic and baseline disease characteristics

Evaluation	Body weight group			All patients N = 310
	5 to < 10 kg N = 154	10 to < 15 kg N = 110	15 to 25 kg N = 46	
Sex, male/female, n (%)	77 (50) / 77 (50)	60 (54) / 50 (46)	24 (52) / 22 (48)	161 (52) / 149 (48)
Median age, years (range)	1.1 (0.2 - 3.1)	2.8 (0.8 - 6.8)	6.1 (2.9 - 9.9)	2.0 (0.2 - 9.9)
Parasite density, asexual forms/µL				
Median	17,581	20,929	14,726	18,488
Mean ± SD	32,394 ± 32,868	35,860 ± 34,124	28,530 ± 30,524	33,050 ± 32,976
Range	1,080 - 100,000	1,373 - 137,760	1,000 - 104,919	1,000 - 137,760
Median temperature (range), °C	38.5 (37.5 – 40.9)	38.5 (37.5 – 40.9)	38.8 (37.6 – 40.1)	38.5 (37.5 – 40.9)

Table 6-6 summarizes the efficacy results by patient body weight. The 28-day parasitological cure rates were high, particularly when PCR-corrected for re-infection, which was more frequent in this study than in other studies performed in Thailand because it was performed in areas with high transmission rates. Similar efficacy was observed regardless of body weight.

Table 6-6 Study A2403 - efficacy in pediatic patients ≤ 16 years

Evaluation	Body weight group			All patients N = 310
	5 to < 15 kg	15 to 25 kg	25 to 35kg	
28-day uncorrected parasitological cure rate				
mITT population n/N (%)	227/264 (86.0)	39/44 (88.6)	2/2 (100.0)	268/310 (86.5)
(95% CI)	(84.1 - 92.3)	(77.4 - 97.3)	(15.8 - 100.0)	(84.9 - 92.3)
Evaluable patients n/M (%)	227/256 (88.7)	38/42 (90.5)	2/2 (100.0)	267/300 (89.0)
(95% CI)	(81.2 - 89.9)	(75.4 - 96.2)	(15.8 - 100.0)	(82.1 - 90.1)
28-day PCR-corrected parasitological cure rate				
mITT population n/N (%)	248/264 (93.9)	40/43 (93.0)	2/2 (100.0)	290/309 (93.9)
(95% CI)	(90.3 - 96.5)	(80.9 - 98.5)	(15.8 - 100.0)	(90.6 - 96.3)
Evaluable patients n/M (%)	248/256 (96.9)	39/41 (95.1)	2/2 (100.0)	289/299 (96.7)
(95% CI)	(93.9 - 98.6)	(83.5 - 99.4)	(15.8 - 100.0)	(93.9 - 98.4)
7-day uncorrected cure rate				
mITT population n/N (%)	260/264 (98.5)	44/44 (100.0)	2/2 (100.0)	306/310 (98.7)
(95% CI)	(96.2 - 99.6)	(92.0 - 100.0)	(15.8 - 100.0)	(96.7 - 99.6)
Evaluable patients n/M (%)	260/260 (100.0)	43/43 (100.0)	2/2 (100.0)	305/305 (100.0)

Evaluation	Body weight group			All patients N = 310
	5 to < 15 kg	15 to 25 kg	25 to 35kg	
(95% CI)	(98.6 - 100.0)	(91.8 - 100.0)	(15.8 - 100.0)	(98.8 - 100.0)
Median time to fever clearance (95% CI)[2], hours	263	44	2	309
mITT population	7.9 (7.8-7.9)	7.8 (7.8-8.0)	15.8 (7.8-23.8)	7.8 (7.8-7.9)
Median time to parasite clearance (95% CI)[2], hours	264	44	2	310
mITT population	24.1 (24.0-35.6)	24.0 (23.8-24.2)	41.9 (35.9-47.9)	24.0 (24.0-35.4)
Percent parasite reduction at 24 hours (mITT population)				
n	260	43	2	305
median	-100.0	-100.0	-95.5	-100.0
25 – 75th percentiles	-100.0 -97.2	-100.0 -99.6	-97.0 -94.0	-100.0 -97.8
Patients with parasite reduction < 75% at 48 hrs				
mITT population n/N (%)	0/262 (0.0)	0/44 (0.0)	0/2 (0.0)	0/308 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]				
mITT population n/N (%)	0/262 (0.0)	0/44 (0.0)	0/2 (0.0)	0/308 (0.0)
Asexual forms of *P falciparum* present, n/N (%) (mITT)				
Day 2 Negative slide	139/260 (53.5)	31/43 (72.1)	0/2 (0.0)	170/305 (55.7)
Day 3 Negative slide	258/262 (98.5)	43/44 (97.7)	2/2 (100.0)	303/308 (98.4)
Day 4 Negative slide	260/260 (100.0)	44/44 (100.0)	2/2 (100.0)	306/306 (100.0)
Patients with recrudescence of *P falciparum* during the study, n/N (%)				
mITT population	9/264 (3.4)	2/44 (4.5)	0/2 (0.0)	11/310 (3.5)

1 Without imputing missing data.
2 Based on Kaplan Meier estimates.

Study B2303

Study B2303 was an investigator-blind, randomized, parallel group, multicenter trial in which 899 infants and children (≤ 12 years of age, body weight ≥ 5 kg and < 35 kg) with microscopically confirmed acute uncomplicated *P falciparum* malaria were randomized to treatment with the 6-dose regimen using either the standard Coartem tablet (crushed for administration) or a dispersible tablet. The study was performed at 8 centers in sub-Saharan Africa: 1 in Bénin, 3 in Kenya, 1 in Mali, 1 in Mozambique, and 2 in Tanzania.

The primary objective of the study was to demonstrate non-inferiority of the dispersible tablet compared with the crushed tablet with respect to the 28-day corrected parasitological cure rate. Of note, the dispersible tablet is not included in the current submission.

Baseline demographic and disease characteristics for the patients receiving the crushed tablets are described in Table 6-7. age characteristics by body weight category are shown in Table 6-8.

Table 6-7 Study B2303 - demographics and baseline disease characteristics

Characteristic	Crushed tablet n = 452
Sex, male/female, n (%)	247 (55) / 205 (45)
Median age, years (range)	3 (0 - 12)
Median weight, kg (range)	13.1 (6 - 34)
Parasite density, asexual forms/µL	
Median	32,288
Range	1,581 - 628,571
Median temperature (range), °C	37.9 (35.6 – 41.1)

Table 6-8 Study B2303 – age characteristics by body weight group

	Body weight group		
Age (years)	5- < 15 kg n = 241	15 - < 25 kg n = 138	25 - < 35 kg n = 30
Modified ITT population			
N	546	289	63
Median (Range)	2.0 (0–5)	5.0 (2–12)	10.0 (6–12)
Evaluable population			
N	494	282	59
Median (Range)	2.0 (0–5)	5.0 (2–12)	10.0 (6–12)

Table 6-9 summarizes the efficacy results from the crushed tablet group. As no claim is being made with respect to the dispersible tablet, data for this form of Coartem are not shown here. Very high 28-day PCR-corrected parasitological cure rates were observed in the evaluable population population regardless of body weight, and the 42-day cure rate was also high in the overall evaluable population. In addition, rapid clearance of fever and parasites was observed, and most patients who had gametocytes at baseline cleared them by day 8.

Table 6-9 Study B2303 - summary of 28-day parasitological cure rate in pediatic patients ≤ 16 years

		Body weight group			
Evaluation		5- < 15 kg n = 241	15 - < 25 kg n = 138	25 - < 35 kg n = 30	All patients n = 409
28-day uncorrected parasitological cure rate					
mITT population	n/N (%)	221/264 (83.7)	123/141 (87.2)	30/33 (90.9)	374/438 (85.4)
	(95% CI)	(78.7 - 88.0)	(80.6 - 92.3)	(75.7 - 98.1)	(81.7 - 88.6)
Evaluable population	n/M (%)	218/248 (87.9)	123/140 (87.9)	29/31 (93.5)	370/419 (88.3)

Evaluation		Body weight group 5- < 15 kg n = 241	15 - < 25 kg n = 138	25 - < 35 kg n = 30	All patients n = 409
	(95% CI)	(83.2 - 91.7)	(81.3 - 92.8)	(78.6 - 99.2)	(84.8 - 91.2)
28-day PCR-corrected parasitological cure rate					
mITT population	n/N (%)	242/260 (93.1)	134/139 (96.4)	31/32 (96.9)	407/431 (94.4)
	(95% CI)	(89.3 - 95.8)	(91.8 - 98.8)	(83.8 - 99.9)	(91.8 - 96.4)
Evaluable population	n/M (%)	239/244 (98.0)	134/138 (97.1)	30/30 (100.0)	403/412 (97.8)
	(95% CI)	(95.3 - 99.3)	(92.7 - 99.2)	(88.4 - 100.0)	(95.9 - 99.0)
7-day uncorrected cure rate					
mITT population	n/N (%)	255/268 (95.1)	142/143 (99.3)	33/34 (97.1)	430/445 (96.6)
	(95% CI)	(96.2 - 100.0)	(84.7 - 99.9)	(94.5 - 98.1)	
Evaluable population	n/M (%)	248/248 (100.0)	140/140 (100.0)	31/31 (100.0)	419/419 (100.0)
	(95% CI)	(98.5 - 100.0)	(97.4 - 100.0)	(88.8 - 100.0)	(99.1 - 100.0)
Median time to fever clearance (95% CI)[2], hours		191	105	27	323
mITT population		7.9 (7.8-8.0)	7.8 (7.7-8.0)	7.8 (7.5-8.5)	7.8 (7.8-7.9)
Median time to parasite clearance (95% CI)[2], hours		273	145	34	452
mITT population		35.3 (25.1-35.8)	34.6 (24.2-35.7)	25.8 (24.0-35.6)	34.9 (25.2-35.6)
Percent parasite reduction at 24 hours (mITT population)					
n		265	143	34	442
median		-99.9	-99.9	-99.9	-99.9
25 – 75th percentiles		-100.0 -98.3	100.0 -97.8	-100.0 - 98.8	-100.0 -98.1
Patients with parasite reduction < 75% at 48 hrs					
mITT population	n/N (%)	1/252 (0.4)	1/132 (0.8)	0/32 (0.0)	2/416 (0.5)
Patients with parasitemia 48 hrs > at baseline[1]					
mITT population	n/N (%)	0/252 (0.0)	1/132 (0.8)	0/32 (0.0)	1/416 (0.2)
Asexual forms of *P falciparum* present, n/N (%) (mITT)					
Day 2	Negative slide	121/265 (45.7)	69/143 (48.3)	17/34 (50.0)	207/442 (46.8)
Day 3	Negative slide	241/252 (95.6)	127/132 (96.2)	30/32 (93.8)	398/416 (95.7)
Day 4	Negative slide	213/214 (99.5)	117/117 (100.0)	31/31 (100.0)	361/362 (99.7)
Patients with recrudescence of *P falciparum* during the study, n/N (%)					
mITT population		5/273 (1.8)	6/145 (4.1)	0/34 (0.0)	11/452 (2.4)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

6.3 Efficacy of the 6-Dose Regimen in Non-immune Travelers

One single study (Study A2401) evaluated the efficacy of Coartem in travelers from non-endemic countries. This is the largest study performed to date in non-immune travelers.

Study A2401

Study A2401 was an open-label, uncontrolled study using the Coartem 6-dose regimen to treat non-immune patients from non-endemic regions who contracted acute uncomplicated *P. falciparum* malaria when traveling in endemic regions. Non-immune patients were regarded as those who had not spent the first five years of their life, nor the last five years prior to the study, in a malaria endemic area, and did not have acute *P. falciparum* malaria diagnosed during those past five years. Patients were followed for 28 days after the start of treatment. The study was designed to have 95% confidence that the estimate of the 28-day coartem cure rate was within a precision of ±5% .

Patients were recruited from centers in Europe (Switzerland, Germany, France, Italy, and the Netherlands) and Colombia. The Colombian center had a history of treating 'non-immune' patients (Soto et al 1998), who were defined as residents of regions declared as non-malarial and who had infrequent travel to malarial areas, thus meeting the criteria for the definition of non-immune status for the purposes of this study. This was the largest study performed to date in non-immune travelers.

Table 6-10 summarizes patient demographics and baseline disease characteristics. A total of 165 patients were enrolled. The patient population was generally of higher body weight (mean 73 kg, with a range of 41 to 119 kg) than the populations enrolled in previous studies in adults, which were conducted in South-East Asia. The patients were most commonly of Caucasian race. Patients from the Colombian center were mainly included in the 'other' race group. Most of these patients were described by the investigator as 'Latin complexion'.

In this study baseline parasitemia was determined as asexual parasites per 1,000 erythrocytes. For those patients for whom baseline counts were available, the range was 0-70 asexual parasites per 1,000 erythrocytes (median 2.4). The remaining patients had their parasite counts determined as asexual forms/μL; while summary statistics for parasitemia were not calculated for these patients, their asexual parasite counts ranged from 92-53,900/μL.

Table 6-10 Study A2401 - demographics and baseline disease characteristics

Characteristic	N = 165
Sex, male/female, n (%)	113 (68) / 52 (32)
Race, n (%)	
Caucasian	80 (48.5)
Black	40 (24.2)
Other	45 (27.3)
Median age, years (range)	37 (17-66)
Median weight, kg (range)	73 (41 - 119)
Parasite density per 1,000 RBCs ± SD	
Median	2.4
Mean ± SD	6.2 ± 9.45
Range	0 - 70
Median temperature ± SD (range), °C	38.0 (35.1 – 40.7)

Although most patients (82%) completed the study, and 93% completed treatment, there was a relatively high number of patients lost to follow up or with protocol violations. One patient discontinued treatment after the second dose due to signs of severe malaria, and was treated with rescue medication. Protocol violations were common: 25% of patients had major protocol violations, most commonly incomplete documentation of parasite counts after parasite clearance. Because these cases were counted as treatment failures, the ITT analysis of the 28-day parasitological cure rate underestimated the efficacy of Coartem.

Table 6-11 summarizes the efficacy results. As expected for the reasons noted above, the 28-day cure rate in the ITT population was low. However, a high 28-day cure rate was observed in the PP population. PCR correction for re-infection was only performed in a subset of patients. In practice, however, no cases of re-infection occurred and the PCR-corrected results were identical to the uncorrected results. Parasite and fever clearance times were similar to those observed in other studies. The efficacy results of this study are consistent with those of studies performed in other regions, suggesting that the relatively high body weight of patients in this study, and their immune status did not adversely affect the efficacy of the Coartem 6-dose regimen.

Table 6-11 Study A2401 - efficacy in adults > 16 years

Evaluation		Adults N =165
28-day uncorrected parasitological cure rate		
mITT population	n/N (%)	120/162 (74.1)
	(95% CI)	(66.6 - 80.6)
Evaluable	n/M (%)	119/124 (96.0)
	(95% CI)	(90.8 - 98.7)
28-day PCR-corrected parasitological cure rate		
mITT population	n/N (%)	120/162 (74.1)
	(95% CI)	(66.6 - 80.6)
Evaluable	n/M (%)	119/124 (96.0)
	(95% CI)	(90.8 - 98.7)
7-day uncorrected cure rate		
mITT population	n/N (%)	137/162 (84.6)
	(95% CI)	(78.1 - 89.8)
Evaluable	n/M (%)	123/125 (98.4)
	(95% CI)	(94.3 - 99.8)
Median time to fever clearance (95% CI)[2], hours		100
mITT population		36.5 (27.8-39.5)
Median time to parasite clearance (95% CI)[2], hours		162
ITT population		41.8 (40.3-43.8)
Percent parasite reduction at 24 hours (mITT population)		
n		152
median		-80.0
25 – 75th percentiles		-99.9 -35.0
Patients with parasite reduction < 75% at 48 hrs		
mITT population	n/N (%)	13/155 (8.4)
Patients with parasitemia 48 hrs > at baseline[1]		

Evaluation		Adults N =165
mITT population	n/N (%)	2/155 (1.3)
Asexual forms of *P falciparum* present, n/N (%) (mITT)		
Day 2	Negative slide	34/155 (21.9)
Day 3	Negative slide	114/155 (73.5)
Day 4	Negative slide	64/73 (87.7)
Patients with recrudescence of *P falciparum* during the study, n/N (%)		
mITT population		1/162 (0.6)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates

6.4 Summary of Efficacy

6.4.1 Summary of efficacy in all individual studies

The efficacy of the Coartem 4-dose or 6-dose regimens in the evaluable population, uncorrected by PCR, is summarized in Table 6-12 for all individual studies being part of the clinical program. Except for a few studies conducted in China, Europe and India, the 4-dose regimen provided a 28-day PCR uncorrected cure rate which was around or below 80%. Conversely, the 6-dose regimen provided a 28-day PCR uncorrected cure rate around or above 90% .

Table 6-12 Summary of clinical efficacy studies in patients with 4-dose and 6-dose regimens (evaluable population)

		Coartem	Comparator	
Study No. Region/year/study design/ observation period/	**N**	**28-day uncorrected cure rate [1]**	**Comparator N**	**28-day uncorrected cure rate[1]**
4-dose regimen Adults and adolescents				
A004 Thailand/1995-96/DB/28d	126	69.3%	Mefloquine 126	82.4%
AB/MO1 China/1993/OL/28d	105	96.1%[3]	-	-
AB/MO2 China/1994/DB/28d	53	100%	Artemether 52 Lumefantrine 52	54.5% 92.2%
A005 UK/1996-97/OL,MC/28d	12	100%	Quinine/SP 11	100%
A007 India/1996-97/DB/28d	89	95.4%	Chloroquine 90	19.7%
A008[6] Thailand/1995-96/OL/63d	309	82.1%	MAS 308	97.3%
A012 Thailand/1995/DB,MC/28d	87	76.5%	Coartem 4x2 tablets 87 3x4 tablets 86	 53.9% 53.2%
A014 Europe/1996-97/DB, MC/28d	51	82.2%	Halofantrine 52	100%

		Coartem	Comparator	
Study No. Region/year/study design/ observation period/	**N**	**28-day uncorrected cure rate [1]**	**Comparator N**	**28-day uncorrected cure rate[1]**
A023 China/1996/DB/28d	52	98%	Lumefantrine Tablet 51 Capsule 50	91.8% 95.9%
A025[2,6] Thailand/1996-97/DB/63d	120	80.8%	-	-
4-dose regimen Infants and Children				
A003 Thailand/1995-6/OL, MC/28 d	111	60.8%	Quinine 108	71.8%
A009 Gambia/1995-6/OL/28 d	60	70.9%	-	-
A010 Gambia/1996-7/DB.MC/28 d	144	-[7]	SP 143	-[7]
A011 Tanzania/1996/OL/28 d	130	63.6%	Chloroquine 130	5%
6-dose regimen Adults				
A025[2,6] Thailand/1996-97/DB/63d	118	96.9%	Coartem (6 dose 96 h) 121	98.1%
A026[6] Thailand/1997-98/OL, MC/28d	150	97%	MAS 50	100%
A028[6] Thailand/1998-99/OL, MC/28d	164	95.5%	MAS 55	100%
A2401 Europe/Colombia/2001-05/OL, MC/28d	165	96.0%[4]	-	-
6-dose regimen Infants and Children				
A2403 Africa/2002-3/OL, MC/28 days	310	89.0%	-	-
B2303 Africa/2006-7/IB, MC/42 days	452	90.5%[5]	Coartem dispersible 447	92.1%[5]

DB = double-blind, MC = multicenter, OL = open-label, MAS = mefloquine/artesunate, SP= sulfadoxine-pyrimethamine
N = number of patients that entered the study
[1] Evaluable patients as described in each study protocol, unless specified differently
[2] In Study 025 two different 6-dose regimens were used, with doses given over 3 or 5 days
[3] ITT population as described in each study protocol
[4] Per Protocol population
[5] Primary analysis population
[6] Studies that enrolled both adults and children
[7] day-28 cure rate not available
Source: Studies ABMO1, ABMO2, A003, A004, A005, A007, A008, A009, A010, A011, A012, A014 , A023, A025, A026, A026, A028, A2401, A2403, B2303

6.4.2 Pooled analyis

Analysis Populations

The pooled analysis of the adult population (> 16 years of age) included data from patients receiving the 4 dose regimen in studies A004, AB/MO1, AB/MO2, A005, A007, A008, A012, A014, A023, A025, and patients receiving the 6-dose regimen from studies A025, A026, A028, and A2401 (See Table 6-11). A total of 784 patients were treated with the 4-dose regimen, and 599 were treated with 6-dose regimens (for the purposes of these analyses the two 6-dose regimens used in Study A025 were both included and were treated as equivalent). Most of the patients in the adult pooled population, with the exception of Study A2401, were from studies performed in Thailand. Since only one study included both the 4 and 6 –dose regimen (A025), tables presenting both 4-dose and 6-dose are for supportive information only rather than direct between treatment group comparison. Table 6-13 shows the numbers of patients, by treatment group, in each analysis population. All patients in each treatment group were included in the modified ITT (mITT) population. Approximately 90% of each treatment group were also included in the evaluable patients population, as defined for each of the contributing studies.

Table 6-13 Number of patients in each analysis population (adult patients> 16 years of age)

	Coartem regimen	
Population	**4-dose**	**6-dose**
Modified ITT (mITT)	784	599
Evaluable for 28-day cure rate	693	513

Table 6-13 shows the numbers of adult patients, by treatment group, in each analysis population. All patients in each treatment group were included in the modified ITT (mITT) population. Because the 28-day cure rate was not evaluated in Study A010, patients from this study were not included in the evaluable patient population for that endpoint, which meant that only 62% of the Coartem 4-dose regimen group were included in this population.

The pooled analysis of the pediatric population included data from patients receiving the 4-dose regimen from studies AB/MO1, AB/MO2, A003, A004, A007, A008, A009, A010, A011, A012, A023, A025, and from patients receiving the 6 dose regimen from studies A025, A026, A028, A2403, and B2303 (see Table 6-14). Since only one study included both the 4 and 6–dose regimens (A025), tables presenting both 4-dose and 6-dose regimen groups are shown as supportive information only rather than direct between treatment group comparison.

Table 6-14 Number of patients in each analysis population (pediatric patients ≤ 16 years)

	Coartem	
Population	**4-dose**	**6-dose**
Modified ITT	650	877
Evaluable for 28-day cure rate	450	828

Adults > 16 years of age

Table 6-15 shows the results from the pooled efficacy analysis for the adult population (> 16 years of age). The 28-day PCR corrected cure rate in the evaluable population was 85.6% and 97.1% for the 4-dose and 6-dose regimen , respectively.

Table 6-15 Efficacy results (pooled analysis*, adult patients >16 years of age)

Efficacy parameter	Coartem 4-dose n = 784	Coartem 6-dose n = 599
28-day cure rate, n/M (%) (mITT)		
Uncorrected	593/784 (75.6)	497/599 (83.0)
Corrected	331/450 (73.6)	499/598 (83.4)
28-day cure rate, n/M (%) (evaluable)		
Uncorrected	588/693 (84.8)	494/511 (96.7)
Corrected	328/383 (85.6)	495/510 (97.1)
Median PCT, hours (95% CI) (mITT)	36.0 (33.5, 36.0)	42.3 (41.5, 43.2)
Median FCT, hours (95% CI) (mITT)	24.0 (24.0, 29.0)	28.5 (22.3, 34.0)

* excluding the 4x2 and 3x4 dose regimen groups from study A012
mITT = modified intent to treat population; PCT = parasite clearance time; FCT = fever clearance time
[1]Fisher's exact test.

Pediatric patients (≤ 16 years of age)

Table 6-16 shows the results from the pooled efficacy analysis for the pediatric population (≤ 16 years of age). The 28- day PCR corrected cure rate in the evaluable population was of 77.8% and 97.3% for the 4-dose and 6-dose regimen , respectively. In contrast with the adult population, the 28-day uncorrected cure rate in the pediatric population was somewhat lower than the PCR-corrected cure rate with the 6-dose regimen. This reflects that most of pediatric patients were enrolled in Africa which has higher endemicity for malaria than South-east Asia.

Table 6-16 Efficacy results (pooled analysis*, pediatric patients ≤ 16 years of age)

Efficacy parameter	Coartem 4-dose n = 650	Coartem 6-dose n = 877
28-day cure rate, n/M (%) (mITT)		
Uncorrected	213/319 (66.8)	743/863 (86.1)
95% CI	(61.3 - 71.9)	(83.6 - 88.3)
p-value	-	<.0001
Corrected	156/248 (62.9)	798/854 (93.4)
95% CI	(56.6 - 68.9)	(91.6 - 95.0)
p-value	-	<.0001
28-day cure rate, n/M (%) (evaluable)		
Uncorrected	210/273 (76.9)	737/823 (89.6)
95% CI	(71.5 – 81.8)	(87.3 – 91.6)
p-value	-	<.0001
Corrected	156/202 (75.7)	792/814 (97.3)
95% CI	(69.2 – 81.5)	(95.9- 98.3)
p-value	-	<.0001

Efficacy parameter	Coartem 4-dose n = 650	Coartem 6-dose n = 877
7-day cure rate, Uncorrected n/M (%)(mITT)	NA	736/755 (97.5)
95% CI	-	(96.1 - 98.5)
7-day cure rate, Uncorrected n/M (%) (evaluable)	NA	724/724 (100.0)
95% CI	-	(99.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		
mITT population	27.8 (25.7 - 35.0)	7.9 (7.9 - 8.0)
Median time to parasite clearance (95% CI)[2], hours		
mITT population	42.0 (40.0 - 45.0)	35.3 (31.7 - 35.7)
Number (%) of patients with parasite clearance by hours		
PCT ≤24 h	131 (28.5)	350 (39.9)
PCT >24-≤48 h	272 (59.1)	442 (50.4)
PCT >48 h	33 (7.2)	60 (6.8)
Parasite clearance not achieved	24 (5.2)	25 (2.9)
7-day cure rate, Uncorrected n/M (%)(mITT)	NA	736/755 (97.5)
95% CI		(96.1 - 98.5)
7-day cure rate, Uncorrected n/M (%) (evaluable)	NA	724/724 (100.0)
95% CI		(99.5 - 100.0)
Median time to fever clearance (95% CI)[2], hours		
mITT population	27.8 (25.7 - 35.0)	7.9 (7.9 - 8.0)
Median time to parasite clearance (95% CI)[2], hours		
mITT population	42.0 (40.0 - 45.0)	35.3 (31.7 - 35.7)
Number (%) of patients with parasite clearance by hours		
PCT ≤24 h	131 (28.5)	350 (39.9)
PCT >24-≤ 48 h	272 (59.1)	442 (50.4)
PCT >48 h	33 (7.2)	60 (6.8)
Parasite clearance not achieved	24 (5.2)	25 (2.9)

*excluding studies A009 & A011
mITT = modified intent to treat population; PCT = parasite clearance time; FCT = fever clearance time
[1]Fisher's exact test.

Table 6-17 shows pooled efficacy data for all pediatric patients enrolled in the 8 key studies by bodyweight group. The higher incidence of day-28 uncorrected cure rate in the two highest body weight groups may be explained by the less likelihood of new infection due to immunization acquired with age.

Table 6-17 Pooled efficacy analysis of 8 key studies (pediatric patients ≤ 16 years of age) by weight group

Evaluation		Body weight group			
		5 - < 15 kg	15 - < 25 kg	25 - < 35 kg	≥ 35 kg
28-day uncorrected parasitological cure rate					
mITT population	n/N (%)	455/538 (84.6)	187/213 (87.8)	50/56 (89.3)	51/56 (91.1)
	(95% CI)	(81.2 - 87.5)	(82.6 - 91.9)	(78.1 - 96.0)	(80.4 - 97.0)
Evaluable patients	n/M (%)	451/512 (88.1)	186/207 (89.9)	49/52 (94.2)	51/52 (98.1)
	(95% CI)	(85.0 - 90.8)	(84.9 - 93.6)	(84.1 - 98.8)	(89.7 - 100.0)
28-day PCR-corrected parasitological cure rate					
mITT population	n/N (%)	497/533 (93.2)	199/210 (94.8)	51/55 (92.7)	51/56 (91.1)
	(95% CI)	(90.8 - 95.2)	(90.8 - 97.4)	(82.4 - 98.0)	(80.4 - 97.0)
Evaluable patients	n/M (%)	493/507 (97.2)	198/204 (97.1)	50/51 (98.0)	51/52 (98.1)
	(95% CI)	(95.4 - 98.5)	(93.7 - 98.9)	(89.6 - 100.0)	(89.7 - 100.0)
7-day uncorrected cure rate					
mITT population	n/N (%)	524/542 (96.7)	214/215 (99.5)	56/57 (98.2)	55/56 (98.2)
	(95% CI)	(94.8 - 98.0)	(97.4 - 100.0)	(90.6 - 100.0)	(90.4 - 100.0)
Evaluable patients	n/M (%)	516/516 (100.0)	208/208 (100.0)	52/52 (100.0)	52/52 (100.0)
	(95% CI)	(99.3 - 100.0)	(98.2 - 100.0)	(93.2 - 100.0)	(93.2 - 100.0)
Median time to fever clearance (95% CI)[2], hours		463	165	42	30
mITT population		7.9 (7.8-7.9)	7.9 (7.8-8.1)	8.6 (7.8-23.5)	42.7 (25.0-45.3)
Median time to parasite clearance (95% CI)[2], hours		547	217	57	56
mITT population		35.0 (24.3-35.6)	34.4 (24.1-35.7)	35.7 (24.8-42.2)	44.6 (42.0-48.0)
Percent parasite reduction at 24 hours (mITT population)					
n		535	214	57	56
median		-100.0	-100.0	-99.5	-99.1
25 – 75th percentiles		-100.0, -97.7	-100.0, -98.1	-100.0 , -97.8	-100.0 , -95.7
Patients with parasite reduction < 75% at 48 hrs					
mITT population	n/N (%)	1/523 (0.2)	1/204 (0.5)	0/55 (0.0)	0/56 (0.0)
Patients with parasitemia 48 hrs > at baseline[1]					
mITT population	n/N (%)	0/523 (0.0)	1/204 (0.5)	0/55 (0.0)	0/56 (0.0)

Evaluation		Body weight group			
		5 - < 15 kg	**15 - < 25 kg**	**25 - < 35 kg**	**≥ 35 kg**
Asexual forms of *P falciparum* present, n/N (%) (mITT)					
Day 2	Negative slide	264/535 (49.3)	107/214 (50.0)	22/57 (38.6)	13/56 (23.2)
Day 3	Negative slide	508/523 (97.1)	197/204 (96.6)	52/55 (94.5)	47/56 (83.9)
Day 4	Negative slide	482/483 (99.8)	186/186 (100.0)	53/54 (98.1)	51/51 (100.0)
Patients with recrudescence of *P falciparum* during the study, n/N (%)					
mITT population		15/547 (2.7)	8/217 (3.7)	1/57 (1.8)	1/56 (1.8)

[1] Without imputing missing data.
[2] Based on Kaplan Meier estimates.

Summary

Review of individual studies provides further evidence of the better efficacy of the 6-dose regimen compared to the 4-dose regimen.

These two pooled analysis further supports the efficacy of the Coartem 6-dose regimen. The PCR-corrected cure rate achieved in the evaluable population was > 95% in both adult and pediatric patients.

6.5 Efficacy in Patients With Mixed Infections

Seven of the 8 key studies included patients with mixed infections, which were defined as infection with *P falciparum* plus one or more other *Plasmodium* species. Table 6-18 summarizes the mixed infections among patients treated with Coartem in each of the key studies and the outcome of treatment.

Table 6-18 Summary of mixed infections among Coartem-treated patients

Study	Study location	Coartem N	*Plasmodium* species	n	Time to parasite clearance (hr)	Relapse
A023	China	52	*P vivax*	1	8	None
A025	Thailand	120	*P vivax*	20	48	6 pts on or before day 29 1 pt each on day 18 & 28 4 pts on day 29 3 pts between day 29 and 42 1 pt each on day 39, 40, & 41
A026	Thailand	150	*P vivax*	5	24	1 pt at day 29 1 pt at day 49
A028	Thailand	164	*P vivax*	16	42	3 pts on or before day 29 1 pt each on day 24, 25, & 29
B2303	Africa	452	*P ovale*	3		
			P malariae	2	24	None
			Unidentified	1		
A2401	Europe, Colombia	165	*P vivax*	2	24	None
			P malariae	6	48	1 pt on day 28

Summary

Although data from patients with mixed infections are relatively limited, the available data indicate that most other *Plasmodium* species are also rapidly cleared from the blood along with *P. falciparum.* Coartem does not provide a radical cure for *P. vivax* or *P. ovale* because it does not have any effect on hypnozoites, but it appears to effectively eliminate circulating parasites.

6.6 Evidence from published data

A number of publications report studies performed with Coartem but not previously described in this document, and not conducted by Novartis. The studies were performed in a wide range of geographical areas, and in populations of both adults and children. The design and location of these studies are shown in Table 6-19 and Table 6-20 and their findings are described below. It should be noted that efficacy endpoints and analysis populations varied between studies. These studies provide most of the available information on the efficacy of the Coartem 6-dose regimen as compared with that of other antimalarials and combinations of antimalarials, including other ACTs. These studies confirm the efficacy of Coartem

6.6.1 Studies in Africa

6.6.1.1 Studies versus artesunate plus amodiaquine

Adjei et al (2008) report a randomized trial comparing the efficacy and safety of ASAQ and co-artemether when used to treat multiple episodes of malaria in children aged 6 months to 14 years in Ghana. Patients were followed up initially for 28 days, and then monthly for up to 1 year. Any subsequent episodes of uncomplicated malaria after 28 days were treated with the regimen as assigned at randomization. For the co-artemether group, adequate clinical and parasitological response was reported in 97.1% at Day 14 and 94.2% at Day 28; corresponding figures for ASAQ were 98.2% and 95.3%. Both treatment groups had similar rates of malaria episodes (0.34 and 0.37, respectively) in the year following recruitment.

Burkirwa et al 2006 compared Coartem and ASAQ in children in an area of high malaria transmission in Uganda. In this study, the primary efficacy outcome was the 28-day risk of recurrent symptomatic malaria and recurrent parasitemia. The risks of both recurrent symptomatic malaria and recurrent parsitemia (unadjusted for re-infection) were both lower with Coartem (27% and 51%, respecively) than ASAQ (42% and 66%, respectively), the between-treatment differences being statistically significant ($p = 0.001$ in each case). Time to recurrent malaria was shorter with ASAQ than Coartem. When corrected for re-infection using PCR, the risks for both recurrent symptomatic malaria and parasitemia were 0 for ASAQ and 1% for Coartem (equivalent to PCR-adjusted 28-day parasitological cure rates of 100% and 99%, respectively), illustrating the high rate of re-infection in the area studied.

Dorsey et al 2007 in a study of children in Uganda, found PCR-corrected 28-day cure rates of 99% with Coartem, 95.4% with ASAQ and 85.9% with AQSP. The differences between Coartem and AQSP, and between ASAQ and AQSP were statistically significant ($p < 0.001$ and $p = 0.08$, respectively). Coartem was associated with lower rates of early treatment failure, late clinical failure, and late parasitological failure, and a higher rate of

adequate clinical and parasitological response, than either of the comparator treatments. Clearance of fever, sexual parasites and gametocytes were similar in the Coartem and ASAQ groups but slower in the AQSP group.

Falade et al 2008, in another study in children in Nigeria, found PCR-corrected 28-day parasitological cure rates of 100% for Coartem and 98.4% for ASAQ. Uncorrected 28-day parasitological cure rates were 95% and 93%, respectively, suggesting relatively low rates of re-infection in this study.

Faye et al 2007 evaluated the use of three ACTs, namely Coartem (as both 4-dose and 6-dose regimens), ASAQ, and mefloquine plus artesunate (MAS), and AQSP in a population of adults and children in Senegal. PCR corrected 28-day parasitological cure rates were 100% for all treatments other than Coartem 4-dose (96.4%). The difference between the Coartem 4-dose group and the MAS and AQSP groups was statistically significant. Parasite clearance was observed to be more rapid with all ACTs than with AQSP. Initial reduction of gametocyte carriage also appeared to be more rapid with the ACTs than with AQSP, although all patients were free of gametocytes by Day 21.

Guthman et al 2006 found PCR-corrected 28-day parasitological cure rates of 100% for both Coartem and ASAQ in a study in children in Angola. In both treatment groups the incidence of anemia showed a large decrease from baseline to 28 days (from 54.1% to 13.4% in the Coartem group, and from 53.1% to 15.9% in the ASAQ group).

Kabanywanyi et al 2007 performed a study in children at 2 centers in Tanzania, with patients at one center receiving Coartem and at the other receiving ASAQ. At 28 days, the PCR-corrected rates of adequate clinical and parasitological response were 100% for Coartem and 93.8% for ASAQ. Late parasitological failures, in all cases due to re-infection rather than recrudescence, occurred in 12% and 29% of each group, respectively. There were no early treatment failures and only 1 late clinical failure (due to re-infection) with Coartem, compared with 1 and 4 (2 due to re-infection), respectively, with ASAQ.

Koram et al 2005 found PCR –corrected 28-day cure rates of 25% for chloroquine, 60% for SP, 100% for ASAQ, and 97.5% for Coartem in infants and children in Ghana. Both artemisinin-based regimens in the study were associated with rapid clearance of fever and parasites.

Martensson et al 2005 found statistically significantly higher PCR-corrected parasitological cure rates with Coartem than ASAQ at 28 days (97% vs. 91%, $p = 0.001$) and 42 days (92% vs 88%, $p = 0.045$), together with a significantly lower re-infection rate at 42 days (17% for Coartem vs 36% for ASAQ, $p<0.001$) in infants and children in Zanzibar. Parasite and fever clearance were rapid with both treatments, and gametocyte carriage was low in both groups.

Meremikwu et al 2006 found that ASAQ and Coartem were highly effective with similar rates of adequate clinical and parasitological response, early treatment failure, late clinical failure and late parasitological failure at 14 days in children in an area of Nigeria with known high levels of resistance to chloroquine and SP in *P. falciparum*. Both treatments had rapid clearance of fever and parasites.

Mutabingwa et al 2005, in a study in children in Tanzania included control groups treated with ASAQ; amodiaquine plus sulfadoxine-pyrimethamine (AQSP); and amodiaquine (AQ) monotherapy. Recruitment to the AQ group was stopped early by the data and

safety monitoring board of the trial due to a high treatment failure rate. Day 14 parasitological failure rates were AQ, 42%; AQSP, 20%; ASAQ, 11%: and Coartem, 1%. Day 28 failure rates 76%, 61%, 40%, and 21%, respectively. The differences between each treatment group and the next best treatment were statistically significant ($p<0.001$) in every case. PCR corrected 28-day parasitological cure rates were 51.6% for AQ, 65.5% for AQSP, 88.8% for ASAQ, and 97.2% for Coartem.

Ndayiragije et al 2004 found similar 14-day rates of adequate clinical and parasitological response with Coartem (140/141, 99.3%) and ASAQ (142/149, 95.3%) and similar effects on gametocyte carriage in children in Burundi.

Owusu-Agyei et al (2008) describe a randomized study comparing the efficacy of co-artemether, ASAQ and artesunate plus chlorproguanil-dapsone (ASCD) in children (aged 6 months to 10 years) in Ghana. A per-protocol analysis showed a lower PCR-corrected parasitological and clinical failure rate at day 28 in the ASAQ group (6.6%) compared to the co-artemether group (13.8%) or ASCD group (13.8%).

Van den Broek et al 2006 performed a study in the Republic of Congo, comparing the efficacy of Coartem, ASAQ and artesunate plus SP (ASSP) in a population of children. PCR-corrected 28-day parasitological cure rates were 100% for Coartem, 98.5% for ASAQ and 90.1% for ASSP. The differences in cure rates between Coartem and ASSP, and between ASAQ and ASSP were statistically significant. Clearance of asexual parasites, gametocytes and fever were rapid in all three treatment groups.

Wiseman et al 2006 evaluated the cost-effectiveness of treatment on the basis of the same study, and concluded that the two ACTs used were more cost effective than the other treatments in areas of high drug resistance, although this might not be the case in areas where amodiaquine or SP (or their combination) remain effective.

Table 6-19 Published studies with the 6-dose regimen of Coartem in Africa

Authors	Country	Design patient population	Comparator(s) No. of patients
Region: East Africa			
Bukirwa et al 2006	Uganda	Randomized, single-blind, single center in children (1 to 10 years)	Coartem (n = 208) ASAQ (n = 211)
Depoortere et al 2004	Sudan	Single centre, non-comparative, in children (12-60 months)	Coartem (n = 98)
Dorsey et al 2007	Uganda	Single-blind, randomized, single center in children (1-10 years)	Coartem (n = 105) AQSP (n = 111) ASAQ (n = 113)
Fogg et al 2004	Uganda	Single centre, non-comparative, in adults and children (≥ 10 kg)	Coartem (n = 235)
Gurkov et al 2008	Ethiopia	One center, comparative in adults and children > 5 years of age	Coartem (n= 30) Quinine (n= 35) Atovaquone/Proguanil (n=32)
Kabanywanyi et al 2007	Tanzania	Randomized, open-label, 2-center in children (6 – 59 months)	Coartem (n = 99) ASAQ (n = 76)
Kamya et al 2007	Uganda	Single-blind, randomized, single center in children (6 months to 10 years)	Coartem (n = 210) DP (n = 211)
Martensson et al 2005	Zanzibar	Multicenter, randomized, open-label in children (6-59 months)[1]	Coartem (n = 200) ASAQ (n = 208)
Martensson et al	Tanzania	Randomized, single center, open-label study	Coartem (n = 50)

2007		in children	SP (n = 56)
Mohamed et al 2006	Sudan	2-center, open-label, treatment assigned by center, in children and adults	Coartem (n = 72) ASSP (n = 71)
Mukhtar et al 2007	Sudan	Randomized, single center, open-label study in children & adults	Coartem (n = 80) ASSP (n = 77)
Mutabingwa et al 2005 and Wiseman et al 2006	Tanzania	Randomized, single center, open-label study in children	Coartem (n = 519) ASAQ (n = 515) AQSP (n = 507) AQ (n = 270)
Piola et al 2005	Uganda	Randomized, open-label, single center, in adults & children (> 10 kg)	Coartem: Supervised (n = 313) Unsupervised (n = 644)
Yeka et al 2008	Uganda	Randomised ,one center, single-blinded , in children aged 6 months – 10 years	Coartem (n= 227) DP (n= 234)
Region: Southern Africa			
Mulenga et al 2006	Zambia	Randomized, open-label, multicenter, in adults	Coartem (n = 485) SP (n = 486)
Toovey 2008	Mozam-bique	Non-comparative, open-label, single center in adults	Coartem (n = 54)

CQ: Chloroquine, SP: Sulfadoxine plus pyrimethamine, CQSP: Chloroquine plus sulfadoxine plus pyrimethamine, AS: Artesunate, AQ: Amodiaquine, ASAQ: Amodiaquine plus artesunate
AQSP: Amodiaquine plus sulfadoxine-pyrimethamine, DP: dihydroartemisinin plus piperaquine, MAS: mefloquine plus artesunate

Table 6-20 Published studies with the 6-dose regimen of Coartem in Africa (continued)

Authors	Country	Design patient population	Comparator(s) No. of patients
Region: West Africa			
Adjei GO et al 2008	Ghana	Randomized, open label	AL (n=111) AS+AQ (n=116)
Falade et al 2008	Nigeria	Randomized, open label, single center in children (6 months to 10 years)	Coartem (n = 66) ASAQ (n = 66)
Faye et al 2007	Senegal	Randomized, open-label, multicenter in children and adults	ASAQ (n = 360) AQSP (n = 161) MAS (n = 145) Coartem (6 dose) (n = 149) Coartem (4-dose) (n = 140)
Koram et al 2005	Ghana	Multicenter, randomized, open-label in children (6-59 months)	Coartem (n = 51) CQ (n = 36) SP (n = 27) ASAQ (n = 54)
Meremikwu et al 2006	Nigeria	Randomized, open-label, single center, in children (6 – 59 months)	Coartem (n = 60) ASAQ (n = 59)
Owusi-Agyei et al 2008	Ghana	Randomised, open label in children aged 6month -10years	Coartem (n= 223) ASAQ (n= 220) ASCD(n= 178)
Sagara et al 2006	Mali	Randomized, single center, open-label study in children (≥ 6 months) and adults	Coartem (n = 303) AS plus sulfa-methoxypyrazine plus pyrimethamine (n = 303)
Sowunmi et al 2007a, Sowunmi et al 2007b	Nigeria	Randomized, open-label, single center, in children (≤ 10 years)	Coartem (n = 90) AQ plus sulfalene plus pyrimethamine (n = 91)
Sutherland et al	The	Randomized, single center, single-blind, in	Coartem (n = 406)

2005	Gambia	children (1-10 years)	CQSP (n = 91)
Zongo et al 2007a	Burkina Faso	Multicenter, randomized, open-label in children (6 months – 10 years)	Coartem (n = 261) AQSP (n = 260)
Zongo et al 2007b	Burkina Faso	Multicenter, randomized, open-label in children (≥ 6 months)	Coartem (n = 188) AQSP (n = 184) DP (n = 187)
Region: Central Africa			
Fanello et al 2007	Rwanda	Randomized, open-label, 2-center in children (12-59 months)	Coartem (n = 251) AQSP (n = 249)
Guthman et al 2006	Angola	Randomized, open-label, single center in children (6 to 59 months)	Coartem (n = 61) ASAQ (n = 64)
Ndayiragije et al 2004	Burundi	Multicenter, randomized, open-label in children (< 5 years)	Coartem (n =142) ASAQ (n = 153)
Van den Broek et al 2006	Republic of Congo	Randomized, single center, open-label study in children (6-59 months)	Coartem (n = 106) ASAQ (n = 101) ASSP (n = 91)

CQ: Chloroquine, SP: Sulfadoxine plus pyrimethamine, CQSP: Chloroquine plus sulfadoxine plus pyrimethamine, AS: Artesunate, AQ: Amodiaquine, ASAQ: Amodiaquine plus artesunate
AQSP: Amodiaquine plus sulfadoxine-pyrimethamine, DP: dihydroartemisinin plus piperaquine, MAS: mefloquine plus artesunate

Studies versus artesunate plus sulfadoxine-pyrimethamine

Mohamed et al 2006, in a study in an area of low malaria transmission Sudan where treatment was assigned by center, found that both Coartem and ASSP were associated with adequate clinical and parasitological response rates of 100% at Day 28.

Mukhtar et al 2007, also in a study in Sudan, found PCR-corrected rates of adequate clinical and parasitological response of 93.4% for ASSP and 91.3% for Coartem. The treatment regimen used was not clear. The authors commented that the higher rate of treatment failure with Coartem observed in this study compared with other published studies may be due to the low-fat diets of the rural population being treated.

Studies versus dihydroartemisinin plus piperaquine

Kamya et al 2007 in a study in children in an area of Uganda with very high malaria transmission, found that the PCR-corrected risk of recurrent parasitemia at Day 28 was significantly lower with DP than with Coartem (1.9% vs. 8.9%); this was also the case at Day 42 (6.9% vs. 16%). The authors note, however, that due to the complexity of infection in this area of very high transmission, leading to difficulty in distinguishing between new and recrudescent infections, the risks of recrudescence are probably overstated. Times to clearance of fever and parasites were similar in the two treatment groups, although DP was associated with better control of gametocytes.

Yeka et al (2008) compared the efficacy of co-artemether with that of dihydroartemisinin-piperaquine (DP) in a randomized trial in children aged 6 months to 10 years with uncomplicated falciparum malaria in Uganda. At 42 days there was no statistically significant difference in the risk of recrudescence (5.8% for co-artemether vs. 2.0% for DP; risk difference = 3.8%, 95% CI -0.2-7.8%), although recurrent parasitemia (uncorrected for re-infection) was more frequent with co-artemether (33.2% vs. 12.2% for DP).

Zongo et al 2007a report a study in children in Burkina Faso, in which patients received Coartem, DP or AQSP. PCR-corrected risks of reinfection at Day 28 were 3.4%, 2.2% and 3.9%, respectively, with corresponding figures at Day 42 of 4.1%, 2.2% and 3.9%. The risks of re-infection, however, were higher with Coartem than with AQSP or DP. Fever clearance was more rapid with AQSP and DP, but prasite clearance was faster with Coartem and DP than with AQSP.

Study versus artesunate plus sulfamethoxypyrazine plus pyrimethamine

Sagara et al 2006 compared Coartem with artesunate plus sulfamethoxypyrazine plus pyrimethamine in a study in adults and children in Mali. The 28-day PCR-corrected parasitological cure rates were 100% for artesunate plus sulfamethoxypyrazine plus pyrimethamine, and 99% for Coartem. Re-infection rates at 28-days were 1.3% and 9.4%, respectively ($p < 0.001$). Clearance of asexual parasites was rapid in both treatment groups, with no statistically significant differences between them. Similarly, gametocyte clearance was similar in the two treatment groups. Fever clearance appeared to be slightly more rapid with artesunate plus sulfamethoxypyrazine plus pyrimethamine.

Studies versus combinations of amodiaquine with non-artemisinin antimalarials

Combinations of amodiaquine with other (non-artemisinin) antimalarials were also used as controls in several studies in Africa. Amodiaquine plus SP (AQSP) was used in two studies, in addition to those already described that included AQSP and other control groups:

Fanello et al 2007, in a study in children in Rwanda, found that Coartem was associated with a statistically significantly higher rate of PCR-adjusted adequate clinical and parasitological response at Day 28 than AQSP (96.8% vs. 79.4%, $p < 0.0001$), as well as statistically significantly more rapid clearance of asexual parasites (2.8% of Coartem patients were parasitemic at Day 2 compared with 47.0% of AQSP patient, $p < 0.0001$; corresponding figures at Day 3 were 0 and 6.4%, $p < 0.0001$). Gametocyte carriage was significantly lower in the Coartem group at all post-baseline time points.

Sowunmi et al 2007a compared Coartem with amodiaquine plus sulfalene plus pyrimethamine in a study in 187 children in an area of intense malaria transmission in Nigeria. PCR-corrected parasitological cure rates at 42 days were 93.3% for Coartem and 98.9% for amodiaquine plus sulfalene plus pyrimethamine. Fever clearance times were similar in the two treatment groups, but parasite clearance was statistically significantly faster with Coartem than with amodiaquine plus sulfalene plus pyrimethamine(mean 1.7 days vs 2.1 days $p = 0.0001$). Gametocyte carriage was similar in the two treatment groups. A second publication from this study (Sowunmi et al 2007b) examined the effects of treatment on malaria-associated hepatomegaly. Hepatomegaly reduction ratios and hepatomegaly resolution rates were similar in the two treatment groups.

Sutherland et al 2005, in a study performed in children in the Gambia, compared Coartem with chloroquine plus sulfadoxine plus pyrimethamine (CQSP), focusing on gametocyte carriage and transmission to mosquitoes. PCR-corrected 28-day cure rates were 96.1% for Coartem and 91.1% for CQSP. Coartem-treated patients were statistically significantly less likely to carry gametocytes at Day 28 than those who received CQSP (8% vs 49%, $p < 0.0001$), and carriers in the Coartem group harbored gametocytes at lower densities, for

shorter periods (0.3 d versus 4.2 d $p < 0.0001$) and were less infectious to mosquitoes at day 7 ($p < 0.001$) than carriers in the CQSP group.

Zongo et al 2007b report a study in children in Burkina Faso, in which the crude (uncorrected for re-infection) risk of recurrent malaria at 28 days was significantly higher with Coartem than AQSP (10.2% vs. 1.7%, $p < 0.0001$); PCR correction gave risks of recurrent malaria of 1.2% and 0.4%, with the between-group difference not being statistically significant. PCR-corrected risks of recurrent parasitemia were 1.6% for Coartem and 0.4% for AQSP; again, the between-group difference was not statistically significant. Coartem was associated with significantly faster parasite clearance (on Day 2, 27% of AQSP patients had parasitemia, compared with 4.6% of Coartem patients, $p < 0.0001$). Fever clearance, in contrast, was faster with AQSP: 25% of Coartem patients were febrile 1 day after the start of treatment, compared with 13% of AQSP patients ($p= 0.0004$). Almost all patients were apyretic by Day 2.

Studies versus sulfadoxine plus pyrimethamine

Sulfadoxine plus pyrimethamine (SP), in addition to being combined with other antimalarials in some of the studies described above, was used as monotherapy in two studies.

Martensson et al 2007, in a study performed in Tanzania in order to evaluate the effects of different sampling schedules on PCR genotyping results, also assessed the efficacy of Coartem and SP treatment in a population of children. The PCR corrected 42-day parasitological cure rates were 98 or 94% in the Coartem group (depending on whether standard or enhanced PCR was used); corresponding figures in the SP group were 70 and 66%, respectively.

Mulenga et al 2006 found that Coartem was associated with significantly faster clearance of fever, parasitemia and gametocytes than SP, and a higher Day 45 PCR-corrected cure rate (94.6% vs. 80.7%, $p < 0.001$).

Studies versus Atovaquone-Proguanil

Gurkov et al (2008) reported the results of a randomized, open-label study comparing the ototoxicity, tolerability, and efficacy of co-artemether, quinine or atovaquone/proguanil in 97 patients (at least 5 years of age) with falciparum malaria in south-west Ethiopia. Patients were followed up for 90 days after initiating treatment.At 28-days, there were no treatment failures in the co-artemether group, but the PCR-confirmed recrudescence rates in the quinine and atovaquone/proguanil groups were 9% and 6%, respectively. One co-artemether-treated patients had a recrudescence at Day 70; this also occurred at Day 40 in one patient receiving quinine.

Studies of adherence to the Coartem 6-dose regimen

Three studies evaluated adherence to the 6-dose regimen of Coartem:

Depoortere et al 2004 assessed adherence in children in southern Sudan whose caregivers were provided with a pack of Coartem treatment and instructions as to how to administer it. Approximately 60% of patients were found to be adherent to treatment.

Fogg et al 2004 in a study in Uganda assessed adherence by administering the first dose of Coartem in the clinic then discharging patients home to complete the treatment course.

Home visits (of which the patients and their families were hitherto unaware) were then made to assess adherence to treatment and determine blood lumefantrine levels. Adherence to treatment was found to be very good (90% of patients were 'probably adherent'). Lumefantrine levels were lower in non-adherent patients than adherent patients, but the difference was not statistically significant. No efficacy data were reported in this publication.

Piola et al 2005 compared in-patient (supervised) treatment, with outpatient (unsupervised) treatment in children and adults in Uganda. The 28 day cure rates were very similar (98% in both groups in the ITT analysis, 100% in an evaluable patients analysis). The only difference between supervised and unsupervised treatment was that blood lumefantrine levels in the unsupervised patients were statistically significantly lower ($p < 0.001$) at Days 3 and 7

Non-comparative studies

Non-comparative studies of the efficacy of Coartem have also been reported:

Jima et al 2005 found a 99.1% parasitological cure rate (not PCR corrected) in adults and children in Ethiopia.

Toovey et al 2008 found a 28-day parasitological cure rate of 100% in a study in adult patients in Mozambique.

Summary of studies performed in Africa

In summary, the studies reported from Africa demonstrate the good efficacy of the 6-dose regimen of Coartem, which appears to be at least as effective as most other ACTs included in the comparative studies and was generally more effective than other, non-ACT comparators used in the studies. In the few studies where comparators were associated with lower risks of treatment failure than Coartem, the studies were typically conducted in areas with very intense malaria transmission, and the comparators included antimalarials with a long half-life, which could prevent re-infection late in the study; indeed, the lower crude failure rates with the comparators in these few studies are the result of lower re-infection rates – recrudescence rates were generally similar for Coartem and comparators.

Several of these publications report the potent effects on ACT treatment on gametocyte carriage. One study, gametocyte carriage was investigated in detail and it was found that in Coartem-treated patients, not only was the rate of carriage of gametocytes significantly reduced as compared to that in patients receiving CQSP, but the carriage time of gametocytes, and the infectivity of the gametocytes for mosquitoes were also significantly decreased. These findings potentially have considerable implications for public health, given the possibility of reducing transmission of malaria by extensive use of ACTs.

Adoption of Coartem as a standard treatment in Kwazulu Natal, South Africa, in combination with stronger vector control, was associated with an 99% decrease in malaria cases and a 97% decrease in deaths related to malaria between 2000 and 2003 (Barnes et al 2005). While these findings may not be directly applicable to hyperendemic regions or countries with less well-developed public health infrastructure than South Africa, they do demonstrate the great

potential benefits of a combination of improved mosquito control coupled with prompt treatment of infected patients with ACTs.

6.6.2 Studies in Asia

A number of publications report studies performed in South or South-East Asia with the 6-dose regimen of Coartem. Table 6-21 shows the design and location of each study, together with the numbers of patients treated.

Table 6-21 Published studies with the 6-dose regimen of Coartem in Asia

Authors	Country	Design patient population	Comparator(s) No. of patients
South-East Asia			
Krudsood et al 2003	Thailand	Randomized, open-label, single center in adults	Coartem (n = 41) DNP (n = 89)
Rojanawatsirivej et al 2003	Thailand	Open-label, multicenter, adults & children (10-74 years), treatment by area (all treatment groups also received primaquine)	Coartem (n = 33) MAS (199)[1] Mefloquine (n = 318)
Stohrer et al 2004	Laos	Randomized, open-label, single center, in adults & children (≥ 10 kg)	Coartem (n = 53) MAS (n = 55)
Mayxay et al 2004	Laos	Randomized, open-label, single center, in adolescents and adults (12-19 years)	Coartem (n = 110) MAS (n = 110) CQSP (n = 110)
Ratcliff et al 2007	Indonesia	Randomized, open-label, 2-center in children (body weight ≥ 10 kg) and adults with *P. falciparum*, *P. vivax*, or mixed infections	Coartem (n = 387) Dihydroartemisinin plus piperaquine (n = 387)
Hutagalung 2005	Thailand	Randomized, open-label, 2-center, in children (> 10 kg) and adults	Coartem (n = 245) MAS (n = 245)
South Asia			
van den Broek et al 2005	Bangladesh	Randomized, open-label, single center, in adults & children (≥ 1 year)	Coartem (n = 121) MAS (n = 121) CQSP (n = 122)
Haque et al 2007	Bangladesh	Open-label, non-comparative, 2-center in adults (≥ 18 years)	Coartem (n = 67)
Thapa et al 2007	Nepal	Randomized, open-label, single center, in adults & children (> 5 years)	Coartem (n = 66) SP (n = 33)

[1]Includes 2 MAS regimens (mefloquine at 25 mg/kg, n = 153, and 15 mg/kg, n = 46)
SP: sulfadoxine plus pyrimethamine; CQSP: Chloroquine plus sulfadoxine pyrimethamine; DNP: dihydroartemisinin, napthoquine and trimethoprim; MAS: mefloquine plus artesunate

6.6.2.1 Studies in South-East Asia

A number of studies with Coartem in South-East Asia have also been reported. These studies also support the good efficacy of the 6-dose regimen in a range of geographical areas. Two studies were performed in the Lao People's Democratic Republic. Both were open randomized studies comparing the 6-dose regimen of Coartem and MAS:

Mayxay et al 2004 compared Coartem with CQSP and with MAS in adolescent patients. The 42-day PCR-corrected parasitological cure rates were 97% for Coartem, 100% for MAS and 93% for CQSP. The difference in cure rates between MAS and CQSP was statistically significant. Mean fever clearance time and parasite clearance time were

significantly longer in the CQSP group than in the MAS and Coartem groups and gametocyte carriage at any time point following treatment was significantly higher in the CQSP group than in the MAS and Coartem groups. There were no statistically significant differences in efficacy between Coartem and MAS.

Stohrer et al 2004 found PCR-corrected cure rates at Day 42 of 93.6% for Coartem and 100% for MAS, in a population of children and adults. The difference between treatment groups was not statistically significant. Day 28 cure rates were identical to those at Day 42. No statistically significant differences in rates of parasite clearance or gametocyte carriage were observed.

Three publications provide data on the efficacy of Coartem in Thailand:

Hutagalung et al 2005 compared Coartem and MAS. Both treatments were associated with rapid clearance of fever and parasitemia, and 42-day parasitological cure rates were 98.8% for Coartem and 96.3% for MAS. Effects on gametocyte carriage were similar. No statistically significant differences between treatments were observed.

Krudsood et al 2003 compared the 6-dose regimen of Coartem with a combination of dihydroartemisinin, napthoquine and trimethoprim (DNP). The 28-day parasitological cure rates (not PCR corrected) were 99% for DNP and 97% for Coartem. Mean fever clearance and parasite clearance times were also similar between treatments.

Rojanawatsirivej et al 2003 published data from a study monitoring the efficacy of antimalarials in several areas. According to the Thai National Drug Policy, patients who were treated with the 6-dose regimen of Coartem also received primaquine 30 mg given over 3 days to achieve a radical cure in case of *P. vivax* co-infection. Coartem plus primaquine was used in the Ratchaburi area, as was mefloquine (15 mg/kg) plus primaquine. All 33 (100%) patients treated with Coartem plus primaquine had adequate clinical response (i.e. parasitological cure at Day 28), compared with 86.3% of the 80 patients who received mefloquine plus primaquine.

Finally, one study in southern Papua, Indonesia compared the efficacy of Coartem and DP in adult and pediatric patients with *P. falciparum*, *P. vivax* and mixed infections:

Ratcliff et al 2007 found that for *P. falciparum* infections, rates of recrudescence at 42 days (PCR-corrected) were 4.7% with Coartem and 4.1% with DP. No differences between treatments were observed in effects on *P. falciparum* gametocyte carriage. For *P. vivax*, however, Coartem was significantly less effective than DP, with a higher rate of treatment failure at 42 days (57% vs. 14%, $p < 0.0001$). As PCR genotyping is not currently possible for *P. vivax*, it is not clear whether these failures represent true recrudescence, relapse from hypnozoites or re-infections (in the latter case DP would appear to offer a longer period of protection from re-infection with *P. vivax* than Coartem, due to the longer half-life of piperaquine than lumefantrine).

The studies reported from South-East Asia in general show that Coartem is associated with similar efficacy to other ACTs in the treatment of *P. falciparum* malaria, with high parasitological cure rates and rapid clearance of parasitemia and resolution of fever. In one study in which *P. vivax* infections were included, the comparator ACT (DP) was significantly more effective in terms of reducing the risk of recurrent *P. vivax* infection, probably due to the long half-life of piperaquine offering protection against re-infection for longer than

lumefantrine: in the same study PCR-corrected *P. falciparum* parasitological cure rates were almost identical for Coartem and DP (Ratcliff et al 2007).

6.6.2.2 South Asia

Three studies reported efficacy in South Asia:

Haque et al 2007 reported rapid fever and parasite clearance, and PCR-corrected 28- and 42-day parasitological cure rates of 98.3% and 94.3% with the 6-dose regimen of Coartem in a non-comparative study in adult patients in Bangladesh.

Thapa et al 2007 compared Coartem with SP in adults and children in Nepal. Parasite clearance was significantly more rapid with Coartem than SP (mean PCT 31 vs 67 hours $p < 0.001$), as was time to fever clearance (median FCT 24 vs 48 hours, $p = 0.017$). Gametocyte clearance was also more rapid with Coartem. The 28-day PCR corrected parasitological cure rate for Coartem was 100%, compared with 87.9% in the SP group ($p = 0.011$).

Van den Broek et al 2005 compared the 6-dose regimen of Coartem with MAS and CQSP in adults and children in Bangladesh . Day 42 PCR-corrected cure rates were 62.4% for CQSP, 100% for MAS and 97.1% for Coartem. The cure rate in the CQSP group was statistically significantly lower than that in the other treatment groups. The efficacy of Coartem treatment was similar in different age groups.

These studies show high parasitological cure rates and rapid clearance of fever and parasitemia with the 6-dose regimen of Coartem, comparable with those for MAS in the one study where this combination was used as a comparator. Coartem was more effective than non-ACT comparators in these studies.

6.6.3 Meta-analysis of Coartem efficacy

A recent meta-analysis (Jansen et al 2007) evaluated the efficacy of ACTs, using a Bayesian random effects approach, included data from 32 published randomized studies performed predominantly in Africa but also in South America and Asia. The analysis showed that Coartem was one of the most effective ACT, with a 97.4% PCR-corrected parasitological cure rate at Day 28 (Table 6-22).

Table 6-22 28-day PCR-corrected parasitological cure rates achieved with combination therapy in the evaluable population

Treatment combination	28-day PCR-corrected cure rate, %
Artemether/lumefantrine	97.4
Mefloquine + artesunate	96.9
Amodiaquine + artesunate	88.5
Amodiaquine + sulfadoxine-pyrimethamine	85.7
Sulfadoxine-pyrimethamine + artesunate	82.6

Treatment combination	28-day PCR-corrected cure rate, %
Chloroquine+ sulfadoxine-pyrimethamine	72.1
Chloroquine + artesunate	45.3

6.7 Summary of Clinical Efficacy

- The combination of artemether and lumefantrine contained in Coartem Tablets is more effective than either drug used alone. Coartem produced a higher parasitological cure rate than artemether alone and cleared parasitemia and fever more rapidly than lumefantrine alone.
- Study 025 demonstrated that the 6-dose regimen is superior to the 4-dose regimen.
- In non-immune adult travelers with *P falciparum* malaria, the 28-day cure rate (uncorrected) was also > 95% in the per protocol population , consistent with the efficacy demonstrated in adult patients living in endemic regions.
- The efficacy of Coartem was similar across bodyweight groups in infants and children.
- Coartem also consistently achieved rapid clearance of parasitemia and fever across multiple studies.
- Although data from patients with mixed infections are relatively limited, the available data indicate that most other *Plasmodium* species are also rapidly cleared from the blood along with *P falciparum*. However, Coartem does not provide a radical cure for *P vivax* or *P ovale* as it does not have any effect on hypnozoites, the liver dormant forms of the parasite.
- The efficacy of Coartem 6-dose regimen was also demonstrated in a large number of studies performed by institutions others than Novartis and reported in the scientific literature and also showed that it is at least as effective as other artemisinin based combination therapies and combination of antimalarials across a wide range of geographical regions and patient population.

7 Overview of Clinical Safety

The clinical safety database is comprised of patients enrolled in 20 Novartis-sponsored studies. Safety information from ongoing safety studies and post-marketing experience with Coartem are also described.

7.1 Safety Evaluations

Adverse events were reported in all clinical trials. Important to note, there were between-study differences in methods of collecting AE data. Pre-printed AE CRF forms were used in all the 4 dose regimen studies (except for studies AB/MO1 and AB/MO2) as opposed to only part of the 6 dose regimen studies (studies A025, A026, A028). These pages, which were otherwise standard AE CRF pages, were pre-printed with specific adverse events, typically those related to malaria signs and symptoms or neurological adverse events. Because of the difference in AEs reporting across studies and since only one study (A025) includes both the 4- and 6-dose groups, AE tables presenting both the 4-dose and 6-dose data as supportive

information only rather than direct between-treatment groups comparisons. Clinical laboratory parameters, including hematologic, hepatic, and renal parameters, were assessed in all studies, although the range of laboratory assessments evaluated was relatively limited in some studies as a result of limited resources at some study centers, and the parameters evaluated varied between studies.

ECG evaluations were performed in most studies included in the pooled safety populations with the exception of A008, A010, A011 and A2412. The time points at which ECGs were performed, the method of reading ECGs, and the number of assessments varied between studies. In some studies, ECGs were analyzed independently by a specialist CRO (eResearch Technologies, East Bridgewater, NJ, USA). In other studies, some ECGs (typically those with QTc > 450 msec, or if there were other concerns) were peer reviewed by an independent cardiologist in addition to the analysis performed by the investigators. In other studies, ECGs were read only by the investigators. The pooled analyses presented here include data analyzed by eResearch Technologies where available and investigator-analyzed data. Peer reviewed ECG data were not included in these pooled analyses.

Systematic neurologic examinations were also included in some studies and audiological tests, including pure tone threshold, tympanometry, and auditory brainstem response (ABR) Wave III latency were performed in Study A2412 and in the ongoing Study A2417.

7.2 Safety Population

Two pooled safety analyses were performed, one in adults (> 16 years of age) and one in pediatric patients (≤ 16 years of age). These analyses included 1572 adult patients and 2026 pediatric patients were treated with Coartem (Table 7-1). Pooled 4-dose and pooled 6 –dose data are based on studies described described in Table 7-1 and in Table 7-2.

The pooled populations included patients enrolled in a wide range of studies in which patients were treated with either the 4-dose or 6-dose Coartem regimens or with a variety of other antimalarial drugs used as active comparators. Some studies used double-blind designs, others were investigator-blind or open-label, and some trials were non-comparative. There were a number of differences between the studies, chiefly resulting from the very long duration of the development program (the studies included in the pooled populations were performed between 1993 and 2007). These included differences in entry criteria, in the safety assessments performed (for example some studies included neurological examinations and others did not), in the use of concomitant medications (notably antipyretics), and in the way that AEs were reported (e.g. in some studies the Case Report Forms included pages pre-printed specific adverse events, typically those related to malaria signs and symptoms). Also of note, very few patients from studies AB/MO1 and AB/MO2 (far fewer than in other studies) reported adverse events. The reason for this is not known, as the protocols specified that adverse events should be recorded at each visit. All of these factors mean that between-group comparisons should be interpreted with caution and regarded as purely descriptive.

Table 7-1 Clinical trials which contributed safety data to the adult and adolescent (>16 years) pooled safety analyses

	Number of patients (Entered study population)		
Study	**Coartem 4-dose**	**Coartem 6-dose**	**Total Coartem[1]**
A004	106	0	106
A005	12	0	12
A007	89	0	89
A008	197	0	197
A012	210	0	210
A014	51	0	51
A023	42	0	42
A025	99	180	279
A026	0	109	109
A028	0	149	149
A2401	0	165	165
A2412[2]	0	44	44
ABM01	78	0	78
ABM02	41	0	41
Total	**925**	**647**	**1572**

[1] includes pediatric patients who received the Coartem dispersible tablet.
A012 patients included those receiving 3 doses of 4 tablets and 4 doses of 2 tablets, as well as those using the standard 4-dose regimen of 4 doses of 4 tablets.
[2]One patient entered the study but did not receive treatment.

Table 7-2 Clinical trials which contributed safety data to the pediatric (≤16years) pooled safety analyses

	Number of patients (Entered study population)		
Study	**Coartem 4-dose**	**Coartem 6-dose**	**Total Coartem[1]**
A003	111	0	111
A004	20	0	20
A007	0	0	0
A008	112	0	112
A009[2]	60	0	60
A010	144	0	144
A011	130	0	130
A012	50	0	50
A023	10	0	10
A025	21	59	80
A026	0	41	41
A028	0	15	15
A2403	0	310	310
A2412	0	9	9
AB/MO1	24	0	24
AB/MO2	12	0	12
B2303		452	899
Total	**694**	**886**	**2027**

[1] includes pediatric patients who received the Coartem dispersible tablet.

7.2.1 Patient Disposition and Exposure

Adult patients (> 16 years of age)

Patient disposition in the adult pooled safety population is summarized in Table 7-3. In these tables 'discontinuation' refers to discontinuation at any point during the studies, not just discontinuation of treatment (treatment periods were brief, typically 2-3 days, but patients were followed by a longer observation period). Most patients in all treatment groups completed the studies. The premature discontinuation rate was lower for the Coartem 6-dose regimen (17%) than the 4-dose regimen (32%); this difference appeared to be almost entirely due to a difference in the proportions of patients discontinuing due to unsatisfactory therapeutic effect (4% of those treated with the 6-dose regimen and 19% of those treated with the 4-dose regimen). Unsatisfactory therapeutic effect most commonly referred to re-appearance of parasites after clearance; only two Coartem-treated patient (one in the 4-dose group, one in the 6-dose group) discontinued treatment due to worsening of the initial episode of malaria and received rescue therapy.

Table 7-3 Patient disposition - adult pooled safety analyses (Entered study population)

	Patients, n (%)		
	4-dose n = 925	**6-dose n = 647**	**Total N = 1572**
Entered study	925 (100.0)	647 (100.0)	1572 (100.0)
Safety population (received ≥ 1 dose)	925 (100.0)	647 (100.0)	1572 (100.0)
Completed study	633 (68.4)	539 (83.3)	1172 (74.6)
Discontinued study	292 (31.6)	108 (16.7)	400 (25.4)
Adverse event(s)	0	1 (0.2)	1 (0.1)
Abnormal test procedure result(s)	0	2 (0.3)	2 (0.1)
Unsatisfactory therapeutic effect	173 (18.7)	24 (3.7)	197 (12.5)
P vivax rescue medication	1 (0.1)	0	1 (0.1)
Subject's condition no longer requires study drug	0	1 (0.2)	1 (0.1)
Protocol violation	4 (0.4)	7 (1.1)	11 (0.7)
Subject withdrew consent	2 (0.2)	2 (0.3)	4 (0.3)
Lost to follow-up	100 (10.8)	69 (10.7)	169 (10.8)
Administrative problems	1 (0.1)	1 (0.2)	2 (0.1)
Death	3 (0.3)	0	3 (0.2)
Non-compliance	8 (0.9)	1 (0.2)	9 (0.6)

Exposure to Coartem components in the adult pooled safety population is shown in Table 7-4. Median exposure to both artemether and lumefantrine, for both the 4-dose and 6-dose regimens, was as expected for patients weighing over 35 kg and thus receiving 4 tablets per dose. Mean exposure to both components was similar to the median.

Table 7-4 Total dose of artemether and lumefantrine, adult pooled safety population

	Coartem 4-dose n = 925		Coartem 6-dose n = 647	
	Artemether	**Lumefantrine**	**Artemether**	**Lumefantrine**
Total dose, mg				
Mean (SD)	297.8 (50.68)	1786.8 (304.07)	472.8 (44.10)	2836.8 (264.61)
Median	320.0	1920.0	480.0	2880.0
Range	80 - 320	480 - 1920	80 - 480	480 - 2880
Total dose per body weight (mg/kg)				
Mean (SD)	5.81 (1.290)	34.87 (7.740)	8.70 (1.914)	52.18 (11.482)
Median	6.04	36.23	8.89	53.53
Range	1.07 – 10.00	6.40 – 60.00	0.82 – 13.71	4.95 – 82.29

Pediatric patients

For the pediatric pooled safety population, patient disposition is summarized in Table 7-5. In all Coartem treatment groups most patients completed the studies as planned. The rate of premature discontinuation from the studies was higher in the 4-dose group (26%) than the 6-dose group (11%); this difference appeared to be mainly due to differences in rates of discontinuation due to unsatisfactory therapeutic effect (14% vs. 0.5%, respectively), and loss to follow-up (8% vs. 3%, respectively). 'Unsatisfactory therapeutic effect' referred to re-appearance of parasites after clearance in all but one Coartem patient; who took the 4-dose regimen, discontinued during treatment and received rescue medication.

Premature discontinuation for safety-related reasons was more common with the 6-dose regimen than the 4-dose regimen: AE-related discontinuation occurred in 71 patients (5.3%) receiving the 6-dose regimen. In most (70 of 71) cases these were patients from study B2303; the remaining patient was from Study A2403. Of the 71 patients, 21 discontinued treatment, the remainder discontinued during the observation period after the end of treatment. Most of the patients who discontinued treatment (20 of 21) were in Study B2303 and 17 of these discontinued due to vomiting medication doses – this study discontinued patients if they either developed severe vomiting or if they vomited more than two doses of study drug within 1 hour of administration or vomited the replacement dose within 2 hours of intake. The single patient who discontinued treatment due to an AE in Study A2403 did so as a result of an urticarial rash. The 50 patients who discontinued from the study due to AEs after completing the treatment period most commonly did so following re-appearance of parasites (reported as *P falciparum* infection). AE-related discontinuation also occurred in 0.8% of patients receiving the 4-dose regimen.

Table 7-5 Patient disposition, pediatric pooled safety analyses (Entered study population)

	Coartem		
	4-dose n = 694 n (%)	**6-dose n = 1332 n (%)**	**Total n = 2026 n (%)**
Entered study	694 (100.0)	1333 (100.0)	2027 (100.0)
Safety population (received at least one dose)	694 (100.0)	1332 (99.9)	2026 (100.0)
Completed study	513 (73.9)	1190 (89.3)	1703 (84.0)
Discontinued study prematurely	181(26.1)	143 (10.7)	324 (16.0)
Adverse Event(s)	4 (0.6)	71 (5.3)	75 (3.7)
Unsatisfactory therapeutic effect	99 (14.3)	6 (0.5)	105 (5.2)
Protocol violation	12 (1.7)	2 (0.2)	14 (0.7)
Subject withdrew consent	4 (0.6)	19 (1.4)	23 (1.1)
Lost to follow-up	55 (7.9)	40 (3.0)	95 (4.7)
Administrative problems	5 (0.7)	0	5 (0.2)
Death	0	4 (0.3)	4 (0.2)
Non-compliance	2 (0.3)	0	2 (0.1)

Dosages of artemether and lumefantrine, and dosage in mg/kg body weight, for the pediatric pooled safety population are shown in Table 7-6. Pediatric patients were dosed according to body weight. On a mg/kg basis, the dosage received in the 6-dose regimen group was higher relative to that in the 4-dose group than would be expected, but this is probably related to differences in body weight ranges between the studies contributing to the two treatment groups, and to the use of the pediatric tablet in two of the studies contributing to the 4-dose regimen.

Table 7-6 Total dose of artemether and lumefantrine, pediatric pooled safety population

	Coartem 4-dose n = 694		**Coartem 6-dose[1] n = 885**		**Coartem 6-dose Dispersible n = 447**	
	Artemether	**Lumefantrine**	**Artemether**	**Lumefantrine**	**Artemether**	**Lumefantrine**
Total dose, mg						
Mean (SD)	143.2 (91.77)	859.2 (550.59)	187.7 (108.26)	1126.1 (649.56)	171.8 (76.96)	1030.6 (461.77)
Median	80.0	480.0	120.0	720.0	120.0	720.0
Range	20 - 320	120 - 1920	20 - 480	120 - 2880	20 - 360	120 - 2160
Total dose per body weight (mg/kg)						
Mean (SD)	6.41 (1.625)	38.45 (9.747)	12.22 (2.942)	73.31 (17.650)	11.97 (2.903)	71.81 (17.418)
Median	6.40	38.40	12.00	72.00	12.00	72.00
Range	1.25 – 11.76	7.50 – 70.59	1.54 – 24.00	9.23 – 144.00	1.79 – 24.00	10.71 – 144.00

[1] does not include patients who received the dispersible tablet

7.3 Overall Safety Profile

The overall safety profile of Coartem in adult patients and in pediatric patients in terms of the most frequently reported AEs by preferred term, serious adverse events, deaths, and discontinuations due to AEs is reported below. Most of the most common AEs were apparently more frequent with the 4-dose regimen. This simply reflect between-study differences in methods of collecting AE data (see Section 7.1)

7.3.1 Adults > 16 Years of Age

Adverse Events

The most frequently reported AEs (occurring in ≥ 1% of patients in any treatment group) are shown in Table 7-7. The most frequently reported AEs were not specific to any particular organ system and were mainly headache, anorexia, dizziness, nausea, chills, fatigue, and asthenia. Many of these were likely related to signs and symptoms of malaria or to febrile conditions.

Table 7-7 Most frequently reported adverse events occurring in ≥ 1% Coartem-treated patients in the adult safety population

	Patients, n (%)		
Preferred term	4-dose n = 925	6-dose n = 647	Total Coartem n = 1572
Headache	675 (73.0)	360 (55.6)	1035 (65.8)
Anorexia	569 (61.5)	260 (40.2)	829 (52.7)
Dizziness	527 (57.0)	253 (39.1)	780 (49.6)
Nausea	415 (44.9)	169 (26.1)	584 (37.2)
Chills	399 (43.1)	147 (22.7)	546 (34.7)
Fatigue	375 (40.5)	111 (17.2)	486 (30.9)
Asthenia	352 (38.1)	243 (37.6)	595 (37.8)
Sleep disorder	344 (37.2)	144 (22.3)	488 (31.0)
Hepatomegaly	281 (30.4)	59 (9.1)	340 (21.6)
Vomiting	272 (29.4)	113 (17.5)	385 (24.5)
Splenomegaly	270 (29.2)	57 (8.8)	327 (20.8)
Abdominal pain	259 (28.0)	112 (17.3)	371 (23.6)
Arthralgia	250 (27.0)	219 (33.8)	469 (29.8)
Myalgia	249 (26.9)	206 (31.8)	455 (28.9)
Palpitations	213 (23.0)	115 (17.8)	328 (20.9)
Diarrhea	91 (9.8)	46 (7.1)	137 (8.7)
Pruritus	38 (4.1)	24 (3.7)	62 (3.9)
Rash	37 (4.0)	21 (3.2)	58 (3.7)
Cough	35 (3.8)	37 (5.7)	72 (4.6)
Anemia	34 (3.7)	23 (3.6)	57 (3.6)
Paraesthenia	32 (3.5)	0 (0.0)	32 (2.0)
Tremor	23 (2.5)	16 (2.5)	39 (2.5)
Gait disturbance	15 (1.6)	3 (0.5)	18 (1.1)
Ataxia	11 (1.2)	3 (0.5)	14 (0.9)
Hypoacusis	11 (1.2)	0 (0.0)	11 (0.7)

	Patients, n (%)		
Preferred term	**4-dose n = 925**	**6-dose n = 647**	**Total Coartem n = 1572**
Insomnia	11 (1.2)	32 (4.9)	43 (2.7)
Nasopharyngitis	9 (1.0)	17 (2.6)	26 (1.7)
Pharyngolaryngeal pain	9 (1.0)	15 (2.3)	24 (1.5)
P falciparum infection	6 (0.6)	13 (2.0)	19 (1.2)
Clonus	5 (0.5)	16 (2.5)	21 (1.3)
Helminthis infection	5 (0.5)	10 (1.5)	15 (1.0)
Hyperhidrosis	4 (0.4)	10 (1.5)	14 (0.9)
Dyspepsia	3 (0.3)	10 (1.5)	13 (0.8)
Malaise	0 (0.0)	20 (3.1)	20 (1.3)
Malaria	0 (0.0)	18 (2.8)	18 (1.1)
Pyrexia	0 (0.0)	159 (24.6)	159 (10.1)
Vertigo	0 (0.0)	21 (3.2)	21 (1.3)

Only two patients > 65 years of age were treated with the 6-dose regimen, and only one patient reported an adverse event (pyrexia).

Deaths, SAEs and Adverse Events Leading to Study Discontinuation

Deaths, serious adverse events, and adverse events leading to study discontinuation are summarized in Table 7-8.

Table 7-8 Number of patients who died, had other serious adverse events or discontinued study due to AEs in the adult pooled safety population (>16 years of age)

	4-dose n = 925	**6-dose n = 647**	**Total Coartem n = 1572**
Serious or significant AEs			
Death	3 (0.2)	0 (-)	3 (0.2)
Serious AE	6 (0.6)	9 (1.4)	15 (1.0)
AE leading to study drug discontinuation	0 (-)	0 (-)[1]	0 (-)[1]

[1]Study completion data showed that one adult patient enrolled in Study A2401 discontinued after the first dose after experiencing mild abdominal pain and mild diarrhea that resolved without intervention.

Three deaths occurred in the adult pooled safety population and these are summarized in Table 7-9. All Coartem-treated patients in the adult pooled safety population who died had received the 4-dose regimen. In all three cases, death was due to violence or accidental trauma.

Table 7-9 Deaths in the adult pooled safety population (>16 years of age)

Study	**Age/Sex[1]**	**Day of last dose**	**Day of death**	**Cause of death (preferred term)**
Coartem 4-dose regimen				
A008	20/Male	3	9	Gun shot wound
A025	37/Male	3	15	Gun shot wound
A025	36/Male	3	20	Land mine

[1]No race information was available for any of the patients in this table.

Serious adverse events in the adult pooled safety population are summarized below by dosing regimen. Among patients treated with the 4-dose regimen, 6 (0.6%) patients reported SAEs, and among patients treated with the 6-dose regimen, nine (1.3%) patients experienced a SAE (Table 7-10). Except for one patient with a diagnosis of progression to severe malaria after administration of the first two doses, none of these SAEs occurred during treatment. The reported SAEs did not present any common pattern or raised any specific safety signal.

Table 7-10 Serious adverse events occurring in the adult pooled safety population

Study No	Age/sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
4-dose regimen					
A014	35/M	Anemia (severe)	15	Ongoing	Yes
A014	37/M	Malaria relapse (severe)	21	24	Yes
A014	49/M	Viral hepatitis (severe)	29	Ongoing	No
A014	25/F	*Falciparum* malaria (severe)	19	21	No
A025	20/M	Chronic hepatitis (mild)	29	40	No
A025	28/M	Abnormal lab values (severe)	1	30	No
		Malaria (severe)	2	30	No
6-dose regimen					
A025	20/M	Typhoid fever (moderate)	8	19	No
A026	17/M	Febrile coma (life-threatening)	14	24	No
A028	28/M	Dyspnoea (severe)	2	4	No
		Pulmonary edema due to fluid overload (severe)	2	5	No
A2401	30/M	Hematuria (mild)	1	5	No
		Malaise (mild)	1	8	No
		Abdominal pain (moderate)	2	39	Unknown
		Elevated liver tests (moderate)	4	26	Yes
		Thrombocytopenia (moderate)	4	8	No
A2401	55/F	Disease progression (severe)	2	7	Yes
		Increased bilirubin (moderate)	2	7	Yes
		Increased transaminases (moderate)	2	7	Yes
		Mental impairment (moderate)	2	4	Yes
		Vomiting (moderate)	2	3	Yes
A2401	62/F	Chills (moderate)	23	27	No
		Fever (moderate)	23	27	No
		Headache (moderate)	23	27	No
		Malaria (severe)	23	Ongoing	No
A2401	55/M	Endocarditis (moderate)	3	43	No
A2401	37/F	Liver cell injury (moderate)	8	16	No
A2401	54/M	Malaria recrudescence (severe)	21	29	Yes
		ECG abnormal T wave (severe)	22	Ongoing	Unknown

7.3.2 Pediatric Patients ≤ 16 Years of Age

Adverse Events

The most frequently reported AEs (occurring in ≥ 1% of patients in any treatment group) are shown in Table 7-11.The most frequently reported AEs were not specific to any particular organ system and were mainly headache, anorexia, vomiting, fatigue, splenomegaly, chills,

abdominal pain, dizziness, nausea, and hepatomegaly. Many of these were likely related to signs and symptoms of malaria or to febrile conditions.

P. falciparum infection was reported much more frequently as an AE in the pediatric pooled safety population than in the adult pooled safety population. This is probably the result of the different regions in which studies contributing patients to the two safety populations were performed. Studies in adults were performed primarily in regions of low or no malaria endemicity (i.e. China, Thailand, and Europe), whereas the studies in children and infants were predominantly performed in sub-Saharan African with high malaria transmission rates.

In each of the Coartem groups, cough was a very common AE, and unlike most of the other common AEs, an analysis of time of onset showed a relatively even distribution throughout the follow-up period of the studies. This strongly suggests that cough is probably related neither to malaria nor to Coartem treatment. It is worth noting that respiratory infections are very common in African children presenting with malaria (O'Dempsey et al 1993). In Studies A003, A010 and A011, in which the 4-dose regimen of Coartem was compared with quinine, SP or chloroquine, no between-group difference in the incidence of cough was observed.

Table 7-11 Most frequently reported adverse events occurring in ≥ 1% patients in the pediatric pooled safety population

Preferred term	4-dose n = 694	Total 6-dose n = 1332	Total Coartem n = 2026
Headache	314 (45.2)	168 (12.6)	482 (23.8)
Anorexia	269 (38.8)	175 (13.1)	444 (21.9)
Vomiting	209 (30.1)	242 (18.2)	451 (22.3)
Fatigue	214 (30.8)	46 (3.5)	260 (12.8)
Splenomegaly	205 (29.5)	124 (9.3)	329 (16.2)
Chills	195 (28.1)	72 (5.4)	267 (13.2)
Abdominal pain	182 (26.2)	112 (8.4)	294 (14.5)
Dizziness	179 (25.8)	56 (4.2)	235 (11.6)
Nausea	176 (25.4)	61 (4.6)	237 (11.7)
Hepatomegaly	174 (25.1)	75 (5.6)	249 (12.3)
Sleep disorder	170 (24.5)	27 (2.0)	197 (9.7)
Anemia	145 (20.9)	115 (8.6)	260 (12.8)
Asthenia	133 (19.2)	63 (4.7)	196 (9.7)
Cough	106 (15.3)	302 (22.7)	408 (20.1)
Diarrhea	76 (11.0)	100 (7.5)	176 (8.7)
Palpitations	64 (9.2)	24 (1.8)	88 (4.3)
Arthralgia	59 (8.5)	39 (2.9)	98 (4.8)
Myalgia	56 (8.1)	39 (2.9)	95 (4.7)
Hypokinesia	44 (6.3)	0 (0.0)	44 (2.2)
Pyrexia	36 (5.2)	381 (28.6)	417 (20.6)
Lethargy	34 (4.9)	0 (0.0)	34 (1.7)
Speech disorder	33 (4.8)	0 (0.0)	33 (1.6)
Rhinorrhoea	25 (3.6)	11 (0.8)	36 (1.8)
Upper respiratory tract infection	25 (3.6)	32 (2.4)	57 (2.8)
Rash	22 (3.2)	38 (2.9)	60 (3.0)
Feeding disorder	14 (2.0)	0 (0.0)	14 (0.7)

Preferred term	4-dose n = 694	Total 6-dose n = 1332	Total Coartem n = 2026
Mood swings	13 (1.9)	15 (1.1)	28 (1.4)
Conjunctivitis	12 (1.7)	20 (1.5)	32 (1.6)
Helminthic infection	11 (1.6)	22 (1.7)	33 (1.6)
Pneumonia	11 (1.6)	20 (1.5)	31 (1.5)
Nasopharyngitis	10 (1.4)	14 (1.1)	24 (1.2)
Pruritus	10 (1.4)	7 (0.5)	17 (0.8)
Fine motor delay	8 (1.2)	0 (0.0)	8 (0.4)
Clonus	7 (1.0)	11 (0.8)	18 (0.9)
Gait disturbance	7 (1.0)	0 (0.0)	7 (0.3)
Heat rash	7 (1.0)	5 (0.4)	12 (0.6)
Impetigo	7 (1.0)	8 (0.6)	15 (0.7)
Urinary tract infection	7 (1.0)	2 (0.2)	9 (0.4)
Acarodermatitis	6 (0.9)	15 (1.1)	21 (1.0)
Respiratory tract infection	2 (0.3)	28 (2.1)	30 (1.5)
Bronchitis	1 (0.1)	26 (2.0)	27 (1.3)
Insomnia	1 (0.1)	13 (1.0)	14 (0.7)
Aspartate aminotransferase increased	0 (0.0)	51 (3.8)	51 (2.5)
Ear infection	0 (0.0)	17 (1.3)	17 (0.8)
Eosinophilia	0 (0.0)	13 (1.0)	13 (0.6)
Lower respiratory tract infections	0 (0.0)	15 (1.1)	15 (0.7)
P falciparum infection	0 (0.0)	224 (16.8)	224 (11.1)
Platelet count decreased	0 (0.0)	20 (1.5)	20 (1.0)
Rhinitis	0 (0.0)	51 (3.8)	51 (2.5)
White blood cell count decreased	0 (0.0)	13 (1.0)	13 (0.6)

Adverse events reported by pediatric patients treated with the 6-dose regimen by age group are shown in Table 7-12.

Table 7-12 Adverse events reported in ≥ 1% of pediatric patients in the Coartem 6-dose group by age

Preferred term	Age group, years			
	≤ 2 n = 587	> 2 to ≤ 6 n = 473	> 6 to ≤ 12 n = 207	> 12 to ≤ 16 n = 65
Cough	159 (27.1)	105 (22.2)	37 (17.9)	1 (1.5)
Pyrexia	154 (26.2)	147 (31.1)	65 (31.4)	15 (23.1)
Vomiting	122 (20.8)	66 (14.0)	34 (16.4)	20 (30.8)
P falciparum infection	92 (15.7)	94 (19.9)	37 (17.9)	1 (1.5)
Diarrhea	71 (12.1)	22 (4.7)	6 (2.9)	1 (1.5)
Anemia	70 (11.9)	32 (6.8)	9 (4.3)	4 (6.2)
Anorexia	59 (10.1)	39 (8.2)	40 (19.3)	37 (56.9)
Rhinitis	34 (5.8)	16 (3.4)	1 (0.5)	0 (0.0)
Splenomegaly	31 (5.3)	50 (10.6)	38 (18.4)	5 (7.7)
Rash	22 (3.7)	14 (3.0)	0 (0.0)	2 (3.1)
Respiratory tract infection	24 (4.1)	3 (0.6)	1 (0.5)	0 (0.0)
Hepatomegaly	23 (3.9)	21 (4.4)	17 (8.2)	14 (21.5)
Upper respiratory tract	21 (3.6)	10 (2.1)	1 (0.5)	0 (0.0)

Preferred term	Age group, years			
	≤ 2 n = 587	> 2 to ≤ 6 n = 473	> 6 to ≤ 12 n = 207	> 12 to ≤ 16 n = 65
infection				
Aspartate aminotransferase increased	17 (2.9)	29 (6.1)	5 (2.4)	0 (0.0)
Fatigue	13 (2.2)	12 (2.5)	6 (2.9)	15 (23.1)
Acarodermatitis	12 (2.0)	3 (0.6)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	12 (2.0)	3 (0.6)	0 (0.0)	0 (0.0)
Eosinophilia	11 (1.9)	2 (0.4)	0 (0.0)	0 (0.0)
Chills	10 (1.7)	15 (3.2)	24 (11.6)	23 (35.4)
Conjunctivitis	10 (1.7)	8 (1.7)	1 (0.5)	1 (1.5)
Bronchitis	9 (1.5)	14 (3.0)	3 (1.4)	0 (0.0)
Clonus	9 (1.5)	1 (0.2)	0 (0.0)	1 (1.5)
Constipation	9 (1.5)	2 (0.4)	0 (0.0)	0 (0.0)
Gastroenteritis	9 (1.5)	2 (0.4)	0 (0.0)	0 (0.0)
Insomnia	9 (1.5)	3 (0.6)	0 (0.0)	1 (1.5)
Pneumonia	9 (1.5)	9 (1.9)	2 (1.0)	0 (0.0)
Abdominal Pain	8 (1.4)	49 (10.4)	34 (16.4)	21 (32.3)
Hemoglobin decreased	8 (1.4)	2 (0.4)	0 (0.0)	0 (0.0)
Mood swings	8 (1.4)	6 (1.3)	1 (0.5)	0 (0.0)
Rhinorrhoea	8 (1.4)	2 (0.4)	1 (0.5)	0 (0.0)
Agitation	7 (1.2)	4 (0.8)	0 (0.0)	0 (0.0)
Lymphocyte morphology abnormal	7 (1.2)	1 (0.2)	1 (0.5)	0 (0.0)
Nasopharyngitis	7 (1.2)	3 (0.6)	1 (0.5)	3 (4.6)
Otitis media	7 (1.2)	3 (0.6)	0 (0.0)	0 (0.0)
Platelet count decreased	7 (1.2)	11 (2.3)	2 (1.0)	0 (0.0)
Ear infection	6 (1.0)	7 (1.5)	4 (1.9)	0 (0.0)
Hypothermia	6 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	6 (1.0)	6 (1.3)	23 (11.1)	26 (40.0)
Headache	4 (0.7)	46 (9.7)	71 (34.3)	47 (72.3)
Helminthic infection	5 (0.9)	10 (2.1)	4 (1.9)	3 (4.6)
Hematocrit decreased	5 (0.9)	7 (1.5)	0 (0.0)	0 (0.0)
Influenza	5 (0.9)	6 (1.3)	0 (0.0)	0 (0.0)
Asthenia	3 (0.5)	1 (0.2)	23 (11.1)	36 (55.4)
Alanine aminotransferase increased	2 (0.3)	6 (1.3)	3 (1.4)	0 (0.0)
Dysphagia	2 (0.3)	5 (1.1)	5 (2.4)	0 (0.0)
Pruritus	2 (0.3)	1 (0.2)	1 (0.5)	3 (4.6)
Abscess	1 (0.2)	1 (0.2)	0 (0.0)	1 (1.5)
Arrhythmia	1 (0.2)	4 (0.8)	2 (1.0)	0 (0.0)
Cellulitis	1 (0.2)	1 (0.2)	0 (0.0)	1 (1.5)
Dizziness	1 (0.2)	2 (0.4)	17 (8.2)	36 (55.4)
Eosinophil count increased	1 (0.2)	1 (0.2)	2 (1.0)	0 (0.0)
Fungal infection	1 (0.2)	0 (0.0)	0 (0.0)	1 (1.5)
Gamma-glutamyltransferase increased	1 (0.2)	6 (1.3)	1 (0.5)	0 (0.0)

Preferred term	Age group, years			
	≤ 2 n = 587	> 2 to ≤ 6 n = 473	> 6 to ≤ 12 n = 207	> 12 to ≤ 16 n = 65
Abscess limb	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Arthralgia	0 (0.0)	1 (0.2)	13 (6.3)	25 (38.5)
Ascariasis	0 (0.0)	0 (0.0)	2 (1.0)	1 (1.5)
Ataxia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Blood potassium decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Hookworm infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Myalgia	0 (0.0)	0 (0.0)	16 (7.7)	23 (35.4)
Nystagmus	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Oliguria	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Oral herpes	0 (0.0)	1 (0.2)	1 (0.5)	1 (1.5)
Palpitations	0 (0.0)	0 (0.0)	5 (2.4)	19 (29.2)
Parasite gastroenteritis	0 (0.0)	0 (0.0)	9 (4.3)	3 (4.6)
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (0.5)	2 (3.1)
Sleep disorder	0 (0.0)	2 (0.4)	9 (4.3)	16 (24.6)
Tremor	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.5)
Trichuriasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
White blood cell count decreased	0 (0.0)	9 (1.9)	4 (1.9)	0 (0.0)

The overall incidence of AEs in patients of ≤ 2 years of age was similar to that in the >2-≤ 12 years age group, but the profile of AEs observed showed some differences. The infants ≤ 2 years of age had higher rates of cough, respiratory tract infection, anemia, and diarrhea than older children. Other AEs that occurred at lower rates in children ≤ 2 years of age were those such as fatigue, chills, abdominal pain that needs to be verbalized and therefore that smaller children may have been less able to report than older patients..Generally reporting of this type of AEs increased with age. For example, anorexia, nausea, headache, asthenia, arthralgia, myalgia were more frequent in children > 12 to ≤ 16.

Deaths, Serious Adverse Events and adverse events leading to study discontinuation

Deaths, serious adverse events and adverse events leading to study discontinuation are summarized for the pediatric pooled safety population in Table 7-13.

Table 7-13 Number of patients who died, had other serious adverse events or discontinued study due to AEs in pediatric pooled safety population

Serious or significant AE	4-dose n = 694	Total 6-dose n = 1332	Total Coartem n = 2026
Death	0	4 (0.3)	4 (0.2)
Serious AE	7 (1.0)	17 (1.3)	24 (1.2)
AE leading to study drug discontinuation	0	21 (1.6)	21 (1.0)

Four deaths occurred in the pediatric pooled safety population and these are summarized in Table 7-14. All of the deaths occurred in patients treated with the 6-dose Coartem regimen and in all but one case the cause of death was infection.

Table 7-14 Deaths in pediatric pooled safety population

Study	Age/Sex/Race	Day of last dose	Day of death	Cause of death (preferred term)
Coartem 6-dose regimen				
A2403	4 yrs/Female/Black	4	9	Gastroenteritis
B2303	5 mo/Male/Black	4	31	*P. falciparum* infection
B2303	2 yrs/Male/Black	4	7	Haemorrhage
B2303	4 mo/Male/Black	2	3	Infection

None of the deaths on study were suspected by the investigators to be related to study treatment. The following narratives briefly describe the cause and circumstances surrounding each of these deaths.

- One patient died due to severe gastroenteritis, having received the full course of Coartem treatment, during which (Day 1-2) she had moderate diarrhea, suspected to be related to study medication, which was treated with oral rehydration therapy. The patient was clear of parasites at Day 7. On Day 9 she developed severe gastroenteritis and died at home on the same day.
- One patient died due to unspecified infection. This patient had discontinued study drug due to vomiting on Day 2, and was clear of parasites at this time. A severe infection (with no further details given) developed, with pyrexia, complicated by dehydration. The infection was treated with quinine, paracetamol, metoclopramide and amoxicillin, but worsened and the patient died on Day 3.
- One patient died due to malaria. This patient cleared parasites within 24 hours, and was still clear of parasites at Day 14. Reappearance of parasites occurred on Day 29, with severe malaria reported as an SAE, and the patient died on Day 31. No PCR was available to determine if this was re-infection or recrudescence of the original infection.
- The remaining patient died as a result of hemorrhage. The patient entered the study with low hemoglobin, hemotocrit and reticulocyte count, and had decreases from baseline in hemoglobin, hematocrit and erythrocyte count, and splenomegaly at Day 4; the platelet count was within the normal range. The patient left the center and was treated with iron-folic acid, then was taken to a traditional therapist and received traditional surgery (scarification) on Day 5. On day 6, the patient was hospitalized for anemia and died due to hemorrhage on Day 7.

Serious adverse events in the pediatric pooled safety population are summarized below by regimen (Table 7-15). Among patients treated with the 4-dose regimen, 7 (1.0%) patients reported SAEs, most commonly anemia. Two cases were reported in patients who had hemoglobin levels of 5.1 gram per deciliter and of 3.4 gram per deciliter at study entry . The remaining patient was treated by chloramphenicol for suspission of typhoid when severe anemia was diagnosed. Among patients treated with the 6-dose regimen, 10 (0.7%) patients experienced an SAE. The most frequently reported SAE was severe malaria. However, it is important to note that 2 patients developed early signs of severe malaria, but retrospectively it was determined that these patients presented with signs and symptoms of severe malaria at study entry with hemoglobin levels below 5 grams per deciliter. The remaining 3 patients developed severe malaria after clearing parasites. In all cases, it was confirmed that it was due

to a new infection. None of these SAEs were considered related to study drug with the exception of 1 case of urticarial rash.

Table 7-15 Serious adverse events occurring in the pediatric pooled safety population

Study No	Age[1]/sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
4-dose regimen					
A009	2/F	Anemia (severe)	15	17	No
A010	1/M	Conjunctivitis (severe)	2	15	No
A010	3/F	Vomiting (severe)	1	3	No
A011	1/F	Bronchopneumonia (moderate)	29	Ongoing	No
A011	1/M	Anemia (life-threatening)	4	Ongoing	Yes
A011	1/M	Pneumonia (moderate)	17	30	No
A011	3/M	Anemia (life-threatening)	4	15	Yes
6-dose regimen					
A2403	8 mo/F	Convulsion (moderate)	28	28	No
		Malaria (severe)	28	Ongoing	No
A2403	1/M	Viral hepatitis (severe)	2	Ongoing	No
A2403	4/F	Urticarial rash (severe)	2	6	Yes
		Atypical pneumonia (moderate)	22	29	No
A2403	4/F	Gastroenteritis (severe)	9	9	No
B2303	4/F	Anemia (severe)	4	15	No
		Fever (severe)	4	15	No
		Facial edema (severe)	6	15	No
B2303	6 mo/M	Acute laryngeal tracheal bronchitis (severe)	22	29	No
B2303	1/M	Malaria (severe)	27	34	No
B2303	2/M	Convulsions (mild)	42	Ongoing	No
		Malaria (severe)	42	Ongoing	No
B2303	5 mo/M	Pneumonia (severe)	26	43	No
		Malaria (severe)	26	32	No
B2303	2 /F	Lower respiratory tract infection	2	4	No
B2303	9 mo/M	Severe malaria (P falciparum infection)	2	3	No
		Severe anemia (iron deficiency)	2	29	No
B2303	7 mo/M	Severe malaria (P falciparum infection)	1	8	No
		Severe anemia	1	29	No
B2303	1/F	Dehydration	43	Ongoing	No
		Diarrhea	43	Ongoing	No
		Vomiting	43	Ongoing	No
B2303	5 /M	Convulsions	29	30	No
		Pyrexia	29	30	No

[1]Years (unless otherwise specified)

7.3.3 Comparison of Safety of 4-dose and 6-dose Regimen

Only one study (Study A025) compared the 4-dose and 6-dose regimens head-to-head in a single randomized, double-blind study. This study showed that the Coartem 6-dose regimen was at least as well tolerated as the 4-dose regimen (Table 7-16).

Table 7-16 Most frequently reported adverse events occurring in ≥ 1% of patients in Study A025 by treatment group

	Patients, n (%)	
Preferred term	**Coartem 6-dose n = 118**	**Coartem 4-dose n = 120**
Headache	29 (24.6)	43 (35.8)
Dizziness	23 (19.5)	24 (20.0)
Anorexia	16 (13.6)	22 (18.3)
Infestation parasitic	16 (13.6)	9 (7.5)
Asthenia	15 (12.7)	20 (16.7)
Myalgia	12 (10.2)	14 (11.7)
Sleep disorders	10 (8.5)	12 (10.0)
Arthralgia	8 (6.8)	13 (10.8)
Palpitations	8 (6.8)	7 (5.8)
Abdominal pain	7 (5.9)	10 (8.3)
Fatigue	6 (5.1)	4 (3.3)
Nausea	5 (4.2)	7 (5.8)
Rigors	5 (4.2)	8 (6.7)
Anemia	4 (3.4)	6 (5.0)
Vomiting	3 (2.5)	4 (3.3)

7.3.4 Safety of 6-dose regimen versus comparators

The safety of the Coartem 6-dose regimen was compared in two open-label randomized trials (Studies A026 and A028) with the combination of mefloquine and artesunate. For the purpose of the comparison the data from both studies were pooled. This analysis summarized in Table 7-17 showed that the Coartem 6-dose regimen had a similar safety profile was at least as well tolerated as the combination of mefloquine with artesunate.

Table 7-17 Most frequently reported adverse events occurring in ≥ 1% patients in studies A026 and A028

	n (%) patients	
Preferred term	**Coartem 6-dose N=314**	**Mefloquine Artesunate N=105**
Any primary system organ class	267 (85.0)	91 (86.7)
Blood and lymphatic system disorders	45 (14.3)	16 (15.2)
Splenomegaly	40 (12.7)	12 (11.4)
Anaemia	10 (3.2)	4 (3.8)
Cardiac disorders	55 (17.5)	17 (16.2)
Palpitations	55 (17.5)	17 (16.2)
Ear and labyrinth disorders	1 (0.3)	1 (1.0)
Ear pruritus	0 (0.0)	1 (1.0)
Eye disorders	1 (0.3)	1 (1.0)
Strabismus	0 (0.0)	1 (1.0)
Gastrointestinal disorders	123 (39.2)	50 (47.6)
Nausea	82 (26.1)	34 (32.4)
Abdominal pain	61 (19.4)	20 (19.0)
Vomiting	50 (15.9)	22 (21.0)

	n (%) patients	
Preferred term	**Coartem 6-dose N=314**	**Mefloquine Artesunate N=105**
Diarrhoea	11 (3.5)	2 (1.9)
Dyspepsia	10 (3.2)	5 (4.8)
General disorders and administration site conditions	219 (69.7)	75 (71.4)
Pyrexia	183 (58.3)	63 (60.0)
Asthenia	108 (34.4)	33 (31.4)
Chills	67 (21.3)	20 (19.0)
Fatigue	34 (10.8)	8 (7.6)
Chest pain	1 (0.3)	1 (1.0)
Gait disturbance	1 (0.3)	1 (1.0)
Hepatobiliary disorders	50 (15.9)	8 (7.6)
Hepatomegaly	48 (15.3)	8 (7.6)
Jaundice	3 (1.0)	0 (0.0)
Infections and infestations	34 (10.8)	12 (11.4)
Nasopharyngitis	8 (2.5)	4 (3.8)
Hookworm infection	4 (1.3)	0 (0.0)
Ascariasis	3 (1.0)	0 (0.0)
Respiratory tract infection	3 (1.0)	1 (1.0)
Subcutaneous abscess	3 (1.0)	1 (1.0)
Trichuriasis	3 (1.0)	1 (1.0)
Urinary tract infection	2 (0.6)	1 (1.0)
Abscess limb	1 (0.3)	1 (1.0)
Cystitis escherichia	1 (0.3)	1 (1.0)
Fungal infection	1 (0.3)	0 (0.0)
Gingival abscess	1 (0.3)	0 (0.0)
Bronchitis	0 (0.0)	1 (1.0)
Nematodiasis	0 (0.0)	1 (1.0)
Parasitic gastroenteritis	0 (0.0)	1 (1.0)
Pulmonary tuberculosis	0 (0.0)	1 (1.0)
Injury, poisoning and procedural complications	0 (0.0)	3 (2.9)
Overdose	0 (0.0)	3 (2.9)
Metabolism and nutrition disorders	114 (36.3)	40 (38.1)
Anorexia	108 (34.4)	37 (35.2)
Hypokalaemia	4 (1.3)	2 (1.9)
Diabetes mellitus	0 (0.0)	1 (1.0)
Hyperlipidaemia	0 (0.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	104 (33.1)	31 (29.5)
Arthralgia	99 (31.5)	31 (29.5)
Myalgia	74 (23.6)	19 (18.1)
Nervous system disorders	177 (56.4)	50 (47.6)
Headache	166 (52.9)	46 (43.8)
Dizziness	123 (39.2)	37 (35.2)
Tremor	1 (0.3)	1 (1.0)
Psychiatric disorders	70 (22.3)	30 (28.6)
Sleep disorder	70 (22.3)	30 (28.6)
Respiratory, thoracic mediastinal and disorders	19 (6.1)	10 (9.5)

	n (%) patients	
Preferred term	**Coartem 6-dose N=314**	**Mefloquine Artesunate N=105**
Cough	12 (3.8)	2 (1.9)
Pharyngolaryngeal pain	9 (2.9)	4 (3.8)
Epistaxis	1 (0.3)	4 (3.8)
Asthma	0 (0.0)	2 (1.9)
Lung infiltration	0 (0.0)	1 (1.0)
Skin and subcutaneous tissue disorders	13 (4.1)	5 (4.8)
Pruritus	9 (2.9)	4 (3.8)
Rash	6 (1.9)	3 (2.9)
Urticaria	2 (0.6)	2 (1.9)
Vascular disorders	4 (1.3)	0 (0.0)
Pallor	3 (1.0)	0 (0.0)

7.3.5 Post Marketing Experience

Between October 1998 (first approval) and August 31, 2008, 150 spontaneous cases were reported to Novartis, including 68 serious cases. Most of them were coming from Africa with only 18% reported reported in children ≤16 years of age despite the fact that the vast majority of patients treated with Coartem were children. Most cases were related to the "General disorders" and "Infections and infestations" System Organ Classes and were due to persistence or recurrence of malaria (37 cases). Hypersentivity has been identified as a possible adverse reaction to Coartem (a total of 24 cases of hypersensitivity and skin reactions were reported) and it is therefore mentioned in the proposed labeling.

Repeated administration of artemether lumefantrine was not associated with an increased risk of adverse events and in particular of neurological side effects (Adjei 2008, Maiteki-Sebuguzi 2008).

7.4 Safety Topics of Special Interest

A number of specific subsets of adverse events were specifically investigated, on the basis of findings in animal studies or known class effects of artemisinin or fluorine derivatives. These included adverse events related to the nervous system or ear and labyrinth and those potentially related to prolongation of the QTc interval. In addition, hematological (anemia) and hemolysis-related adverse events were assessed in greater detail.

7.4.1 Nervous System or Ear and Labyrinth Disorders

7.4.1.1 Preclinical Data

Specific studies to confirm artemether neurotoxicity, including its clinical and histopathologic presentation have been performed. While the rat exhibits the brain lesion following a 25 mg/kg/day i.m. artemether dose for 7 or 14 days, most studies have been in the dog which provides more flexibility than the rat for i.m. dose administration and toxicokinetic measurements. Specifically, 20 mg/kg/day i.m. doses for 5 or 30 days were administered to dogs; toxicokinetic measurement, clinical neurologic assessments, hearing tests, and histopathologic evaluation of the brains at the conclusion of the study were performed. While

microscopic brain lesions mainly in the brain stem and cerebellur roof nuclei were observed following 30 days of treatment, no changes were observed in animals treated for 5 days except a slight thymic atrophy in one animal. Clinical data showed tremors in one animal and convulsions in another animal after > 27 days of treatment; no animals in any groups showed changed in clinical neurologic parameters. Additional studies at doses ranging from 10 to 80 mg/kg/day for 5 to 8 days of treatment have confirmed that brain lesions are observed following i.m. doses in the dog when animals are treated for 8 or more days at high doses. Daily 10 mg/kg/day i.m. dosing for 8 days did not cause brain lesions.

Oral doses showed no brain lesions and no clinical evidence of neurotoxicity (eg. no seizures or tremors) in the dog at up to 300 mg/kg/day of artemether for 13 weeks. An early study of artemether oral doses of up to 600 mg/kg/day for 8 days showed vomiting but no microscopic brain changes. To confirm that neurotoxicity does not pose a risk following oral dosing, oral artemether and Coartem doses were administered to dogs and the brains were prepared specifically to evaluate the lesion validated following i.m. administration. Artemether doses of up to 600 mg/kg (reduced to 300 mg/kg on Day 2) and Coartem doses of up to 1000 mg/kg (containing 143 mg/kg artemether) were administered and the animals were evaluated for neurologic and hearing changes prior to necropsy followed by brain fixation and histopathology evaluation. The oral 600 mg/kg artemether dose animals exhibited tremors and vomiting, and thereafter sporadic vomiting was noted at the 300 mg/kg/day dose. There were no other neurologic effects, hearing tests revealed minimal hearing loss at 20 dB which would not impair the hearing of a dog, this change was not accompanied by any histopathologic changes in the brain. The Coartem animals showed no changes in any parameter.

The only neurologic effect following oral artemether dosing was in juvenile rats aged 7 days postpartum when artemether treatment was initiated. In that study mortality was observed in animals in the 100 mg/kg/day group after 4-11 days of treatment. Surviving animals were sacrificed and their brains showed significant amount of hemorrhage. In the 30 mg/kg/day group, one animal died, and brain hemorrhage was observed in this animal. No other 30 mg/kg/day or any 10 mg/kg/day animal showed brain lesions. While brain hemorrhage is certainly neurotoxicity, it is significantly different than the brain stem and auditory pathway changes seen following i.m. dosing in the rat and dog which occurred with no clinical symptoms other than occasionally tremor or seizure at high doses and relatively long treatment duration. Thus, the brain hemorrhage in juvenile rats (< 21 days old) may be a more general toxicity of artemether in these young animals. No other oral doses of artemether alone or in combination with lumefantrine have produced neurotoxicity.

The most striking difference in the data available for i.m. and oral artemether studies are the toxicokinetic results. In dogs, artemether exposure is considerably higher following i.m. doses compared to oral exposure. Furthermore, after oral dosing, artemether and DHA exposures decline while exposure following i.m. dosing remains relatively constant. Thus the route of administration affects the circulating levels of artemether and DHA, resulting in substantially higher levels which are sustained when the i.m. route of administration is employed. This exposure difference is likely responsible for the artemether neurotoxicity specific to the i.m. route of administration.

7.4.1.2 Artemether Exposure in Dogs and Humans

Dogs

The disposition of artemether in the dog, including metabolism, was investigated using radiolabeled artemether. Metabolism was rapid and extensive, with formation of numerous metabolites. Strong binding of radioactivity to blood constituents indicated formation of reactive intermediates from the peroxide group in artemether and dihydroartemisinin (DHA). The artemether or DHA concentrations at artemether doses of ≤ 150 mg/kg in dogs were difficult to measure due to the very rapid first-pass metabolism and elimination of both compounds. Artemether and DHA concentrations were erratic and near or below the lower limit of quantification (LLOQ) (10 ng/mL). More recent toxicokinetics studies in dogs were performed using a more sensitive and specific LC-MS/MS method for quantification of artemether and DHA in plasma (Souppart et al 2002). The LLOQ for artemether and DHA was 5-10 ng/mL using a plasma sample of 0.5 mL for both compounds.

Multiple oral dosing of artemether or Coartem induced its own metabolism in dogs. Mutiple oral dosing of 143 mg/kg/day artemether (as Coartem) for three consecutive days in dogs, decreased the artemether AUC by *approx.* 25-fold compared to AUC at Day 1. Mechanistic *in vivo* and *in vitro* studies with artemisinin in rats and mice indicated that induction may be mediated *via* the nuclear constitutive androstane receptor (CAR) (Simonsson et al 2006).

Humans

In humans, radiotracer studies were judged not to be feasible. Thus no detailed data exist on the metabolism of artemether in humans *in vivo* (except formation of DHA). Instead, human metabolism was investigated *in vitro*, showing similar metabolism as in the nonclinical species, including the dog.

In male healthy human subjects, after oral administration of 80 mg artemether (as Coartem), artemether was absorbed fairly rapidly with peak plasma concentrations (C_{max}) reached about 2 hours after dosing. Food enhances the absorption and bioavailability of both artemether and lumefantrine, as AUC increased by a factor of 2.4 in subjects after a meal (Lefèvre and Thomsen 1999) .

As observed in dogs, multiple oral dosing of artemether or Coartem induced its own metabolism in humans. In a multiple dose study in healthy volunteers in which artemether was given orally for five consecutive days (2x50 mg tablets, Artenam®), artemether induced CYP3A4 activity *approx.* 1.5-fold (Asimus et al 2007).

The human exposure to artemether has been assessed in a number of studies in malaria patients. The most relevant mean $AUC_{(0\text{-}8h)}$ value was 535 ng·h/mL, measured on Day 1 (after the first dose) in malaria patients treated with the standard 6-dose regimen over 3 days (Study A028), and C_{max} was 186 ng/mL. For DHA, the relevant mean $AUC_{(0\text{-}8h)}$ value was 604 ng·h/mL (Study A028) measured on Day 3 (after the last dose; DHA concentrations were higher after the last than after the first dose), and C_{max} was 205 ng/mL. Due to the fast elimination of artemether and DHA ($t_{1/2}$ about 2 h), $AUC_{(0\text{-}8h)}$ was assumed to be equal to $AUC_{(0\text{-}inf)}$ and $AUC_{(0\text{-}24h)}$ for twice daily dosing was estimated as 2 times $AUC_{(0\text{-}8h)}$. Thus for

twice daily dosing, the $AUC_{(0\text{-}24h)}$ of artemether was estimated as 1070 ng·h/mL and the $AUC_{(0\text{-}24h)}$ of DHA was estimated as 1208 ng·h/mL.

Comparison of systemic exposure between dog and human

Comparison of systemic exposure between dog and human has therefore to be made using the 300 and 600 mg/kg oral doses in the dog as well as the 20 mg/kg i.m. dose.

The comparison of systemic exposure between dog and human is provided in Table 7-18. The exposure of the dogs to artemether at 300 mg/kg dose of where no neurologic symptoms were observed was similar to that in humans. For artemether, the exposure multiples were slightly lower than 1, whereas they were greater than 1 for DHA.

It is noteworthy that the oral exposure of the dog to artemether and DHA at 600 mg/kg/day was not double that at 300 mg/kg/day but showed a marked over-proportional increase by at least one order of magnitude. So comparison of the exposure of the dogs at the 600 mg/kg/day to the human therapeutic exposure shows a substantial margin with a factor of 11 to 21.

The i.m. data show that artemether exposure increases with dose, while DHA levels are low and relatively constant regardless of the dose. After a single 20 mg/kg i.m. dose, artemether AUC values were 2.1 times higher than exposure in humans, while the exposure at Day 7 was 8.7 times greater than in humans. C_{max} values were only slightly higher in the dogs compared to humans, and were only slightly higher on Day 7 compared to Day 1. The ratio of dog C_{max} values to human C_{max} values was 1.2 and 1.6 on Day 1 and Day 7, respectively.

Table 7-18 Exposure to artemether and dihydroartemisinin in dogs and comparison to humans

Species Study no.	Artemether Dose (mg/kg/day)	Route	Day	Gender	$AUC_{0\text{-}24h}$ (ng.h/mL)	C_{max} (ng/mL)	Exposure multiple [a] (revised)	
							Based on $AUC_{0\text{-}24h}$	Based on C_{max}
Artemether								
Dog 7-day PK	50	p.o.	1	Male	ND [b]	ND [b]	-	-
Study DMPK (F) 1998/014	150	p.o.	1	Male	ND [b]	ND [b]	-	-
	600	p.o.	1	Male	1730	208	1.6	1.1
Dog	600 [c]	p.o.	1	Male	22479	3358	21.0	18.1
Study DMPK R0510009B	300	p.o.	3	Male	602	130	0.6	0.7
Dog	20	i.m.	1	Male	2290	219	2.1	1.2
Study 970024	20	i.m.	7	Male	9340	294	8.7	1.6
	40	i.m.	1	Male	6540	461	6.1	2.5
	40	i.m.	7	Male	18200	825	17.0	4.4
	80	i.m.	1	Male	12700	985	11.9	5.3
	80	i.m.	7	Male	39000	1180	36.4	6.3

Species Study no.	Artemether Dose (mg/kg/day)	Route	Day	Gender	AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)	Exposure multiple [a] (revised) Based on AUC_{0-24h}	Exposure multiple [a] (revised) Based on C_{max}
Dihydroartemisinin								
Dog 7-day PK	50	p.o.	1	Male	ND [b]	ND [b]	-	-
Study DMPK (F) 1998/014	150	p.o.	1	Male	ND [b]	ND [b]	-	-
	600	p.o.	1	Male	6600	795	5.5	3.9
Dog	600 [c]	p.o.	1	Male	13375	2572	11.1	12.5
Study DMPK R0510009B	300	p.o.	3	Male	1389	609	1.1	3.0
Dog	20	i.m.	1	Male	314	40.3	0.3	0.2
Study 970024	20	i.m.	7	Male	307	19.0	0.3	0.1
	40	i.m.	1	Male	370	41.4	0.3	0.2
	40	i.m.	7	Male	335	20.4	0.3	0.1
	80	i.m.	1	Male	937	85.0	0.8	0.4
	80	i.m.	7	Male	456	33.7	0.4	0.2

[a] comparison to human daily dose of 2x80 mg oral dose of artemether (as Coartem); human reference values for AUC and C_{max} of artemether and DHA see text. No human i.m. data is available.

[b] below LOQ of 10 ng/mL.

[c] the dose of artemether was reduced from 600 to 300 mg/kg as of Day 2..

7.4.1.3 Clinical data

7.4.1.3.1 Systematic Neurological Examinations

Systematic neurological examinations were performed at one site only in both studies A025 and A026, in study A2403 and in study B2303.

In studies A025, A026 and 2403, neurological abnormalities, commonly tandem walk and gait abnormal, clonus, nystagmus, tremor, Romberg test positive, were reported in a limited number of patients at baseline ; these symptoms were generally attributed to malaria. Most abnormalities still observed post-baseline were mild and resolved by Day 8. In two patients in Study A2403, neurological abnormalities were still present at Day 28; these were hyperreflexia and/or clonus, and are included in the cases described previously.

Results of neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any post-baseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

7.4.1.3.2 Adverse events

Nervous system disorders

Adults (> 16 years of age)

Adverse events related to nervous system disorders are summarized in Table 7-19. Headache and dizziness were the most frequently reported AEs. The vast majority of these AEs was of mild intensity, transient and resolved spontaneously.

Table 7-19 Nervous system disorders in the adult pooled safety population

	Patients, n (%)		
Preferred term	**4-dose n = 925**	**6-dose n = 647**	**Total Coartem n = 1572**
Headache	675 (75.0)	360 (55.6)	1035 (65.8)
Dizziness	527 (57.0)	253 (39.1)	780 (49.6)
Tremor	23 (2.5)	16 (2.5)	39 (2.5)
Paresthesia	32 (3.5)	0 (0.0)	32 (2.0)
Ataxia	11 (1.2)	3 (0.5)	14 (0.9)
Nystagmus	8 (0.9)	5 (0.8)	13 (0.8)
Clonus	5 (0.5)	16 (2.5)	21 (1.3)
Hypoesthesia	3 (0.3)	4 (0.6)	7 (0.4)
Convulsion	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia	1 (0.1)	0 (0.0)	1 (0.1)
Hypersomnia	1 (0.1)	0 (0.0)	1 (0.1)
Lethargy	1 (0.1)	0 (0.0)	1 (0.1)
Somnolence	1 (0.1)	3 (0.5)	4 (0.3)
Syncope vasovagal	1 (0.1)	0 (0.0)	1 (0.1)
Coma	0 (0.0)	1 (0.2)	1 (0.1)
Fine motor delay	0 (0.0)	2 (0.3)	2 (0.1)
Mental impairment	0 (0.0)	1 (0.2)	1 (0.1)

Headache and dizziness were the most frequently reported AEs. The vast majority of these AEs was of mild intensity, transient and resolved spontaneously.

Pediatric (≤ 16 years of age)

Adverse events related to nervous system disorders are summarized in Table 7-20 and by age group in Table 7-21. Headache and dizziness were the most frequently reported AEs. The vast majority of these AEs was of mild intensity, transient and resolved spontaneously. Most cases of convulsions represented febrile convulsions. A break down of nervous system disorders by age group in the pediatric population receiving the 6-dose regimen showed no clinically relevant differences between age groups. However, any firm conclusion for this analysis is limited by the small number of events. It is important to note that the reporting of adverse events, such as headache and dizziness, that require verbalization, was higher in older children. Convulsions were more frequently reported in younger children which are more proned to febrile convulsions.

Table 7-20 Nervous system disorders in the pediatric pooled safety population

	Patients, n (%)		
Preferred term	**4-dose n = 694**	**Total 6-dose n = 1332**	**Total Coartem n = 2026**
Headache	314 (45.2)	168 (12.6)	482 (23.8)
Dizziness	179 (25.8)	56 (4.2)	235 (11.6)
Hypokinesia	44 (6.3)	0 (0.0)	44 (22)
Lethargy	34 (4.9)	0 (0.0)	34 (1.7)
Speech disorder	33 (4.8)	0 (0.0)	33 (1.6)
Fine motor delay	8 (1.2)	0 (0.0)	8 (0.4)
Clonus	7 (1.0)	11 (0.8)	18 (0.9)
Convulsion	6 (0.9)	4 (0.3)	10 (0.5)
Nystagmus	4 (0.6)	1 (0.1)	5 (0.2)
Paraesthesia	4 (0.6)	0 (0.0)	4 (0.2)
Ataxia	3 (0.4)	1 (0.1)	4 (0.2)
Tremor	3 (0.4)	2 (0.2)	5 (0.2)
Coordination abnormal	2 (0.3)	0 (0.0)	2 (0.1)
Hyperreflexia	2 (0.3)	6 (0.5)	8 (0.4)
Somnolence	2 (0.3)	4 (0.3)	6 (0.3)
Aphasia	1 (0.1)	0 (0.0)	1 (0.0)
Facial palsy	1 (0.1)	0 (0.0)	1 (0.0)
Febrile convulsion	1 (0.1)	0 (0.0)	1 (0.0)
Hypersomnia	1 (0.1)	0 (0.0)	1 (0.0)
Dyskinesia	0 (0.0)	1 (0.1)	1 (0.0)
Epilepsy	0 (0.0)	1 (0.1)	1 (0.0)
Myoclonus	0 (0.0)	3 (0.2)	3 (0.1)

Headache and dizziness were the most frequently reported AEs. The vast majority of these AEs was of mild intensity, transient and resolved spontaneously.

Table 7-21 Nervous system disorders among patients in the pediatric pooled safety population treated with the 6-dose regimen by age group

	Age group (years)			
Preferred term	**≤ 2 n = 587**	**> 2 to ≤ 6 n = 473**	**> 6 to ≤ 12 n = 207**	**> 12 to ≤ 16 n = 65**
Headache	4 (0.7)	46 (9.7)	71 (34.3)	47 (72.3)
Dizziness	1 (0.2)	2 (0.4)	17 (8.2)	36 (55.4)
Clonus	9 (1.5)	1 (0.2)	0 (0.0)	1 (1.5)
Hyperrreflexia	5 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
Convulsion	2 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)
Somnolence	0 (0.0)	3 (0.6)	1 (0.5)	0 (0.0)
Myoclonus	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)
Tremor	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.5)
Ataxia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Dyskinesia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Nystagmus	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)

Ear and labyrinth disorders

Adults (> 16 years of age)

Adverse events related to ear and labyrinth disorders are summarized in Table 7-22. Vertigo, hypoacusis and tinnitus were most commonly reported and all cases were of mild intensity, transient and resolved spontaneously. One patient with the 6-dose regimen reported deafness which was in fact a mild worsening of hearing loss which was present at baseline.

Table 7-22 Ear and labyrinth disorders occurring in the adult pooled safety population

	Patients, n (%)		
Preferred term	**4-dose n = 925**	**6-dose n = 647**	**Total Coartem n = 1572**
Hypoacusis	11 (1.2)	0 (0.0)	11 (0.7)
Tinnitus	3 (0.3)	4 (0.6)	7 (0.4)
Deafness[1]	0 (0.0)	1 (0.2)	1 (0.1)
Middle ear infection	0 (0.0)	1 (0.2)	1 (0.1)
Motion sickness	0 (0.0)	2 (0.3)	2 (0.1)
Vertigo	0 (0.0)	21 (3.2)	21 (1.3)

[1] Patient in Study A2401 reported mild worsening of hearing loss that was present at baseline.

The majority of these AEs was of mild intensity, transient and resolved spontaneously.

Pediatric patients

Adverse events related to ear and labyrinth disorders are summarized in Table 7-23 and by age group in Table 7-24. The most commonly reported ear and labyrinth disoerder was hypoacusis which was observed only with the 4 dose regimen. All cases were mild in severity, and transient.

Table 7-23 Ear and labyrinth disorders occurring in the pediatric pooled safety population

Preferred term	**4-dose n = 694**	**6-dose n = 1332**	**Total Coartem n = 2026**
Hypoacusis	5 (0.7)	0 (0.0)	5 (0.2)
Cerumen impaction	0 (0.0)	1 (0.1)	1 (0.0)
Ear pain	0 (0.0)	3 (0.2)	3 (0.1)
Ear pruritus	0 (0.0)	1 (0.1)	1 (0.0)
Otorrhoea	0 (0.0)	1 (0.1)	1 (0.0)

Table 7-24 Ear and labyrinth disorders in the 6-dose pediatric pooled safety population by age group

	Age group (years)			
Preferred term	**≤ 2 n = 587**	**> 2 to ≤ 6 n = 473**	**> 6 to ≤ 12 n = 207**	**> 12 to ≤ 16 n = 65**
Ear pain	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Cerumen impaction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ear pruritus	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

		Age group (years)		
Otorrhoea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

7.4.1.4 Post marketing information

The search in the Novartis global safety database for all cases including at least one event coding under the MedDRA "Nervous System Disorders" and "Ear and Labyrinth Disorders" Systems Organs Classes (SOCs), and reported cumulatively up to 31 August 2008 retrieved 26 spontaneous reports, and 61 reports of serious adverse events (SAEs) from clinical trials.

No case was reported suggesting impairment of the auditory or vestibular functions, except for one event, vertigo that occurred in a 37-year-old male patient concomitantly with abnormal behavior, euphoric mood, vertigo, dysarthria and an abnormal coordination 2 days after the last Coartem dose. Brain magnetic resonance imaging (MRI) and blood tests were normal.

The most frequently reported neurological events in adult patients were headache, and dizziness. In children, convulsions sometimes qualified as febrile, and all occurring in a context of pyrexia were the most frequently reported events.

Very few cases of gait disturbance were reported (2 in adult and one in a child).

Two cases, which occurred after the treatment was completed, could suggest a post-malaria neurological syndrome (PMNS) which has been described following recovery from severe *P. falciparum* malaria (Nguyen et al 1996 , Zambito et al 2006).

The review of the serious cases does not show any pattern suggesting any safety signal.

7.4.1.5 Additional information on effect of Coartem on auditory function

Study 2412

Study A2412 was conducted specifically to evaluate possible effects of Coartem treatment on the auditory system. This open-label single-center study used audiological measurements, including pure-tone air conduction thresholds and ABR, to evaluate the effects of Coartem, atovaquone-proguanil and MAS on auditory function following the treatment of acute uncomplicated *P falciparum* malaria. Although this was an open-label study, measures were taken to ensure that the audiology technician remained blinded to the treatment the patients were receiving. Adult patients were randomized in a 3:1:1 ratio (Coartem: atovaquone-proguanil: MAS). The study was terminated prematurely for administrative reasons with 87 of the planned 265 patients randomized, which limits the conclusions that can be drawn. However, the analysis rejected the null hypothesis, that the proportion of patients with ABR Wave III latency changes at Day 7 in the Coartem group is $\geq$ 15%, utilizing a level of significance of 5%, as shown by one-sided 95% confidence intervals and p-value (0.042). Four patients in the Coartem group and one patient in the MAS group had post-baseline increases in ABR Wave III and/or V latencies of > 0.3 msec. These changes were not suggestive of drug-related effects, as they tended to be transient and unilateral. Evaluation of drug levels showed no relationship between ABR wave latency increases and artemether, dihydroartemisinin or lumefantrine levels. Due to the small sample size in this study, the result of the premature termination and the large proportion of patients without valid ABR

assessments, this finding needs to be confirmed in a larger study. Novartis is currently performing a very similar study (A2417) to confirm these findings.

Review of the literature

Extensive clinical and pathological studies (Price 2000; Ribiero and Olliario 1998; Kissinger et al 2000; Hien et al 2003) have found no evidence to date of similar lesions observed in animals in human malaria patients.

There have been case reports of neurological problems (including ataxia, nystagmus, tremor and slurred speech), occurring after administration of herbal artemisinin (Panossian et al 2005) or artesunate monotherapy (Miller and Panosian 1997, Franco-Paredes et al 2005), in one case following five 10-day courses of the drug (Franco-Paredes et al 2005), but in each case the attribution of neurotoxicity to artemisinin treatment was questionable (White et al 2006; Davis et al 1997; Newton et al 2005). In 2004, however, the results of an audiometry study of workers at a construction site in Mozambique was published (Toovey and Jameson 2004). This retrospective case-control study found that workers who developed malaria and were treated with Coartem were found to have significantly greater increases in pure-tone thresholds (although the changes were subclinical) than matched control patients who had not had malaria and were not treated with Coartem. The methodology of this study has been criticized, however, (Winstanley and Molyneux 2004; Mehta et al 2004) and the results were not supported by other case-control studies in which evaluation of auditory brainstem responses (ABR) and other audiological measurements were performed in patients exposed to several courses of artemisinin derivatives (Kissinger et al 2000; Van Vugt et al 2000) or in patients treated with Coartem (Hutagalung et al 2006). A study in volunteers with experimental malaria treated with Coartem also found no evidence of drug-related damage to hearing (McCall et al 2006). In a recent sudy perfomed in malaria patients in Ethiopia with the aim of comparing audiotoxicity, tolerability and efficacy of Coartem with that of quinine and atovaquone/proguanil, the evaluation of pure tone audiometry and distortion product otoaccoustic emissions revealed transient significant cochlear hearing loss in patients treated with quinine but not in those treated with Coartem or atovaquone-proguanil. There was no evidence of drug-induced brain stem lesions evaluated by brain stem evoked response audiometry (Gurkov et al 2008).

7.4.2 Cardiac Safety

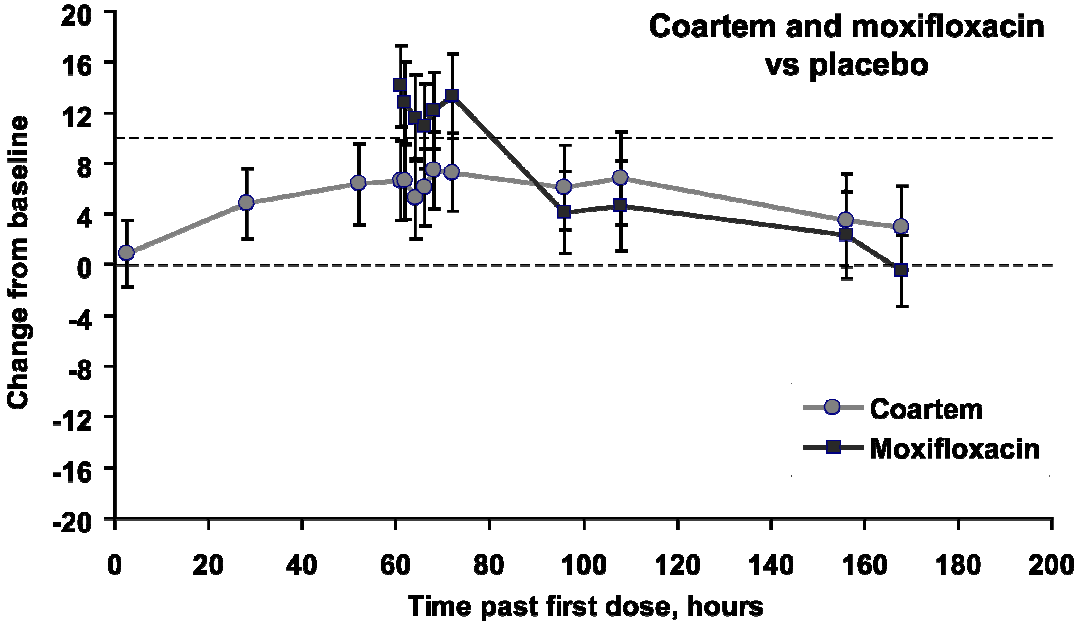
Lumefantrine is chemically related to halofantrine, an antimalarial known to be associated with significant prolongation of the QTc interval. Therefore, particular attention was paid to cardiac safety in the Coartem clinical development program.

Definitive QTc study in healthy volunteers

A definitive, parallel-group, QTc study was performed in healthy volunteers and included both a placebo and a moxifloxacin control group (n = 42 per group). This study showed that the Coartem 6-dose regimen was associated with prolongation of QTc (Fridericia). Following Coartem administration, the mean changes from baseline in QTc(F), relative to placebo, were 7.45, 7.29, 6.12, and 6.84 msec at 68, 72, 96 and 108 hours post-dose (Figure 7-1). At 156 and 168 hours post-dose, the changes from baseline in QTc(F) were not significantly different

from baseline. No subject had a > 30 msec increase from baseline nor an absolute increase to > 500 msec. The moxifloxacin positive control was associated with a maximal QTc(F) increase, relative to placebo, of 14.1 msec at 1 hour post-dose with continued increases for 12 hours post-dose.

Figure 7-1 Mean change from time-averaged baseline in QTc (Fridericia) by timepoint



In addition, there was a formal analysis of the effect of Cmax on the change in QTcF and lumefantrine exposure . This analysis demonstrated that the 95% confidence limits for the mean Cmax of lumefantrine do not cross the upper confidence band of the threshold of relevance for QTc change (10 msec vs placebo).

Malaria Patients

No patient died of cardiovascular causes, and no adverse events related to QTc prolongation, such as torsade de pointe or arrhythmia, have been reported.

Pooled QTc (Fridericia) data from adult, adolescent and pediatric patients enrolled in key studies AB/MO2, A023, A025, A026, A028, A2401, A2403, and B2303 are summarized in Table 7-25. This table shows change from baseline QTc (F) to highest post-baseline value and absolute post-baseline QTc(F).

Table 7-25 Pooled analysis of QTc (Fridericia) for patients enrolled in studies AB/MO2, A023, A025, A026, A028, A2401, A2403, and B2303

	Coartem regimen			
	4-dose N = 225	6-dose N = 1480	Total 6-dose N = 1927	Total N = 2152
QTc (Fridericia) increases between baseline and highest post-baseline value				
n/M (%) patients				
≤0 msec	14/135 (10.4)	215/1270 (16.9)	316/1699 (18.6)	330/1834 (18.0)

	Coartem regimen			
	4-dose N = 225	6-dose N = 1480	Total 6-dose N = 1927	Total N = 2152
>0 - <30 msec	51/135 (37.8)	580/1270 (45.7)	770/1699 (45.3)	821/1834 (44.8)
30 - 60 msec	50/135 (37.0)	333/1270 (26.2)	454/1699 (26.7)	504/1834 (27.5)
>30 msec	63/135 (46.7)	395/1270 (31.1)	522/1699 (30.7)	585/1834 (31.9)
>60 msec	15/135 (11.1)	77/1270 (6.1)	92/1699 (5.4)	107/1834 (5.8)
Baseline missing	5/135 (3.7)	65/1270 (5.1)	67/1699 (3.9)	72/1834 (3.9)
Any post-baseline QTc (Fridericia) prior to or on Day 4:				
>450 msec	11/134 (8.2)	26/1234 (2.1)	27/1663 (1.6)	38/1797 (2.1)
>480 msec	2/134 (1.5)	2/1234 (0.2)	2/1663 (0.1)	4/1797 (0.2)
>500 msec	2/134 (1.5)	0/1234 (0.0)	0/1663 (0.0)	2/1797 (0.1)

This pooled analysis showed that the maximum increase from baseline was < 30 msec in the majority of patients, and very few patients had a post-baseline QTc(F) > 450 msec.

It should be noted that malaria itself and its associated stress and anemia, and recovery from malaria appears to have some effects on cardiac electrophysiology and in particular on lengthening of the QT interval (White 2007). This is also confounded by the fact that QT correction formulae are based on a normal heart rate of 60 beats/minute, and patients with malaria tend to have elevated heart rates that decrease with successful treatment and defervescence. This leads to a trend to overcorrect QT. This is even more pronounced in small children which typically have heart rates well above 60 beats/minute in healthy conditions.

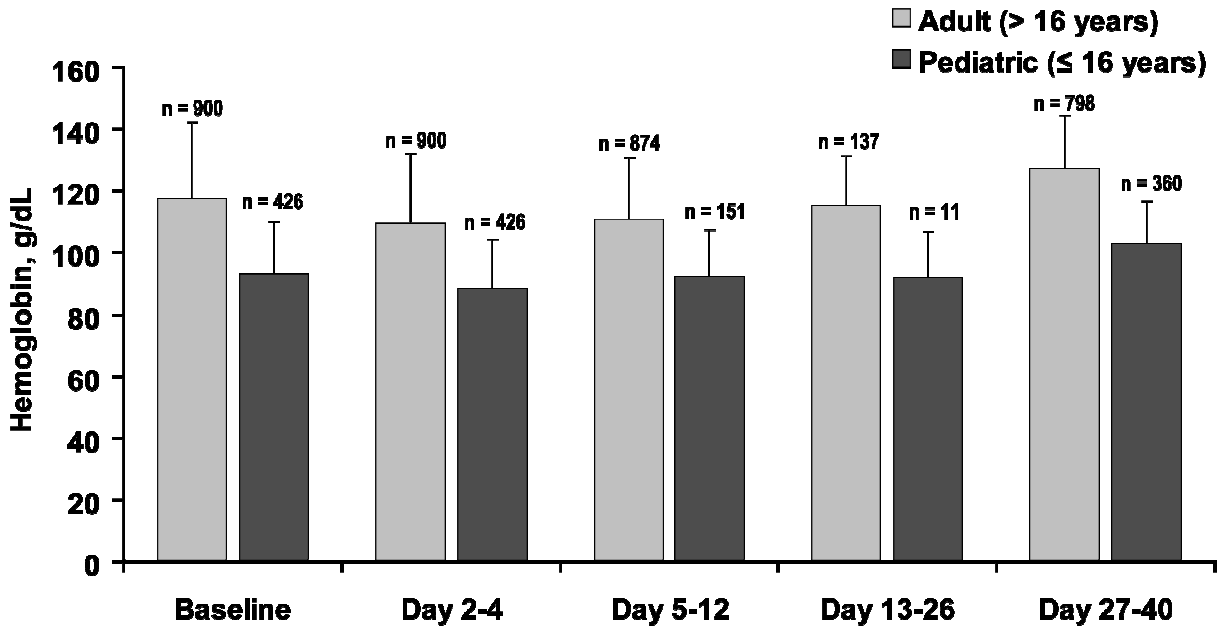
7.4.3 Hematologic Safety

Based on preclinical studies suggesting that repeated exposure to Coartem may affect blood cell counts, particular attention was given to hemoglobin levels and Hematologic AEs.

Hemoglobin

Summary statistics for hemoglobin among all patients treated with Coartem showed small mean decreases from baseline in the earlier time windows followed by small mean increases from baseline at the day 27-40 window (Figure 7-2). The observed changes in hemoglobin (initial decrease followed by an increase) are consistent with successful treatment and resolution of malaria. A similar pattern was observed in both the adult pooled safety population and the pediatric pooled safety population. Most of the comparator antimalarials groups appeared to show similar patterns of changes, but in some cases relatively few patients had assessments.

Figure 7-2 Mean hemoglobin by time window in pooled safety populations



Hematologic and hemolysis-related adverse events

Clinically relevant AEs related to hematology or hemolysis occurring in the adult pooled safety population are shown in Table 7-26. Anemia was the only such AE reported for more than a single patient in any treatment group, and occurred at similar rates in each group. No AEs related to hemolysis were reported in the adult pooled safety population.

Table 7-26 Hematologic and hemolysis-related adverse events of clinical relevance in the adult pooled safety population (>16 years)

Preferred term	Patients, n (%)		
	Coartem 4-dose N = 694	Coartem 6-dose N = 885	Total Coartem N = 2026
Hematology-related AE	35 (3.8)	23 (3.6)	58 (3.7)
Anaemia	34 (3.7)	23 (3.6)	57 (3.6)
Microcytic anaemia	0 (0.0)	1 (0.2)	1 (0.1)
Neutropenia	1 (0.1)	1 (0.2)	2 (0.1)
Thrombocytopenia	0 (0.0)	1 (0.2)	1 (0.1)

Clinically relevant AEs related to hematology or hemolysis occurring in the pediatric pooled safety population are shown in Table 7-27. As in the adult population, anemia was by far the most common AE in this category. The only potentially hemolysis-related AE reported was increased reticulocyte count, observed in four patients treated with the Coartem 6-dose regimen. These patients were all from Study B2303. In three cases the reticulocyte increases were reported as mild, only one case was reported as moderate and all were reported as not related to study drug. None of the patients with reticulocyte increases had severe anemia: hemoglobin levels for these patients at the time the reticulocyte increases were reported were as follows: 79-84 g/L; 85-94 g/L; 71-98 g/L; and 93-103 g/L.

Table 7-27 Hematologic and hemolysis-related adverse events of clinical relevance in the pediatric pooled safety population (≤16 years)

	Patients, n (%)		
Preferred term	**Coartem 4-dose N = 694**	**Coartem 6-dose N = 885**	**Total Coartem N = 2026**
Haemolytic-disorder-related AE	0 (0.0)	3 (0.3)	4 (0.2)
Reticulocyte count increased	0 (0.0)	3 (0.3)	4 (0.2)
Hematology-related AE	145 (20.9)	124 (14.0)	308 (15.2)
Anaemia	145 (20.9)	104 (11.8)	260 (12.8)
Eosinophil count decreased	0 (0.0)	0 (0.0)	1 (0.0)
Haematocrit decreased	0 (0.0)	6 (0.7)	12 (0.6)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	1 (0.0)
Neutropenia	0 (0.0)	2 (0.2)	2 (0.1)
Neutrophil count decreased	0 (0.0)	1 (0.1)	3 (0.1)
Platelet count decreased	0 (0.0)	10 (1.1)	20 (1.0)
Red blood cell count decreased	0 (0.0)	1 (0.1)	2 (0.1)
Reticulocyte count decreased	0 (0.0)	2 (0.2)	3 (0.1)
Thrombocytopenia	0 (0.0)	1 (0.1)	3 (0.1)
White blood cell count decreased	0 (0.0)	2 (0.2)	13 (0.6)

7.5 Ongoing Safety Studies

Two safety studies are ongoing. Study A2417 is exploring the effects of Coartem on the auditory function in patients with malaria; and Study A2407, an observational pregnancy study conducted in Zambia.

Study A2417

Study A2417 is an open-label study similar to Study A2412 (described in Section 7.4.1) that is evaluating the effects of Coartem, atovaquone-proguanil and mefloquine plus artesunate on auditory function following the treatment of acute uncomplicated *P falciparum* malaria based on audiological measurements, including pure-tone air conduction thresholds, tympanometry and ABR Wave III latency, in patients ≥ 8 years of age.

Study A2407

The safety of Coartem in pregnancy is being evaluated in a multicenter, prospective observational study set up in collaboration with the WHO in Zambia. Pregnant women who had used Coartem or SP to treat symptomatic malaria were assigned to exposure groups based on the antimalarial treatment they had received for the treatment of the most recent malaria episode prior to registry entry. Patients were followed up at seven visits to antenatal clinics, mothers were followed up until 6 weeks after birth, babies until 12 months after birth..

The study is still ongoing, but a preliminary report based on outcomes up to 6 weeks after birth has shown no effects of treatment with Coartem on perinatal or neonatal mortality. Rates

of birth defects were low in both exposure groups, and no major malformations, apart from in one patient with a chromosomal abnormality, were reported.

7.6 Summary of Clinical Safety

In summary, based on pooled analyses of data from over 3,500 patients and detailed assessment of specific safety topics of interest in selected studies:

- Coartem treatment appeared to be safe and well-tolerated in diverse patients populations, including children with body weight ≥ 5 kg and from two months of age upwards.
- Many of the observed adverse events were not specific to any organ class and were likely associated with the signs and symptoms of malaria or concomitant infections .
- There were few deaths or serious adverse events. None of the deaths were considered to be related to Coartem treatment. Most serious adverse events were considered not to be related to Coartem treatment.
- The vast majority of adverse events in the nervous system disorder system and ear and labyrinth disorder system was transient and reversible.
- There were no adverse events associated with QTc prolongation.
- There was no evidence of hematologic or hemolytic toxicity as well as no evidence of hepatic or renal toxicity.

There were some differences in the adverse events observed in the adult pooled safety population compared with the pediatric pooled safety population, but these most likely reflect differences in the ability of patients to report symptoms and different types of concomitant medical conditions. In addition, the pediatric population was mainly from studies conducted in Africa, and the adult population was drawn predominantly from studies conducted in Asia and Europe; therefore, differences in AEs between geographic regions resulting, for example, from differing malaria endemicity and different living conditions likely contributed to this observation.

Beside some cases of skin reactions and hypersensitivity, the post marketing experience did not identify any new specific safety concerns. Repeated administration did not seem to be associated with an increased risk of adverse drug reactions, in particular with regards to neurological side effects.

8 Indications and Usage

Coartem is proposed for use in the treatment of malaria in patients of 5 kg bodyweight and above with acute, uncomplicated infections due to *P. falciparum* or mixed infections including *P. falciparum*. The Coartem 6-dose regimen is effective against both drug-sensitive and drug-resistant *P. falciparum* and is recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

9 Overall Benefit/Risk Assessment

Coartem is the first fixed-dose oral artemisinin-based combination therapy (ACT) for acute uncomplicated *Plasmodium falciparum* malaria that was pre-qualified by the World Health Organisation (WHO).

The superiority in efficacy of the combination of artemether and lumefantrine over the individual components has been demonstrated in two studies. Artemether allows for fast fever and parasite clearance, thus ensuring fast recovery from malaria symptoms while lumefantrine provides efficacy sustained in the long term thereby avoiding recrudescence

No formal dose finding studies have been performed, however different dosing regimens have been evaluated, in particular the 4-dose versus the 6-dose regimen. The recommended dose regimen has proved to provide highly effective, safe and well-tolerated treatment in a range of patient populations with similar efficacy different levels of immunity including non immune adults and infants and children.

The efficacy of recommended 6-dose regimen of Coartem has been demonstrated in clinical studies performed and reported by the sponsor, and in a large number of trials performed by third parties and published in the scientific literature, to be highly effective in the treatment of acute uncomplicated *Plasmodium falciparum* malaria, and mixed infections including *P. falciparum*, in adults, adolescents, children and infants in a wide range of endemic countries and in residents of non-malarial areas who acquire the infection when traveling in endemic regions. Across the development program, efficacy has been established in a range of patient populations with varying degrees of expected immunity based on age and local endemicity of malaria at the trial sites. The 28-day PCR-corrected parasitological cure rates with the 6-dose regimen in the evaluable population of Coartem in clinical studies were consistently 95% or higher.

The clinical development program for Coartem was largely in line with the 2007 FDA draft guidance on development of antimalarials, even though most of the program was performed long before the guidelines were issued.

No clinical resistance has been seen to date. The combination of antimalarials used in Coartem should limit the development of resistance, and providing a fixed combination in a single tablet that is easy and convenient for patients to take should help to ensure compliance to treatment (which in turn should help limit the development of resistance) as well as ensuring optimal efficacy.

Coartem is included in the UK and French treatment guidelines (Lalloo et al 2007, Société de Pathologie Infectieuse de Langue Française 2007) for imported uncomplicated *Plasmodium falciparum* malaria in adults and children.

Coartem appears to be safe and well-tolerated on the basis of data from clinical trials (in which over 3500 patients received Coartem, including almost 2000 treated with the 6-dose regimen), extensive post-marketing experience and including repeated administration.

An infection that if not treated effectively can rapidly progress into a severe and often fatal form, *Plasmodium falciparum* malaria is one the world's most important health issues, and one which is not confined to endemic countries. In the USA, malaria is primarily a problem for travelers to endemic areas. With increasing international travel, the numbers of patients

with malaria returning to the United States from endemic countries is set to increase, particularly as increasing drug resistance in *P. falciparum* makes effective chemoprophylaxis more difficult.

No artemisinin based combination therapy is currently registered in the United States despite a clear therapeutic benefit and the fact that it is recommended by the WHO (Magill and Panosian 2005). Only one oral fixed combination therapy is available in the United States, and resistance to this therapy has been described recently. This therapy is also recommended for prophylaxis. It would therefore prove worthwhile to have an alternative treatment available.

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Appendix

Appendix Table 1 Summary of pharmacokinetic studies in healthy volunteers and studies with PK component in malaria patients

Study No.	Region/Year/Design/ Objective/Population	No. of Subjects[1]	Treatment Duration	Medication dose
Healthy volunteers				
A006	Switzerland/1994-95/ Open-label, 2-period, crossover (fasted)/ Comparison of two oral formulations/Males (Caucasian)	12	Single dose (80/480 mg)	Coartem 4 tablets
A020	China/1995-96/Open-label, 2-period crossover/Food interaction study (fed vs fasted)/Males (Chinese)	16	Single dose (80/480 mg)	Coartem 4 tablets
A022	Switzerland/1996/Single dose Open, pilot, parallel group (fed)/Evaluation of cardiac (QTc) effects/Males	6	Single dose (80/480 mg)	Coartem 4 tablets
A024	Switzerland/1996/Double-blind, double-dummy, 2-period, crossover (fed)/Evaluation of cardiac (QTc) effects/Males (Caucasian)	14	Single dose (80/480 mg)	Coartem 4 tablets
A027	Germany/1998/Double-blind, parallel-group (fed)/Drug-drug interaction study with mefloquine/Males (Caucasian)	42	6-dose regimen over 3 days	Coartem 6x4 tablets
A2301	Northern Ireland/2001/ Open-label, 2-period, crossover (fed)/Drug-drug interaction study with ketoconazole/Males and females (Caucasian)	16	Single dose (80/480 mg)	Coartem 4 tablets
A2302	UK/2000/Double-blind, parallel-group (fed)/Drug-drug interaction study with quinine/Males (Caucasian)	42	6-dose regimen over 3 days	Coartem 6x4 tablets
B2102	Germany/2004/ Open-label, 2-period, crossover (fed)/Relative bioavailability of standard tablet vs powder-in-bottle/Males and females (Caucasian)	48	Single dose (80/480 mg)	Coartem 4 tablets/ Coartem powder-in-bottle for suspension
B2104	France/2005-06/Open-label, 3-period, 2-sequence, crossover (fed)/BAV study of dispersible tablet for suspension vs standard intact and crushed tablet/Males and females (Caucasian)	48	Single dose (80/480 mg)	Coartem 4 tablets, intact, crushed and dispersible
A2101	France/2005-06/6-dose regimen/Single-blind, parallel group (fed)/Thorough evaluation of cardiac (QTc) effects/Males and females (Caucasian)	126	Coartem 6-dose regimen over 3 days	Coartem 6x4 tablets
Malaria patients				
AB/MO1	China/1993/Open-label, non-comparative confirmatory efficacy/safety trial/Males and females	102 (24)	4-dose regimen over 2 days	Coartem 4x4 tablets
AB/MO2	China/1994/Double-blind, randomized (1/1), parallel group comparative efficacy-safety trial of Coartem vs its individual components artemether and lumefantrine	157 (36)	4-dose regimen over 2 days vs monotherapies	Coartem 4x4 tablets
A004	Thailand/1995-96/Double-blind, randomized (1/1), parallel group comparative efficacy/safety trial of Coartem vs mefloquine	252 (126)	4-dose regimen over 2 days	Coartem 4x4 tablets

Study No.	Region/Year/Design/ Objective/Population	No. of Subjects[1]	Treatment Duration	Medication dose
	(only one PK sample was taken at 56 h post first dose)/Males and females			
A012	Thailand/1995/Double-blind, randomized (1/1), parallel group comparative efficacy/safety trial of 3 dose-regimens of Coartem (dose optimization study)/Males and females	260 (42)	4-dose regimen (4x4 tablets) vs 4x2 and 3x4 tablets regimens	Coartem 4x4, 4x2 and 3x4 tablets
A014	Europe/1996-97/Double-blind, randomized (1/1), parallel group comparative efficacy/safety trial of Coartem vs halofantrine/Males and females	103 (56)	4-dose regimen over 2 days	Coartem 4x4 tablets
A023	China/1996/Double-blind, randomized (1/1) comparative efficacy/safety trial of Coartem vs lumefantrine alone (powder and capsule)/Males and females	153 (37)	4-dose regimen (4x4 tablets) over 2 days vs lumefantrine alone	Coartem 4x4 tablets Lumefantrine 4x4 tablets
A025	Thailand/1996-97/Double-blind, randomized (1/1), parallel group comparative efficacy/safety trial of 3 dose regimens of Coartem/Adults males and females	359 (52)	4-dose regimen (4x4 tablets) over 2 days, and 6-dose regimen over 3 or 5 days	Coartem 4x4 and 6x4 tablets
A026	Thailand/1997-98/ Open-label, randomized (3/1), parallel group confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine-artesunate/Adults and children (n = 34, 2-12 yrs) males and females	200 (148)	6-dose regimen over 3 days	Coartem 6x4 tablets
A028	Thailand/1998-99/Open-label, randomized (3/1), parallel group confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine-artesunate/Adults males and females	219 (25)	6-dose regimen over 3 days	Coartem 6x4 tablets
A2401	Europe, Colombia/2001-05/Open-label, non-comparative efficacy/safety trial in non-immune patients/Adults males and females	165 (15)	6-dose regimen over 3 days	Coartem 6x4 tablets
A2403	Africa/2002-03/Open-label, non-comparative efficacy/safety trial in children (5-25 kg bodyweight)/Children males and females	310 (181)	6-dose regimen over 3 days	Coartem 6x4 tablets
B2303	Africa/2006-07/ Investigator-blind, randomized, parallel group efficacy/safety trial in infants and children (5-35 kg bodyweight)/ Children males and females	899 (625)	6-dose regimen over 3 days crushed tablet vs. dispersible tablet	Coartem 6x4 tablets

[1] Total number of subjects enrolled, with number of PK subjects in brackets when different from total