

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-268

MEDICAL REVIEW(S)

REVIEW OF REQUEST FOR PRIORITY REVIEW

To: Edward Cox, MD, MPH
Director, Office of Antimicrobial Products

Through: Renata Albrecht, M.D
Director, DSPTP, OAP

From: Joette M. Meyer, Pharm.D.
Acting Medical Team Leader, DSPTP, OAP

NDA: 22-268

Submission Date: 6/27/08

Date Review Completed 7/25/08

Product: Coartem (artemether/lumefantrine)

Sponsor: Novartis Pharmaceuticals Corporation
East Hanover, NJ

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

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

Abbreviations

A	artemether
ACT	artemisinin-based combination therapy
AL	artemether-lumefantrine combination
AQ	amodiaquine
AS	artesunate
AS+AQ	artesunate + amodiaquine combination
AS+MQ	artesunate + mefloquine combination
AS+SP	artesunate + sulfadoxine-pyrimethamine combination
L	lumefantrine
MAS	mefloquine artesunate combination
MQ	mefloquine
SP	sulfadoxine-pyrimethamine
RCT	randomized controlled trial
WHO	World Health Organization

WHO Levels of Evidence for Treatment Guidelines

S	formal systematic reviews, such as a Cochrane Review, including more than one randomized controlled trial;
T	comparative trials without formal systematic review;
O	observational studies (e.g. surveillance or pharmacological data);
E	expert opinion/consensus.

Coartem® (co-artemether; artemether-lumefantrine; also marketed as Riamet® mainly in countries where malaria is not endemic), is a combination of 20 mg artemether (an artemisinin derivative) and 120 mg lumefantrine (a racemic mixture of a synthetic racemic fluorine derivative formerly known as benflumetol). Co-artemether acts as a blood schizonticide and its components show complementary pharmacokinetics and have dissimilar modes of action providing synergistic activity against *Plasmodium falciparum*.

Coartem is registered and available in over 80 countries world wide to treat malaria.

The NDA is for registration of the 6-dose regimen of co-artemether in the treatment of acute uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

The sponsor was granted Fast Track status on January 14, 2008 and began submission of their rolling review in November 2007. On June 19, 2008 the applicant submitted a request for a Priority Review. This stated, in part:

For a number of reasons, Coartem will be an important addition to the few medications available in the US to treat malaria. No new treatment for malaria has been approved in the US since 2000. Coartem provides a significant improvement in terms of lack of resistance and patient compliance, has an acceptable safety profile and is a highly effective treatment for a life-threatening parasitological disease. Novartis concurs with your statements cited above [FDA letter granting Fast Track designation] that Coartem will fill an unmet medical need for patients who do not respond to or who may not tolerate other available antimalarials, or who have an infection with P. falciparum that is resistant to other treatments. For these reasons, Novartis requests that the Agency assign Priority Review to the Coartem NDA 22-268."

On July 2, 2008 the division requested further clarification from the applicant:

We note in your request for NDA Priority review that you state "Coartem provides a significant improvement in the treatment of life-threatening malaria in terms of lack of resistance and patient compliance, is highly effective, and has an acceptable safety profile. "Coartem meets an unmet medical need for patients unresponsive to or intolerant of other antimalarials."

According to the CDER Manual of Policies and Procedures (MaPP) Review Classification Policy: Priority (P) and Standard (S) [6020.3], a determination for Priority review should be based on whether the drug product provides safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement compared to marketed products in treating, preventing, or diagnosing disease.

In order to aid in our determination of the designation of Coartem, please provide additional information to address your assertion that Coartem provides a significant improvement compared to marketed products. Significant improvement can be interpreted to mean:

1. *Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease*
2. *Elimination or substantial reduction of a treatment-limiting drug reaction*
3. *Documented enhancement of patient compliance*
4. *Evidence of safety and effectiveness in a new subpopulation.*

Evidence to support your justification can come from clinical trials comparing a marketed product(s) with Coartem or from other scientifically valid information.

On July 17, 2008 the applicant submitted additional information, as requested. The updated request focuses on three points:

1. *Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease*

The applicant states:

Coartem provides significant improvement over marketed products for malaria in that the product is an artemisinin-based combination therapy (ACT), the first to be available in the US, and it shows no resistance to date (Guidelines for the treatment of malaria, WHO, 2006 - Annex 6, Resistance to Antimalarials). This significant improvement is underscored by the World Health Organization's (WHO) prequalification of Coartem in 2004. To date, one ACT – (Coartem®) – has been pre-qualified.

(http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm#n)

The applicant cites the following supporting data:

- Guidelines for the Treatment of Malaria, WHO, 2006
- World Health Organization's (WHO) prequalification of Coartem in 2004.
(http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm#n3)

The WHO Guidelines recommend ACTs as the “best current treatment for uncomplicated falciparum malaria.”

In addition:

Artemisinin and its derivatives (artesunate, artemether, artemotil, dihydroartemisinin) produce rapid clearance of parasitaemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10 000 in each asexual cycle, which is more than other current antimalarials (which reduce parasite numbers 100- to 1000-fold per cycle). Artemisinin and its derivatives are eliminated rapidly. When given in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment with an artemisinin compound is required; but when given in combination with slowly eliminated antimalarials, shorter courses of treatment (3 days) are effective. The evidence of their superiority in comparison to monotherapies has been clearly documented.

Reviewer's Comment: WHO Guidelines cite the superiority of combining oral AS with oral AQ, MQ, or SP vs. oral AS alone based on a meta-analysis. No trial included for A vs. AL is discussed (Annex 7.1). However, in the NDA, Study ABMO2 compares A (46%) vs. 4-dose regimen of AL (94%); $p < 0.001$

WHO document goes on to state:

EVIDENCE: trials comparing ACTs^a

Interventions: oral AL, AS+AQ, AS+MQ, AS+SP

Summary of RCTs: AL 6-dose regimen compared with 4-dose regimen; 6 doses resulted in higher cure rate in 1 trial in Thailand (RR: 0.19; 95% CI: 0.06–0.62).

AS+MQ compared with AL 6-dose regimen; systematic review including 2 small RCTs from Thailand. Higher proportion of patients with parasitaemia at day 28 with AL but difference not statistically significant. One additional RCT in Lao People's Democratic Republic also reported higher proportions of patients with parasitaemia at day 42 with AL but also not statistically significant.

AS+AQ compared with AL 6-dose regimen; 1 trial in Tanzania found a significantly higher proportion of parasitological failures on day 28 with AS+AQ.

No trials of AL compared with AS+SP.

Expert comment: the efficacy of ACTs with AQ or SP as partner medicines is insufficient where cure rates with these medicines as monotherapies is less than 80%. The efficacy of AL and AS+MQ generally exceeds 90% except at the Thai-Cambodian border, where AL failure rate was 15%.

Basis of decision: expert opinion.

Recommendations

1. Use the following ACTs: AL (6-dose regimen), AS+AQ, AS+MQ, AS+SP.
2. In areas with AQ and SP resistance exceeding 20% (PCR-corrected at day 28 of follow-up), use AS+MQ or AL.

Reviewer's Comment: The trial discussed in the table above of AL 6-dose vs. 4-dose regimen in which 6-doses resulted in higher cure rate in one trial in Thailand is Study A025 in the NDA submission.

AS+ MQ compared to AL in Thailand submitted as Studies A026 and A028 in the NDA.

Study 026: 97% for AL vs. 100% for AS + MQ at 28 days

Study 028: 95.5% for AL vs. 100% for AS + MQ at 28 days

There are insufficient data on the efficacy of AS + MQ to support a non-inferiority margin. WHO bases support of AS + MQ as first line therapy on these two trials. No other data available.

AS+AQ vs. AL in Tanzania – RCT with a 14-day follow-up period; 295 children < 5 years of age Burundi 2001-2002. Clinical and parasitological response at Day 14:

99% [95% CI 98%, 100%] for AL vs. 95% [95% CI 92%, 99%] for AS + AQ; p value not reported.

Reference:

Ndayiragije A et al. Efficacité de combinaisons thérapeutiques avec les dérivés de l'artémisinine dans le traitement de l'accès palustre non-complicé au Burundi. [Efficacy of therapeutic combinations with artemisinin derivatives in the treatment of non complicated malaria in Burundi.] *Tropical Medicine and International Health*, 2004, 9:673–679.

Summary of WHO recommendations on treatment of uncomplicated falciparum malaria:

RECOMMENDATIONS	LEVEL OF EVIDENCE
The treatment of choice for uncomplicated falciparum malaria is a combination of two or more antimalarials with different mechanisms of action.	S, T, O
ACTs are the recommended treatments for uncomplicated falciparum malaria.	S
The following ACTs are currently recommended: – artemether-lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine.	S, T, O
The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination: – in areas of multidrug resistance (South-East Asia), artesunate + mefloquine or artemether-lumefantrine – in Africa, artemether-lumefantrine, artesunate + amodiaquine; artesunate + sulfadoxine-pyrimethamine.	E S
The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.	S
Artemether-lumefantrine should be used with a 6-dose regimen.	T, E
Amodiaquine + sulfadoxine-pyrimethamine may be considered as an interim option in situations where ACTs cannot be made available.	E

ACTS are also recommended as first-line treatment for infants and young children [Level of Evidence T, O, and E] and AL is specifically recommended for use in travelers returning to non-endemic countries (along with Malarone and quinine + doxycycline or clindamycin) [Level of Evidence O and E].

(b) (4)



WHO document discusses practical aspects with artemether-lumefantrine treatment:

An advantage of this combination is that lumefantrine is not available as a monotherapy and has never been used by itself for the treatment of malaria. Recent evidence indicates that the therapeutic response and safety profile in young children of less than 10 kg is similar to that in older children, and artemether-lumefantrine is now recommended for patients ≥ 5 kg. Lumefantrine absorption is enhanced by co-administration with fat. Low blood levels, with resultant treatment failure, could potentially result from inadequate fat intake, and so it is essential that patients or carers are informed of the need to take this ACT with milk or fat-containing food – particularly on the second and third days of treatment.

WHO Facts on ACTs – January 2006 update

http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm#n

Since 2001, a total of 56 countries have adopted one of the WHO recommended artemisinin-based combination therapies, several as first-line treatment and a few as second-line (see table below, last updated on 1st November 2005).

Appears This Way On Original

Continent	Countries	Options	Line
AFRICA	Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Ghana, Guinea, Liberia, Madagascar, Senegal, Sao Tome and Principe, Sierra Leone, Sudan (S), Zanzibar	AS + AQ	1st
	Angola, Benin, Burkina Faso, Comoros, Ethiopia, Gambia, Guinea Bissau, Kenya, Mali, Namibia, Niger, Nigeria, Rwanda, Uganda, South Africa (Kwa Zulu Natal), Tanzania, Togo, Zambia	AL	1st
	Côte d'Ivoire, Gabon, Mozambique, Sudan (N), Sao Tome and Principe, Zanzibar	AL	2nd
	Mozambique, Sudan (N), South Africa (Mpumalanga)	AS + SP	1st
ASIA	Cambodia, Thailand	AS + MQ	1st
	Bangladesh, Bhutan, Laos, Myanmar	AL	1st
	Indonesia	AS + AQ	1st
	Afghanistan, India (5 Provinces), Iran, Tajikistan, Yemen	AS + SP	1st
	Viet Nam	DP	1st
	Papua New Guinea	AS + SP	2nd
	Philippines, Iran	AL	2nd
SOUTH AMERICA	Ecuador, Peru	AS + SP	1st
	Bolivia, Peru, Venezuela	AS + MQ	1st
	Brazil, Guyana, Suriname	AL	1s

AS+AQ = artesunate+amodiaquine; AS+SP = artesunate+sulfadoxine/pyrimethamine;
AS+MQ = artesunate+mefloquine; AL = artemether/lumefantrine; DP = dihydroartemisinin/piperaquine

2. Evidence of safety and effectiveness in a new subpopulation.

- Resistance to Malarone® has been detected

Reports of resistance even to atovaquone-proguanil (Malarone®) have been published in recent years for malaria acquired in Africa as well as in South America. A total of 12 published cases of resistance to atovaquone-proguanil have been summarized by 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. In 7 out of 12 cases, isolates with genetically confirmed markers of resistance, notably mutations in the cytochrome b gene have been identified.

Reviewer's Comment: Malarone was not used as the comparator in any of the clinical trials that were included in the application.
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WHO Guidelines do not recommend Malarone as first line treatment. “Atovaquone-proguanil has been shown to be safe and effective as a combination partner in one large study, but is not included in these recommendations for deployment in endemic areas because of its very high cost.”

The WHO’s recommendations for second-line treatment of uncomplicated falciparum malaria, do include ACTs:

On the basis of the evidence from current practice and the consensus opinion of the Guidelines Development Group, the following second-line treatments are recommended, in order of preference:

- *alternative ACT known to be effective in the region,*
- *artesunate + tetracycline or doxycycline or clindamycin,*
- *quinine + tetracycline or doxycycline or clindamycin.*

The alternative ACT has the advantages of simplicity, and where available, coformulation to improve adherence. The 7-day quinine regimes are not well tolerated and adherence is likely to be poor if treatment is not observed.

[Level of Evidence O for all three alternative regimens]

The applicant cited the following supportive data:

- **Boggild 2007¹**

The authors state:

*Outside of treatment trials, reports of AP treatment failure are rare. As of July 2005, there have been 12 published cases of AP failure for the treatment of *P. falciparum* malaria,³⁴⁻⁴¹ only 7 of which have had isolates with genetically confirmed markers of resistance, notably mutations in the cytochrome *b* gene (Table 3). A small number of reported failures have been reported with parasites possessing wild-type cytochrome *b*; however, to date, these cases have been less definitive, for example, not all of these cases ensured directly observed therapy, adequate drug levels, and none of these isolates has been cultured to confirm resistance in vitro. Alternative molecular mechanisms of resistance other than mutations in cytochrome *b* have yet to be defined. Seven cases of AP treatment failure have been documented 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 (Table 3).*

Reviewer’s Comment: Table 3 from Reference #1 has adapted by the Reviewer to include salvage treatment and 2 additional cases from Reference #9. Applicant cites

¹ Boggild AK, Parise ME, Lewis LS, et al. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). *Am J Trop Med Hyg* 2007;76(2):208-23.

References Schwarz et al 2003 (#3), Kuhn et al 2005 (#15), and Legrand et al 2007 (#16) in their request. Other references obtained by the Reviewer.

Patient age, sex	Immune status	Atovaquone/proguanil Treatment dose, duration	Country of acquisition	Molecular marker of resistance	Salvage Treatment
45, M ²	Semi-immune	Four adult tabs daily, 3 days	Nigeria	Cyt b Tyr268Asn	Oral quinine (600 mg TID) x 3 days and doxycycline (100 mg BID) x 7 days
24, F ³	Non-immune traveler	Four adult tabs daily, 3 days	Kenya	Cyt b Tyr268Ser	Oral quinine (600 mg TID) x 3 days and doxycycline (100 mg BID) x 7 days
28, M ⁴	Non-immune traveler	Four adult tabs daily, 3 days	Mali	Cyt b Tyr268Ser	Riamet [®] (lumefantrine and artemether).
28, M ⁵	Non-immune traveler	Four adult tabs daily, 3 days	Cameroon	Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108	Mefloquine 1500 mg over 2 days
1.5, M ⁶	Non-immune traveler	One adult tab daily, 3 days	Ivory Coast	Wt cyt b and DHFR	Mefloquine
4, M ⁷	Non-immune traveler	One adult tab daily, 3 days	Ivory Coast	Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108	Mefloquine
Adult, F ⁸	Semi-immune	Four adult tabs daily, 3 days	Ivory Coast	Cyt b Tyr268Ser	Atovaquone and proguanil
38, F ⁹	Semi-immune	Four adult tabs daily, 3 days	Democratic	Wt cyt b	6-dose regime of

² Fivelman QL, Butcher GA, Adagu IS, Warhurst D, Pasvol G, 2002. Malarone treatment failure and *in vitro* confirmation of resistance of *Plasmodium falciparum* isolate from Lagos, Nigeria. *Malaria J* 1: 1–4.

³ Schwartz E, Bujanover S, Kain KC, 2003. Genetic confirmation of atovaquone-proguanil resistant *Plasmodium falciparum* malaria acquired by a nonimmune traveler to East Africa. *Clin Infect Dis* 37: 450–451.

⁴ Schwobel B, Alifrangis M, Salanti A, Jelinek T, 2003. Different mutation patterns of atovaquone resistance to *Plasmodium falciparum* *in vitro* and *in vivo*: Rapid detection of codon 268 polymorphisms in the cytochrome b as a potential *in vivo* resistance marker. *Malaria J* 2: 5–11.

⁵ David KP, Alifrangis M, Salanti A, Vestergaard LS, Ronn A, Bygbjerg IB, 2003. Atovaquone/proguanil resistance in Africa: A case report. *Scand J Infect Dis* 35: 898–899.

⁶ Farnert A, Lindberg J, Gil P, Swedberg G, Berqvist Y, Thapar M, Lindegardh N, Berezcky S, Bjorkman A, 2003. Evidence of *Plasmodium falciparum* malaria resistant to atovaquone and proguanil hydrochloride: case reports. *BMJ* 326: 628–629.

⁷ Ibid #5

⁸ Ibid #5

⁹ Wichmann O, Muehlen M, Gruss H, Mockenhaupt FP, Suttorp N, Jelinek T, 2004. Malarone treatment failure not associated with previously described mutations in the cytochrome b gene. *Malaria J* 3: 14–16.

Patient age, sex	Immune status	Atovaquone/proguanil Treatment dose, duration	Country of acquisition	Molecular marker of resistance	Salvage Treatment
			Republic of Congo		co-artemether (20 mg artemether and 120 mg lumefantrine)
30, M ¹⁰	Semi-immune	Four adult tabs daily, 3 days	Gambia	Wt cyt b	Mefloquine
28, M ¹¹	Non-immune traveler	“adequate doses”	Mali	Cyt b Tyr268Ser	Coartemether (artemether and lumefantrine)
33, M ¹²	Non-immune traveler	Four adult tabs daily, 3 days	Kenya, Tanzania	Wt cyt b	Coartemether (artemether and lumefantrine)
56, M ¹³	Semi-immune	Four adult tabs daily, 3 days	Nigeria	Wt cyt b	Coartemether (artemether and lumefantrine)
38, F ¹⁴	Semi-immune	“standard treatment course”	Kinshasa	Not done MIC above therapeutic (17.2 µg/ml)	Artemisinin-based combination (not coartemether)
25, F ¹⁵	Non-immune traveler	Two adult tabs twice a day, 3 days	Sierra Leone	Cyt b Tyr268Ser DHFR C59R, S108N	Oral quinine (600 mg TID) and doxycycline (100 mg BID) x 7 days

Reviewer’s Comment: In summary, patients with resistance were treated with Coartem (N=5) or available medications, such as quinine and doxycycline (N=3) or mefloquine (N=3). And all responded to salvage therapy.

One additional case was reported in South America by Legrand et al.¹⁶

A nonimmune P. falciparum patient was infected during a 5-day visit without prophylaxis in Maripasoula, a region of malaria endemicity, and while residing in a malaria-free area, the patient experienced three malaria episodes on day 0 (treated with halofantrine [Halfan]), day 25 (treated with atovaquone-proguanil), and day 49 (treated with quinine-doxycycline). All treatments were well tolerated. Plasma atovaquone concentration,

¹⁰ Wichmann O, Muehlberger N, Jelinek T, et al. 2004. Screening for mutations related to atovaquone/proguanil resistance in treatment failures and other imported isolates of *Plasmodium falciparum* in Europe. *J Infect Dis* 190: 1541– 1546.

¹¹ Ibid #9

¹² Ibid #9

¹³ Ibid #9

¹⁴ Ibid #9

¹⁵ Kuhn S, Gill MJ, Kain KC, 2005. Emergence of atovaquone-proguanil resistance during treatment of *Plasmodium falciparum* malaria acquired by a non-immune North American traveler to West Africa. *Am J Trop Med Hyg* 72: 407– 409.

¹⁶ Legrand E, Demar M, Volney, et al. First case of emergence of atovaquone resistance in *Plasmodium falciparum* during second-line atovaquone-proguanil treatment in South America. *Antimicrob Agent Chemother* 2007;51:2280-81.

measured 1 day after atovaquone-proguanil administration, was 1.45 µg/ml, indicating adequate drug absorption.

... The day 49 parasites presented elevated IC50 levels for atovaquone and a 268S mutant Cyt b, a mutation consistently associated with in vitro resistance to atovaquone and therapeutic failures...The resistance mutation was undetected in both pretreatment samples, indicating the emergence of resistant parasites during the course of the atovaquone-proguanil treatment.

Reviewer's Comment: Patient responded to salvage treatment with quinine-doxycycline.

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The applicant states:

The recommended 6-dose regimen of co-artemether has been demonstrated in clinical studies performed and reported by Novartis and in 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. Currently available malaria treatments are not approved for use in mixed plasmodium infections.

Supporting Data cited by applicant:

- **NDA Studies – Clinical Overview**

Reviewer's Comment: Overview section of NDA does not discuss results for mixed infections separately. Only by reading individual study summaries can the numbers be determined. The study reports also are often vague in reporting results of the mixed infections. See table created by Reviewer from NDA data below.

Study #	Design	Number/Type of Infection Mixed with falciparum in Coartem arm	Outcome
A025	6 dose regimen vs. 4 dose regimen	20 with mixed, including vivax (8 patients ≤ 12 years of age)	All cleared vivax within 48 hours; 9/20 patients had recrudescence of vivax during trial (6 on or before Day 28 and 3 between Days 28 and Day 42)
A026	6 dose vs. mefloquine/artesunate	5 with mixed, including vivax (all > 12 years of age)	All cleared by 24 hrs; 2/5 had recrudescence of vivax (Day 29 and Day 49)

A028	6 dose vs. mefloquine/artesunate	16 with mixed, including vivax	All cleared within 48 hours; 3/16 had recrudescence of vivax
B2303	Tablet vs. dispersible tablet in infants and children	6 with mixed (5-9 years): 3 ovale, 2 malariae, and 1 unidentified	All cleared by Day 2; 0/6 recrudescence
A2401	6 dose non-comparative in non-immune	8 mixed – 6 with malariae and 2 with vivax	All cleared by 48 hours; 1/6 with malariae had recrudescence on Day 28; 0/2 with vivax relapsed

- **Ratcliff et al 2007¹⁷**

Summary

Background: The burden of Plasmodium vivax infections has been underappreciated, especially in southeast Asia where chloroquine resistant strains have emerged. Our aim was to compare the safety and efficacy of dihydroartemisinin-piperaquine with that of artemether-lumefantrine in patients with uncomplicated malaria caused by multidrug-resistant P. falciparum and P. vivax.

Methods: 774 patients in southern Papua, Indonesia, with slide-confirmed malaria were randomly assigned to receive either artemether-lumefantrine or dihydroartemisinin-piperaquine and followed up for at least 42 days. The primary endpoint was the overall cumulative risk of parasitological failure at day 42 with a modified intention-to-treat analysis.

Findings: Of the 754 evaluable patients enrolled, 466 had infections with P. falciparum, 175 with P. vivax, and 113 with a mixture of both species. The overall risk of failure at day 42 was 43% (95% CI 38–48) for artemether-lumefantrine and 19% (14–23) for dihydroartemisinin-piperaquine (hazard ratio=3.0, 95% CI 2.2–4.1, p<0.0001). After correcting for reinfections, the risk of recrudescence of P. falciparum was 4.4% (2.6–6.2) with no difference between regimens. Recurrence of vivax occurred in 38% (33–44) of patients given artemether-lumefantrine compared with 10% (6.9–14.0) given dihydroartemisinin-piperaquine (p<0.0001). At the end of the study, patients receiving dihydroartemisinin-piperaquine were 2.0 times (1.2–3.6) less likely to be anaemic and 6.6 times (2.8–16) less likely to carry vivax gametocytes than were those given artemether-lumefantrine.

Interpretation: Both dihydroartemisinin-piperaquine and artemether-lumefantrine were safe and effective for the treatment of multidrug-resistant uncomplicated malaria. However, dihydroartemisinin-piperaquine provided greater post-treatment prophylaxis than did artemether-lumefantrine, reducing P. falciparum reinfections and P. vivax recurrences, the clinical public-health importance of which should not be ignored.

¹⁷ Ratcliff A, Siswantoro H, Kenangalem E, Maristela, R, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. Lancet 2007;369:757-65.

Reviewer's Comment: Mixed infections (vivax and falciparum) at baseline in 56/375 in the artemether-lumefantrine arm. Outcome was not reported separately for those with mixed infections at baseline.

- **Krudsood et al, 2007¹⁸**

Abstract: Chloroquine remains the drug of choice for the treatment of vivax malaria in Thailand. Mixed infections of falciparum and vivax malaria are also common in South-East Asia. Laboratory confirmation of malaria species is not generally available. This study aimed to find alternative regimens for treating both malaria species by using falciparum antimalarial drugs. From June 2004 to May 2005, 98 patients with *Plasmodium vivax* were randomly treated with either artemether-lumefantrine (n = 47) or chloroquine (n = 51). Both treatments were followed by 15 mg of primaquine over 14 days. Adverse events and clinical and parasitological outcomes were recorded and revealed similar in both groups. The cure rate was 97.4% for the artemether-lumefantrine treated group and 100% for the chloroquine treated group. We concluded that the combination of artemether-lumefantrine and primaquine was well tolerated, as effective as chloroquine and primaquine, and can be an alternative regimen for treatment of vivax malaria especially in the event that a mixed infection of falciparum and vivax malaria could not be ruled out.

Reviewer's Comment: All patients had documented vivax infection at baseline. It is not clear if any patient was co-infected with falciparum or not, but assumed not to be co-infected, based on the methods described in this paper.

WHO Guidelines state that "Where ACT has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate + sulfadoxine-pyrimethamine is the exception as it will not be effective against *P. vivax* in many places." [Level of Evidence O and E]

The applicant is not proposing use of Coartem in combination with primaquine for the treatment of mixed infections in the US label.

Also for mixed infections WHO states:

Mixed malaria infections are common. In Thailand, despite low levels of malaria transmission, one-third of patients with acute P. falciparum infection are co-infected with P. vivax, and 8% of patients with acute vivax malaria have simultaneous P. falciparum infection. Mixed infections are underestimated by routine microscopy...ACTs are effective against all malaria species and are the treatment of choice. Radical treatment with primaquine should be given to patients with confirmed P. vivax and P. ovale

¹⁸ Krudsood S, Tangpukdee N, Muangnoicharoen S, et al. Clinical efficacy of chloroquine versus artemether-lumefantrine for Plasmodium vivax treatment in Thailand. Korean Journal of Parasitology. 2007;45;111-4.

infections except in high transmission settings where the risk of re-infection is high.

Conclusions from applicant's June 19th and July 17th 2008 submissions requesting Priority Review: The applicant has not submitted an adequate justification to support a Priority Review under the 6020.3 MaPP. Specifically, the applicant has not provided evidence, in the form of clinical data, that Coartem demonstrates a significant improvement over marketed products.

On July 25, 2008 the Division spoke to the applicant and stated that we required additional information (clinical data) to address their assertion that Coartem provides a significant improvement compared to marketed products. The Division said that Coartem must show an advantage on a clinically meaningful endpoint. In addition, if the applicant was able to show a correlation between a clinical parasitological endpoint, their request for a priority review would be further strengthened.

On August 4, 2008 the applicant provided a new document which states that "*Coartem demonstrates evidence of safety and effectiveness in the pediatric subpopulation.*"

To support their assertion, the applicant provided a summary of efficacy in the pediatric population (≤ 12 years of age with body weight as low as 5 kg) shown in Tables 2-1 and 2-2 in the Appendix.

Reviewer's Comment:

The Statistical Team Leader created separate tables for the efficacy results in children using data from the 4 dose supportive studies and the eight key 6-dose studies – see FDA Tables 1 and 2 below. Of note, the numbers in these tables were obtained directly from the study reports and efficacy datasets in the NDA. If possible, the results from the ITT population are reported. The resulting data are similar, but not the same as the results in the applicant's Table 2-1.

The 4-dose pediatric studies in FDA Table 1 (A003, 008, 009, 010, and 011) are considered to be supportive of the 6-dose regimen. The applicant had not provided raw data in the NDA for these studies. Four of these studies are comparative (Studies 003, 008, 010, and 011). The results suggest that 4 doses of Coartem result in a greater reduction in parasite burden at 24 hours (95% to 99%) compared to quinine in Study 003 (67%), SP in Study 010 (62%), and chloroquine in Study 011 (59%). Parasite reduction at 24 hours was not reported in Study 008 which used MAS as the comparator. The only comparative study to evaluate parasite clearance time (PCT) was Study 003 and Coartem achieved a greater PCT (40 hours) compared to quinine (77 hours). Median fever clearance time (FCT) was 52 hours for Coartem compared to 88 hours for quinine in Study 003. FCT was reported as "normal by day 2" in 88% of the Coartem patients in Study 010 compared to 48% of the SP-treated patients. FCT was not reported in Studies 008 or 011. Parasitological cure at 28 days with Coartem was better with Coartem than with chloroquine (64% vs. 5%, respectively in Study 011), slightly lower than quinine (43% vs. 47% in Study 003), and substantially lower than with SP (77% vs. 87% in Study 010) or MAS (80% vs. 95% Study 008).

The pooled parasitological cure rate at 28 days in children across all the 4-dose studies was 60% [95% CI (54%, 65%)] as shown in the applicant's Table 2-2.

Four studies in the NDA evaluate the efficacy of the 6-dose regimen in children of body weight of 5 kg and above (Studies A025, A026, A2403 and B2303). These are 4 of the 8 studies considered to be key efficacy studies in the NDA (with raw data included). As shown in FDA Table 2, only Study 026 was a comparative study (9 patients treated with MAS). In these studies, Coartem achieved a median PCT of 24 to 44 hours and a median FCT of 7.6 to 44 hours.

The pooled parasitological cure rate at 28 days in children across all the 6-dose studies was 86% [95% CI (83%, 88%)] as shown in the applicant's Table 2-2.

In summary, Coartem 4-doses in children resulted in an earlier reduction in parasite burden in comparative studies than quinine, SP, and chloroquine and a more rapid FCT than quinine and SP. Overall parasitological cure at 28 days was lower with Coartem compared to quinine, SP, and MAS, but data from the 6-dose studies suggests that the two additional doses may increase efficacy (60% compared to 86% in the pooled analysis).

Additional studies in adults support the conclusion that Coartem has a more rapid PCT and FCT compared to all controls studied with the exception of MAS, which is not an approved comparator. The other approved comparators included chloroquine, SP, quinine plus SP, mefloquine, quinine plus doxycycline, and halofantrine. The data in adults also support an acceptable 28-day cure rate for the 6-dose regimen of Coartem.

Therefore, the limited evidence from pediatric studies along with supportive evidence from adult studies supports the initial assessment that Coartem has efficacy, especially for the endpoints of fever and parasite clearance time. This efficacy was better than the approved comparators used in the applicant's NDA studies.

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

Study	Treatment arm n	28 day cure	Median PCT hours	Median FCT hours	Parasite reduction at 24 hours
003	Coartem 4 dose n=111 Quinine n = 108	48/111 (43.2) 51/108 (47.2)	40 77	52 88	98.6% 67.3%
008	Coartem 4 dose (n = 64) MAS	79.6% (n=48?) 94.6%			

	(n = 64)	(n=52?)			
010	Coartem 4 dose N=144 SP N=143	14-day Cure rate 111/144 (77.1%) 125/143 (87.4%)		Normal by day 2: 88.2% 48.2%	94.9% 62.4%
011	Coartem 4 dose N=130 Chloroquine N=130	Evaluable 75/118 (63.6%) 6/119 (5%)			97.5% 59%
009	Coartem 4 dose N = 60	71.7%	36	36 (n=58)	94.7

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FDA Table 2
Efficacy Results for Subjects ≤ 12 years in 6-dose Key Studies

Study	Treatment arm n	28 day cure non-PCR corrected	28 day cure PCR corrected	Median PCT hours	Median FCT hours
025	Coartem 6 dose (n = 18)	14/18 (77.8)	14/18 (77.8)	42.5	19.75 (n = 9)
	Coartem 6 dose (96 hours) (n = 13)	12/13 (92.3)	12/13 (92.3)	42.77	20.25 (n=9)
	Coartem 4 dose (n = 12)	11/12 (91.7)	11/12 (91.7)	44.1	20.6 (n=8)
026	Coartem 6 dose (n = 25)	21/25 (84%)	21/24 (87.5)		43.7 (n=16)
	MAS (n = 9)	9/9 (100%)	9/9 (100)		45.49 (n=6)
2403	Coartem 6 dose (n=310)	268/310 (86.5)	291/310 (93.9)	24	7.8
2303	Coartem 6 dose (n=452)	374/430 (87.0)	407/423 (96.2)	34.5 (n=452)	7.6 (n=451)

In addition, the applicant states:

Due to the long time elapsed since the studies were performed and the current submission, acquired resistance has affected most of the comparators used, in particular chloroquine, mefloquine and SP. According to current WHO treatment policies and practice, these comparators are now of limited relevance reinforcing the need for alternative efficacious treatments for this particular patient population

In this context, it is important to note the two recent publications where SP was used as monotherapy in two studies that confirmed the superiority of efficacy of the 6 dose regimen of Co-artemether:

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 co-artemether and SP treatment in a population of children. The PCR corrected 42-day parasitological cure rates were 98 or 94% in the co-artemether group (depending on whether standard or enhanced PCR was used); corresponding figures in the SP group were 70 and 66%, respectively.¹⁹

¹⁹ Martensson A, Ngasala B, Ursing J, et al (2007) Influence of consecutive-day blood sampling on polymerase chain reaction-adjusted parasitological cure rates in an antimalarial-drug trial conducted in Tanzania. J Infect Dis; 195: 597-601.

Mulenga et al 2006 found that co-artemether 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%, $p < 0.001$).²⁰

Regarding safety, the applicant states:

The overall incidence of Adverse Events (AEs) in the pediatric population was less in the Co-artemether groups (4 or 6 dose regimen) than with any of the comparators. This is also true for the incidence of AEs suspected to be drug related (See Table 3-1 in the Appendix).

Reviewer's Comment: The overall incidence of AEs with the 6-dose Coartem regimen (73%) was less than the comparators (90% to 100%) but the 4-dose Coartem regimen had a similar incidence (92%) to the comparators.

Furthermore, Co-artemether has been shown to induce less QTc prolongation compared to Quinine, one of the treatments currently recommended in the United States for uncomplicated P. Falciparum malaria acquired in chloroquine resistance or unknown resistance region (CDC treatment guidelines <http://www.cdc.gov/malaria/pdf/treatmenttable.pdf>). (see Table 3-2 in the Appendix).

Reviewer's Comment: The data in Table 3-2 are from Study 003, which was a 4-dose study of Coartem. It's not stated which correction formula was applied to the data in Table 3-2, but is assumed to be Bazett's correction formula. In the Clinical Overview section of the NDA, the applicant pooled the change from baseline in QTc on Day 1-4 for the 4-dose and 6-dose studies in the pediatric population, but did not include any comparator data (see Table 5-40). The mean change appears similar between the two regimens (Day 1-4 mean change from baseline using Bazett's formula: 10.1 msec for 4-dose Coartem and 8.0 msec for 6-dose Coartem).

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²⁰ Mulenga M, Van geertruyden JP, Mwananyanda L, et al (2006)] Safety and efficacy of lumefantrine-artemether (Coartem®) for the treatment of uncomplicated Plasmodium falciparum malaria in Zambian adults. Malaria Journal; (Internet) Available from: <<http://www.malariajournal.com/content/5/1/73>>

Conclusions and Recommendation

The applicant submitted three requests for a Priority Review. The submission dated August 4, 2008 provides data to support the following criteria as specified in MaPP 6020.3:

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

Children ≤ 12 years of age treated with a Coartem achieve an earlier reduction in parasite burden and a more rapid fever clearance time than other approved comparators, including quinine and sulfadoxine/pyrimethamine. Overall the 28-day cure rates appear similar to approved comparators.

The overall incidence of AEs with the 6-dose Coartem regimen (73%) was less than the comparators (90% to 100%) but the 4-dose Coartem regimen had a similar incidence (92%) to the comparators. Coartem may have less of an effect on QT interval prolongation than quinine.

Therefore, NDA 22-268 for a 6-dose regimen of Coartem to treat acute, uncomplicated *P. falciparum* malaria in adults and children (down to 5 kg) should be granted a Priority Review.

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APPENDIX

Table 2-1 Summary of data in studies including pediatric patients- Demographics and efficacy

Study/ Year/ Country	Treatment arm N (N<=12 years)	Median age in years (median age for patients <=12 years) Range (range for patients <=12 years)	28-day cure Cured n/M (%) 95% CI	Median PCT (hours) 95% CI	Median FCT (hours) 95% CI	Median Parasite reduction at 24hours: 25-75 Percentiles	Fever clearance on Day 2
A003 1995/96 Thailand	Coartem 4 dose: 111	8 2-12	45/74=60.8% ¹ [48.8, 72]%	40 ² [37,40]	52 ¹ [40,88]	98.6% ¹ 87.5-99.9%	-
	Quinine: 108	9 4-12	51/71=71.8% ¹ [59.9, 81.9]%	77 ² [65,89]	88 ¹ [68,112]	67.3% ¹ increase-92.4%	
A008⁷ 1995/96 Thailand	Coartem 4 dose: 309 (64)	20(9.5) 5-66 (5-12)	224/273=82.1% ¹ [77.0, 86.4]%	-	-	100% ² 99-100%	79.29%
	MAS: 308 (64)	20 (8.5) 5-65 (5-12)	257/264=97.3% ¹ [94.6, 98.9]%			100% ² 99.6-100%	84.74%
A009 1995/96 Gambia	Coartem 4 dose: 60	3 1-6	92.7% ⁵ [82.4, 98]%	36 ² [36,36]	36 ¹ [24, 42]	94.7% ² 94.0-95.3%	
A010 1996-97 Gambia	Coartem 4 dose: 144	3 1-5	111/119=93.3% ^{3,1} [87.2, 97.1]%	-	-	94.9% ² 93.5-96.0%	83.33%
	SP: 143	3 0-5	125/128=97.7% ^{3,1} [93.3, 99.5]%			62.4% ² 45.9-78.8%	50.35%

Study/ Year/ Country	Treatment arm N (N≤12 years)	Median age in years (median age for patients ≤12 years) Range (range for patients ≤12 years)	28-day cure Cured n/M (%) 95% CI	Median PCT (hours) 95% CI	Median FCT (hours) 95% CI	Median Parasite reduction at 24hours: 25-75 Percentiles	Fever clearance on Day 2
A011 1996 Tanzania	Coartem 4 dose: 130	2 0-5	75/118=63.6% ¹ [54.2,72.2]%	-	-	97.8% ² 88.7-99.8%	-
	Chloroquine: 130	2 1-4	6/119=5% ¹ [1.9,10.7]%			59% ² increase-79.8%	
A025⁷ 1996/97 Thailand	Coartem 4 dose: 120 (12)	24 (6) 3-75 (3-12)	84/104=80.8% ¹ [71.9, 87.8]%	44 ² [43, 44]	23 ¹ [21, 36]	99.1% ¹ 96.8-99.9%	-
	Coartem 6 dose: 118 (18)	23 (8) 3-62 (3-12)	93/96=96.9% ¹ [91.1, 99.4]%	44 ² [43, 45]	35 ¹ [22, 43]	99.1% ¹ 94.0-100%	
A026⁷ 1997/98 Thailand	Coartem 6 dose: 150 (25)	22 (9) 2-63 (2-12)	130/134=97.0% ¹ [93.3, 99.0]%	-	-	99.1% ¹ 96.5-100%	74.67%(D2) 96% (D3)
	MAS: 50 (9)	25 (7) 3-61 (3-12)	47/47=100% ¹ [93.8, 100]%			99.7% ¹ 98.6-100%	84% (D2) 92% (D3)
A2403 2002/03 Africa	Coartem 6 dose: 310	2.0 0.2-9.9	291/310=93.9% ⁶ [90.6, 96.3]%	24 ² [24.0, 35.4]	7.8 ² [7.8, 7.9]	-	-
B2303 2006/07 Africa	Coartem 6 dose: 452 (crushed arm)	3.0 0.0-12.0	403/409=98.5% ⁴ [97.4, 99.7]%	34.9 ² [25.2, 35.6]	7.8 ² [7.8, 7.9]	-	-
¹ evaluable population							
² ITT population							

Study/ Year/ Country	Treatment arm N (N<=12 years)	Median age in years (median age for patients <=12 years) Range (range for patients <=12 years)	28-day cure Cured n/M (%) 95% CI	Median PCT (hours) 95% CI	Median FCT (hours) 95% CI	Median Parasite reduction at 24hours: 25-75 Percentiles	Fever clearance on Day 2
<p>³ 14 day cure rate ⁴ Primary analysis (PA) population, PCR corrected ⁵ evaluable PCR corrected ⁶ ITT PCR corrected ⁷ Data from studies that included both adult and pediatric population SP = sulfadoxine-pyrimethamine MAS: Mefloquine artesunate FCT: fever clearance time PCT: parasite clearance time</p>							

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Table 2-2 Pooled efficacy analysis in pediatric population (Pediatric [\leq 12 years])

Efficacy parameters	Co-artemether 4-dose regimen	Co-artemether 6- dose regimen	MAS	Quinine	SP	Chloroquine
<i>mITT population</i>						
28-day cure Uncorrected Cured n/M (%) 95% CI	220/369 (59.6) [54.4-64.7]	691/806 (85.7) [83.1-88.1]	67/76 (88.2) [78.7-94.4]	51/106 (48.1) [38.3-58.0]	NA	6/127 (4.7) [1.8-10.0]
28-day cure PCR-corrected Cured n/M (%) 95% CI	242/362 (66.9) [61.7-71.7]	746/797 (93.6) [91.7-95.2]	67/76 (88.2) [78.7-94.4]	51/105 (48.6) [38.7-58.5]	NA	6/125 (4.8) [1.8-10.2]
<i>Evaluable population</i>						
28-day cure Uncorrected Cured n/M (%) 95% CI	213/313 (68.1) [62.6-73.2]	685/770 (89.0) [86.5-91.1]	67/70 (95.7) [88.0-99.1]	51/71 (71.8) [59.9-81.9]	NA	6/119 (5.0) [1.9-10.7]
28-day cure PCR-corrected Cured n/M (%) 95% CI	235/306 (76.8) [71.7-81.4]	740/761 (97.2) [95.8-98.3]	67/70 (95.7) [88.0-99.1]	51/70 (72.9) [60.9-82.8]	NA	6/117 (5.1) [1.9-10.8]
Median PCT (hours) <i>mITT</i> 95% CI	48.0 [45.0 - 48.0]	34.9 [24.7 - 35.6]	24.0 [NE – NE]	77.0 [65.0 - 89.0]	48.0 [NE – NE]	360.0 [168.0 – NE]
Median FCT (hours) <i>mITT</i> 95% CI	24.8 [24.0-26.7]	7.9 [7.8-7.9]	24.2 [23.8-46.8]	80.0 [68.0-112.0]	48.1 [46.0-49.7]	24.0 [7.0-48.0]
Number (%)of patients with <i>P. Falciparum</i> Gametocytes, by time in study and treatment, <i>mITT</i>, n/M (%)						
Baseline	17/500 (3.4)	38/820 (4.6)	3/ 76 (3.9)	4/104 (3.8)	6/143 (4.2)	5/116 (4.3)
>0-72 hours	63/507 (12.4)	78/812 (9.6)	7/ 76 (9.2)	29/105 (27.6)	19/142 (13.4)	13/123 (10.6)
>72 hours - Day 8	21/370 (5.7)	9/775 (1.2)	1/ 69 (1.4)	42/104 (40.4)	7/ 44 (15.9)	12/ 95 (12.6)
>Day 8 (7 days after start of treatment)	25/463 (5.4)	6/791 (0.8)	0/ 72 (0.0)	24/ 83 (28.9)	39/135 (28.9)	6/ 82 (7.3)
Modified ITT population (<i>mITT</i>): All (randomized) patients with parasitologically confirmed <i>P. falciparum</i> malaria who received at least one dose of study drug						
Confidence intervals (CI) were calculated according to the Pearson-Clopper method						

NA: not applicable, 28-day parasitological cure rates were not determined in Study A010, which provided all SP patients.

NE: not estimable

Percentages are based on the number of patients with a measurement during the respective time interval (=M)

Source: CO Appendix-Table 4.1-12, CO Appendix-Table 4.1-16, CO Appendix-Table 4.1-20, CO Appendix-Table 4.1-22.

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Table 3-1 Overview of all adverse events, by treatment, Safety population (Pediatric [\leq 12 years])

	Co-artemether				MAS	Quinine	SP	Chloroquine
	4-dose	6-dose	Total 6-dose	Total				
	N=521	N=820	N=1267	N=1788	N=78	N=108	N=143	N=130
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	479 (91.9)	600 (73.2)	910 (71.8)	1389 (77.7)	77 (98.7)	100 (92.6)	129 (90.2)	130 (100)
Any AE suspected to be study drug related	79 (15.2)	146 (17.8)	188 (14.8)	267 (14.9)	45 (57.7)	4 (3.7)	25 (17.5)	76 (58.5)
Any AE leading to study drug discontinuation	0 (0.0)	12 (1.5)	21 (1.7)	21 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any serious AE	7 (1.3)	10 (1.2)	17 (1.3)	24 (1.3)	0 (0.0)	0 (0.0)	3 (2.1)	2 (1.5)

Source: CO appendix table 5.2-2

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Table 3-2**Absolute Change in QTc (msec)**

	Co-artemether 4 dose	Quinine
Day 2		
N	27	26
Mean	5.2	11.5
SD	28.1	23.0
Day 4		
N	27	26
Mean	9.0	20.2
SD	24.2	20.1
Day 8		
N	27	26
Mean	4.9	32.0
SD	23.7	23.2
Day 29		
N	21	18
Mean	8.2	20.4
SD	20.6	25.8
Source: CSR A003 table 9.5-3		

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MEDICAL OFFICER

Review of Pregnancy Section of the Coartem[®] Prescribing Information

This document contains a brief overview of the pregnancy section (8.0) of the Coartem prescribing information (label).

Background

Malaria in pregnancy carries significant morbidity and mortality for both the mother and her unborn child. Pregnant patients are at increased risk of developing severe malaria and recrudescence following conventional anti-malarial treatment. The published medical literature contains limited information regarding the efficacy of artemisinins and for the treatment of malaria in pregnancy. The NDA 22-268 did not contain efficacy data for artemether-lumefantrine for the treatment of *P. falciparum* malaria in pregnancy. Safety data from two observational studies in pregnancy were submitted for review and results are included in the current draft label. During the review of the submission, there was no available published information on efficacy of artemether-lumefantrine in pregnancy.

Following completion of the Advisory Committee meeting and clinical reviews of the NDA in mid December 2008, McGready *et al*¹ reported results from a trial of Coartem[®] in pregnant patients conducted at the Shoklo Malaria Research Unit in northwestern Thailand, which is an area of multi-resistant *Plasmodium falciparum*. This study was an open-label, randomized, controlled trial comparing treatment with artemether-lumefantrine (AL) for three days or artesunate (AS) monotherapy for seven days in women with uncomplicated *P. falciparum* malaria during the second and third trimesters of pregnancy. The current standard six-dose artemether-lumefantrine regimen was found to be well tolerated and safe in pregnant patients with uncomplicated *P. falciparum* malaria, but efficacy was inferior to seven days of artesunate monotherapy. The cure rates (95% CI) in the intention to treat (ITT) population were: AS 89.2% (82.3%–96.1%) and AL 82.0% (74.8%–89.3%), $p = 0.054$ (ITT); and AS 89.7% (82.6%–96.8%) and AL 81.2% (73.6%–88.8%), $p=0.031$ in the per-protocol population. Patients were followed for risk of recrudescence and one-third of the PCR-confirmed recrudescence cases occurred after 42 days of follow-up. No pregnant woman or newborn infants died from malaria during the trial. Birth outcomes and infant (up to age 1 year) outcomes did not differ significantly between the two groups.

The authors concluded that reduced efficacy probably resulted from low lumefantrine concentrations in later pregnancy. They also stated the results may not be applicable to pregnant women in areas of high malaria transmission and thus higher levels of immunity. The authors suggested that a longer or more frequent artemether-lumefantrine

¹ R. McGready, Saw Oo Tan, EA Ashley *et al*. A Randomised Controlled Trial of Artemether-Lumefantrine Versus Artesunate for Uncomplicated *Plasmodium falciparum* Treatment in Pregnancy. *PLoS Med* 5(12): e253. doi:10.1371/journal.pmed.0050253

dose regimen may be needed to treat pregnant women effectively and should be evaluated in another clinical trial.

Clinical Reviewer's Comments on clinical trial by McGready *et al.*

The authors report that in an area of multi-drug resistance, the lower lumefantrine plasma levels found in pregnant women result in a lower parasitological efficacy. At this time, the results of population pharmacokinetics from the trial have not been published but a publication is planned. The trial was conducted in northwestern Thailand which is an area of highly resistant malaria where *P. falciparum* has gained resistance to all available antimalarials.² Immunity to malaria contributes significantly to the treatment outcome with antimalarials. Northwestern Thailand is an area of low transmission and thus low immunity which may contribute to the lower efficacy rates observed in the context of low lumefantrine levels.

A comparison is not feasible between this study and studies 025, 026 and 028 (Coartem, NDA 22268) conducted in the same area of Thailand because follow-up was for 28 days and most relapses in the study by McGready *et al.* occurred after 28 days. There was no comparator arm containing non-pregnant women in the study and since the PK data is not yet published, it is not known how PK in the pregnant population compares to PK of the drug in non-pregnant women in the NDA studies. It is also important to note that PK of lumefantrine is known to be highly variable.

A similar trial in another region of endemic malaria could yield different results depending on the level of resistance to anti-malarials and the level of immunity in the population under study. Efficacy rates could be higher (even in the presence of low levels of lumefantrine) in populations with higher levels of immunity, e.g. in Africa.

The clinical reviewer agrees with the authors that the results of this trial may not be generalizable to other populations and further evaluation of the efficacy and pharmacokinetics of artemether-lumefantrine in pregnancy is warranted.

Draft Artemether-Lumefantrine, Coartem[®] Label

The current draft label (subsection 8.1) for artemether-lumefantrine, Coartem[®] contains information regarding the use of the drug in pregnancy. The label includes safety information from two observational studies in pregnancy but does not include efficacy data. The efficacy of Coartem Tablets was not evaluated in the observational studies.

² R. McGready and F. Nosten. The Thai-Burmese border: drug studies of *Plasmodium falciparum* in pregnancy. *Ann Trop Med Parasit*, Vol. 93, Supplement No. 1, S19 - S23 (1999)

Excerpt from the proposed label prior to the publication by McGready *et al.*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)



Current proposed pregnancy section of the label following the publication by McGready *et al.*:

8.1 Pregnancy

“Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Coartem Tablets (including a third of patients who were exposed in the first trimester), and published data of over 1000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of Coartem Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Coartem Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

Future Studies

A study of artemether-lumefantrine in pregnant patients uncomplicated *P. falciparum* malaria arriving in the U.S.A. with would not be feasible because of low numbers of patients. There are usually less than 1,500 cases of malaria per year in travelers (men, women and children) returning to the USA. The CDC received reports of 1,324 cases of malaria, including four fatal cases, in 2004 among persons in the United States or one of its territories. This number represented an increase of 3.6% from the 1,278 cases reported for 2003. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 49.6%, 23.8%, 3.6%, and 2.0% of cases, respectively. Seventeen patients (1.3% of total) were infected by two or more species. The infecting species was unreported or undetermined in 262 (19.8%) cases.³

³ MMWR, May 26, 2006 / 55(SS04);23-37

NDA 22-268

Artemether/Lumefantrine, Coartem[®]

The division consulted with the Maternal Health Team (MHT) and they advised that the division does not have authority under current FDA regulations to require a post-marketing study of artemether-lumefantrine in pregnancy outside the U.S.A. Novartis was contacted by the division to ask if studies of Coartem[®] in pregnancy were planned. Novartis stated that there is on-going communication between Novartis and the clinical investigators at the Shoklo Malaria Research Unit in Thailand but that studies of malaria in pregnancy are not planned at this time.

Conclusion

Additional treatment outcome information and pharmacokinetic information on Coartem is needed in pregnant patients with uncomplicated *P. falciparum* malaria^{(b) (4)}

A statement regarding the lack of efficacy data in pregnancy was added to the draft label. Updates can be made to the drug label as more clinical data on efficacy become available.

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Elizabeth OShaughnessy
3/11/2009 04:57:25 PM
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Joette Meyer
3/11/2009 05:08:20 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date:

From: Eric Bastings, M.D., Deputy Division Director
Division of Neurology Drug Products, HFD-120

Subject: Coartem

To: DSPTP

Document type: Consultative Review
ODE1 number:

Joette Meyer, Acting Clinical Team Leader in DSPTP consulted DNP regarding the neurological toxicity of Coartem.

Coartem is an oral fixed-dose combination of artemether 20mg and lumefantrine 120mg. DSPTP is reviewing an NDA application for the treatment of uncomplicated falciparum malaria infection in adults and in pediatric patients.

DSPTP asked several questions to this division, all related to the known neurotoxic effects of the product in non clinical studies, and the potential for neurotoxicity in humans.

Dr. Dave Hawver and Dr. Kenneth Bergmann respectively reviewed the nonclinical and the clinical material that was provided to this division, and this memorandum is based on their comments, and represents the division's position. Please refer to their reviews filed separately for further details.

1. Upon review, do you consider the applicant's non clinical and clinical evaluation of neurotoxicity to be adequate?

Non clinical: No. The potential for neurotoxicity induced by the combination of lumefantrine, artemether, and dihydroartemesinin (DHA) at (and at multiples above) plasma exposures expected in humans given the recommended clinical dosage of Coartem has not been adequately evaluated in nonclinical studies.

Clinical: We note that there is a very limited safety margin between exposure and treatment duration causing neurotoxicity in dogs and the proposed dosing regimen in humans. We note limitations of the safety data provided by the sponsor, with a lack of detailed neurological examination or evaluations, limiting the detection of mild or asymptomatic neurological toxicity. In addition, some of the expected symptoms (e.g. dizziness, vertigo) can be a manifestation of the treated condition (malaria) and not represent neurotoxicity.

With these limitations in mind, the clinical materials provided by DSPTP do not provide evidence suggesting that significant neurotoxicity occurs in human. Dr. Bergmann, DNP Medical Officer, notes that all deaths are convincingly unrelated to drug. Dr. Bergmann observes that CNS SAEs (convulsions, coma, severe headache, mental impairment) are all less than 0.1% and cannot be distinguished from effects of cerebral malaria or severe general illness.

Dr. Bergmann notes that in non clinical studies performed by the Sponsor, as well as in the scientific literature, the most consistent pathology across species is found in the lateral vestibular nucleus (coordination and balance) and the trapezoid auditory brainstem nucleus (sound localization, not hearing per se). Dr. Bergmann observes that there is limited published human data regarding neurotoxicity (the drug is marketed in foreign countries). He could find in a Medline search one single case-control study of patients receiving either artesunate or artemether, and which revealed no safety signal in either audiometry or brainstem auditory evoked potentials. Dr. Bergmann's review of the scientific literature and the Sponsor's information did not identify a single report documenting a neuropathological examination of a person dying after taking an artemisinin-class agent.

Dr. Bergmann believes that serious human toxicity is likely rare. He notes that the denominator for occurrence rate are the estimated ^{(b) (4)} patients have been treated with coartemether (the drug has a long marketing history outside of the United States). This must be contrasted to the lack of reported CNS serious adverse event in the literature. I generally agree with that assessment, but also note the limitations of post-marketing reporting, in particular in foreign countries which may not have a reliable post-marketing reporting system, and suspect that the degree of under-reporting may be very severe in this situation.

2. Do you have any concerns or comments about the monitoring for neurological events, or lack of monitoring, in the clinical trials? Do you have any suggestions for testing that should be incorporated into future trials?

I concur with Dr. Bergmann that systematic neurological examination of subjects receiving this drug has not been performed, and that therefore asymptomatic or mild neurological toxicity in human can not be ruled out.

Please see below (response to question 5) for the division's recommendations for a post-marketing safety study.

3. Do you agree with DSPTP's preliminary non clinical and clinical analyses? Do you have any additional comments to add?

Non clinical:

- a. Intramuscular (i.m.) artemether induced degenerative brain lesions when administered to dogs for 8 days at 20, 40, or 80 mg/kg/day, or for 27-30 days at 20 mg/kg/day, but NOT after 8 days at 10 mg/kg/day (N=3M), after 5 days at 40 mg/kg/day (N=3M) or after 3 days at 40 mg/kg/day (\pm 6 day recovery period; N=3M/group).
- b. The evidence suggests that the neurotoxicity observed in dogs and rats given artemether i.m. correlates better with the level of sustained plasma exposures to artemether and its active metabolite (DHA) over several days rather than with the maximal plasma exposures.
- c. The lowest artemether exposure ($AUC_{0-24 \text{ hr}}$) associated with brain lesions was observed in dogs treated for 8 days at 20 mg/kg/day i.m., and ranged from 1340-5920 ng*hr/mL, increasing over the 8 days of treatment. The NOEL for brain lesions in dogs (10 mg/kg/day i.m. for 8 days) resulted in exposures ranging from 537-2560 ng*hr/mL. Estimated human plasma exposure to artemether at the maximum recommended dose of 80 mg BID p.o. is 1070 ng*hr/mL.
- d. Repeated intramuscular administration of artemether to dogs has allowed evaluation of artemether plasma exposures several-fold above those expected in humans given the recommended dosage of Coartem, but the DHA plasma exposures in these studies have generally been lower than those expected in humans.
- e. Repeated oral administration of artemether to dogs results in rapid dramatic reduction in plasma exposure to artemether and DHA due to induction of metabolic enzymes; by 7 days of dosing at 300 or 600 mg/kg/day, plasma exposures to artemether and DHA were much lower than those expected in humans given the recommended dosage of Coartem.
- f. The mechanism of action of the neurotoxicity induced by artemether and DHA is not clear; therefore, it possible that other metabolites whose concentrations have not been measured may contribute to the toxicity.
- g. The possibility that co-treatment with lumefantrine may alter the level or duration of plasma exposure of artemether/DHA needed to induce brain lesions in dogs has not been evaluated.

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

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

Clinical: please see above under response to question 1.

4. Do you have any comments regarding labeling of this product if it were approved for the treatment of acute, uncomplicated malaria in adults and children as a 3 day regimen?

We believe that labeling should include a description of the findings of degenerative brain lesions in rats and dogs, and a statement that these lesions were seen at exposure levels close to that of the human dosing regimen, but that no serious drug related neurotoxicity was observed in clinical trials.

We also suggest to describe that grapefruit juice led to a two-fold increase in AUC of artemether and DHA.

5. DSPTP is planning to request two non clinical studies as post-marketing commitments (PMCs). Are there other non clinical or clinical studies you would recommend, either prior to approval or as PMCs?

Non clinical:

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

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

Clinical:

The requirement for a post-marketing clinical trial must be balanced with the risk/benefit profile of the product and the availability of other less toxic drug products to treat malaria. If the product is believed to have a robust efficacy, there is no safer alternative, and the potential for mild or asymptomatic neurotoxicity is acceptable considering the drug's efficacy, it may be reasonable not to require a clinical trial.

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

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

Eric P. Bastings, MD
Deputy Division Director

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/s/

Eric Bastings

12/19/2008 10:27:28 AM

MEDICAL OFFICER

Please also see separate non clinical review by Dr.
Hawver, and clinical review by Dr. Bergmann.

ADDENDUM: CLINICAL REVIEW OF EFFICACY

Application Type NDA
Submission Number 22-268
Submission Code 000

Letter Date June 27th, 2008
PDUFA Goal Date December 27th, 2008

Reviewer Name Elizabeth O'Shaughnessy, MD
Team Leader Joette Meyer, Pharm D
Review Completion Date 12.14.2008

Established Name Artemether/Lumefantrine
(Proposed) Trade Name Coartem
Therapeutic Class Anti-malarial drug
Applicant Novartis Pharmaceuticals Corp.

Priority Designation Priority
Formulation oral tablet
Dosing Regimen Three day treatment with a total of six doses and dosed based on body weight
Indication Treatment of malaria in patients of 5 kg body weight and above with acute uncomplicated malaria due to *Plasmodium falciparum* or mixed infections including *P. falciparum*
Intended Population Adults and Children

Efficacy in Patients with Renal or Hepatic Impairment

On Nov 19th, 2008, the applicant submitted an analysis of efficacy in patients with *P. falciparum* infection and renal and hepatic impairment at baseline to support labeling recommendations. The majority of patients (adult and pediatric) in the mITT population had mild to moderate renal or hepatic impairment. The degree of hepatic or renal impairment at baseline may reflect more severe malaria in these patients.

Renal Impairment

Adult Patients

Renal function was assessed by the applicant using the *Cockcroft and Gault* formula (1976): Creatinine clearance, (CrCl) in ml/min, was defined as follows: normal (> 80 ml/min); mild (50 – 80 ml/min), moderate (30 - < 50 ml/min), and severe < 30 ml/min). The majority of patients had mild renal impairment and there were no adult patients with severe renal impairment.

The efficacy of Coartem in adults and children with renal impairment are summarized in the following tables. The 28-day cure rate and Parasite Clearance Times (PCT) were similar between the patients with normal renal function and those with mild to moderate renal impairment. Fever Clearance Time (FCT) were slightly shorter in patients with moderate renal impairment but the ranges were comparable in all groups.

Table 1: Efficacy in Patients > 16 years old with Normal vs. Impaired Renal Function

	Renal Impairment at Baseline			
	Normal	Mild	Moderate	Severe
28-day Cure Rate* n/N (%) [95% CI]	182/223 (81.6) (75.9-86.5)	119/143 (83.2) (76.1-88.9)	9/ 9 (100.0) (66.4, 100.0)	NA
PCT, hours Median (range)	32.0 (24.0-36.5)	37.0 (31.3-40.3)	39.5 (13.5-47.0)	NA
FCT, hours Median (range)	40.5 (40.0-42.0)	40.0 (37.0-42.0)	28.5 (20.0-48.0)	NA

*PCR uncorrected results; NA=not applicable.

Source: Table adapted from the applicants submission, 11.19.08

Pediatric Patients

Renal function in pediatric patients was assessed using the *Shull* or *Schwartz* formula if the weight of the patient was not available. A total of 64% of patients had normal or mild renal impairment and 36% of patients had moderate to severe renal impairment. The 28-day cure rate and Fever Clearance Time (FCT) was similar between the patients with all levels of renal impairment. It is unclear why the median Parasite Clearance Time (PCT)

was shorter (24 hours vs. 36 hours)) in patients with severe renal impairment compared to patients with normal renal function.

Table 2: Efficacy in Patients \leq 16 years old with Impaired Renal Function

	Renal Impairment at Baseline			
	Normal	Mild	Moderate	Severe
28-day Cure Rate* n/N% [95% CI]	159/177 (89.8) [84.4 ,93.9]	267/315 (84.8) [80.3, 88.5]	163/190 (85.8) [80.0 , 90.4]	79/ 92 (85.9) [77.0]
PCT, hours Median (range)	35.6 (24.1-35.8)	35.6 (34.3-35.8)	34.5 (24.2 -35.4)	23.8 (23.8 - 24)
FCT, hours Median (range)	7.8 (NE,NE)	7.9 (7.87.9)	7.9 (7.8 8.1)	8.0 (7.8,23.5)

*PCR uncorrected results; NE = not estimable.

Source: Table adapted from the applicant's submission, 11.19.08

Overall, patients with renal impairment had similar 28-day cure rates to patients with normal baseline renal function. The degree of renal impairment at baseline may reflect more severe malaria with or without dehydration in these patients. In these studies, all patients with renal impairment cleared parasites within 48 hours and had similar clinical outcomes based on the 28-day cure rate to patients with normal renal function.

Hepatic Impairment

The applicant assessed patients in the clinical trials as having mild, moderate or severe hepatic impairment as follows:

Normal: Total bilirubin = ULN and AST = ULN (or regardless of AST value if missing)

Mild: Either Total bilirubin = ULN and AST > ULN or Total bilirubin > ULN – 1.5xULN (regardless of AST value)

Moderate: Total bilirubin > 1.5x – 3x ULN (regardless of AST value)

Severe: Total bilirubin > 3x ULN (regardless of AST value)

Missing: Baseline for total bilirubin is missing (regardless of whether AST value is missing or not)

Most patients with acute *P. falciparum* infection present with some degree of related hepatic impairment. Baseline abnormalities in liver function tests improved in nearly all patients after treatment with Coartem Tablets. The efficacy of Coartem in adults and children with hepatic impairment are summarized in the following tables.

Adults

In adults, the 28-day cure rate decreased, and PCT and FCT were slower as baseline hepatic impairment declined from mild, moderate, and severe compared to patients with normal hepatic function. An assessment of efficacy in patients with severe hepatic

function impairment base is limited due to the low numbers of patients in the severe hepatic impairment group.

Table 3: Efficacy in Patients > 16 years old with Normal vs. Impaired Hepatic Function

	Hepatic Impairment at Baseline			
	Normal	Mild	Moderate	Severe
28-day Cure Rate* n/N% [95% CI]	146/164 (89.0) [83.2, 93.4]	101/121 (83.5) [75.6, 89.6]	45/ 60 (75.0) [62.1, 85.3]	9/ 17 (52.9) [27.8, 77.0]
PCT, Hours Median (range)	19.7 (16.5-29.0)	36.3 (31.0-40.0)	36.3 (32.0 -43.8)	64.8 (47.5-152.5)
FCT, Hours Median (range)	19.7 (16.5-29.0)	36.3 (31.0-40.0)	36.3 (32.0 -43.8)	64.8 (47.5-152.5)

*PCR uncorrected results

Source: Table adapted from the applicant's submission, 11.19.08

Pediatric Patients

In pediatric patients, no clear effects of baseline hepatic function on efficacy were apparent in patients with mild to moderate hepatic impairment compared to those with normal hepatic function. PCT and FCT were slower in patients with moderate to severe hepatic impairment. There were too few patients with severe impairment (n = 2) to make a definitive conclusion on efficacy in patients with severe hepatic impairment.

Table 4: Efficacy in Patients ≤ 16 years old with Impaired Hepatic Function

	Hepatic Impairment at Baseline			
	Normal	Mild	Moderate	Severe
28-day Cure Rate n/N%	127/144(88.2)	149/170 (87.6)	20/ 24 (83.3)	1/ 2 (50.0)
95% CI	[81.8, 93.0]	[81.7 , 92.2]	[62.6, 95.3]	[1.3 , 98.7]
PCT, hours Median (range)	24.2 (24.0-35.8)	24.0 (23.9-35.3)	36.0 (35.9-47.8)	41.7 (35.4-48.0)
FCT, hours Median (range)	7.8 (7.8-7.9)	7.9 (7.8-8.0)	23.5 (7.8 -23.9)	22.1 (NE, NE)

PCR uncorrected; NE: not estimable

Source: Table adapted from the applicant's submission, 11.19.08

Overall, hepatic function improved in most patients with hepatic function impairment at baseline, therefore the lower cure rate and the slower PCT and FCT compared to patients with normal hepatic function is more likely an indicator of severity of malaria rather than lack of efficacy of Coartem.

Summary and Conclusions

In adult patients with mild to moderate renal impairment, the 28-day cure rate and Parasite Clearance Times (PCT) and Fever Clearance Time (FCT) were similar between groups. In pediatric patients, there were no clear effects on the 28-day cure rate and FCT between patients with mild, moderate or severe renal impairment. It is unclear why PCT

NDA 22-268

Addendum to clinical review of efficacy

Coartem®, artemether/lumefantrine

was shorter in pediatric patients with severe renal impairment nonetheless, all patients with renal impairment cleared blood parasites within 48 hours.

The patients with severe hepatic impairment had decreased cure rates and longer time to parasite clearance. However, hepatic function improved in the majority of patients who were treated with Coartem suggesting that hepatic impairment at baseline was due to *P. falciparum* infection.

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

The following information is from the safety reviews by S. Lim, MD and O. Belen, MD. In clinical studies, the adverse event profile did not differ in patients with or without mild or moderate hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with Coartem Tablets. Therefore, no specific dose adjustments are needed for patients with mild or moderate hepatic insufficiency. In clinical studies, the adverse event profile did not differ in patients with or without mild or moderate renal impairment. No specific dose adjustments are needed for patients with mild to moderate renal impairment. Caution should be exercised when administering Coartem Tablets in patients with severe renal or severe hepatic impairment. (*S. Lim MD*)

In study 2403 and 2303 (pediatric studies) laboratory evaluations and specifically liver transaminases were evaluated. Inquiry of AST values (at study completion) identified 11 patients with AST values > 100 U/L and one patient with over 500 U/L (i.e. 10x ULN). ... There were no serious adverse events reported as a result of these changes in the liver transaminases. However, there was a single case with hepatic enzyme increase with grade 4 toxicity (ALT >15.0 x ULN) which resolved by Day 43. (*O. Belen, MD*)

Labeling Recommendation: Coartem Tablets can be labeled for adult and pediatric patients with mild to moderate renal or hepatic impairment without dosage adjustment. However, few patients were studied with severe renal or hepatic impairment to allow for dosing recommendations to be made in these populations.

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Elizabeth OShaughnessy
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MEDICAL OFFICER

Joette Meyer
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-268
Submission Code 000

Letter Date June 27th, 2008
Stamp Date June 27th, 2008
PDUFA Goal Date December 27th, 2008
Review Date November 17, 2008

Reviewer Name Ozlem Belen, MD, MSc, MPH
Team Leader Joette Meyer, Pharm D
Review Completion Date November 24, 2008

Established Name Artemether/Lumefantrine
(Proposed) Trade Name Coartem
Therapeutic Class Anti-malarial drug
Applicant Novartis Pharmaceuticals Corp.

Priority Designation Priority
Formulation oral tablet
Dosing Regimen Three day treatment with a total of 6 doses and dosed based on body weight
Indication Treatment of malaria in patients of 5 kg body weight and above with acute uncomplicated malaria in due to *Plasmodium falciparum* or mixed infections including *P. falciparum*

Intended Population Adults and Children

Table of Contents

1	EXECUTIVE SUMMARY.....	3
	1.1 SUMMARY OF CLINICAL FINDINGS.....	3
	1.2 RECOMMENDATION ON REGULATORY ACTION.....	6
	1.3 RECOMMENDATION ON POST-MARKETING ACTIONS.....	7
2	INTRODUCTION AND BACKGROUND.....	7
	2.1 PRODUCT INFORMATION.....	7
	2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	7
	2.3 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS.....	8
	2.4 SOURCES OF CLINICAL SAFETY DATA.....	9
3	REVIEW STRATEGY.....	10
	3.1 DATA QUALITY AND INTEGRITY.....	10
	3.2 INTEGRATED REVIEW OF EFFICACY.....	10
4	REVIEW OF INDIVIDUAL STUDY REPORTS.....	10
	4.1 SAFETY REVIEW STUDY A2403.....	10
	4.1.1 STUDY DESIGN.....	10
	4.1.2 SAFETY ASSESSMENTS.....	11
	4.1.3 SAFETY RESULTS.....	12
	4.1.4 SUMMARY AND CONCLUSIONS FOR STUDY A2403.....	23
	4.2 SAFETY REVIEW STUDY B2303.....	24
	4.2.1 STUDY OBJECTIVES AND DESIGN.....	24
	4.2.2 SAFETY EVALUATION.....	26
	4.2.3 SAFETY RESULTS.....	28
	4.2.4 SUMMARY AND CONCLUSIONS FOR STUDY B2303.....	40

1. Executive Summary

1.1 Summary of Clinical Safety Findings

Coartem is an oral fixed-dose combination tablet, containing artemether 20 mg and lumefantrine 120 mg; both compounds are blood schizonticidal in the life-cycle of *Plasmodium* species. Artemether has a short half-life and a rapid onset of action and lumefantrine has a slow onset of action. The six-dose regimen (3 day regimen) of Coartem is approved in approximately 80 countries. The WHO (WHO Malaria Treatment Guidelines, 2006) recommends the standard six-dose treatment of Coartem everywhere irrespective of the immune status of the patient and/or of the multi-drug resistance status in the country.

In animal models, artemisinin derivatives such as artemether, have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. In view of findings from animal models, neurological AEs were specifically evaluated, as were AEs affecting the auditory system. In addition, specific neurological examinations were undertaken in most studies to detect specific pre-defined neurological signs and symptoms.

As lumefantrine is chemically related to halofantrine, an antimalarial associated with prolongation of the QTc interval, particular attention was also paid to adverse events affecting the cardiovascular system, and ECG evaluations were made in most studies in malaria patients with the 6-dose regimen and some studies with the 4-dose regimen.

This review concentrates on the safety results of the two large pediatric studies, A2403 and B2303, which were counted as 2 of the eight key studies for the NDA. The pooled pediatric safety population is evaluated by Dr. Sue Lim.

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

The Study A2403 was performed to evaluate the safety and efficacy of 6-dose regimen of Coartem in the treatment of uncomplicated *Plasmodium falciparum* malaria in African infants and children with body weight 5 to 25 kg. The age groups into which most patients fell were 12-24 months and 2 to 4 years. This younger age group is at high risk of malaria and its complications, including death. The study enrolled over 300 children and over 98% of patients received 6-dose course of treatment.

The safety evaluations have to be taken into consideration within the limits of the study design, namely, an open-label, uncontrolled study.

One (4 year old female) patients died as a result of severe gastroenteritis. Malaria was noted to be cured and patient completed therapy without significant events. Therefore her death is not likely to be related to study drug. Six patients experienced severe AEs: these were anemia (2 patients), gastroenteritis (1 case), (viral) hepatitis (one case), urticaria (1 case), malaria (1 case). Except for the two cases of anemia and one case of malaria which was assessed as related to baseline disorder, the remaining three were categorized as SAEs. One patient discontinued due to an SAE of urticaria which is most likely to be related to study drug.

The most common body systems affected were ‘infections and infestations’, ‘blood and lymphatic system disorders’, respiratory, thoracic and mediastinal disorders’ and ‘gastrointestinal disorders’. This was expected in this population given the age group and the underlying disease. Developing or worsening diarrhea, cough, rash or clonus was identified in some small number patients. Special attention was given to neurological adverse events and specifically to clonus; except for one patient clonus reported in any patient at any time point during study had resolved by the end of study (Day 28). All patients were part of the same study center in Nigeria, with no other cases reported from other study centers.

Among laboratory values, special attention was paid to the increases in liver transaminases, specifically AST: twelve cases were identified with higher than baseline values at Day 28 and a final AST value of more than 2x ULN. Other than three patients with normal AST at baseline, all had values outside the normal range at baseline. Given the age and the number of patients in this study with malaria in the study, the changes in the AST evaluations are within the expected range in this population and did not result in serious adverse events or discontinuations.

Study B2303 was a randomized, partially blinded, multicenter, parallel-group study to compare efficacy, safety and tolerability of Coartem dispersible tablet formulation vs. Coartem 6-dose crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children. Comparator groups were designed to compare to assess efficacy of Coartem 6-dose dispersible versus 6-dose crushed tablets and for evaluation of safety, both arms still include study drug under investigation, i.e. 6-dose regimen of artemether/lumefantrine, and therefore is not a randomized study in this sense (other than by formulation). Approximately 60% of the patients fell into the 5- < 15 kg body weight group and over half were 2- <6 year old representing the higher incidence of malaria in this particular age group.

Approximately 87% of patients of the total study population completed the study.

It was noted that AEs leading to discontinuation is less in the safety population than the randomized patient population (70 in the randomized population vs. 20 in the safety population). Many cases discontinued from the study due to vomiting and *P. falciparum* infection before the administration of the first dose of the study drug.

The most frequently affected primary system organ classes were general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders. The most frequent AEs were pyrexia, cough, *P. falciparum* infection and vomiting.

There were three deaths during the study: in the dispersible tablet group, one patient died from hemorrhage and another from an infection. One patient in the crushed tablet group died from

severe *P. falciparum* infection. None of the deaths were likely to be related due to the administration of the study drug.

Excluding deaths, there were ten additional serious adverse events; case narratives were reviewed and did seem likely to be related to study drug administration. The most frequent AE leading to discontinuation was vomiting as it would be expected in this age group with underlying illness. Nevertheless, a course of action when vomiting occurs should be described in the label in the event that the drug is not tolerated. No AEs related to auditory system were reported; unlike Study 2403, clonus was not reported as TEAE.

There were some mild increase in the QTc interval, it is hard to evaluate these effects without a comparator group with known effects since dehydration and resulting electrolyte disturbances may result in changes in QTc interval. The medical reviewer will defer to IRT consult for labeling proposals regarding Coartem effects on QTc interval.

Inquiry of AST values (at study completion) identified one patient with over 500 U/L ($\geq 10x$ ULN). Given the patient population is at risk for increases in AST due to underlying disease process and the size of the study, the increases in the AST values observed in this patient population would be expected. There were no serious adverse events reported as a result of these changes in the liver transaminases. However, there was a single case with hepatic enzyme increase with grade 4 toxicity (ALT > 15.0 x ULN) which resolved by Day 43.

One patient in the dispersible tablet group and one patient in the crushed tablet group had convulsions reported as an SAE. One patient, aged 5 (dispersible tablet group) had convulsions that were severe, also reported as an SAE, (reported on Day 29, fever also reported), an event lasting two days whereas 2 patients (one of whom had active pneumonia and anemia) in the crushed tablet group had either mild or moderate convulsions (reported on Day 42 and Day 2). Febrile seizure would not be unexpected in the in the age (2 – 5 years old) group given the underlying infectious disease process.

Over 770 pediatric patients up to 12 years of age were treated with Coartem and 434 pediatric patients treated with Coartem dispersible tablet. Overall, when both of these large pediatric studies taken into account together, they present acceptable safety profile in the pediatric age group defined, in the treatment of children down to 5 kg with acute uncomplicated *P. falciparum* infection, especially since this younger age group is at high risk of malaria and its complications, including death. The safety evaluations have to be taken into consideration within the limits of the study design, being the lack of a comparator to evaluate the background rates in this patient population.

1.2 Recommendation on Regulatory Action

Coartem administered as a 6-dose treatment regimen over 3 days has been shown to be safe for the treatment of malaria in children of 5 kg body weight and above with acute uncomplicated *P. falciparum* infection. Approval is recommended for the following Coartem dosing regimen based on the review of two pediatric studies reviewed (Study A2403 and Study B2303).

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

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

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

A recommendation regarding approval of Coartem for the treatment of acute uncomplicated malaria in patients with mixed infections including *P. falciparum* is pending discussion at the Anti-Infectives Advisory Committee Meeting on December 3, 2008.

1.3 Recommendation on Post-marketing Actions

There are no recommendations for risk management activity or Phase 4 requirements / commitments at this time.

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2. Introduction and Background

2.1. Product Information

Coartem is an oral fixed-dose combination tablet, containing artemether 20 mg and lumefantrine 120 mg; both compounds are blood schizonticidal in the life-cycle of *Plasmodium* species. Artemether has a short half-life and a rapid onset of action and lumefantrine has a slow onset of action and the combination of these two compounds may reduce the emergence of resistance. Coartem has shown efficacy against drug-sensitive and drug-resistant *P. falciparum* malaria. The six-dose regimen (3 day regimen) of Coartem is approved in approximately 80 countries. The WHO (WHO Malaria Treatment Guidelines, 2006) recommends the standard six-dose treatment of Coartem everywhere irrespective of the immune status of the patient and/or of the multi-drug resistance status in the country.

A WHO report on the safety of artesunate and other artemisinin derivatives from 169 studies (15,567 patients) showed that artesunate had a good tolerability profile. Gastrointestinal side effects are the most common reported adverse events. Reduction in reticulocyte counts, anemia, neutropenia, and elevated transaminases were reported to be mild and transient. Neuropsychiatric adverse events were reported in a few patients and resolved without intervention; these adverse effects require further study because some of the studies lack information on neurological evaluations. Headache and dizziness were reported to be common neurological side-effects but may also be related to underlying malaria. Due to the chemical similarity of lumefantrine to halofantrine, there has been a concern for potential QT interval prolongation.

2.2. Currently Available Treatment for Indications

The antimalarial drugs (oral) currently approved for treatment and marketed in the U.S. are

- **chloroquine (Aralen®)**
- **sulfadoxine-pyrimethamine (Fansidar®)**
- **mefloquine (Lariam®)**
- **atovoquone/proguanil, (Malarone®)**
- **primaquine phosphate,**
- **quinine sulfate (Qualaquin®)**
- **Halofantrine (Halfan®)**

Halofantrine is FDA-approved, but not currently available in the U.S. The use of halofantrine in this country has been limited by its known cardiotoxicity related to QTc prolongation, and reports of death in young individuals without a cardiac history.

The use of chloroquine for treatment of *P. falciparum* malaria is limited to areas of where the parasite is susceptible, namely Central America west of the Panama Canal, the Dominican Republic, Haiti, Mexico, and some areas in the Middle East.

The use of sulfadoxine-pyrimethamine (Fansidar®) has been used for malaria self-treatment, but its use is also limited to malaria acquired in areas where the parasite is sensitive.

Mefloquine (single dose regimen) can still be used in most geographical regions for treatment of uncomplicated *P. falciparum* malaria, except in certain areas of Thailand, particularly the Thai-Myanmar and Thai-Cambodia border, and some local areas in South America. Mefloquine, is indicated for the treatment of mild to moderate acute malaria caused by *P. falciparum*, and is not available as an intravenous preparation for severe *P. falciparum* malaria in the U.S. Neuropsychiatric AEs are associated with the use of mefloquine and can contribute to non-completion of a full course of therapy.

Malarone (a 3-day regimen) is indicated for the treatment of acute uncomplicated *P. falciparum* malaria, and has been shown to be effective where chloroquine, halofantrine, mefloquine and amiodaquine have high failure rates. Vomiting is associated with malarone and mefloquine, especially in children.

Quinine sulfate oral tablets or capsules have been available in the United States since prior to the Food, Drug, and Cosmetic Act of 1938. To preserve the availability of quinine for the treatment of malaria while proceeding to regulate the unsafe over-the-counter use of quinine for nocturnal leg cramps, the FDA approved Quinine sulfate, 324 mg capsules for the treatment of uncomplicated *P. falciparum* malaria. The product was marketed in December 2006. Parenteral quinine sulfate for treatment of severe *P. falciparum* malaria is not available in the U.S., although IV quinidine, the diastereomer of quinine, is available and approved for treatment of severe malaria caused by *P. falciparum*. Quinine sulfate must be combined with another anti-malarial drug to ensure eradication of parasites. Common side effects associated with quinine include cinchonism, headache, dizziness and GI symptoms. Rare but serious AEs include DIC, thrombocytopenia, hypoglycemia, blindness, deafness, hepatitis, renal failure, QT interval prolongation, hypotension and adverse drug-drug interactions with CYP3A4 inhibitors.

The Centers for Disease Control and Prevention (CDC) guidelines for treatment of malaria recommend the use of oral quinine sulfate in combination with doxycycline, tetracycline, or clindamycin for *P. falciparum* malaria acquired in areas of chloroquine resistance or unknown resistance (CDC 2004 Guidelines for Treatment of Malaria in the U.S.). The only intravenous products available for the treatment of severe malaria are IV quinidine and IV artesunate, which are available for compassionate use under IND from the CDC.

2.3. Important Issues with Pharmacologically Related Products

Specific safety topics:

In animal models, artemisinin derivatives such as artemether, have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. In view of findings from animal models, neurological AEs were specifically evaluated, as were AEs affecting the auditory system. In addition, specific neurological examinations were undertaken in most studies to detect specific pre-defined neurological signs and symptoms.

As lumefantrine is chemically related to halofantrine, an antimalarial associated with prolongation of the QTc interval, particular attention was also paid to adverse events affecting the cardiovascular system, and ECG evaluations were made in most studies in malaria patients with the 6-dose regimen and some studies with the 4-dose regimen. A definitive QTc study with Coartem was performed in healthy adult volunteers (Study A2101).

Clinical laboratory parameters were also assessed in all studies, although the range of parameters evaluated as relatively limited and varied between studies as a result of the limited availability of clinical laboratory resources at the study centers.

2.4. Sources of Clinical Safety Data

NDA 22-268 is an electronic submission. Efficacy and safety data as well as the CRFs and other supporting data for the NDA, such as JMP data files, financial disclosure statements, proposed labeling, and non-clinical data were included in the electronic file.

In the Novartis clinical development program, 20 studies were conducted between 1993 and 2007, most of which 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 by body weight ranges. Although the 4-dose regimen initially appeared promising based on studies in China, the 6-dose regimen was ultimately selected for further clinical development based on evidence that it provided superior efficacy to the 4-dose regimen in Thailand. Of these 20 studies, 8 were selected (primarily based on demonstration of efficacy) through discussions between Novartis and the FDA to act as key studies to support registration of the 6-dose regimen.

The pooled pediatric safety population (defined in the FDA analysis as patients ≤ 16 years of age) includes patients from 4-dose studies: A003, A008 (pediatric patients only), A009, A010, A011, A025; and from 6-dose studies: A026, A028, A2403, B2303, and is evaluated in the review by medical reviewer Dr. Sue Lim.

This review will concentrate on safety results of the two large pediatric studies, A2403 and B2303, which were counted as 2 of the eight key studies for the NDA.

These two studies were conducted in African children. Study A2403 was an open-label, single arm, multicenter study conducted in Kenya, Nigeria, and Tanzania to obtain information on the use of Coartem in young children with body weights as low as 5 kg. Study B2303 was a partially blinded, randomized multicenter trial of Coartem tablets (crushed for administration)

compared to Coartem dispersible tablets in children weighing 5 to < 35 kg in sub-Saharan Africa. The applicant is not requesting approval of the dispersible tablet in this NDA application.

Study	Region/year/study design/ Coartem regimen	Population	Patients (n)	
			Coartem	Comparator
A2403	Kenya,Nigeria,Tanzania/ 2002-2003/OL/MC/6-dose	Children (5-25 kg)	310	None
B 2303	Kenya, Mali, Tanzania, Zanzibar, Benin, Mozambique/MC/6 dose	Children (5-35 kgs)	447	Coartem dispersible (434)

3. Review Strategy

The efficacy studies for NDA 22-268 were reviewed by Dr. Elizabeth O-Shaughnessy and adult safety data (in addition to pooled pediatric safety data) by Dr. Sue Lim.

3.1. Data Quality and Integrity

A consult with the Division of Scientific Integrity (DSI) was requested to inspect sites as per Dr. Elizabeth O’Shaughnessy, Medical Reviewer.

3.2. Integrated Review of Efficacy

Reference is made to efficacy review by Dr. Elizabeth O’Shaughnessy.

4. Review of Individual Study Reports

4.1. NDA 22, 268/Coartem Safety Review Study A2403

Title: Open label, multicenter study for the evaluation of safety and efficacy of Coartem® (artemether-lumefantrine) tablets (6-dose regimen) in African infants and children in the treatment of acute uncomplicated falciparum malaria.

Study dates: July 2002 - February 2003.

Study Center(s): One center in each of Nigeria, Kenya and Tanzania

4.1.1. Study Design

This was an open label, non-comparative multicenter study to assess the safety and efficacy of Coartem® 6-dose regimen under supervised treatment in 300 infants and children weighing ≥ 5 kg - ≤ 25 kg.

The Coartem® dose was based on body weight groups as follows:

- 5 - < 10 kg (BWG 1) = 6 doses of 1 tablet
- 10 - < 15 kg (BWG 2) = 6 doses of 1 tablet
- 15 - ≤ 25 kg (BWG 3) = 6 doses of 2 tablets

Tablets were given with food or drink when possible as appropriate; in case the infant or when a child was unable to swallow tablets, the tablets were dissolved and given according to the procedure described in the protocol.

The primary objective of this study was to investigate the safety of the 6-dose regimen in infants down to 5 kg of body weight. The study was performed because the WHO wanted to evaluate whether the 6-dose regimen of Coartem could replace the 4-dose regimen in those countries in which it is registered. In addition, WHO wanted to evaluate a 6-dose regimen for use in young children (BW 5kg) in Africa who are likely to be non-immune and are at high risk of death due to falciparum malaria.

An open-label, non-comparative design was selected due concerns of insufficient efficacy of the first-line products in non-immune children.

Patients who had signs of severe malaria or who had other *Plasmodium* infections (*P. vivax*, *P. ovale*, *P. malariae*) were excluded. Male or non-menarche females weighing between 5 kg and ≤ kg who were suffering from uncomplicated *P. falciparum* infection confirmed by microscopy using Giemsa-stained thick film with lower and upper limits of parasitemia of 1,000 and 100,000 parasites/mm³ respectively and who had fever were included in this study.

Patients who discontinued prematurely during the treatment phase due to reasons other than “unsatisfactory therapeutic effect” and “adverse events” (such for “lost to follow up”, “withdrew consent” or “non-compliance” were replaced. The replaced patient would belong to the same body weight group (BWG) for safety assessment to be feasible in this group.

Coartem was provided in blisters containing 8 tablets; six tablets were for the regular treatment (according to body weight) and two were replacement tablets in case of vomiting.

Medical Reviewer’s Comments: *Reference is made to the review by Dr. O’Shaughnessy for more in depth study design description including inclusion/exclusion criteria.*

4.1.2. Safety Assessments

Monitoring and recording of all adverse events, including hematology, chemistry and urine laboratory values, measurement of vital signs and physical and specific neurological examinations and ECG recordings were part of safety assessments.

The Safety and ITT populations were comprised of the same patients. For consistency with standard presentations, all safety summaries were referenced using the Safety population and all appropriate efficacy summaries were referenced using the ITT population.

A serious adverse event was defined as fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, constituted a congenital anomaly or a birth defect or was medically significant in that it jeopardized the patient or required medical or surgical intervention. Any serious event which occurred after the patient provided informed consent until 4 weeks after the patient stopped study participation had to be reported.

All laboratory specimens were processed and analyzed in the local laboratory. The following parameters were assessed:

- Hematology – hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, platelet count.
- Biochemistry – glucose, bilirubin, creatinine (serum), ALT (SGPT), AST (SGOT), serum- γ -glutamyl transferase, G6PD (at baseline only).
- Urine measurements were collected only if deemed necessary by the investigator-hemoglobinuria, proteinuria, and sediment.

Vital signs were measured at study entry and all study visits. ECG was recorded at baseline and Day 3 as a standard 12-lead ECG (25 mm/sec) followed by a tracing for rhythm evaluation. QT and corrected QT (QTc) was a significant clinical safety endpoint and QTc was calculated using Bazett's and Fridericia's formula. Attention was given to the change in QTc from baseline, and absolute QTc value.

Full physical examinations were carried out at baseline and Days 3, 7, 14 and Day 28 or at time of withdrawal. A full neurological examination was performed at baseline, Days 3, 7, 14 and Day 28.

Adverse events that appeared as a new event or worsened from baseline were deemed Treatment Emergent Signs and Symptoms (provided they occurred before recurrence of acute malaria/parasitemia) to exclude any potential bias in individual investigators' reporting of AEs.

4.1.3. Safety Results

Source is provided below the table unless generated by the reviewer (from datasets or post-text tables in the study report).

The table below summarizes the baseline demographic characteristics of the patient population by age and body weight.

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Table 1. Demographic summary age distribution and weight group in total (ITT population)

	5 - < 10kg (N=154)	10 - < 15 kg (N=110)	15 - ≤ 25 kg (N=46)	Total (N=310)
Age (Years)				
N	154	110	46	310
Mean ± SD	1.1 ± 0.59	3 ± 1.06	6.1 ± 1.72	2.5 ± 1.98
Median	1.1	2.8	6.1	2
Range	0.2 -3.1	0.8 -6.8	2.9 - 9.9	0.2 - 9.9
Age distribution n (%)				
≤ 6 months*	26 (16.9)	0	0	26 (8.4)
>6-12 months	49 (31.8)	2 (1.8)	0	51 (16.5)
>12-24 months	65 (42.2)	14 (12.7)	0	79 (25.5)
>2-4 years	14 (9.1)	77 (70)	6 (13)	97 (31.3)
4-6 yrs	0	15 (13.6)	17 (37)	32 (10.3)
> 6 yrs	0	2 (1.8)	23 (50)	25 (8.1)
Body weight				
N	154	110	46	310
Mean ± SD	8.2 ± 1.2	12.1 ± 1.38	18.4 ± 2.8	11.1 ± 3.88
Median	8.3	12	18	10
Range	5 - 9.9	10 - 14.5	15 - 25	5 - 25

* Analysis of demographics dataset showed there were two patients shown as 0.17 year old (approx. 2 months old) and three patients 0.25 year old (approximately 3 months old).

**Source: Modified from Table 7-4 of the study report.

Overall exposure by body weight groups in the total population is summarized in the table below. Over 98% of patients received 6-dose course of treatment.

Table 2. Overall exposure by body weight group and in total (ITT population)

	5 - < 10kg (N=154)	10 - < 15 kg (N=110)	15 - ≤ 25 kg (N=46)	Total (N=310)
Exposure n(%)				
1 dose	2 (1.3)	0	0	2 (0.6)
4 doses	0	1 (0.9)	0	1 (0.3)
5 doses	1 (0.6)	0	0	1 (0.3)
6 doses	151 (98.1)	109 (99.1)	46 (100)	306 (98.7)
Number of vomited doses n(%)				
1 dose	20 (13)	7 (6.4)	3 (6.5)	30 (9.7)
2 dose	1 (0.6)	1 (0.9)	1 (2.2)	3 (1)
> 2 doses	1 (0.6)	0	0	1 (0.3)
Number of patients received replacement doses – n (%)				
1 dose	19 (12.3)	7 (6.4)	3 (6.5)	29 (9.4)
2 doses	1 (0.6)	1 (0.9)	1 (2.2)	3 (1)
> 2 doses	1 (0.6)	0	0	1 (0.3)

* 2 (0.6%) patients switched to recue (one patient 5 - < 10 kg weight group and one in 1 - < 15 kg weight group).

*Source: Modified from Table 8-1 of the study report.

The table below shows the patient disposition for each body weight group. Total of four patients discontinued treatment prematurely, one due to adverse event, two withdrew consent, and one was withdrawn due to a protocol violation.

Disposition of Patients

Table 3. Patient disposition for each body weight group and in total (safety)

	5 - < 10kg	10 - < 15 kg	15 - ≤ 25 kg	Total
Total No. of patients – n (%)				
Enrolled	154	110	46	310
Treated (ITT)	154(100)	110(100)	46(100)	310(100)
Completed treatment	151(98.1)	109(99.1)	46(100)	306(98.7)
Completed follow-up period	152 (98.7)	108(98.2)	46(100)	306(98.7)
Discontinuations from treatment				
Total	3(1.9)	1(0.9)	0	4(1.3)
Primary reason				
○ W/D consent	2(1.3)	0	0	2(0.6)
○ Protocol violation	1(0.6)	0	0	1(0.3)
○ Adverse events	1(0)	1(0.9)	0	1(0.3)
Discontinuations from follow-up				
Total	1(0.6)	2(1.8)	0	3(1)
Primary reason				
○ Lost to f/u	1(0.6)	1(0.9)	0	2(0.6)
○ Death	0	1(0.9)	0	1(0.3)

*Source: Modified from Table 7-1 of the study report.

Deaths and other serious adverse events

The number of patients who died, had other serious (or clinically significant) AEs or discontinued for safety reasons are summarized in the table below.

Table 4. Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of AEs (safety population)

	5 - < 10kg	10 - < 15 kg	15 - ≤ 25 kg	Total
Total No. of patients studied				
	154(100)	110(100)	46(100)	310(100)
Serious or significant events				
-Death	0	1(0.9)	0	1(0.3)
-Serious non-fatal adverse events	2(1.3)	1(0.9)	0	3(1)
-Discontinuation due to AEs	0	1(0.9)	0	1(0.3)

*Source: Table 10-4 of the study report.

Summary case narrative involving death (NGA/002 00204): The patient was a 4 year old black female weighing 4 years old with no recorded relevant prior medical history. She received a full course of Coartem treatment (6 doses of 1 tablet). At baseline, in addition to receiving paracetamol to treat pyrexia, she received oral rehydration therapy to treat moderate diarrhea. Malaria signs and symptoms at baseline were mild; her baseline parasite count was 2555/μL with no detectable parasites in subsequent blood films. Her malaria was assessed as cured at Day 7. On Day 7 she developed a mild cough. On Day 8, she developed severe gastroenteritis and died at home on the same day. No treatment for the gastroenteritis was recorded. All ECG parameters

were reported within normal range at Baseline and on Day 3; recorded vital signs and laboratory results were noted to be unremarkable.

Medical Reviewer’s Comments: *Based on the summary narrative above, death was related to severe gastroenteritis. Malaria was noted to be cured and patient completed therapy without significant events.*

Table 5. Listing of serious adverse events

Country/Center/Subject	Age/Sex/Race	Adverse Event Preferred Term System Organ Class	Start Day	Severity
KEN/001.00145	0.67/F/Black	Convulsions NOS Nervous system disorders Malaria Infections and Infestations	Day 27 – ongoing Day 27 - ongoing	moderate
KEN/001.00149	1.58/M/Black	Hepatitis viral Infections and Infestations	Day 1 - ongoing	severe
KEN/001.00222	4.33/F/Black	Urticaria NOS Skin and subcutaneous tissue disorders Pneumonia primary atypical Infections and Infestations	Day 1- Day 5 Day 21 - Day 28	severe moderate
NGA/002.00204*	4.00/F/Black	Gastroenteritis NOS Infection and Infestations	Day 8	severe

*Patient died due to this adverse event / discussed above.

*Source: Modified from Table 10-5 of the study report.

Summary Narratives of Serious Adverse Events:

Six patients experienced severe AEs: these were anemia (2 patients), gastroenteritis (1 case), (viral) hepatitis (one case), urticaria (1 case), malaria (1 case). Except for the two cases of anemia and one case of malaria which was assessed as related to baseline disorder, these events were categorized as SAEs and are described below.

The table below summarizes number of patients with severe AEs after baseline by primary system organ class, preferred term, and body weight group in Safety population.

Table 6. Number (%) of patients with Severe AEs after baseline by system organ class (Safety population).

System organ class	Preferred term	5 - <10 kg (n=154)	10 - <15 kg (n=110)	15 - ≤ 25 kg (n=46)	Total (n=310)
Any primary system	Total	3 (1.9)	3 (2.7)	0	6 (1.9)
Blood and lymphatic system	Total	1 (0.6)	1 (0.9)	0	2 (0.6)
	-Anemia	1 (0.6)	1 (0.9)	0	2 (0.6)
Infections and infestations	Total	2 (1.3)	1 (0.9)	0	3 (1)
	-Gastroenteritis	0	1 (0.9)	0	1 (0.3)
	-Hepatitis viral	1 (0.6)	0	0	1 (0.3)
	-Malaria	1 (0.6)	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	Total	0	1 (0.9)	0	1 (0.3)
	-Urticaria	0	1 (0.9)	0	1 (0.3)

KEN/001.00145 (8 month old black female, 8.1 kg): This patient had a previous history of malaria 1 month before the study entry. No other medical history was reported. She received chloroquine treatment at an unspecified date during the month prior to study entry. She completed 6 doses of full artemether treatment as planned and was reported as cured at Day 7 and 14. The patient was diagnosed with severe malaria and experienced convulsions on Day 27. No treatment was noted for the convulsions, which occurred only on Day 27 and the malaria episode was ongoing at the end of the study. PCR analysis suggested this was a new infection rather than a recrudescence of the original infection. The patient did not have any neurological exam that was reported.

KEN/001.00149 (1.6 year old black male, 8.8 kg): This patient had a previous malaria infection reported 1 month prior to study entry and received amodiaquine treatment for malaria which was discontinued 2 days before entering the study. He completed full course of Coartem treatment and the malaria was reported as cured at the evaluations on Day 7, 14, 28. On Day 1 he developed hepatitis which was ongoing at the end of the study. SGPT and SGOT levels were elevated throughout the study with the highest reported on Day 1 (prior to the first dose of the study drug). Total bilirubin levels were recorded as elevated on Day 1 and 3 (36 and 145 µmol/L respectively). Jaundice, hepatomegaly, anorexia, chromaturia, abdominal distension were reported. Other medications received included paracetamol (baseline to Day 2), amoxicillin (Days 3-7), metronidazole (Days 3-7), lactulose (Days 4-8) and glucose infusions (Days 6-8).

Medical Reviewer's Comments: *Although this event was categorized as viral hepatitis, there were no laboratory parameters to support this conclusion. The fact that the SAE started prior to first dose of artemether makes it less likely to be related the study drug.*

KEN/001.00222 (4.3 years old black female, 12.8 kg): The patient experienced malaria, with her last episode occurring 4 months prior to the study entry. She took the first 4 doses of Coartem and on Day 1; she developed severe urticaria which was accompanied by mild pruritus. The urticaria was treated with chlorpheniramine and resolved by Day 5. Study medication was discontinued after the 4th dose of the study medication, and amodiaquine rescue medication was started.

Medical Reviewer's Comments: *This SAE (urticaria) is likely to be related to the study medication.*

Table 7. Discontinuations due to adverse events, regardless of study drug relationship, by primary system organ class, preferred term and body weight group

MedDRA system organ class Adverse events (MedDRA PT)	5 - <10 kg (n=154)	10 - <15 kg (n=110)	15 - ≤ 25 kg (n=46)	Total (n=310)
Any primary system organ class	0	1 (0.9)	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (0.9)	0	1 (0.3)
Urticaria	0	1 (0.9)	0	1 (0.3)

One patient discontinued due to an adverse event (KEN/001 000222) who discontinued due to an SAE of urticaria. Case narrative for this patient is summarized amongst serious adverse events previously.

Overall experience of adverse events (AEs)

System organ classes (MedDRA version was not identified in the study report) affected by AEs, irrespective of causality are shown in the table below. The most common body systems affected were 'infections and infestations', 'blood and lymphatic system disorders', respiratory, thoracic and mediastinal disorders' and 'gastrointestinal disorders'.

Table 8. Number of patients (%) with AEs (after baseline, before recurrence) overall, by system organ class, by body weight (total safety population)

	5 - <10 kg	10 - <15 kg	15 - ≤ 25 kg	Total
Patients studied				
Total no. of patients	154	110	46	310
Total no. of patients with AEs	116 (75.3)	79 (71.8)	30 (65.2)	225 (72.6)
System organ class affected				
Infections and infestations	65 (42.2)	36 (32.7)	13 (28.3)	114 (36.8)
Blood and lymphatic system	51 (33.1)	37 (33.6)	10 (21.7)	98 (31.6)
Respiratory, thoracic and mediastinal	50 (32.5)	36 (32.7)	5 (10.9)	91 (29.4)
Gastrointestinal	48 (31.2)	26 (23.6)	16 (34.8)	90 (29)
Metabolism and nutrition	17 (11)	15 (13.6)	5 (10.9)	37 (11.9)
Skin and subcutaneous tissue	20 (13)	10 (9.1)	1 (2.2)	31 (10)
Hepatobiliary disorders	11 (7.1)	13 (11.8)	5 (10.9)	29 (9.4)
Nervous system disorders	10 (6.5)	8 (7.3)	5 (10.9)	23 (7.4)
Psychiatric disorders	15 (9.7)	6 (5.5)	1 (2.2)	22 (7.1)
General / administrative site	7 (4.5)	8 (7.3)	2 (4.3)	17 (5.5)
Investigations	5 (3.2)	6 (5.5)	0	11 (3.5)
Eye disorders	4 (2.6)	4 (3.6)	1 (2.2)	9 (2.9)
Injury, poisoning and procedural	5 (3.2)	1 (0.9)	0	6 (1.9)
Ear and labyrinth disorders	3 (1.9)	1 (0.9)	0	4 (1.3)
Vascular disorders	2 (1.3)	1 (0.9)	1 (2.2)	4 (1.3)
Cardiac disorders	0	1 (0.9)	0	1 (0.3)
Renal and urinary disorders	1 (0.6)	0	0	1 (0.3)

*Patients are only counted once in each body system regardless of the number of AEs experienced in that body system.

*Source: Table 10-1 of the study report.

The following table shows the most frequent AEs (irrespective of causality), by preferred term, occurring in >3% of the population by body weight group.

Table 9. Number (%) of patients with most frequent AEs (after baseline but before recurrence, > 3% of safety population)

Adverse events (MedDRA PT)	5 - <10 kg (n=154)	10 - <15 kg (n=110)	15 - ≤ 25 kg (n=46)	Total (n=310)
Cough	44 (28.6)	28 (25.5)	5 (10.9)	77 (24.8)
Anemia	41 (26.6)	21 (19.1)	9 (19.6)	71 (22.9)
Vomiting	25 (16.2)	12 (10.9)	8 (17.4)	45 (14.5)
Anorexia	17 (11)	15 (13.6)	5 (10.9)	37 (11.9)
Diarrhea	20 (13)	10 (9.1)	3 (6.5)	33 (10.6)
Hepatomegaly	10 (6.5)	12 (10.9)	5 (10.9)	27 (8.7)
Splenomegaly	11 (7.1)	13 (11.8)	2 (4.3)	26 (8.4)
Respiratory tract infections	19 (12.3)	6 (5.5)	0	25 (8.1)
Rash	13 (8.4)	11 (10)	0	20 (6.5)
Rhinitis	13 (8.4)	5 (4.5)	0	19 (6.1)
Malaria	15 (9.7)	6 (5.5)	4 (8.7)	30 (9.7)
Upper respiratory tract infections	6 (3.9)	11 (5.5)	4 (8.7)	15 (4.8)
Eosinophilia	7 (4.5)	5 (4.5)	0	13 (4.2)
Clonus	7 (4.5)	6 (5.5)	1 (2.2)	13 (4.2)
Pyrexia	4 (2.6)	5 (4.5)	1 (2.2)	12 (3.9)
Lower respiratory tract infections	9 (5.8)	7 (6.4)	1 (2.2)	12 (3.9)
Scabies infection	7 (4.5)	2 (1.8)	1 (2.2)	12 (3.9)
Constipation	5 (3.2)	4 (3.6)	0	11 (3.5)
Insomnia	7 (4.5)	6 (5.5)	1 (2.2)	11 (3.5)

*Source: Modified from Table 10-2 of the study report.

Medical Reviewer's Comments: *Cough, anemia, vomiting anorexia and diarrhea were the AE's reported in more than 10% of the overall safety population. The increased AEs in the 5- <10 kg body is expected within the corresponding age group.*

Hepatomegaly and splenomegaly were reported in 8-9% of patients. One patient experienced an AE affecting the cardiovascular system, sinus arrhythmia (the ECG showed sinus rhythm with marked sinus arrhythmia). This adverse event began on Day 3 and lasted for 5 days. No action was taken and arrhythmia resolved spontaneously.

The investigators reported that 25% of patients experienced AEs that were suspected to be related to the study medication. The most frequent were gastrointestinal disorders, vomiting and diarrhea, blood and lymphatic disorders, anemia and eosinophilia, nervous system disorders, clonus.

Table 10. N (%) patients with AEs (after baseline but before recurrence) suspected to be related to study drug (Safety population) Laboratory Values

MedDRA system organ class Adverse events (MedDRA PT)	5 - <10 kg (n=154)	10 - <15 kg (n=110)	15 - ≤ 25 kg (n=46)	Total (n=310)
Blood and lymphatic system disorders	14 (9.1)	12(10.9)	1 (2.2)	27 (8.7)
Anemia	8 (5.2)	6 (5.5)	1 (2.2)	15 (4.8)
Eosinophilia	6 (3.9)	6 (5.5)	0	12 (3.9)
Neutropenia	0	1 (0.9)	0	1 (0.3)
Cardiac disorders	0	1 (0.9)	0	1 (0.3)
Sinus arrhythmia	0	1 (0.9)	0	1 (0.3)
Gastrointestinal disorders	19 (12.3)	10 (9.1)	5 (10.9)	34 (11)
Vomiting	10 (6.5)	0	4 (8.7)	14 (4.5)
Diarrhea	5 (3.2)	5(4.5)	1 (2.2)	11 (3.5)
Constipation	2 (1.3)	3 (2.7)	0	5 (1.6)
Abdominal pain	0	2 (1.8)	0	2 (0.6)
Nausea	2 (1.3)	0	0	2 (0.6)
Abdominal distention	1 (0.6)	0	0	1 (0.3)
Procedural complications	2 (1.3)	0	0	2 (0.6)
Hypothermia	2 (1.3)	0	0	2 (0.6)
Investigations	0	2 (1.8)	0	2 (0.6)
Hemoglobin decreased	0	1 (0.9)	0	1 (0.3)
Transaminases increased	0	1 (0.9)	0	1 (0.3)
Metabolism and nutrition disorders	2 (1.3)	0	0	2 (0.6)
Anorexia	2 (1.3)	0	0	2 (0.6)
Nervous system disorders	7 (4.5)	6 (5.5)	1 (2.2)	14 (4.5)
Clonus	7 (4.5)	5 (4.5)	1 (2.2)	13 (4.2)
Hyperreflexia	1 (0.6)	2 (1.8)	1 (2.2)	4 (1.3)
Psychiatric disorders	1 (0.6)	0	0	1 (0.3)
Insomnia	1 (0.6)	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (1.3)	1 (0.9)	0	3 (1)
Cough	2 (1.3)	1 (0.9)	0	3 (1)
Catarrh	1 (0.6)	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	6 (3.9)	4 (3.6)	0	10 (3.2)
Rash	6 (3.9)	3 (2.7)	0	9 (2.90)
Urticaria	0	1 (0.9)	0	1 (0.3)

*Source: Table 10-3 of the study report.

Medical Reviewers' Comments: *Out of nervous system disorders, clonus is specifically further evaluated in the review. Clonus was observed in 13 patients post-baseline overall. The lack of comparator group makes it difficult to assess causality.*

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Table 11. Treatment emergent adverse events (AEs) observed in > 2 patients

Adverse Event (PT)	N of patients
Abdominal Distension	3
Abdominal Pain	7
Acute Coryza	11
Acute Respiratory Infection	7
Agitation	3
Anaemia	56
Anemia	8
Ankle clonus	3
Anorexia	37
ARI (Acute Respiratory Infection)	5
Asymptomatic Parasitemia	4
Boil	4
Catarrh	9
Chills	4
Clonus	10
Concunctivitis	6
Constipation	10
Cough	78
Coughing	6
Diarrhea	31
Eosinophilia	13
Excessive crying	3
Fever	7
Fever due to malaria	4
Headache	6
Heat Rash	3
Helminthiasis	4
Hepatomegaly	27
Hyperreflexia	6
Hypothermia	6
Insomnia	11
Irritability	7
LRTI	5
Malaria	21
Mild anemia	4
Nausea	6
None	85
Oral Moniliasis	4
Otitis media	4
Pityriasis veriscolor	3
Rash	12
Rashes	3
Rhinitis	6
Rigors	4
Scabies	8
Skin rash	3
Splenomegaly	26
URTI	8
Vomiting	45

Clinical laboratory evaluations

Hematology

Hemoglobin levels, hematocrit and erythrocyte counts decreased from baseline to Day 3, but increased from baseline to Day 28 consistent with the resolution of malarial infection. Platelet counts increased from baseline to Day 28. No significant changes were observed in total leukocyte counts.

A total of 13 (4.2%) patients had partial G-6-PD deficiency, and one patient had total G-6-PD deficiency. These patients had no post-baseline measurements of hemoglobin levels; in two patients for whom the data were available (both with partial G-6-PD deficiency) no adverse effects on the hemoglobin recovery levels were reported.

Medical Reviewer’s Comments: *Evaluation of the post-text listings confirmed the findings described above.*

Biochemistry

Analysis from baseline shift based on normal ranges showed biochemistry parameters shifting normal from baseline to Day 28 with the exception of creatinine (approximately 25% of patients who were normal at baseline shifted to low levels by Day 28) and, AST (approximately 35% of patients who were normal at baseline had high levels at Day 28). Most of these high levels at Day 28 were not clinically significant since limits for abnormalities were based on the normal range. In addition to the single patient with serious adverse event who had hepatitis (KEN/0001.00149) who was described in the narrative above, 12 additional cases were identified with higher than baseline values at Day 28 and a final AST value of more than 2x ULN. These cases are summarized in the table below.

Table 12. Patient patients with high levels of AST at Day 28 (>2x ULN)

Country/Center/Subject	Age/Sex	AST (U/L)		
		Day 0, pre-dose 1	Day 3	Day 28
KEN/0001.00140	0.58/M	59.4	30.9	139.6
KEN/0001.00146	0.92/M	72.5	34.5	139.2
NGA/0002.00121	1.92/F	73	32	591
NGA/0002.00124	0.82/F	80	131	117
NGA/0002.00132	1.17/M	39	79	109
NGA/0002.00137	0.92/M	83	54	128
KEN/0001.00209	4.42/F	181.7	100.4	282.4
KEN/0001.00223*	2.42/M	42.1	136.6	101.8
KEN/0001.00233*	4.17/F	40.8	56.8	100.5
NGA/0002.00228	5/F	-	34	157
TZA/0003.00226	3.58/M	47.4	62.8	97.3
NGA/0002.00308*	8.67/M	29	22	136

*Patients with normal SGOT values at baseline.

Medical Reviewer’s Comments: *Most patients listed in the table above had levels outside of the normal range at baseline. Most significant shift in the AST value occurred in one patient (NGA/0002.00121); this patient was not cited among cases with serious adverse events.*

ECG Evaluations

Patients were evaluated using a standard 12-lead ECG at baseline and Day 3. Heart rate (subsequently R-R interval were found to decrease from baseline); PR, QRS and QT intervals all showed slight increases.

Shift from baseline analyses of QTc interval (based on Bazett's formula) showed one patient with normal baseline QTc interval, one patient (0.4%) had QTc prolongation at Day 3 (male patient had an increase from 403 to 454 msec) and 19 (7%) were borderline. Out of the three patients with QTc prolongation at baseline, all but one had normal QTc at Day 3 and the remaining patient (male) had a change from 451 msec at baseline to 468 msec at Day 3.

Seventeen patients had borderline QTc at baseline (431-450 msec in males, 451-470 msec in females), all but two remained borderline at Day 3, two patients had QTc prolongation (one female patient had an increase from 456 to 480 msec, and one male patient had increase from 438 to 470 msec). All patients who had QTc shifting into the prolonged range at Day 3 were in the 5 < 10 kg body weight group, all were 2 years of age or younger. Analysis of QTc interval based on Fridericia's formula, showed no patients with QTc prolongation at baseline or Day 3.

Medical Reviewer's Comments: In general, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates. Patients with malaria often have elevated heart rates until parasitemia begins to resolve (as indicated in this study by the PR intervals decreasing from baseline), therefore, QT correction by Fridericia's formula is thought to be the more appropriate correction formula for this study..

The medical reviewer will defer to IRT consult for labeling proposals regarding Coartem effects on the QTc interval.

Treatment-emergent signs and symptoms

Treatment Emergent Signs and Symptoms (TESS) of malaria were collected at baseline and at each follow-up visit (on a specific CRF). Developing or worsening diarrhea, cough, rash or clonus was identified in some small number patients. Hepatomegaly and splenomegaly were slower to resolve and had not resolved in all of the patients by Day 28.

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Table 13. Treatment-emergent signs and symptoms – Clonus (Safety patients)

Country/Center/Subject	Age/Sex	Clonus						
		Day 0	Day 1	Day 2	Day 3	Day 7	Day 14	End (Day 28)
5 - < 10 kg								
NGA/0002.00109	0.75/M	-	-	+	-	-	-	-
NGA/0002.00114	0.92/M	-	+	+	+	-	-	-
NGA/0002.00117	1.33/F	-	-	+	-	-	-	Not done
NGA/0002.00122	1.17/F	+	-	-	-	-	-	-
NGA/0002.00132	1.17/M	-	-	+	+	+	-	-
NGA/0002.00134	1.42/F	-	+	+	-	-	-	-
NGA/0002.00125	0.58/F	-	-	+	+	-	-	-
NGA/0002.00136	1.50/F	+	-	+	+	-	-	-
10- < 15 kg								
NGA/0002.00215	2.08/M	-	-	-	+	-	-	-
NGA/0002.00217	4.42/M	-	-	+	+	-	-	-
NGA/0002.00219	6.75/M	-	+	+	-	-	-	-
NGA/0002.00222	2.67/M	-	-	+	-	-	-	-
NGA/0002.00229	2.33/F	-	-	-	-	-	+	-
15 - ≤25 kg								
NGA/0002.00313	5.75/F	-	+	+	+	+	+	+

*No patients with clonus at Day 1, pre-dose 1.

Medical Reviewer’s Comments: *Except for one patient in the 15 to ≤25 kg weight group, clonus reported in any patient at any time point during study had resolved by the end of study (Day 28). All patients were part of the same study center in Nigeria.*

4.1.4. Summary and Conclusions Regarding Study A2403

The study (A2403) was performed to evaluate the safety and efficacy of 6-dose regimen of Coartem in the treatment of uncomplicated *Plasmodium falciparum* malaria in African infants and children with body weight 5 to 25 kg. The study enrolled over 300 children. Over 98% of patients received 6-dose course of treatment. The age groups into which most patients fell were 12-24 months and 2 to 4 years. This younger age group is at high risk of malaria and its complications, including death.

The safety evaluations have to be taken into consideration within the limits of the study design, namely, open-label, uncontrolled study.

One (4 year old female) patients died as a result of severe gastroenteritis. Malaria was noted to be cured and patient completed therapy without significant events. Therefore her death is not likely to be related to study drug. Six patients experienced severe AEs: these were anemia (2 patients), gastroenteritis (1 case), (viral) hepatitis (one case), urticaria (1 case), malaria (1 case). Except for the two cases of anemia and one case of malaria which was assessed as related to baseline disorder, the remaining three were categorized as SAEs. One patient discontinued due to an SAE of urticaria which is most likely to be related to study drug.

The most common body systems affected were ‘infections and infestations’, ‘blood and lymphatic system disorders’, respiratory, thoracic and mediastinal disorders’ and ‘gastrointestinal disorders’. This was expected in this population given the age group and the underlying disease.

Treatment Emergent Signs and Symptoms of malaria were collected at baseline and at each follow-up visit. Developing or worsening diarrhea, cough, rash or clonus was identified in some small number patients. Special attention was given to neurological adverse events and specifically to clonus; except for one patient clonus reported in any patient at any time point during study had resolved by the end of study (Day 28). All patients were part of the same study center in Nigeria, with no other cases reported from other study centers.

Among laboratory values, special attention was paid to the increases in liver transaminases, specifically AST: twelve cases were identified with higher than baseline values at Day 28 and a final AST value of more than 2x ULN. Other than three patients with normal AST at baseline, all had values outside the normal range at baseline. Most significant shift in AST was observed in one patient. Given the age and the number of patients in this study with malaria in the study, the changes in the AST evaluations are within the expected range in this population and did not result in serious adverse events or discontinuations.

4.2. SAFETY REVIEW STUDY B2303

Study No: CCOA566B2303

Title: A randomized, investigator-blinded, multicenter, parallel-group study to compare efficacy, safety and tolerability of Coartem® dispersible tablet formulation vs. Coartem® 6-dose crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children.

Study dates: Aug-2006 through Mar-2007

Study Center(s): The study was conducted in three centers in Kenya, one center in Mozambique, two centers in Tanzania, one center in Mali, and in one center in Republic of Benin.

4.2.1. Study Objectives and Design

The primary objective was to confirm the efficacy of the Coartem dispersible tablet in infants and children with a body weight of ≥ 5 kg and < 35 kg and ≤ 12 years of age suffering from *P. falciparum* malaria by testing the hypothesis that Coartem 6-dose dispersible tablet is non-inferior to the presently used Coartem 6-dose regimen of crushed tablet on the 28-day PCR-corrected parasitological cure rate.

The secondary objectives included (not listing all):

- To compare the safety and tolerability profile of the two treatment groups (AEs, general laboratory, vital signs, and ECG measurements).

This study design was a randomized, investigator-blinded, multi-center, parallel-group design to assess the efficacy, safety and tolerability of a Coartem 6-dose regimen of dispersible tablet vs.

Coartem 6-dose crushed tablets under supervised treatment (each tablet or dispersible tablet containing 20 mg artemether and 120 mg lumefantrine).
 A total of 890 male and female infants and children (≤ 12 years of age) with acute uncomplicated *P. falciparum* malaria were required.

Medical Reviewer’s Comments: *Reference is made to clinical efficacy review by Dr. Elizabeth O’Shaughnessy for further details in study objectives and design. Comparator groups were designed to compare to assess efficacy of Coartem 6-dose dispersible versus 6-dose crushed tablets and for evaluation of safety, both arms still include study drug under investigation, i.e. 6-dose regimen of artemether/lumefantrine, and therefore is not a randomized study in this sense (other than by formulation).*

Patients were admitted to hospital for the first 3 days and all treatments were given under hospital supervision. All randomized patients remained under medical surveillance (if possible within hospital grounds) for the following 4 days (until Day 7) until the results of the interim analysis were known. These patients were then followed until Day 42 and accounted for the primary and secondary assessment of the study.
 Study medication was followed by food/drink whenever possible. Patients who vomited a dose within 1 hour of trial drug administration were given a replacement dose. During the entire treatment phase no more than two doses were to be replaced.

Table 14. Study Design

Visit	1	2	3	4	5	6	7	8	9	10	11
Evaluation	Pre-treatment	Treatment Phase					Follow-up phase				
Day	1	2		3			4	7	14	28	42
Hours		0	8	24	36	48	60				
Dosing		X	X	X	X	X	X				
Screening	X										
Randomization	X										
Study Completion form											X

*Source: Modified from Table 10-3 of the study report.

Patients were assigned to one of the following 2 treatment arms in a ratio of 1:1 and received active treatment based on body weight as follows:

- BWG 1: ≥ 5 kg – < 15 kg = 6 doses of 1 tablet
- BWG 2: ≥ 15 kg – < 25 kg = 6 doses of 2 tablets
- BWG 3: ≥ 25 kg – < 35 kg = 6 doses of 3 tablets

Patients were not replaced if treatment was not well tolerated during the first 3 days of dosing and the investigators were to attempt recruiting patients so that all weight groups were adequately represented (e.g. at least 25% in each weight group).

4.2.2. Safety Evaluation and definition of safety population

Baseline demographics characteristics for the safety population are presented in the table below. Approximately 60% of the patients fell into the 5 - < 15 kg body weight group and over a half of the patients were 2 to 6 years of age.

Table 15. Baseline demographic summary (Safety population)

	Dispersible tablet (N=447)	Crushed tablet (N=452)	Total (N=899)
Age (Years)			
N	447	452	899
Mean ± SD	3.6 ± 2.69	3.7 ± 2.84	3.6 ± 2.69
Median	3	3	3
Age distribution n (%)			
< 3 months*	1 (0.2)	1 (0.2)	2 (0.2)
3 - < 6 months	6 (1.3)	7 (1.5)	13 (1.4)
12 - < 24 months	23 (5.1)	28 (6.2)	51 (5.7)
2 - < 4 yrs	81 (18.1)	73 (16.2)	154 (17.1)
4-6 yrs	92 (20.6)	15 (13.6)	181 (20.1)
6 -12 yrs	99 (22.1)	2 (1.8)	204 (22.7)
Body weight			
N	447	452	899
Mean ± SD	14.4 ± 5.51	14.5 ± 5.53	14.4 ± 5.52
Median	13	13.1	13
Range	5 - 34	6 - 34	5 - 34

Source Table 7- 4 of the study report.

* Demographics dataset in the submission was reviewed for the age range; there was one patient 0.2 year old (approximately 2.4 months old), and 8 patients 0.3 year old (approximately 3.5 months old)

All adverse event summaries included adverse events that newly occurred or increased in intensity after the first dose of study medication until 42 days thereafter.

Adverse events (AEs) were summarized for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and each individual AE (preferred term). Adverse events were also summarized by maximum intensity, primary system organ class, and preferred term.

Treatment emergent signs of symptoms of malaria (TESS) were tabulated by worst intensity. Listings and summaries of serious adverse events, of adverse events leading to discontinuation of study drug, and adverse events leading to interruption of study drug were summarized.

Medical history/current medical conditions and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology (Version 10.0).

Safety assessments consisted of:

- monitoring and recording all adverse events, pregnancies
- the monitoring of hematology, blood chemistry, including liver function test (urine values)
- regular measurement of vital signs

- physical and specific neurological examinations
- ECG recordings at study entry and on Day 3 (6 – 10 hours) after last dose.

Safety population included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment; patients were analyzed according to treatment received. A patient who vomited the first dose of study medication as well as its replacement dose was considered having received at least one dose of study drug for the safety analysis.

Patient Disposition

Patient disposition is presented in the table below. Over 85% of patients in each treatment group completed the study.

Table 16. Patient disposition (Randomized population)

	Dispersible tablet	Crushed tablet	Total
Total number of patients- n(%)			
Randomized	447 (100)	452 (100)	899 (100)
Treated (at least one dose)	447 (100)	452 (100)	899 (100)
Treated (at least one full dose)*	444 (99.3)	446 (98.7)	890 (99)
Completed treatment period	431 (96.4)	435 (96.2)	866 (96.3)
Completed study	394 (88.1)	388 (85.8)	782 (87)
Discontinuations- n (%)			
Total	53 (11.9)	64 (14.2)	117 (13)
Primary reason			
Adverse events	30 (6.7)	40 (8.8)	70 (7.8)
Lost to follow-up	15 (3.4)	12 (2.7)	27 (3)
Subject withdrew consent	6 (1.3)	11 (2.4)	17 (1.9)
Death	1 (0.4)	1 (0.2)	3 (0.3)

*A dose that was not vomited, or a dose that was vomited and replaced and the replacement was not vomited was considered a full dose.

*Source: Table 10-3 of the study report.

Patient exposure to Coartem is presented in the table below for the safety population. The majority of patients received the full 6-dose course of treatment. Most patients who vomited a dose only vomited one dose and the majority of vomited doses were replaced. The vomiting of replacement doses was less common. The proportion of patients who switched to rescue medication due to vomiting of study medication was less than 2.5%.

Table 17. Overall study drug exposure (Safety population)

	Dispersible tablet N=447 n(%)	Crushed tablet N=452 n(%)
Patients took		
1 dose	5 (1.1)	8 (1.8)
2 doses	6 (1.3)	5 (1.1)
3 doses	3 (0.7)	2 (0.4)
4 doses	1(0.2)	1 (0.2)
5 doses	1 (0.2)	1 (0.2)
6 doses	431 (96.4)	435 (96.2)

Coartem®/ artemether/lumefantrine

Patients who vomited		
No dose	404 (90.4)	394 (87.2)
One dose	33 (7.4)	47 (10.4)
Two doses	9 (2)	11 (2.4)
> Two doses	1 (0.2)	0

*Source: Modified from Table 8-1 of the study report.

The incidence of deaths, serious or significant AEs, AEs requiring study drug adjustment or interruption, and discontinuations due to AEs are presented in the table below.

4.2.3. Safety Results

The incidence of deaths, serious or significant AEs, AEs requiring study drug adjustment/interruption, and discontinuations due to AEs are presented in the table below. There were 3 deaths in the study, all case narratives summarized in the course of this review.

Table 18. Number (%) of patients who died, had serious or other significant AEs or discontinued because of them (Safety population)

	Dispersible tablet N=447 n(%)	Crushed tablet N=452 n(%)
Patients studied		
-Total no. of patients with AEs	307 (68.7)	318 (70.4)
-Total no. of patients with serious - significant adverse events	12 (2.7)	17 (3.8)
Serious or significant AEs		
-Deaths	2 (0.4)	1 (0.2)
-SAEs	7 (1.6)	6 (1.3)
-AEs leading to discontinuation	9 (2)	11 (2.4)
-AEs requiring dose adjustment or study drug interruption	0	0

*Source: Table 10-3 of the study report.

Medical Reviewer’s Comments: *It is noted that AEs leading to discontinuation is less in the safety population than the randomized patient population (70 in the randomized population vs. 20 in the safety population). A closer look later in the course of the review revealed that many cases discontinued from the study due to vomiting and P. falciparum infection before the administration of the first dose of the study drug.*

For the purposes of this safety review, numbers of SAEs and AEs leading to discontinuation in the safety population is more helpful.

The most frequently affected primary system organ classes were general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders. The most frequent AEs were pyrexia, cough, *P. falciparum* infection and vomiting. Splenomegaly was reported in 6.7% of patients. This AE was pre-existing in 21% of patients at baseline. The proportion of patients with diarrhea was slightly higher in the dispersible tablet group in comparison to the crushed tablet group. Other frequent AEs were abdominal pain, headache, and anorexia observed in both treatment groups.

One case of ear pain was reported and the event occurred in the crushed tablet group. Ear infections were reported in 2.0% of patients in the dispersible tablet group and in 1.5% of patients in the crushed tablet group. There were no other AEs related to the auditory system. Five patients (1.1%) in the dispersible tablet group and 3 patients (0.7%) in the crushed tablet group reported cardiac disorder AEs which will be discussed in greater detail.

Table 19. Number (%) of patients with most frequent AEs (5% in any treatment group) by primary system organ class and preferred term (Safety population)

	Dispersible tablet n(%)	Crushed n(%)
Patients studied		
Total no. of patients	447	452
Total no. patients with AEs	307 (68.7)	318 (70.4)
System organ class/ AE		
Blood and lymphatic system disorders	44 (9.8)	46 (10.2)
Splenomegaly	30 (6.7)	30 (6.6)
Gastrointestinal disorders	125 (28)	119 (26.3)
Vomiting	75 (16.8)	76 (16.8)
Abdominal pain	37 (8.3)	31 (6.9)
Diarrhea	36 (8.1)	26 (5.8)
General disorders	169 (37.8)	169 (37.4)
Pyrexia	167 (37.4)	165 (36.5)
Infections and infestations	164 (36.7)	158 (35)
<i>Plasmodium falciparum</i> infection	86 (19.2)	101 (22.3)
Investigations	55 (12.3)	50 (11.1)
Aspartate aminotransferase (AST) increased	27 (6)	20 (4.4)
4 (2.4)Metabolism and nutrition disorders	31 (6.9)	31 (6.9)
Anorexia	28 (6.3)	30 (6.6)
Nervous disorders	36 (8.1)	38 (8.4)
Headache	33 (7.4)	33 (7.3)
Respiratory, thoracic and mediastinal disorders	107 (23.9)	117 (25.9)
Cough	105 (23.5)	113 (25)

*All adverse events that occurred on the first study drug administration (Day 1) until Day 43 inclusive were included.

*Source: Table 10-1 of the study report.

Severe AEs were reported by 8.3% of the patients in the dispersible tablet group and 7.3% of patients in the crushed tablet group.

The most frequent AE that was assessed as related to the study drug administration was vomiting, 7.4% in the dispersible tablet group vs. 9.3% in the crushed tablet group.

All adverse events after baseline, regardless of study-drug relationship, by MedDRA primary system organ class and preferred term (PT), by body weight group (BWG) and treatment (in Safety population) is presented in the table below.

Table 20. All adverse events after baseline, regardless of study drug relationship, by system organ class, PT and by BWG

Primary system organ class Preferred term (>2%)	5 - <10 kg (n=168) n (%)	10 - <15 kg (n=379) n (%)	15 - ≤ 25 kg (n=289) n (%)	25 - < 35 kg (n=63) n(%)
Any primary system organ class	125 (74.4)	265 (69.9)	196 (67.8)	39 (61.9)
Blood and lymphatic system disorders	19 (11.3)	39 (10.3)	29 (10)	3 (4.8)
Cardiac disorders	1 (0.6)	3 (0.8)	3 (1)	1 (1.6)
Arrhythmia	1 (0.6)	2 (0.5)	3 (1)	1 (1.6)
Tachycardia	0	1 (0.3)	0	0
Ear and labyrinth disorders	0	0	1 (0.3)	1 (1.6)
Ear pain			1 (0.3)	1 (1.6)
Eye disorders	4 (2.4)	2 (0.5)	6 (2.1)	1 (1.6)
Conjunctivitis	4 (2.4)	2 (0.5)	6 (2.1)	1 (1.6)
Gastrointestinal disorders	70 (41.7)	98 (25.9)	66 (22.8)	10 (15.9)
Vomiting	54 (32.1)	62 (16.4)	33 (11.4)	2 (3.2)
Abdominal pain	2 (1.2)	26 (6.9)	35 (12.1)	5 (7.9)
Diarrhea	29 (17.3)	24 (6.3)	8 (2.8)	1 (1.6)
General disorders	72 (42.9)	145 (38.3)	104 (36)	15 (23.8)
Fever	71 (42.3)	10 (2.6)	101 (34.9)	15 (23.8)
Hepatobiliary disorders	4 (2.4)	6 (1.6)	2 (0.7)	0
Infections and Infestations	60 (35.7)	144 (38)	97 (33.6)	21 (33.3)
<i>Plasmodium falciparum</i> infection	28 (16.7)	76 (20.1)	67 (23.2)	16 (25.4)
Rhinitis	10 (6)	17 (4.5)	4 (1.4)	0
URTI	7 (4.2)	8 (2.1)	2 (0.7)	0
Ear infection	2 (1.2)	8 (2.1)	5 (1.7)	1 (1.6)
Pneumonia	2 (1.2)	11 (2.9)	1 (0.3)	0
Investigations	15 (8.9)	43 (11.3)	43 (14.9)	4 (6.3)
AST increased	5 (3)	18 (4.7)	22 (7.6)	2 (3.2)
Platelet count decreased	2 (1.2)	9 (2.4)	8 (2.8)	0
Metabolism and nutrition disorder	19 (11.3)	26 (6.9)	16 (5.5)	1 (1.6)
Anorexia	16 (9.5)	25 (6.6)	16 (5.5)	1 (1.6)
Nervous system disorders	1 (0.6)	19 (5)	42 (14.5)	12 (19)
Headache	1 (0.6)	14 (3.7)	39 (13.5)	12 (19)
Convulsion	0	1 (0.3)	2 (0.7)	0
Psychiatric disorders	10 (6)	14 (3.7)	3 (1)	0
Mood swings	4 (2.4)	8 (2.1)	3 (1)	0
Agitation	4 (2.4)	3 (0.8)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	52(31)	102 (26.9)	60 (20.8)	9 (14.3)
Cough	50 (29.8)	100 (26.4)	59 (20.4)	1 (1.6)
Skin and subcutaneous tissue disorders	9 (5.4)	15 (4)	7 (2.4)	1 (1.6)
Rash	4 (2.4)	11 (2.9)	3 (1)	0
Dermatitis	2 (1.2)	1 (0.3)	2 (0.7)	0

*Summarized from analysis output 6.1.1, Appendix 8.1.

Medical Reviewer's Comments: *The table reflects the age specific differences between the body weight groups which would be expected. For example anorexia, is most common in the 5 - <10 kg which is expected to be most common in the corresponding age group. The table also*

helps visualization of adverse events of concern by primary organ class such as nervous system disorders and did not report unusual findings by body weight groups.

Deaths, other serious and significant adverse events

The incidence of deaths, serious or significant AEs, AEs requiring study drug adjustment/interruption, and discontinuations due to AEs are presented in the table below.

There were 3 deaths during the study.

MLI/0601/00203 (dispersible tablet): 4 month old black male (weight: 6.2 kg)

Infection, vomiting

The patient had past medical history of bronchitis treated with amoxicillin and presented with cough, diarrhea, fever and vomiting.

The patient vomited after ingestion of the first and second dose of the study medication. The dose was repeated within one hour on both occasions. On the Study Day 2, he had another episode of vomiting within one hour of dosing and the study medication was permanently discontinued. On the same day, the patient developed moderate fever (38.9°C) and was diagnosed with severe infection complicated by dehydration. He received paracetamol and amoxicillin and metoclopramide for vomiting. He started quinine as a rescue medication for malaria on the same day. On study Day 3, his condition worsened and died due to infection and dehydration.

BEN/0801/00047 (dispersible tablet): 2.4 year old, black male (10 kg)

Hemorrhage, hemoglobin decreased

The patient did not have any significant past medical history. He was only noted to have splenomegaly at study entry. He received the first dose of the study medication on Study Day 1, when his hemoglobin level was 7.8 mg/dL, his platelet count ($300 \times 10^9/L$).

The patient received the last dose of study medication on Study Day 4 and the parasite clearance was confirmed on Study Day 3.

On Study Day 3, the patient developed moderate fever and was treated with paracetamol. The fever subsided on Study Day 4, but the patient was noted to have decreased hemoglobin (5.1 g/dL). On the same day, he received the last dose of the study medication and he had an episode of mild vomiting after the last dose. He was treated with iron-folic acid for the event of decreased hemoglobin.

On Study Day 5, he was taken to a traditional therapist who performed a traditional abdominal surgery on his left hypochondrium (Scarification). This event was considered medically significant. On Study Day 6, the patient was hospitalized with the diagnosis of anemia (hemoglobin 7.8 g/dL) and continuing splenomegaly. On Study Day 7, his condition worsened and he died due to fatal hemorrhage.

TZA/0301/00203 (crushed tablet): 5 month old black male (6 kg).

P. falciparum infection (severe), pyrexia, convulsion

The patient did not have any active and significant past medical history at the study entry. His concomitant medication included paracetamol for fever.

He received the first dose of study medication on Study Day 1, when his hemoglobin level was 7.4 g/dL. He received the last dose of the study medication on Study Day 4 and the parasite clearance was confirmed on Study Day 2.

On Study Day 29, the patient developed severe pyrexia and he was hospitalized the next day with diagnosis of severe *P. falciparum* infection. He was noted with severe anemia (hemoglobin level of 3.1 g/dL) and his platelet count was $28 \times 10^9/L$. His body temperature was 36°C, pulse was 125 bpm, and BP was 132/62 mm of Hg and his asexual parasite count was 8446/μl. On admission, the patient had constant convulsions and he showed no significant neurological findings. No details of treatment given were available. On Study Day 31, the patient's condition worsened and he died due to pyrexia, convulsion and the disease (malaria) progression.

Medical Reviewer's Comments: *The death of these three patients described were not likely to be related to the study drug: the first patient died due dehydration secondary to his infection, the second patient died due to hemorrhage secondary traditional medical practices, and the third patient due to malaria after his first episode seemed to be adequately treated.*

The two tables below summarize the patients with serious adverse events.

Table 21. Serious adverse events (including deaths) regardless of study-drug relationship, by primary system organ class, preferred term (Safety population)

Primary system organ class Preferred term	Dispersible tablet N=447	Crushed tablet N=452
Investigations	1 (0.2)	0
Hemoglobin decreased	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Dehydration	1 (0.2)	0
Oral intake reduced	1 (0.2)	0
Nervous system disorders	1 (0.2)	1 (0.2)
Convulsion	1 (0.2)	1 (0.2)
Vascular disorders	1 (0.2)	0
Hemorrhage	1 (0.2)	0

Table 22. Summary of Patients with Serious Adverse Events (excluding deaths)

Patient no.	Age/race/gender	Weight (kg)	Adverse Event	Outcome
Coartem dispersible tablet				
KEN/0101/00084	2y/ B/ F	8.1	Lower respiratory tract infection	Recovery
KEN/0101/00106	9m/ B/ M	6.6	<i>P. falciparum</i> infection, anemia	Ongoing
KEN/0102/00009	7m/ B/ M	8	<i>P. falciparum</i> infection, anemia	Recovery
KEN/0102/00026	1.6y/B/F	8	Dehydration, diarrhea, vomiting	Recovery
MLI/0601/00046	5.2/ B/ M	17	Convulsion, fever, epilepsy	Partial Recovery
Coartem crushed tablet				
KEN/0101/00044	6m/ B/ M	7.9	Laryngotacheobronchitis	Recovery
KEN/0102/00011	1.9y/ B/ M	12	<i>P. falciparum</i> infection	Recovery
KEN/0102/00022	2.8y/ B/ M	15	<i>P. falciparum</i> infection, convulsion	Ongoing
KEN/0102/00031	5m/ B/M	7	<i>P. falciparum</i> infection, pneumonia	Recovery
BEN/0801/00051	4.2y/ B/ F	11.5	Fever, anemia, facial edema	Recovery

Medical Reviewer’s Comments: *In depth review of each case revealed that the serious adverse event was not likely due to the study medication. In case of the patient with facial edema, the event occurred 2 days after the last dose of the study drug as administered. There was one case of convulsion in each formulation group. A 5.2 year old black male (dispersible tablet group) was diagnosed to have epilepsy twenty days after completion of study based on EEG changes; he was afebrile at the onset of his first seizure episode. Another 2.8 year old black male patient (crushed tablet group) developed severe P. falciparum infection and was hospitalized on Study Day 42 with fever, vomiting and convulsions after his initial parasite clearance was confirmed on Day 2 of the study. The convulsion was reported to be associated with fever and a new onset P. falciparum infection.*

The following two tables summarize the cases of discontinuations due adverse events.

Table 23. Discontinuations due to adverse events (regardless of study-drug relationship) by primary system organ class and preferred term (Safety population)

Primary system organ class Preferred term	Dispersible tablet N=447 (%)	Crushed tablet N=452 (%)
Any primary system organ class	9 (2)	11 (2.4)
Blood and lymphatic system disorders	2 (0.40)	0
Anemia	1 (0.2)	0
Iron deficiency anemia	1 (0.2)	0
Gastrointestinal disorders	6 (1.3)	11 (2.4)
Vomiting	6 (1.3)	11 (2.4)
Infections and infestations	3 (0.7)	0
Plasmodium falciparum infection	2 (0.4)	0
Lower respiratory tract infection	1 (0.2)	0

* Source: Post-text table 10.2-4 of the study report.

Table 24. Summary of Case Narratives for Discontinuations due to Adverse Events (Randomized population)

Patient no.	Age/race/gender	Weight (kg)	Adverse Event	Outcome
Coartem dispersible tablet				
KEN/0101/00001	1.7y/ B/ F	11.1	Vomiting	Recovery
KEN/0101/00015	3.2y/ B/F	3.2	Vomiting	Recovery
MOZ/0201/00088	3.3y/ B/ M	11	Vomiting	Recovery
MLI/0601/00042	4.8y/ B/M	19	Vomiting	Recovery
MLI/0601/00205	11m/ B/ M	8.5	Vomiting	Recovery
TZA/0301/00141	2.3y/B/ F	12	<i>P. falciparum</i> infection, fever, vomiting	Recovery
MLI/0601/00003	7.1/ B/ F	20	<i>P. falciparum</i> infection, fever, headache, vomiting, abdominal pain	Recovery
MLI/0601/00009	7.1/B/M	25	<i>P. falciparum</i> infection, fever, headache	Recovery
MLI/0601/00010	8.1y/ B/ M	23	<i>P. falciparum</i> infection	Recovery
MLI/0601/00011	6.1y/ B/ M	19	<i>P. falciparum</i> infection	Recovery
MLI/0601/00013	9.2y/ B/ M	22	<i>P. falciparum</i> infection, fever, headache	Recovery
MLI/0601/00030	1.3y/ B/ M	9.5	<i>P. falciparum</i> infection, fever	Recovery
MLI/0601/00040	4.5y/ B/ M	13	<i>P. falciparum</i> infection, cough, fever, nausea	Recovery
MLI/0601/00063	7.9/ B/ M	25	<i>P. falciparum</i> infection, headache, nausea	Recovery

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MLI/0601/00074	6.3y/ B/F	20	<i>P. falciparum</i> infection, headache, fever, chills, abdominal pain	Recovery
MLI/0601/00077	8.3y/B/M	21	<i>P. falciparum</i> infection, headache	Recovery
MLI/0601/00080	9.3y/ B/M	27	<i>P. falciparum</i> infection, headache, chills, fever	Recovery
MLI/0601/00082	6.3y/ B/ M	19	<i>P. falciparum</i> infection, splenomegaly	Recovery
MLI/0601/00093	4.3y/ B/ F	17	<i>P. falciparum</i> infection, fever	Recovery
MLI/0601/00094	4.6y/ B/ M	13	<i>P. falciparum</i> infection, fever, splenomegaly, abdominal pain, headache	Recovery
MLI/0601/00097	3.3y/ B/ M	14	<i>P. falciparum</i> infection, vomiting, abdominal pain, splenomegaly	Recovery
MLI/0601/000110	5.2y/ B/F	16	<i>P. falciparum</i> infection	Recovery
MLI/0601/000114	4.8y/ B/ F	14	<i>P. falciparum</i> infection, fever, abdominal pain	Recovery
MLI/0601/000116	3.6y/ B/ F	12	<i>P. falciparum</i> infection, cough	Recovery
MLI/0601/000116	10.3y/ B/ M	34	<i>P. falciparum</i> infection	Recovery
BEN/0801/00013	2.7y/B/M	12	<i>P. falciparum</i> infection, vomiting, fever, ear infection, anorexia, cough, mood swings	Recovery
BEN/0801/00034	1.2y/ B/ M	13	<i>P. falciparum</i> infection, fever	Recovery
BEN/0801/00064	4.8y/ B/ M	16	<i>P. falciparum</i> infection, cough, anemia	Ongoing
BEN/0801/00101	7.3y/ B/ F	17.5	<i>P. falciparum</i> infection, fever, vomiting, anorexia	Recovery
Coartem crushed tablet				
KEN/0101/00010	1y/ F/ M	8.7	Vomiting	Recovery
KEN/0101/00035	1.1y/ B/ M	7.1	Vomiting	Recovery
KEN/0101/00058	1.3y/ B/ M	9.5	Vomiting	Recovery
KEN/0101/00029	1.5y/ B/ F	11	Vomiting	Recovery
TZA/0301/00050	3.8y/ B/ F	13	Vomiting	Recovery
MLI/0601/00075	2y/ B/ F	9.5	Vomiting	Recovery
MLI/0601/00085	4.3y/B/ F	17	Vomiting	Recovery
MLI/0601/00099	9m/ B/ F	8	Vomiting	Recovery
MLI/0601/00151	2.3y/ B/ F	10	Vomiting	Recovery
MLI/0601/00157	8m/ B/ M	8	Vomiting	Recovery
MLI/0601/00185	1y/ B/ M	8	Vomiting	Recovery
TZA/0301/00118	6.7y/ B/ F	21	<i>P. falciparum</i> infection	Recovery
TZA/0301/00155	4.5y/ B/ F	12.5	<i>P. falciparum</i> infection, fever	Recovery
TZA/0301/00163	8.8y/ B/ F	25	<i>P. falciparum</i> infection, fever	Recovery
MLI/0601/00005	5.6y/ B/ M	18	<i>P. falciparum</i> infection, fever, headache, splenomegaly	Recovery
MLI/0601/00006	4.8y/ B/ M	18	<i>P. falciparum</i> infection	Recovery
MLI/0601/00007	9.1y/ B/ M	26	<i>P. falciparum</i> infection, fever, abdominal pain	Recovery
MLI/0601/00012	4y/ B/ M	13	<i>P. falciparum</i> infection	Recovery
MLI/0601/00015	3.2y/ B/ F	11	<i>P. falciparum</i> infection	Recovery
MLI/0601/00017	4.9y/ B/ F	15	<i>P. falciparum</i> infection, headache	Recovery
MLI/0601/00018	1.7/ B/ M	10	<i>P. falciparum</i> infection, fever, chills, abdominal pain, anorexia, diarrhea, cough	Recovery
MLI/0601/00022	2.2y/ B/ M	11	<i>P. falciparum</i> infection, fever, splenomegaly	Partial recovery
MLI/0601/00025	7.8y/ B/ M	20	<i>P. falciparum</i> infection, fever, abdominal pain, headache, diarrhea	Recovery
MLI/0601/00029	4.2y/ B/ M	17	<i>P. falciparum</i> infection, abdominal pain	Recovery

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MLI/0601/00031	7.2y/ B/ M	21	<i>P. falciparum</i> infection, abdominal pain	Recovery
MLI/0601/00038	4.3y/ B/ M	14	<i>P. falciparum</i> infection, cough, headache	Recovery
MLI/0601/00041	2.6y/ B/ F	12	<i>P. falciparum</i> infection, fever, chills, abdominal pain, headache, anxiety, anorexia	Recovery
MLI/0601/00043	2.7y/ B/ F	13	<i>P. falciparum</i> infection, fever, chills, fatigue, anorexia	Recovery
MLI/0601/00047	5.5y/ B/ M	22	<i>P. falciparum</i> infection, cough, chills, headache, vomiting, nausea, abdominal pain, anorexia	Recovery
MLI/0601/00048	8.2y/ B/ M	21	<i>P. falciparum</i> infection, headache	Recovery
MLI/0601/00056	10.2y/ B/ M	26	<i>P. falciparum</i> infection	Recovery
MLI/0601/00090	7.3 y/ B/ M	18	<i>P. falciparum</i> infection, fever	Recovery
MLI/0601/00091	4.3y/ B/ M	20	<i>P. falciparum</i> infection	Recovery
MLI/0601/00092	7.3y/ B/ M	23	<i>P. falciparum</i> infection, fever, headache	Recovery
MLI/0601/00098	8m/ B/ M	8.5	<i>P. falciparum</i> infection	Recovery
MLI/0601/00102	2.7y/ B/M	10	<i>P. falciparum</i> infection, diarrhea	Recovery
MLI/0601/00109	4.3y/ B/ M	14	<i>P. falciparum</i> infection, splenomegaly, fever, headache	Recovery
MLI/0601/00117	6.3y/ B/M	18	<i>P. falciparum</i> infection, splenomegaly, abdominal pain, fever	Recovery
MLI/0601/00117	1y/ B/ M	9.3	<i>P. falciparum</i> infection, diarrhea, fever	Recovery
MLI/0601/00122	5.4y/ B/ F	19	<i>P. falciparum</i> infection	Recovery
BEN/ 0801/00004	7.1y/ B/ M	20	<i>P. falciparum</i> infection*, pyrexia, vomiting	Partial recovery
BEN/ 0801/00033	4.1y/ B/ F	14	<i>P. falciparum</i> infection	Recovery
BEN/ 0801/00053	3.4y/ B/ M	19	<i>P. falciparum</i> infection, fever, anorexia, abdominal pain, fatigue, mood swings, headache	Recovery

*Ongoing AE at the time of last available report.

The most frequent AE leading to discontinuation was vomiting: 1.3% of the dispersible tablets, and 2.4% of the crushed tablet patients.

Medical Reviewer’s Comments: *The table above summarizes (randomized) patients who discontinued due to adverse event. The table includes all randomized patients and therefore many patients were not able to get the study drug due to vomiting and/or P. falciparum infection. Almost all patients did recover with rescue antimalarial treatment and other measures.*

Laboratory values

Hematology

Mean hemoglobin and RBC levels decreased from baseline to Day 3 (48 hours) and Day 7, but increased from baseline to Day 28 and Day 42. At Day 42, hemoglobin had increased from baseline by 10.8 g/L in the dispersible tablet group and by 10.5 g/L in the crushed tablet group. Reticulocytes increased from baseline to 48 hours and Day 7, but decreased from baseline to Day 28 and Day 42, corresponding with the simultaneous increase in hemoglobin.

Approximately 37% of patients had low hemoglobin and 29% of patients had low hematocrit at baseline; in those patients with normal hemoglobin and normal hematocrit at baseline, the majority also had normal levels at Day 3. Shifts from normal baseline to low or normal baseline

to high values at the last post-baseline value occurred in less than 10% of patients in either treatment group for hemoglobin, hematocrit, and RBC.

Biochemistry

- There were small decreases in glucose levels from baseline, mostly with some recovery on Day 28 and Day 42.
- There were no major changes in creatinine. Approximately 69% of patients had normal creatinine levels at baseline, of these patients over 84% had normal levels at Day 3.
- AST and ALT levels decreased, the greatest mean decreases from baseline occurring on Day 7 (-16.0 U/L) in the dispersible tablet group and (-24.7 U/L) in the crushed tablet group for AST, (-11.8 U/L) in the dispersible tablet group and (-15.4 U/L) in the crushed tablet group for ALT.
- Over 60% of patients had normal AST levels and approximately 36% had high AST levels at baseline. Shifts from normal baseline to high for AST occurred in approximately 17% of patients.
- No noticeable shifts from normal baseline were observed for ALT.

Laboratory values of toxicity grade 3 or 4

The proportion of patients with newly occurring laboratory values of toxicity grade 3 or 4 is presented in the table below. All newly occurring Grade 4 laboratory values were queried and were deemed not clinically significant and not warranting reporting as a SAE.

Grade 4 toxicity laboratory values were observed in 12 patients in the crushed tablet group (2 absolute neutrophil count decrease, 4 platelet count decrease, and 6 blood glucose decrease). Grade 4 toxicity laboratory values were observed in 14 patients in the dispersible tablet group (3 platelet count decreased, 1 hepatic enzyme increase, 9 blood glucose decrease and 1 absolute neutrophil count decrease).

Table 25. Number (%) of patients with newly occurring laboratory values of toxicity grade 3 or 4 during the study (Safety population)

Parameter	Dispersible tablet (N=447) n/M (%)	Crushed tablet (N=452) n/M (%)
Hemoglobin	39/439 (8.9)	36/441 (8.2)
WBC (total)	0/439 (0.0)	0/441 (0.0)
Absolute neutrophils	2/404 (0.5)	2/410 (0.5)
Platelet count	11/439 (2.5)	17/441 (3.9)
SGOT (AST)	0/438 (0.0)	1/441 (0.2)
SGPT (ALT)	1/438 (0.2)	1/442 (0.2)
Gamma-GT	0/434 (0.0)	0/440 (0.0)
Creatinine	0/438 (0.0)	2/442 (0.5)
Hypoglycemia	28/395 (7.1)	31/394 (7.9)
Hyperglycemia	1/395 (0.3)	2/394 (0.5)

*percentages are calculated using the total number of patients with a post-baseline laboratory as a denominator.

* Source Table 10-4 of the study report.

There were four patients in the dispersible tablet group with Grade 3 or 4 levels of AST and/or ALT. In all but one patient, these were Grade 3 values observed at baseline with subsequent improvement. In the remaining patient, a Grade 4 value of SGPT ALT (summarized below) occurred at Day 29 only, with a value within the normal range at Day 42.

In the crushed tablet group, three patients had Grade 3 or 4 levels of AST and/or ALT. In all but one patient, the worst values were observed at baseline with subsequent improvement. In the remaining patient, Grade 3 levels of both AST and ALT were observed at Day 43 (all previous values were within the normal range).

The case narrative for the only patient with hepatic enzyme increase with grade 4 toxicity is summarized below.

TZA/0302/00017 – Hepatic enzyme increased

Treatment group: Coartem dispersible tablet

The patient was 3.5 year old, Black, female (weight 9.9 kg).

This patient entered the study with a diagnosis of acute uncomplicated *P. falciparum* malaria, confirmed by a blood smear. She did not have any active and significant medical history at the study entry. Her concomitant medications included paracetamol for fever.

She received the first dose of the study medication on Study Day 1, when her hemoglobin level was 6.6 g/dL, and ALT 15 U/L. She received the last dose of the study medication on Study Day 4 and the parasite clearance was confirmed on Study Day 3.

From Study Day 2 to Study Day 29 the patient was treated with vitamins-minerals-ginseng for anemia low hemoglobin level.

On Study Day 29, the patient's ALT level was noted to have increased to 860 U/L from a baseline of 15 U/L, which met the criteria for Laboratory abnormality with toxicity grade 4 (>15.0 x ULN). The Patient developed also high AST (305 U/L) and GGT (366 U/L) on Study Day 29 of severe intensity. The increase in these parameters was resolved on Study Day 43, ALT was 19.0 U/L, AST (not available) and GGT was 70 U/L.

The patient completed the study on Study Day 43 (07 Feb 2007) and her asexual parasite count and gametocyte count were nil on the same day.

Medical Reviewer's Comments: *The single case of grade 4 hepatic enzyme (ALT) increase occurred 25 days after last dose of study drug administration and resolved by the end of the study.*

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Table 26. Summary of patients with AST > 100 U/L at the last visit

Subject Id No.	Weight Group	Baseline Value	Study Completion
CCOA566B2303_0201_00003	15- < 25 Kg	34	108
CCOA566B2303_0201_00076	15- < 25 kg	57	102
CCOA566B2303_0101_00086	5- < 15 Kg	56	100
CCOA566B2303_0101_00097	15- < 25 Kg	44	117
CCOA566B2303_0101_00099	15- < 25 Kg	37	104
CCOA566B2303_0101_00088	5- < 15 Kg	57	104.7
CCOA566B2303_0101_00130	5- < 15 Kg	689	103.3
CCOA566B2303_0101_00002	15- < 25 Kg	Not available	107
CCOA566B2303_0101_00075	5- < 15 Kg	35	152
CCOA566B2303_0101_00104	15- < 25 Kg	63	173
CCOA566B2303_0101_00110	15- < 25 Kg	49	593

Medical Reviewer’s Comments: *Inquiry of AST values (at study completion) identified AST 11 patients with values > 100 U/L and one patient with over 500 U/L (≥ 10x ULN). Given the patient population is at risk for increases in AST due to underlying disease process and the size of the study, the increases in the AST values observed in the table above would be within the expected range.*

Vital signs

There were some decreases in mean (maximum -2.8 mmHg in the dispersible tablet group and maximum -2.5 mmHg in the crushed tablet group) and median (maximum -1.0 mmHg in the dispersible tablet group and maximum -2.0 mmHg in the crushed tablet group) systolic blood pressure until Day 28 when there were small increases.

Mean diastolic blood pressure was approximately 62 mmHg in the both treatment groups at baseline. There was a decrease in both treatment groups at all time points with a maximum decrease of -2.1 mmHg at 36 hours.

No AEs of bradycardia, hypotension, or hypertension were reported.

Cardiac Disorders and ECG Analysis

A total of 8 patients with cardiac AEs (5 in the dispersible tablet group and 3 in the crushed tablet group) were reported. All were reported by the investigator(s) at one site (in Benin).

In the dispersible tablet group, four patients had an arrhythmia (reported on Day 2, 4, 8, and 43), three of which were reported as mild and one that was reported as moderate in severity; no action were taken as a result of these cardiac AEs. In addition, a 4 year old patient in the dispersible tablet group had tachycardia that began on Day 15 and lasted for one day. A pulse rate of 114 bpm and body temperature of 37.8°C was measured. The AE was reported as mild and no action was taken.

Three 3 cardiac AEs reported in the crushed tablet group were arrhythmia, all of which were mild in severity and no action was taken (one low pulse rate- suspected to be related to the study drug and 2 sinus tachycardia were noted- not suspected to be related to the study drug).

The proportion of patients with QTc signal values based on Bazett’s and Fridericia’s formula is presented in the table below.

There were no patients with QTc intervals >500 msec (by either formula). The proportion of patients with a QTc increase of 30-60 msec (using either formula) was higher in the dispersible tablet group compared to the crushed tablet group.

Table 27. Number (%) of patients with QTc signal values (Safety population)

Parameter	Dispersible tablet (N=447) n/M (%)	Crushed tablet (N=452) n/M (%)
Bazett's formula		
QTc increase from baseline to highest post-baseline value		
≤0 msec	161/429 (37.5)	168/436 (38.5)
>0 - <30 msec	183/429 (42.7)	196/436 (45.0)
30 - 60 msec	80/429 (18.6)	60/436 (13.8)
>60 msec	3/429 (0.7)	10/436 (2.3)
Baseline ECG not done	2/429 (0.5)	2/436 (0.5)
QTc >500 msec	0/429 (0.0)	0/436 (0.0)
Fridericia's formula		
QTc increase from baseline to highest post-baseline value		
≤0 msec	101/429 (23.5)	101/436 (23.2)
>0 - <30 msec	190/429 (44.3)	206/436 (47.2)
30 - 60 msec	121/429 (28.2)	101/436 (23.2)
>60 msec	15/429 (3.5)	26/436 (6.0)
Baseline ECG not done	2/429 (0.5)	2/436 (0.5)
QTc >500 msec	0/429 (0.0)	0/436 (0.0)

*Source: Table 10-6 of the study report.

Medical Reviewer's Comments: *There were some mild increase in the QTc interval; it is hard to evaluate these effects without a comparator group with known effects since dehydration and resulting electrolyte disturbances may result in changes in QTc interval. The medical reviewer will defer to IRT consult for labeling proposals regarding Coartem effects on QTc interval.*

Nervous System Disorders

Headache was the most frequent AE affecting the nervous system, occurring in 7.4% of patients in the dispersible tablet group and 7.3% of patients in the crushed tablet group.

Baseline neurological examination findings were present in small proportion of patients (1.1% dispersible tablet group vs. 0.4% crushed tablet group).

Abnormal gait, tandem walk, and dysdiadochokinesis occurred in 0.4% to 1.1% of patients.

Neurological examinations were systematically performed at each visit during the study.

There were 5 cases in the dispersible tablet group and 2 cases in the crushed tablet group where patients had baseline abnormalities that persisted on Day 1. No further neurological examination abnormalities were found. No hearing loss was reported during neurological examinations.

One patient (0.2%) in the dispersible tablet group and one patient (0.2%) in the crushed tablet group had convulsions reported as an SAE.

One patient, aged 5, in the dispersible tablet group had convulsions that were severe, also reported as an SAE, (reported on Day 29, fever also reported), an event lasting two days whereas 2 patients (one of whom had active pneumonia and anemia) in the crushed tablet group had either mild or moderate convulsions (reported on Day 42 and Day 2).

The patient in the crushed tablet group reported convulsions and severe malaria on Day 42. The patient, aged 2, in the crushed tablet with mild convulsions also had this reported as an SAE.

One patient, aged 3, in the dispersible tablet group had dyskinesia that was reported as mild and lasted for one day (occurring on Day 2). This patient had no neurological examination abnormalities. Epilepsy was reported in one 4 year old patient in the dispersible tablet group and was mild, occurring on Day 41. This patient also had pneumonia reported on the same day and no relevant medical history. One case of dizziness was reported in the crushed tablet group in a patient with active anemia. This AE was reported as mild, occurred during the treatment period and lasted for 2 days. Tremor was reported for one patient in the crushed tablet group. The AE was reported as mild, and started on Day 42, lasted for 2 days.

Medical Reviewers Comments: *Febrile convulsions associated with infections such as malaria is not unexpected in this age group and it would be difficult assign association with the study drug, given the nature of the underlying disease process.*

4.2.4. Summary and Conclusions Regarding Study B2303

Study B2303 was a randomized, investigator-blinded, multicenter, parallel-group study to compare efficacy, safety and tolerability of Coartem dispersible tablet formulation vs. Coartem 6-dose crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children.

Comparator groups were designed to compare to assess efficacy of Coartem 6-dose dispersible versus 6-dose crushed tablets and for evaluation of safety, both arms still include study drug under investigation, i.e. 6-dose regimen of artemether/lumefantrine, and therefore is not a randomized study in this sense (other than by formulation).

Approximately 60% of the patients fell into the 5- < 15 kg body weight group and over half were 2- <6 year old representing the higher incidence of malaria in this particular age group.

Approximately 87% of patients of the total study population completed the study. It was noted that AEs leading to discontinuation is less in the safety population than the randomized patient population (70 in the randomized population vs. 20 in the safety population). Many cases discontinued from the study due to vomiting and *P. falciparum* infection before the administration of the first dose of the study drug and for the purposes of this safety review, numbers of SAEs and AEs leading to discontinuation in the safety population were discussed. The most frequently affected primary system organ classes were general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders. The most frequent AEs were pyrexia, cough, *P. falciparum* infection and vomiting.

There were three deaths during the study: in the dispersible tablet group, one patient died from hemorrhage and another from an infection. One patient in the crushed tablet group died from severe *P. falciparum* infection (also associated with convulsion). None of the deaths were likely to be related due to the administration of the study drug.

Excluding deaths, there were ten additional serious adverse events; case narratives were reviewed and did seem likely to be related to study drug administration. The most frequent AE leading to discontinuation was vomiting as it would be expected in this age group with underlying illness. No AEs related to auditory system were reported; unlike Study 2403, clonus was not reported as TEAE.

There were some mild increase in the QTc interval, it is hard to evaluate these effects without a comparator group with known effects since dehydration and resulting electrolyte disturbances may result in changes in QTc interval. The medical reviewer will defer to IRT consult for labeling proposals regarding Coartem effects on QTc interval.

Laboratory evaluations and specifically liver transaminases were evaluated. Inquiry of AST values (at study completion) identified AST 11 patients with values > 100 U/L and one patient with over 500 U/L ($\geq 10 \times$ ULN). Given the patient population is at risk for increases in AST due to underlying disease process and the size of the study, the increases in the AST values observed in this patient population would be expected. There were no serious adverse events reported as a result of these changes in the liver transaminases. However, there was a single case with hepatic enzyme increase with grade 4 toxicity (ALT >15.0 x ULN) which resolved by Day 43.

One patient in the dispersible tablet group and one patient in the crushed tablet group had convulsions reported as an SAE. One patient, aged 5 (dispersible tablet group) had convulsions that were severe, also reported as an SAE, was diagnosed to have epilepsy twenty days after completion of study based on EEG changes; he was afebrile at the onset of his first seizure episode. Another 2.8 year old black male patient (crushed tablet group) developed severe *P. falciparum* infection and was hospitalized on Study Day 42 with fever, vomiting and convulsions after his initial parasite clearance was confirmed on Day 2 of the study. The convulsion was reported to be associated with fever and a new onset *P. falciparum* infection. Febrile seizure would not be unexpected expected in the in the age (2 – 5 year old) group given the underlying infectious disease process. Lack of a comparator makes it difficult to assign causality.

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/s/

Ozlem Belen
11/25/2008 06:14:33 PM
MEDICAL OFFICER

Joette Meyer
11/25/2008 07:28:55 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-268
Submission Code 000

Letter Date June 27, 2008
Stamp Date June 27, 2008
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Reviewer Name Sue Lim, MD
Review Completion Date November 24, 2008

Established Name Artemether-lumefantrine
(Proposed) Trade Name Coartem
Therapeutic Class Antimalarial
Applicant Novartis

Priority Designation P

Formulation Oral tablet
Dosing Regimen 6 doses over 3 days based on weight
5 kg to < 15 kg: One tablet initially, 1 tablet after 8 hours and 1 tablet twice daily for two days
15 kg to < 25 kg: Two tablets initially, 2 tablets after 8 hours and 2 tablets twice daily for two days
25 kg to < 35 kg: Three tablets initially, 3 tablets after 8 hours and 3 tablets twice daily for two days
35 kg and above: Four tablets initially, 4 tablets after 8 hours and 4 tablets twice daily for two days

Intended Population 5 kg body weight and above

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

Table of Contents

1	EXECUTIVE SUMMARY	4
1.1	RECOMMENDATION ON REGULATORY ACTION	6
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	7
1.2.1	Risk Management Activity	7
1.3	SUMMARY OF CLINICAL FINDINGS	7
1.3.1	Brief Overview of Clinical Program	7
1.3.2	Efficacy	8
1.3.3	Safety	9
1.3.4	Dosing Regimen and Administration	13
1.3.5	Drug-Drug Interactions	14
1.3.6	Special Populations	15
2	INTRODUCTION AND BACKGROUND	16
2.1	PRODUCT INFORMATION	16
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	16
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	18
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	18
2.5	PRESUBMISSION REGULATORY ACTIVITY	18
2.6	OTHER RELEVANT BACKGROUND INFORMATION	19
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	19
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	19
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	19
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	20
4.1	SOURCES OF CLINICAL DATA	20
4.2	TABLES OF CLINICAL STUDIES	20
4.3	REVIEW STRATEGY	23
4.4	DATA QUALITY AND INTEGRITY	23
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES	23
4.6	FINANCIAL DISCLOSURES	23
5	CLINICAL PHARMACOLOGY	23
6	INTEGRATED REVIEW OF EFFICACY	24
7	INTEGRATED REVIEW OF SAFETY	24
7.1	METHODS AND FINDINGS	24
7.1.1	Patient exposure	26
7.1.2	Deaths	28
7.1.3	Other Serious Adverse Events	34
7.1.4	Dropouts and Other Significant Adverse Events	47
7.1.5	Common Adverse Events	50
7.1.6	Less Common Adverse Events	89
7.1.7	Laboratory Findings	89
7.1.8	Vital Signs	94
7.1.9	Electrocardiograms (ECGs)	95
7.1.10	Immunogenicity	117
7.1.11	Human Carcinogenicity	117
7.1.12	Special Safety Studies	118
7.1.13	Withdrawal Phenomena and/or Abuse Potential	119

7.1.14	Human Reproduction and Pregnancy Data	120
7.1.15	Assessment of Effect on Growth.....	126
7.1.16	Overdose Experience	126
7.1.17	Postmarketing Experience.....	126
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	131
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	131
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	136
7.2.3	Adequacy of Overall Clinical Experience	136
7.2.4	Adequacy of Special Animal and/or In Vitro Testing	136
7.2.5	Adequacy of Routine Clinical Testing.....	137
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup.....	137
7.2.7	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	137
7.2.8	Assessment of Quality and Completeness of Data	137
7.2.9	Additional Submissions, Including Safety Update	138
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	138
7.3.1	Pooling Data Across Studies to Estimate and Compare Incidence.....	138
7.3.2	Explorations for Predictive Factors	138
7.3.3	Causality Determination	138
8	ADDITIONAL CLINICAL ISSUES	139
8.1	DOSING REGIMEN AND ADMINISTRATION	139
8.2	DRUG-DRUG INTERACTIONS	140
8.3	SPECIAL POPULATIONS.....	141
8.4	PEDIATRICS	142
8.5	ADVISORY COMMITTEE MEETING	142
8.6	LITERATURE REVIEW	142
8.7	POSTMARKETING RISK MANAGEMENT PLAN	142
8.8	OTHER RELEVANT MATERIALS	142
9	OVERALL ASSESSMENT.....	142
9.1	CONCLUSIONS	142
9.2	RECOMMENDATION ON REGULATORY ACTION	143
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	143
9.3.1	Risk Management Activity	144
9.3.2	Required Phase 4 Commitments.....	144
9.3.3	Other Phase 4 Requests.....	144
9.4	LABELING REVIEW	144
9.5	COMMENTS TO APPLICANT.....	144
10	APPENDICES	145
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS	145
10.2	LINE-BY-LINE LABELING REVIEW.....	204

1 EXECUTIVE SUMMARY

Coartem Tablets (fixed-dose combination tablet of 20 mg artemether and 120 mg lumefantrine) is an artemesinin-based combination therapy registered in over 80 countries for the treatment of acute, uncomplicated malaria due to *Plasmodium falciparum*. Due to increasing resistance to available antimalarial drugs, the WHO currently recommends use of artemesinin-based combination therapy for the treatment of uncomplicated *P. falciparum* malaria.

Novartis Pharmaceuticals Corporation is requesting approval of a 6-dose regimen of Coartem for the treatment of malaria in patients of 5 kg body weight and above with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Coartem should be administered over 3 days for a total of 6 doses: an initial dose, second dose after 8 hours and then twice daily (morning and evening) for the following two days. The number of tablets per dose is dependent upon the patient's bodyweight and ranges from 1 to 4 tablets.

Coartem was granted a Priority review designation based on the following criteria as specified in MaPP 6020.3: Evidence of increased effectiveness in treatment of acute, uncomplicated malaria (faster parasite clearance time in children ≤ 12 years of age compared to other approved comparators), and evidence of safety and effectiveness in a new subpopulation (faster fever clearance time in children compared to approved comparators).

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

The NDA submission included data on the efficacy and safety of Coartem evaluated in male and female, adult and pediatric patients with uncomplicated *P. falciparum* malaria infection in China, Europe, Columbia, Asia, and sub-Saharan Africa. Of the 20 clinical studies performed in the development program, eight were identified as key studies to support the NDA. These eight studies included complete safety and efficacy information, including raw data and electronic data sets. Due to the large amount of information to be submitted, NDA 22-268 was submitted as a rolling submission starting in October 2007 with the final module submitted in June 2008. For the clinical review, the efficacy and safety of Coartem was separated; the following review covers the safety of Coartem only.

For the safety review, patients exposed to either the 4- or 6-dose regimens of Coartem were included in the safety population, but attention was primarily focused on the 6-dose regimen (6 doses based on body weight administered over 3 days) for which the Applicant was seeking approval. The 6-dose regimen population was composed of 1979 patients, 647 adults (older than

16 years) and 1332 children (16 years and younger) exposed to Coartem in mostly non-controlled, open label trials (81% of patients came from these trials). The pediatric data includes patients who received the intact and crushed tablets, as well as the unapproved dispersible tablet. The 6-dose Coartem population was patients with malaria between ages 3 months to 78 years: 67% (1332) were 16 years and younger, and 33% (647) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the pediatric studies were conducted in Africa. Supportive data was obtained from patients exposed to an unapproved 4-dose regimen of Coartem Tablets (4 doses administered over 2 days) in 787 adults and 659 children.

Discontinuation of Coartem due to adverse drug reactions occurred in 4% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 5% (71/1332) in children. The most common adverse drug reaction leading to discontinuation in children was vomiting, which was specified in one study protocol as criteria for discontinuation.

The most frequently reported treatment emergent adverse events (AEs) in both pooled populations were likely related to malaria signs and symptoms. In adult patients, these included headache, anorexia, dizziness, asthenia, arthralgia and myalgia, while in pediatric patients, pyrexia, cough, vomiting, *P. falciparum* infection, anorexia and headache were the most frequently reported AEs. The majority of AEs were of mild intensity. Overall, there were few deaths and SAEs reported; no deaths and few SAEs were possibly related to Coartem.

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

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

Postmarketing data provided additional reassurance on the absence of any specific nervous system, ear/labyrinth and QT safety signals. Data regarding exposure to Coartem during pregnancy was obtained from postmarketing data and a pregnancy registry of over 1000 patients, both of which suggested no increase in teratogenic effects or spontaneous abortions in women who received Coartem during pregnancy.

In conclusion, the overall safety results provide substantial evidence to support the safety of Coartem as a 6-dose regimen in the treatment of adults and children down to 5 kg with acute uncomplicated *P. falciparum* infection. If approved, Coartem would be the first artemesinin-based combination therapy approved in the U.S. and would offer an additional antimalarial choice which is safe and well-tolerated for the treatment of uncomplicated *P. falciparum* malaria.

1.1 Recommendation on Regulatory Action

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

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

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

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

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

This recommendation is based on the pooled safety analyses of 1979 patients exposed to the 6-dose regimen of Coartem (647 adult patients, 1331 pediatric patients), and supported by an additional 1446 patients exposed to the 4-dose regimen of Coartem (787 adult patients, 659 pediatric patients).

A recommendation regarding approval of Coartem for the treatment of acute uncomplicated malaria in patients with mixed infections including *P. falciparum* is pending discussion at the Anti-Infectives Advisory Committee Meeting on December 3, 2008.

Please refer to the Medical Officer review by Dr. Elizabeth O'Shaughnessy for Coartem efficacy analyses and conclusions.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Based on this safety review, no risk management activities, phase 4 commitments or other phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Coartem is a fixed-dose combination tablet of 20 mg artemether and 120 mg lumefantrine in a 1:6 ratio. The components act synergistically, with artemether providing early and rapid parasite clearance, while lumefantrine prevents recrudescence.

In the Novartis clinical development program, 20 studies were conducted between 1993 and 2007, most of which 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 by body weight ranges. Although the 4-dose regimen initially appeared promising based on studies in China, the 6-dose regimen was ultimately selected for further clinical development based on evidence that it provided additional benefit to the 4-dose regimen in Thailand. Of these 20 studies, 8 were selected (primarily based on demonstration of efficacy) through discussions between Novartis and the FDA to act as key studies to support registration of the 6-dose regimen. These are briefly summarized in Table 1.

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Table 1: Summary of 8 key studies

Study No.	Study Design /Objective	No. of patients		Population	Year/ Study location
		Co-artemether	Comparator		
ABM02	Double-blind, randomized (1:1), parallel group comparative efficacy/safety 4-dose regimen co-artemether vs individual components	53	Artemether: 52 Lumefantrine: 52	Adults	1994 China
A023	Double-blind, randomized (1:1) comparative efficacy/safety 4-dose regimen co-artemether vs lumefantrine alone (tablets & capsule)	52	Lumefantrine tablet: 51 Lumefantrine capsule: 50	Adults	1996 China
A025	Double-blind, randomized (1:1) , parallel group comparative efficacy/safety 4-dose regimen vs two 6-dose regimens of co-artemether	120	Co-artemether: 6 dose 60 h: 118 6 dose 96 h: 121	Adults Children (≤12 yrs, n = 43)	1996-97 Thailand
A026	Open-label, randomized (3:1), parallel group confirmatory efficacy/safety 6-dose regimen, comparison with MAS	150	Mefloquine-artesunate: 50	Adults Children (2-12 yrs, n = 34)	1997-98 Thailand
A028	Open-label, randomized (3:1), parallel group, confirmatory efficacy/safety 6-dose regimen, comparison with MAS	164	Mefloquine-artesunate: 55	Adults	1998-99 Thailand
A2401	Open-label, non-comparative efficacy/safety 6-dose regimen in non-immune patients	165	-	Adults	2001-05 Europe, Colombia
A2403	Open-label, non-comparative efficacy/safety 6-dose regimen	310	-	Infants/ children (5-25 kg)	2002-03 3 countries in Africa
B2303	Investigator-blind, randomized (1:1), parallel group efficacy/safety 6-dose regimen	452	Co-artemether dispersible tablet: 447	Infants/ children (5-35 kg)	2006-07 5 countries in Africa

Source: Table 1-1, Novartis Clinical Overview

1.3.2 Efficacy

Please refer to the Medical Officer review by Dr. Elizabeth O’Shaughnessy for Coartem efficacy analyses and conclusions.

1.3.3 Safety

Safety analyses of data obtained from 1979 patients exposed to the 6-dose regimen of Coartem was the basis for regulatory approval. This population was composed of 647 adults (patients greater than 16 years) and 1332 children (16 years and younger). Coartem was studied in both active-controlled and non-controlled, open label trials; for the 6-dose regimen, there were 367 patients studied in active-controlled trials, and 1612 patients from non-controlled, open label trials.

The 6-dose population were patients with malaria between ages 3 months to 78 years: 67% (1332 patients) were 16 years and younger, and 33% (647 patients) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the pediatric studies were conducted in Africa.

Supportive information was obtained from patients exposed to an unapproved regimen of 4 doses administered over 2 days in 787 adults and 659 children.

Tables 2 and 3 show the most frequently reported adverse reactions ($\geq 3\%$) in adults and children respectively who received the 6-dose regimen of Coartem. Adverse reactions collected in clinical trials included signs and symptoms at baseline but only treatment emergent adverse events are presented below. In adults, the most frequently reported adverse reactions were headache, anorexia, dizziness and asthenia. In pediatrics, the adverse reactions were pyrexia, cough, vomiting and *Plasmodium falciparum* infection. Most adverse reactions were mild, and did not lead to discontinuation of study medication. Discontinuation of Coartem due to adverse drug reactions occurred in 4% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 5% (71/1332) in children. The most common adverse drug reaction leading to discontinuation in children was vomiting, which was specified in one study protocol as criteria for discontinuation.

Table 2: Adverse reactions occurring in 3% or more of adult patients treated in clinical trials with the 6-dose regimen (6 dose over 3 days) of Coartem

System Organ Class	Preferred term	Adults* N=647 (%)
Nervous system disorders	Headache	360 (55.6)
	Dizziness	253 (39.1)
Metabolism and nutrition disorders	Anorexia	260 (40.2)
General disorders and administration site conditions	Asthenia	243 (37.6)
	Pyrexia	159 (24.6)
	Chills	147 (22.7)
	Fatigue	111 (17.2)
	Malaise	20 (3.1)
Musculoskeletal and connective tissue disorders	Arthralgia	219 (33.8)
	Myalgia	206 (31.8)

Gastrointestinal disorders	Nausea	169 (26.1)
	Vomiting	113 (17.5)
	Abdominal pain	112 (17.3)
	Diarrhoea	46 (7.1)
Psychiatric disorders	Sleep disorder	144 (22.3)
	Insomnia	32 (4.9)
Cardiac disorders	Palpitations	115 (17.8)
Hepatobiliary disorders	Hepatomegaly	59 (9.1)
Blood and lymphatic system disorders	Splenomegaly	57 (8.8)
	Anaemia	23 (3.6)
Respiratory, thoracic and mediastinal disorders	Cough	37 (5.7)
Skin and subcutaneous tissue disorders	Pruritus	24 (3.7)
	Rash	21 (3.2)
Ear and labyrinth disorders	Vertigo	21 (3.2)

* Adults defined as patients > 16 years

Table 3: Adverse reactions occurring in 3% or more of pediatric patients treated in clinical trials with the 6-dose regimen (6 dose over 3 days) of Coartem

System organ class	Preferred Term	Children* N=1332 (%)
General disorders and administration site conditions	Pyrexia	381 (28.6)
	Chills	72 (5.4)
	Asthenia	63 (4.7)
	Fatigue	46 (3.5)
Respiratory, thoracic and mediastinal disorders	Cough	302 (22.7)
Gastrointestinal disorders	Vomiting	242 (18.2)
	Abdominal pain	112 (8.4)
	Diarrhoea	100 (7.5)
	Nausea	61 (4.6)
Infections and infestations	Plasmodium falciparum infection	224 (16.8)
	Rhinitis	51 (3.8)
Metabolism and nutrition disorders	Anorexia	175 (13.1)
Nervous system disorders	Headache	168 (12.6)
	Dizziness	56 (4.2)
Blood and lymphatic system disorders	Splenomegaly	124 (9.3)
	Anaemia	115 (8.6)
Hepatobiliary disorders	Hepatomegaly	75 (5.6)
Investigations	Aspartate aminotransferase increased	51 (3.8)

* Children defined as patients ≤ 16 years

Tables 4 and 5 show the most frequently reported adverse reactions ($\geq 3\%$) in adults and children respectively from comparative studies which randomized subjects to either the 6-dose regimen of Coartem or an unapproved comparator, mefloquine and artesunate (MAS). The results for adult patients are similar to the pooled adult population data shown in Table 2. Adverse reaction rates for pediatric patients are higher in Table 5 compared to the pooled pediatric population data in Table 2 due to demographic differences (the pooled pediatric population included a larger proportion of younger children and infants unable to express symptoms).

Table 4: Adverse reactions occurring in 3% or more of adult patients treated in clinical trials with Coartem Tablets or mefloquine artesunate (MAS)

System Organ Class	Preferred Term	Coartem Tablets N=257 (%)	Mefloquine Artesunate N=77 (%)
General disorders and administration site conditions	Pyrexia	149 (57.8)	44 (57.1)
	Asthenia	83 (32.2)	25 (32.5)
	Chills	48 (18.6)	16 (20.8)
	Fatigue	29 (11.2)	8 (10.4)
Nervous system disorders	Headache	129 (50.0)	32 (41.6)
	Dizziness	100 (38.8)	28 (36.4)
Musculoskeletal and connective tissue disorders	Arthralgia	82 (31.8)	24 (31.2)
	Myalgia	65 (25.2)	14 (18.2)
Metabolism and nutrition disorders	Anorexia	78 (30.2)	26 (33.8)
Gastrointestinal disorders	Nausea	64 (24.8)	25 (32.5)
	Abdominal pain	44 (17.1)	11 (14.3)
	Vomiting	27 (10.5)	10 (13.0)
	Diarrhoea	11 (4.3)	2 (2.6)
	Dyspepsia	10 (3.9)	4 (5.2)
Psychiatric disorders	Sleep disorder	58 (22.5)	23 (29.9)
Cardiac disorders	Palpitations	45 (17.4)	15 (19.5)
Hepatobiliary disorders	Hepatomegaly	31 (12.0)	4 (5.2)
Blood and lymphatic system disorders	Splenomegaly	22 (8.5)	8 (10.4)
Respiratory, thoracic and mediastinal disorders	Cough	12 (4.7)	1 (1.3)
	Pharyngolaryngeal pain	7 (2.7)	4 (5.2)
Skin and subcutaneous tissue disorders	Pruritus	8 (3.1)	4 (5.2)
	Rash	5 (1.9)	3 (3.9)
Injury, poisoning and procedural complications	Overdose	0	3 (3.9)

Table 5: Adverse reactions occurring in 3% or more of pediatric patients treated in clinical trials with Coartem Tablets or mefloquine artesunate (MAS)

System Organ Class	Preferred Term	Coartem Tablets N=56 (%)	Mefloquine Artesunate N=28 (%)
Nervous system disorders	Headache	37 (66.1)	14 (50.0)
	Dizziness	23 (41.1)	9 (32.1)
General disorders and administration site conditions	Pyrexia	34 (60.7)	19 (67.9)
	Asthenia	25 (44.6)	8 (28.6)
	Chills	19 (33.9)	4 (14.3)
	Fatigue	5 (8.9)	0
Metabolism and nutrition disorders	Anorexia	30 (53.6)	11 (39.3)
Gastrointestinal disorders	Vomiting	23 (41.1)	12 (42.9)
	Nausea	18 (32.1)	9 (32.1)
	Abdominal pain	17 (30.4)	9 (32.1)
	Dyspepsia	0	1 (3.6)
Blood and lymphatic system disorders	Splenomegaly	18 (32.1)	4 (14.3)
	Anaemia	4 (7.1)	2 (7.1)
Hepatobiliary disorders	Hepatomegaly	17 (30.4)	4 (14.3)
Musculoskeletal and connective tissue disorders	Arthralgia	17 (30.4)	7 (25.0)
	Myalgia	9 (16.1)	5 (17.9)
Psychiatric disorders	Sleep disorder	12 (21.4)	7 (25.0)
Cardiac disorders	Palpitations	10 (17.9)	2 (7.1)
Infections and infestations	Respiratory tract infection	2 (3.6)	0
	Nasopharyngitis	1 (1.8)	2 (7.1)
	Bronchitis	0	1 (3.6)
	Parasitic gastroenteritis	0	1 (3.6)
	Subcutaneous abscess	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	2 (3.6)	0
	Cough	0	1 (3.6)
	Epistaxis	0	3 (10.7)
Skin and subcutaneous tissue disorders	Urticaria	0	1 (3.6)

1.3.4 Dosing Regimen and Administration

Administration

Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

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

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

Dosage in Adult Patients (> 16 years of age)

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

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

Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended.

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

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

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

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

Dosage in Patients with Renal or Hepatic Impairment

No specific studies have been carried out in patients with renal or hepatic impairment. Most patients with acute malaria present with some degree of related hepatic impairment. In clinical studies, the adverse event profile did not differ in patients with (b) (4) mild or moderate hepatic impairment (b) (4)

(b) (4) no specific dose adjustments are needed for patients with mild or moderate hepatic (b) (4)

In clinical studies, the adverse event profile did not differ in patients with (b) (4) mild or moderate renal impairment. There were no patients with severe renal impairment in the clinical studies. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe renal or severe hepatic impairment.

1.3.5 Drug-Drug Interactions

(b) (4)

(b) (4)

- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolides, fluoroquinolones, imidazole, and triazole antifungal agents); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride.
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

1.3.6 Special Populations

Geriatric patients

(b) (4)

Pregnancy

The evidence for use in pregnancy came from 4 sources: a pregnancy registry in Zambia (Study A2401, which examined outcomes in women exposed to Coartem or SP for treatment of malaria during pregnancy); preliminary results of Study A2415, an investigator-initiated trial which examined the safety, tolerability and efficacy of artesunate monotherapy versus Coartem in pregnancy; preliminary results of Study A2422, a phase 4, prospective, community-based, longitudinal demographic surveillance study to assess the impact of Coartem when used as national policy first-line treatment on malaria morbidity and mortality in Tanzania; postmarketing experience.

The cumulative data to date suggests that exposure to Coartem during pregnancy does not result in an increase in teratogenic effects or spontaneous abortions.

A Maternal Health Team consult was obtained for direction regarding labeling, the appropriate risk classification regarding use of Coartem in pregnancy, and review of the submitted pregnancy registry data. This review is available in DFS, but the main recommendations included removing the (b) (4), assigning Coartem a Pregnancy Category C due to the increase in embryo-fetal loss in animal studies, the establishment of an international antimalarial pregnancy exposure registry, and post-marketing commitments/requirements of lactation and pharmacokinetic studies in pregnant women which are still under consideration by the Review Division.

INTRODUCTION AND BACKGROUND

1.4 Product Information

Coartem is an oral fixed-dose combination, antimalarial drug containing artemether 20mg and lumefantrine 120mg. Both compounds are blood schizonticidal in the life-cycle of *Plasmodium* species, and have complementary pharmacokinetics which may reduce the emergence of resistance - artemether has a short half-life and a rapid onset of action which produces rapid parasite clearance, while lumefantrine has a slow onset of action and prevents recrudescence. Originally developed by the Academy of Military Medical Sciences in China, Coartem was acquired by Ciba and subsequently by Novartis for further development. The WHO (WHO Malaria Treatment Guidelines, 2006) recommends the standard six-dose treatment of Coartem administered over 3 days everywhere irrespective of the immune status of the patient and/or of the multi-drug resistance status in the country.¹

Coartem was first registered in Gabon on 14 October 1998. The product is marketed under the name Riamet in Europe and as Coartem in the rest of the world and is approved in 82 countries. By the end of March 2008, 172 million co-artemether treatments had been provided to endemic countries according to Novartis. Based on historical data covering both private sector and public distribution, it is estimated that approximately ^{(b) (4)} patients have been treated with Coartem since the first approval for clinical use in 1998. It is estimated that 70% of co-artemether treatment courses have been in children (under 35 kg body weight) and 30% for treatment of adults (above 35 kg bodyweight).

1.5 Currently Available Treatment for Indications

The antimalarial drugs (oral) currently approved for treatment and marketed in the U.S. are the following:

- chloroquine (Aralen®)
- sulfadoxine-pyrimethamine (Fansidar®)
- mefloquine (Lariam®)
- atovoquone/proguanil, (Malarone®)
- primaquine phosphate,
- quinine sulfate (Qualaquin®)
- Halofantrine (Halfan®)

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

Halofantrine is FDA-approved, but not currently available in the U.S. The use of halofantrine in this country has been limited by its known cardiotoxicity related to QTc prolongation, and reports of death in young individuals without a cardiac history.

The use of chloroquine for treatment of *P. falciparum* malaria is limited to areas of where the parasite is susceptible, namely Central America west of the Panama Canal, the Dominican Republic, Haiti, Mexico, and some areas in the Middle East.

The use of sulfadoxine-pyrimethamine (Fansidar®) has been used for malaria self-treatment, but its use is also limited to malaria acquired in areas where the parasite is sensitive.

Mefloquine (single dose regimen) can still be used in most geographical regions for treatment of uncomplicated *P. falciparum* malaria, except in certain areas of Thailand, particularly the Thai-Myanmar and Thai-Cambodia border, and some local areas in South America. Mefloquine, is indicated for the treatment of mild to moderate acute malaria caused by *P. falciparum*, and is not available as an intravenous preparation for severe *P. falciparum* malaria in the U.S. Neuropsychiatric AEs are associated with the use of mefloquine and can contribute to non-completion of a full course of therapy.

Malarone (a 3-day regimen) is indicated for the treatment of acute uncomplicated *P. falciparum* malaria, and has been shown to be effective where chloroquine, halofantrine, mefloquine and amiodaquine have high failure rates. Vomiting is associated with malarone and mefloquine, especially in children.

Quinine sulfate oral tablets or capsules have been available in the United States since prior to the Food, Drug, and Cosmetic Act of 1938. To preserve the availability of quinine for the treatment of malaria while proceeding to regulate the unsafe over-the-counter use of quinine for nocturnal leg cramps, the FDA approved Quinine sulfate, 324 mg capsules for the treatment of uncomplicated *P. falciparum* malaria. The product was marketed in December 2006. Parenteral quinine sulfate for treatment of severe *P. falciparum* malaria is not available in the U.S., although IV quinidine, the diastereomer of quinine, is available and approved for treatment of severe malaria caused by *P. falciparum*. Quinine sulfate must be combined with another anti-malarial drug to ensure eradication of parasites. Common side effects associated with quinine include cinchonism, headache, dizziness and GI symptoms. Rare but serious AEs include DIC, thrombocytopenia, hypoglycemia, blindness, deafness, hepatitis, renal failure, QT interval prolongation, hypotension and adverse drug-drug interactions with CYP3A4 inhibitors.

The Centers for Disease Control and Prevention (CDC) guidelines for treatment of malaria recommend the use of oral quinine sulfate in combination with doxycycline, tetracycline, or clindamycin for *P. falciparum* malaria acquired in areas of chloroquine resistance or unknown resistance (CDC 2004 Guidelines for Treatment of Malaria in the U.S.). The only intravenous products available for the treatment of severe malaria are IV quinidine and IV artesunate, which are available for compassionate use under IND from the CDC.

1.6 Availability of Proposed Active Ingredient in the United States

Artemether and lumefantrine are not currently marketed in the U.S. alone or in combination.

1.7 Important Issues With Pharmacologically Related Products

In animal models, artemisinin derivatives such as artemether have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. AEs related to the nervous system and ear/labyrinth were selected out for further analysis given these previously observed toxicities. As lumefantrine is chemically related to halofantrine, an antimalarial associated with prolongation of the QTc interval, particular attention was also paid to AEs affecting the cardiovascular system, and ECG evaluations were performed in most studies in malaria patients with the 6-dose regimen and some studies with the 4-dose regimen. A thorough QTc study, (Study A2101) was conducted in healthy adult volunteers and is discussed in this review.

1.8 Presubmission Regulatory Activity

On October 30, 2006, Novartis first met with the Division of Special Pathogen and Transplant Products (DSPTP) to discuss filing an NDA seeking approval for Coartem® (artemether/lumefantrine) Tablets for use in the treatment of malaria. Under discussion were the large amount of worldwide clinical data that was used to support regulatory approval in over 80 countries, the applicability of the data to the U.S. population, the quality of the data, and if the cumulative information met FDA standards to support a regulatory submission in the U.S.

On August 31, 2007, the Applicant obtained Orphan Drug designation through the Office of Orphan Drug Development, and submitted questions regarding Fast Track designation. The Agency responded on September 27, 2007, and a second pre-NDA meeting was held on Nov. 9, 2007. The sponsor received Fast Track designation in January, 2008.

A number of issues were discussed prior to the Nov. 2007 pre-NDA meeting, and an agreement was reached in the meeting on the following:

- FDA accepted the list of key studies (i.e., Studies A023, A025, A026, A028, ABM02, A2401, B2303, and A2403). These were considered key studies since case report forms and electronic datasets of raw data were available for analysis.
- FDA agreed to consider the Novartis proposal to integrate ISS and ISE information into the Clinical Overview.
- FDA requested that the summary of safety display both 4- and 6-dose safety data, and pediatric and adult data. The efficacy summary should also present the following data: 4- and 6- dose; adult and pediatric; immune and non-immune; any available special populations, such as geriatrics (over 65 years old), pregnancy (especially first trimester exposure), and patients over 65 kg body weight.

- Novartis confirmed the following: CRFs from the key studies as well as written narratives would be provided for deaths and serious adverse events (SAEs); would provide details of the administration of crushed tablets in clinical studies and as much information on food taken with medication as possible; would provide body weight granularity to support the current dosage recommendation in pediatrics; confirmed that MedDRA 10 would be used as the common dictionary; would submit study reports for all Novartis sponsored clinical studies performed with Coartem (see Section 4.2 Tables of Clinical Studies) including the key studies; would provide a review of safety of the 6-dose regimen in adults and children with reference to clinical study reports supported by relevant pooled analyses and supportive studies leading to the 6-dose recommendation in Europe, Switzerland, and endemic countries as well as with postmarketing experience in the relevant section of the Clinical Overview. Particular attention would be given to neurological, including audiology, and cardiac safety.
- To facilitate and expedite the submission of documents and data for review by the FDA under Fast Track designation, Novartis proposed to follow the current eNDA format and not eCTD format for this rolling submission in which sections would be submitted in 2007 and 2008.
- The first submission module (Pharmacology/toxicology) was submitted October 30, 2007 and the final module (Clinical Summary) was submitted June 27, 2008.

1.9 Other Relevant Background Information

None.

2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1 CMC (and Product Microbiology, if Applicable)

Please see the CMC and CDTL's reviews for details.

2.2 Animal Pharmacology/Toxicology

The nonclinical toxicology program for Coartem was comprehensive, and included safety pharmacology studies, genetic toxicology studies, reproductive toxicology studies, phototoxicity studies as well as single dose, one-month and three-month toxicity studies in rats and dogs. Several studies were conducted to characterize effects of artemether in juvenile animals, including neurotoxicity. The adverse effects of special interest examined were reproductive and neurological toxicity, which were both attributed primarily to artemether. Please see the Pharmacology/toxicology reviews in DFS and CDTL's review for details.

With respect to reproductive toxicology, studies in rats and rabbits suggested risk for fetal loss with exposure during pregnancy. Neurological toxicity appeared related to systemic plasma concentrations of artemether achieved with IM administration; extensive first pass metabolism which occurs with oral administration of artemether in beagle dogs resulted in low concentrations which were not associated with brain histopathology.

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

NDA 22-268 was an electronic submission. Efficacy and safety data, and supporting data such as CRFs, data files, financial disclosure statements, proposed labeling, and non-clinical data were included in the electronic file.

The datasets used in this review, and other safety data can be found in the EDR using the following links:

Individual study data:

Study A023: \\fdswa150\nonectd\N22268\R_007\2008-04-08

Study ABMO2: \\FdsWa150\nonectd\N22268\R_019\2008-06-05

Study A025: \\FdsWa150\nonectd\N22268\R_002\2008-02-11

Study A026: \\FdsWa150\nonectd\N22268\R_003

Study A028: \\FDSWA150\NONECTD\N22268\R_006\2008-03-19

Study A2401: \\FDSWA150\NONECTD\N22268\R_011\2008-05-09

Study A2403: \\FDSWA150\NONECTD\N22268\R_014\2008-05-22

Study B2303: \\FDSWA150\NONECTD\N22268\R_016\2008-05-29

Pooled safety data: \\FdsWa150\NONECTD\N22268\N_000\2008-06-27\crt\datasets\Pool

120 day safety update: \\FDSWA150\NONECTD\N22268\N_000\2008-10-28

Post marketing safety data: \\FDSWA150\NONECTD\N22268\N_000\2008-09-10

Datasets were loaded into the software program Integrated Review for analysis.

The safety evaluation was conducted on 2 pooled populations based on age (adults defined as patients > 16 years but ≤ 65 years of age; pediatric defined as ≤ 16 years of age). Both populations only included patients from studies which used the 4- and 6-dose regimens of Coartem.

3.2 Tables of Clinical Studies

Clinical studies for NDA 22-268 are listed in Table 6 below.

Table 6: Completed clinical studies

Study No.	Region/year/study design/ Coartem Regimen	Population	Patients (n)	
			Coartem	Comparator
4-dose Key Studies				
A023	China/1996/DB/4-dose	Adults	52	Lumefantrine
AB/MO2	China/1994/OL/4-dose	Adults	53	Artemether (52); Lumefantrine (52)
4-dose Supportive Studies				
A003	Thailand/1995-6/OL, MC/4-dose	Children (5-12 years)	111	Quinine (108)
A004	Thailand/1995-96/DB/4-dose	Adults	126	Mefloquine (126)
A005	UK/1996-97/OL,MC/4-dose	Adults	12	Quinine/Fansidar® (11)
A007	India/1996-97/DB/4-dose	Adults	89	Chloroquine (90)
A008	Thailand/1995-6/OL, MC/4-dose	Children (> 5 years) & adults	309	MAS (308)
A010	Gambia/1996-7/DB, MC/4-dose	Children (6-25 kg)	144	Fansidar® (143)
A011	Tanzania/1996/OL/4-dose	Children (≥ 5 kg)	130	Chloroquine (130)
A014	Europe/1996-97/DB, MC/4-dose	Adults	51	Halofantrine (52)
AIC04	Senegal/2000/OL/4-dose	Adults	36	Chloroquine (36)
AIC04	Cameroon/2000/OL/4-dose	Adults	30	Fansidar® (30)
4 dose vs. 6-dose Key Study				
A025*	Thailand/1996-97/DB/4- & 6-dose	Adults	108 & 208	None
6-dose Key Studies				
A026	Thailand/1997-98/OL,MC/6-dose	Adults	125	MAS (41)
A028	Thailand/1998-99/OL,MC/6-dose	Adults	162	MAS (50)
A2401	Europe, Colombia/6-dose	Adults	165	None
A2403	Kenya,Nigeria,Tanzania/ 2002-2003/OL/MC/6-dose	Children (5-25 kg)	310	None
B 2303	Kenya, Mali, Tanzania, Zanzibar, Benin, Mozambique/MC/6 dose	Children (5-35 kgs)	447	Coartem dispersible (434)
6-dose Supportive Studies				
A030	Vietnam/2001/OL/6-dose	Adults	45	MAS (38)
ABD01	Bangladesh/2002-03/OL/6-dose	Adults	103	Quinine/Fansidar® (103)
ABR01	Brazil/2000-02/OL/6-dose	Adults	28	Quinine/doxycycline (31)

AL = Artemether-lumefantrine; DB = double-blind, MC = multicenter, OL = open-label, MAS = mefloquine/artesunate.
 *In study 025 two 6-dose regimens were used, with doses given over 60hours or 96hours

Source: Adapted from Applicant's Clinical Overview Section of NDA

Other studies in the development program:

Study No.	Region/year/study design/regimen	Number of Patients
AMMS 1	China/1997 Determination of optimal artemether: lumefantrine (A:L) ratio (1:5 vs. 1:6) for 4-dose regimen	A:L 1:5: 20 A:L 1:6: 20
AMMS 2	China/1988 Safety & efficacy vs. individual components for 4-dose regimen	Coartem: 20 Lumefantrine: 20 Artemether: 20
AMMS 3	China/1988 Dose finding (comparison of 3 different regimens: 4 doses/3 days – 0, 8, 24, 48 hours; 3 doses/3 days - 0, 24, 48 hours; 4 doses/2 days – 0, 8, 24, 32 hours)	Coartem 4 doses/3 days: 24 3 doses/3 days: 22 4 doses/2 days: 20
AMMS 4	China/1989 Review of 100 cases of malaria in children treated with co-artemether 4-dose, 3-day regimen	Coartem: 100
A012	Thailand/1995/DB,MC/4-dose Safety & efficacy 4-dose regimen in adults vs. lower dose (4 doses of half drug quantity) and shorter treatment (3 doses over 24 hours)	Coartem Full 4-dose: 87 Half-dose: 87 3-dose: 86
AB/MO 1	China/1993/OL/4-dose China/1993/Open-label, non-comparative confirmatory efficacy/safety trial/Adults Males and females	Coartem 4-dose regimen over 2 days: 102
A009	Gambia/1995-6/OL/28 days Children (5-25 kg)	Coartem: 60 Pediatric tablet (each tablet had half the content of each component compared to a standard tablet)

Source: Novartis October 2006 pre-NDA background document

Other studies discussed in this review:

- Study A2101: Definitive QTc study in healthy subjects
- Study A2407: Pregnancy registry in Zambia evaluating the safety profile of Coartem and SP in pregnant women with symptomatic malaria
- Study A2412: An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *P. falciparum* malaria in patients 12 years of age or older

- Study A2417: An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *P. falciparum* malaria in patients 12 years of age or older in Columbia
- Study A2422: an epidemiology study to assess the impact of the introduction of co-artemether as a national treatment policy on all-cause mortality in infants/children < 5 years of age in a rural area of southern Tanzania

3.3 Review Strategy

The 8 efficacy studies for NDA 22-268 were reviewed by Dr. Elizabeth O'Shaughnessy. The pooled safety review was performed by Dr. Sue Lim. The individual study safety reviews of the 8 key studies were completed by Drs. Joette Meyer (4 dose studies A023 and ABM02, brief summaries only), Regina Alivasatos (A025 and A026), Sue Lim (A028 and A2401) and Ozlem Belen (pediatric studies A2403 and B2303). All individual study report reviews are in the Appendix with the exception of the pediatric studies. Please refer to the separate review by Dr. Ozlem Belen for these reviews.

3.4 Data Quality and Integrity

A consult (not for cause) with the Division of Scientific Integrity (DSI) was requested to inspect sites from Studies A023, ABM02, A025, A026, A028 and A2403 (3 centers). Please see CDTL memo for results of inspections. There were no findings of concern at the time of this review.

3.5 Compliance with Good Clinical Practices

The sponsor's statement was submitted and reviewed and appeared to be in compliance with GCP.

3.6 Financial Disclosures

The Applicant obtained certification from each investigator and sub-investigator who enrolled subjects in the clinical trials. No investigator or sub-investigator had any disclosed information to reveal.

4 CLINICAL PHARMACOLOGY

Please refer to the Clinical Pharmacology review.

5 INTEGRATED REVIEW OF EFFICACY

Please refer to the Medical Officer review by Dr. Elizabeth O’Shaughnessy.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

For the integrated safety review, the Clinical Overview provided by the Applicant as the final portion of the rolling NDA, pertinent patient narratives and CRFs were reviewed. Datasets were registered with iReview for safety analyses. All tables unless otherwise noted were created by the reviewer.

In the Clinical Overview, the Applicant presented safety data as two pooled analyses, one for adults and adolescents (patients who were >12 years of age), and the other for children and infants (patients ≤ 12 years of age). Both populations included patients with acute uncomplicated falciparum malaria who received the 4-dose or the 6-dose regimen of Coartem and comparator antimalarials.

With respect to pediatric age categorization, we referred to Guidance E11, “Guidance for Industry: Clinical Investigation of Medicinal Products in the Pediatric Population”. The following pediatric age categorizations were suggested:

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on region))

Given the history of neurologic AEs reported with Coartem and the ongoing neurocognitive development which occurs in adolescence, the FDA chose to include adolescents with pediatric patients, and therefore defined the pediatric population as ≤16 years of age, and adults were defined as >16 years of age. There were only 7 individuals greater than 65 years of age (geriatric patients), and therefore these patients were included with the adult population since the ability to obtain meaningful information from such a small population would be limited. A total of 1434 adult patients and 1991 pediatric patients were exposed to Coartem (Table 7).

Table 7: Patients included the FDA adult and pediatric pooled safety populations

Population	Coartem 4-dose	Coartem 6-dose	Population total
Adult	787	647	1434
Pediatrics	659	1332	1991
Coartem (dose) total	1446	1979	3425

The Applicant also provided an analysis according to these new age categories when requested by the FDA.

The FDA pooled safety populations were used to assess safety in terms of the rate, type, severity and assessment of study drug relationships of AEs; rates of deaths, serious adverse events (SAEs) and other clinically significant AEs; clinical laboratory assessments; electrocardiography; vital signs; and safety in a range of subgroups of each population. AEs in the pooled populations were coded using MedDRA version 10.1.

For the 8 key studies, the only comparator other than the components of Coartem was mefloquine artesunate (MAS) although the 4-dose studies had other comparators (Table 1). Both the FDA and Applicant analyzed selected comparator antimalarials only, since the sample sizes were very small in some cases. For the FDA adult pooled population, the only comparator antimalarial examined was MAS, while MAS and sulfadoxine-pyrimethamine (SP) were examined in the FDA pediatric pooled population. The Applicant correctly cautioned that because of the nature of pooled safety populations, that between-group differences should be interpreted carefully.

In the FDA pediatric pooled safety population, the 6-dose regimen data were summarized for the standard tablet, the dispersible tablet evaluated in Study B2303, and for a “total 6- dose” group that pooled data from patients treated with the standard tablet and the dispersible tablet. It was considered valid to include the latter group as efficacy and drug exposure for the standard and dispersible tablet have been demonstrated to be very similar. (b) (4)

A number of specific subsets of AEs were specifically investigated on the basis of findings in studies with animals, or the chemical nature of the components of artemether and lumefantrine. These include AEs affecting the nervous system, ear and auditory system, and QT prolongation. In addition, AEs affecting the liver, hematological and hemolysis-related AEs were also assessed. While other clinical laboratory parameters were also assessed in the studies, the range of parameters evaluated were few and variable due to limited laboratory resources at the study centers, and the parameters evaluated varied between studies. ECGs were performed in most studies. To standardize the analysis, the Applicant consulted (b) (4) where available, and used investigator-analyzed data. 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.

The pooled populations included a wide range of studies (Table 1) in which patients were treated with the 4-dose or 6-dose regimens of Coartem, or with a variety of other antimalarials used as active comparators. Some studies used double-blind designs, others were investigator-blind or open label, and some trials were non-comparative. Few comparators were used in more than one study, and only a single study included both the 4-dose and 6-dose regimens of Coartem (Study A025). There were a number of differences between the studies due to the very long duration of

the development program, which spanned from 1993 to 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 such as antipyretics, and in the way that AEs were reported. Study differences in collecting AE data may have a significant impact on the interpretation of the data. Pre-printed AE Case Report Forms (CRFs) with tick boxes for specific AEs which were usually those related to malaria signs and symptoms were used in almost all the 4-dose studies and only some of the 6-dose studies. This may account for the generally higher frequency of AEs reported with the 4-dose compared to the 6-dose regimen. Overall, all of these factors mean that between group comparisons between 4- and 6-dose Coartem, and between Coartem and comparator antimalarials, should be interpreted with caution.

Since the Applicant’s submission was for the 6-dose regimen, safety data is presented in greater detail for this dosing regimen although data for the 4-dose and comparator antimalarials are also presented.

6.1.1 Patient exposure

6.1.1.1 Adult patients

The numbers of patients included in the FDA adult pooled safety database is summarized in Table 8. In the Applicant’s original analysis of the pooled adult and adolescent population, there were 1810 patients who had been exposed to Coartem. This was based on defining adults as patients >12 years of age. In the FDA’s analysis, adults were defined as > 16 years of age. With these new age definitions, a total of 1434 adult patients were exposed to Coartem (787 with the 4-dose regimen, 647 with 6-dose). Note that two Coartem dosing regimens were excluded from the safety analysis: Coartem 3-dose (Study A012), and the Coartem 4-dose regimen represented as “Coartem 4*2 tablets”, where only half the dose (2 tablets) was administered at each dosing interval instead of 4 tablets (Study A012). Both of these regimens represented lower exposures to Coartem.

Table 8: Sources of adult* study patients used in the FDA adult pooled safety analysis

Study	Artemether	Atovaquone-Proguanil	Chloroquine	Coartem 3 dose	Coartem 4 dose	Coartem 4*2 tablets	Coartem 6 dose	Halo-fantrine	Lume-fantrine capsules	Lume-fantrine tablets	Mef-loquine	Mef-loquine Artesunate	Quinine/SP
A004					106						109		
A005					12								11
A007			89		89								
A008					197							188	
A012				67	72	71							
A014					51			52					
A023					42				38	42			
A025					99		180						

Study	Artemether	Atovaquone-Proguanil	Chloroquine	Coartem 3 dose	Coartem 4 dose	Coartem 4*2 tablets	Coartem 6 dose	Halo-fantrine	Lumefantrine capsules	Lumefantrine tablets	Mefloquine	Mefloquine Artesunate	Quinine/SP
A026							109					34	
A028							149					43	
A2401							165						
A2412		13					44					15	
ABM01					78								
ABM02	44				41					40			
Total Patients	44	13	89	67	787	71	647	52	38	82	109	280	11

* (>16 and ≤ 65 years of age)

In the FDA adult pooled safety population, Study A2401 conducted in European travelers was included with the other studies that used the 6-dose regimen of Coartem since, unlike efficacy, the non-immune status of the patients in this study was considered unlikely to influence safety and tolerability.

The only comparator antimalarial which was relevant to current practice in the treatment of malaria according to the current WHO recommendations and had been used in a sufficient number of adult patients to allow meaningful comparisons with Coartem was mefloquine plus artesunate (MAS). There were 280 exposures to MAS in the adult pooled population.

The Applicant pointed out that far fewer AEs were reported from ABM01 and ABM02 compared to other studies. The reason for this is not known, as the protocols specified that AEs should be recorded at each visit. Both of these studies were conducted at one site in China, and a DSI investigation of this study site was ordered. The inspection was still ongoing at the time of this review, although nothing of concern had been reported so far.

6.1.1.2 Pediatric patients

Table 9 shows the FDA pediatric pooled safety population. In the Applicant's original analysis of the pooled pediatric population, there were 1788 patients who had been exposed to Coartem. With the new age definition of pediatrics as ≤16 years of age, the updated total of pediatric patients exposed to Coartem as 1991 (659 with the 4-dose regimen, 1332 with 6-dose, which included crushed, dispersible and standard tablet forms). Similar to the adult population, 3-dose and the 4 dose (2 tablets instead of 4, represented as "Coartem 4*2 tablets") regimens were excluded from the safety analysis. It is also noted that patients enrolled in Studies A009 and A011 received an experimental pediatric tablet which administered only half the current standard dose of artemether and lumefantrine (artemether/lumefantrine 10mg/60mg per tablet instead of 20mg/120mg). There were 150 exposures to MAS and 143 exposures to sulfadoxine-pyrimethamine (SP).

Table 9: Sources of pediatric * study patients used in the FDA pediatric pooled safety analysis

Study	Artemether	Atovaquone-Proguanil	Chloroquine	Coartem 3 dose	Coartem 4 dose	Coartem 4*2 tablets	Coartem 6 dose crushed tablet	Coartem 6 dose dispersible tablet	Coartem 6 dose tablet	Lumefantrine capsules	Lumefantrine tablets	Mefloquine	Mefloquine Artesunate	Quinine	SP
A003					111									108	
A004					20							17			
A007			1												
A008					112								120		
A009#					60										
A010					144										143
A011#			130		130										
A012				19	15	16									
A023					10					12	9				
A025					21				59						
A026									41				16		
A028									15				12		
A2403									310						
A2412		4							9				2		
ABM01					24										
ABM02	8				12						12				
B2303							452	447							
Total Patients	8	4	131	19	659	16	452	447	434	12	21	17	150	108	143

* ≤ 16 years of age

used an experimental pediatric formulation which was half the current standard dose of artemether and lumefantrine

Section 7.2.1.2 Demographics describes the baseline characteristics of the adult and pediatric pooled safety populations.

6.1.2 Deaths

6.1.2.1 Adult patients

Deaths, SAEs and AEs leading to premature discontinuation are summarized for the FDA adult pooled safety population in Table 10.

Table 10: Number of patients who died, had other SAEs or discontinued prematurely due to AEs in the FDA adult pooled safety population

Serious or significant AEs	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Total Coartem N=1434 (%)
Death	3 (0.4)	0	3 (0.2)
Serious AE	6 (0.8)	9 (1.4)	15 (1.0)
AE leading to study drug discontinuation	0	1 (0.2)	1 (0.1)

Three deaths (0.2%) occurred in the adult pooled safety population (3/1427 patients treated with Coartem, Table 11). These are summarized in Table 11. All Coartem-treated patients in the adult pooled safety population who died had received the 4-dose regimen, in Studies A008 and A025 in Thailand. In all three cases, death was due to violence or accidental trauma. One patient was shot in a family fight, one was shot by a military group and one was killed when he had an accident at work (stepped on a land mine). One patient taking chloroquine in Study A007 in India also died. This patient died due to cardiorespiratory arrest following cerebral malaria. These events were considered by the investigator to be unlikely to be related to study medication.

Table 11: Deaths in the FDA adult pooled safety population

Study	Patient no.	Age/Sex ¹	Day of last dose	Day of death	Cause of death (preferred term)
Co-artemether 4-dose regimen					
A008	THA/0002/00544	20/Male	3	9	Gun shot wound
A025	THA/0003/00197	37/Male	3	15	Gun shot wound
A025	THA/0003/00420	36/Male	3	20	Accident at work ²
Chloroquine					
A007	IND/0002/00186	40/Male	3	6	Cardio-respiratory arrest

Source: Table 5-29, Novartis Clinical Overview

Narratives of adult patient deaths

1. Study A008, Patient 00544

Age: 20 years Sex: male Weight: 62 kg

Adverse experience/laboratory abnormality: Patient (died) was shot

Relationship to trial treatment: Not related

Prematurely discontinued: Yes ("Death")

Discussion: This patient was randomised to Coartem on 09-July-96 and received 320 mg artemether and 1,920 mg lumefantrine at 0, 8, 24 and 48 hours. (b) (6) after having received the last treatment dose, on (b) (6), the patient was shot in a family fight and died the same day.

2. Study A025, patient 00197

Treatment group: Coartem, 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 37 years Sex: Male Weight: 54 kg

Adverse experience/laboratory abnormality: Shot by military group

Relationship to trial treatment: Not related

Prematurely discontinued: Yes

Discussion: The patient was randomised to the standard 4 dose regimen and started the trial treatment on 17-Oct-96. He received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, and 48 h plus placebo at 36 h and 60 h, 72 h and 96 h to match the other treatment groups. The malaria smear was negative on (b) (6). When the patient did not come back for a follow-up visit, it was found that he had been shot by a military group and died on (b) (6).

3. Study A025, patient 00420

Treatment group: Coartem, 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 36 years Sex: Male Weight: 42 kg

Adverse experience/laboratory abnormality: Injury by foreign body

Relationship to trial treatment: Not related

Prematurely discontinued: Yes

Discussion: The patient was randomised to the standard 4 dose regimen and started the trial treatment on 20-Jan-97. He received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, and 48 h plus placebo at 36 h and 60 h, 72 h and 96 h to match the other treatment groups. He recovered from malaria within 48 hours. On (b) (6) the patient stepped on a mine while walking in the fields and died immediately.

4. Study A007, patient 00186

Treatment group: chloroquine, 600 mg followed by 300 mg at 6-8 hours, 24 hours, and 48 hours (25 mg base/kg total dose)

Age: 40 years Sex: Male Weight: 64 kg

Adverse experience/laboratory abnormality: Cardiorespiratory arrest following cerebral malaria

Relationship to trial treatment: Unlikely

Prematurely discontinued: Yes

Discussion: The patient was admitted to hospital with a three days history of fever. He had a *P. falciparum* infection and satisfied the inclusion criteria. He was randomised to chloroquine and started trial treatment on 04-Dec-96. He received the full treatment course, i.e., 600 mg followed by 300 mg at 6, 24, and 48 hours. On (b) (6) (Day 6), the patient suddenly became tachypnoeic at 8:45 am and was moved to the intensive care unit. His respiration was shallow with a rate of 40/min, the pulse rate was 120/min, and blood pressure was 100/60 mmHg. The patient did not respond coherently to questions asked. A ryle's tube was passed, however there was no evidence of gastrointestinal bleed. The arterial blood gases report showed metabolic acidosis. The patient was started on intravenous therapy with quinine, ranitidine, and sodium bicarbonate. Glucose rose from pre-treatment of 197 mg/dL to 256 mg/dL on (b) (6) prior to death. The patient died despite treatment at 1:15 p.m. in the intensive care unit.

6.1.2.2 Pediatric patients

Deaths, SAEs and AEs leading to premature discontinuation are summarized for the FDA pediatric pooled safety population in Table 12. Deaths are further described in Table 13.

Table 12: Number of patients who died, had other SAEs or discontinued prematurely due to AEs in the FDA pediatric pooled safety population

Serious or significant AEs	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Total Coartem N=1991 (%)	MAS N=150 (%)	SP N=143 (%)
Death	0	4 (0.3)	4 (0.2)	0	0
Serious AE	7 (1.1)	17 (1.3)	24 (1.2)	0	3 (2.1)
AE leading to study drug discontinuation	4 (0.6)	71* (5.3)	75 (3.8)	0	0

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

Table 13: Deaths in the FDA pediatric pooled safety population

Study	Patient no.	Age/Sex/Race	Day of last dose	Day of death	Cause of death (preferred term)
Co-artemether 6-dose regimen, standard tablet					
A2403	NGA/0002/00204	4 yrs/Female/Black	4	9	Gastroenteritis
B2303	TZA/0301/00203	5 mo/Male/Black	4	31	<i>Plasmodium falciparum</i> infection
Co-artemether 6-dose regimen, dispersible tablet					
B2303	BEN/0801/00047	2 yrs/Male/Black	4	7	Haemorrhage
B2303	MLI/0601/00203	4 mo/Male/Black	2	3	Infection

Source: Table 5-30, Novartis Clinical Overview

Four patients died, all of whom were treated with the 6-dose regimen of Coartem (two with the standard tablet, two with the dispersible tablet) in Study A2403 and Study B2303 in Africa. In all but one case the cause of death was infection:

- One patient died due to severe gastroenteritis, having received the full course of Coartem treatment during which time she had moderate diarrhea suspected to be related to study medication (Day 1-2) and 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 from hemorrhage. The patient entered the study with low hemoglobin, hematocrit 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.

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

Narratives of pediatric patient deaths

1. Country Center/Patient number[NGA/002 00204]

Study No.: 2403

Patient: 4 years old, Black, female, 13 kg, 90 cm

Treatment group: Coartem

Event(s): Death (Gastroenteritis NOS)

This patient had no recorded relevant prior medical history, although the investigator noted a fine maculopapular rash on her trunk on entry to the study, which was thought to be heat rash. She received a full course of Coartem treatment (6 doses of 1 tablet). At baseline she had received paracetamol to treat pyrexia, and from Day 1 to Day 2 of treatment she received oral rehydration therapy to treat diarrhea, which was of moderate severity and considered by the investigator to be suspected to be related to study medication. Malaria signs and symptoms at baseline were mild. Her baseline parasite count was 2555/ μ L, but no parasites were detectable in subsequent blood films, including the pre dose 2 sample. Her malaria was reported as cured at Day 7. On Day 7 she developed a mild cough, suspected by the investigator to be related to study medication. No treatment was given for the cough. On Day 8, she developed severe gastroenteritis and died at home on the same day. No treatment for the gastroenteritis was recorded. Her vital signs and laboratory results were unremarkable. All ECG parameters were within the normal range at Baseline and Day 3.

2. Patient CCOA566B2303 – Infection, vomiting

Treatment group: Coartem dispersible tablet

Patient details: 4 month old, Black, male, weight 6.2kg, body temperature 37.2°C, pulse 87 bpm, BP 90/58 mm of Hg, asexual parasite count 33240/ μ l

Event(s): 1. Death (infection); 2. Discontinuation due to AE (vomiting)

This patient entered the study on ^{(b) (6)} (Study Day 1) with the diagnosis of acute uncomplicated *P. falciparum* malaria, confirmed by blood smear. He had a significant past medical history of bronchitis treated with amoxicillin and an active medical history of cough, diarrhea, pyrexia and vomiting. He received the first dose of study medication on Study Day 1 when his hemoglobin level was 91 g/L and blood glucose was 3.480 mmol/L. The patient had an episode of moderate vomiting after ingestion of first and second dose of study medication. The dose was repeated within one hour on both occasions. On the same day, the patient had moderate otitis which was treated with Otoralgil (phenylephrine, lidocaine hydrochloride). On Study Day 2, he had another episode of mild vomiting within one hour of dosing and the. Study medication was permanently discontinued due to this event. On the same day, the patient developed moderate pyrexia (38.9°C) and was then diagnosed with severe infection complicated with

dehydration, with a negative blood smear. He was treated with metoclopramide for vomiting and received paracetamol and amoxicillin for pyrexia. He started on quinine as a rescue medication for malaria on the same day. On Study Day 3, his condition worsened and he died due to infection complicated with dehydration. No autopsy was conducted following death. The investigator suspected a relationship only between vomiting and the study medication.

3. Patient CCOA566B2303 – Hemorrhage, hemoglobin decreased

Treatment group: Coartem dispersible tablet

Patient details: 2.4 year old, Black, male, weight 10kg, body temperature 40.2°C, pulse 199 bpm, BP 70/48 mm of Hg, asexual parasite count 152571/μl

Event(s): 1. Death (hemorrhage); 2. SAE (hemorrhage, hemoglobin decreased)

This patient entered the study on (b) (6) (Study Day 1) with a diagnosis of acute uncomplicated *P. falciparum* malaria, confirmed by blood smear. He did not have any significant past medical history. He was only noted to have splenomegaly at study entry. He received the first dose of the study medication on Study Day 1, when his hemoglobin level was 78 g/L, his platelet count (300 x 10⁹/L), his neutrophils 37.0 % and blood glucose was 6.6 mmol/L. The patient received the last dose of study medication on Study Day 4 and the parasite clearance was confirmed on Study Day 3. On Study Day 3, the patient developed moderate fever and was treated with paracetamol. The fever subsided on Study Day 4, but the patient was noted to have decreased hemoglobin (51 g/L) with associated decreased hematocrit (16.1 %). His RBC count was 2.1 x 10¹²/L and his platelet count 174 x 10⁹/L, his neutrophils 35.0 %. On the same day, he received the last dose of the study medication and he had an episode of mild vomiting after the last dose. He was treated with iron-folic acid (Foldine) for the event of decreased hemoglobin. On Study Day 5, he was taken to a traditional therapist who performed an traditional abdominal surgery on his left hypochondrium (Scarification). This event was considered medically significant. On Study Day 6, the patient was hospitalized with the diagnosis of anemia (hemoglobin 78 g/L) and continuing splenomegaly. On Study Day 7, his condition worsened and he died due to fatal hemorrhage. Autopsy was not performed. The investigator did not suspect a relationship between the events of decreased hemoglobin and hemorrhage and the study medication.

4. Patient CCOA566B2303– *P. falciparum* infection (severe), pyrexia, convulsion

Treatment group: Coartem crushed tablet

Patient details: 5 month, Black, male, weight 6kg, body temperature 37.0°C, pulse 126 bpm, BP 100/52 mm of Hg, asexual parasite count 197877/μl

Event(s): 1. Death (*P. falciparum* infection (severe), pyrexia, convulsion); 2. SAE (*P. falciparum* infection (severe), pyrexia, convulsion)

This patient entered the study on (b) (6) (Study Day 1) with a diagnosis of acute uncomplicated *P. falciparum* malaria, confirmed by blood smear. He did not have any active and significant past medical history at the study entry. His concomitant medication included paracetamol for fever. He received the first dose of study medication on Study Day 1, when his hemoglobin level was 74 g/L and blood glucose was 4.0 mmol/L. He received the last dose of the study medication on Study Day 4 and the parasite clearance was confirmed on Study Day 2. On Study Day 29, the patient developed severe pyrexia and he was hospitalized the next day with diagnosis of severe *P. falciparum* infection. He was noted with severe anemia

(hemoglobin level of 31 g/L, hematocrit 0.10/l), his RBC was 1.4 x10¹²/L and platelet count was 28x10⁹/L. His body temperature was 36°C, pulse was 125 bpm, and BP was 132/62 mm of Hg and his asexual parasite count was 8446/μl. No PCR testing was done on the same day. On admission, the patient had constant convulsions and he showed no significant neurological findings. No details of treatment given were available. On Study Day 31, the patient's condition worsened and he died due to pyrexia, convulsion and the disease progression. Autopsy details are not available. The investigator did not suspect a relationship between the events of *P. falciparum* infection, pyrexia and convulsion and the study medication.

6.1.3 Other Serious Adverse Events

6.1.3.1 Adult patients

SAEs in the FDA adult pooled safety population are summarized in Table 14. Overall, there were few SAEs reported. In the 6-dose Coartem group, 9 patients (1.4%) experienced 22 SAEs, where 6 patients (0.8%) had 7 SAEs in the 4-dose group and 1 patient (10.4%) reported 1 SAE in the MAS group (urticaria, data not shown). Most MedDRA preferred terms (PTs) were reported only once. The most frequently reported SAE was *P. falciparum* infection (3 patients in 4-dose, 2 patients in 6-dose).

Table 14: SAEs in the FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)
Blood and lymphatic system disorders	Anemia	1 (0.1)	0
	Thrombocytopenia	0	1 (0.2)
Gastrointestinal disorders	Abdominal pain	0	1 (0.2)
	Vomiting	0	1 (0.2)
General disorders and administration site conditions	Chills	0	1 (0.2)
	Disease progression	0	1 (0.2)
	Malaise	0	1 (0.2)
	Pyrexia	0	1 (0.2)
Hepatobiliary disorders	Chronic hepatitis	1 (0.1)	0
	Hepatocellular damage	0	1 (0.2)
Infections and infestations	Endocarditis	0	1 (0.2)
	Hepatitis viral	1 (0.1)	0
	<i>Plasmodium falciparum</i> infection	3 (0.4)	2 (0.3)

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)
	Typhoid fever	0	1 (0.2)
Investigations	Blood bilirubin increased	0	1 (0.2)
	Electrocardiogram T wave abnormal	0	1 (0.2)
	Laboratory test abnormal	1 (0.1)	0
	Liver function test abnormal	0	1 (0.2)
	Transaminases increased	0	1 (0.2)
Metabolism and nutrition disorders	Fluid overload	0	1 (0.2)
Nervous system disorders	Coma	0	1 (0.2)
	Headache	0	1 (0.2)
	Mental impairment	0	1 (0.2)
Renal and urinary disorders	Hematuria	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	1 (0.2)
	Total number of patients reporting SAEs	6 (0.8)	9 (1.4)

Of the 9 patients with SAEs in the Coartem 6-dose group, 6 (and 18 of the 22 SAEs) were from Study A2401. The SAEs from this study were categorized as such because they led to hospitalization or prolongation of hospitalization. Table 15 summarizes the SAEs and additional details are provided in the narratives below.

Table 15: Summary of 6-dose SAEs in the FDA adult pooled safety population

Patient number/ Study	SAE	Related to study medication?	Comments
11/A2401	1- liver function test abnormal 2 - haematuria 3 - malaise 4 - abdominal pain 5 -thrombocytopenia	SAEs 1, 2, 3 – no SAEs 4, 5 - unlikely	SAEs 1, 2, 3 were present at baseline Patient had hepatomegaly and splenomegaly on baseline physical exam which could account for SAEs 4,5
7/A2401	1 – blood bilirubin increased 2 – transaminases increased	SAEs 1, 2 – possible SAEs 3, 4, 5 -	SAEs 1, 2 present at baseline but

Patient number/ Study	SAE	Related to study medication?	Comments
	3 – mental impairment 4 – disease progression 5 – vomiting	unlikely	worsened on therapy
2/A2401	1 – chills 2 – pyrexia 3 – headache 4 – plasmodium falciprum infection	Yes – efficacy failure	Efficacy failure
3/A2401	1 – hepatocellular damage	Possible	SGOT elevated at baseline but worsened on therapy with Coartem, paracetamol and metamazole
22/A2401	1 – endocarditis	No	
1/A2401	1 – electrocardiogram abnormal 2 – <i>Plasmodium falciparum</i> infection	SAE 1 – unlikely SAE 2 – efficacy failure	Efficacy failure
41/A025	1- typhoid fever	No	
28/A028	1 – dyspnea 2 – fluid overload	No	Iatrogenic
259/A026	1 – coma	Unlikely	Etiology of coma unknown but unlikely given temporal occurrence and confounders

6-dose Adult SAE narratives

1. Patient 11:

Patient 11 was a 30 year old male enrolled in A2401 with a history of “elevated liver tests” and hepatomegaly and splenomegaly detected on baseline physical exam with the following SAEs: liver function test abnormal (SGPT 156 U/L at baseline), haematuria, malaise, abdominal pain and thrombocytopenia. The first 3 SAEs were present before enrollment or at baseline, and the onset of the abdominal pain and thrombocytopenia were on study days 2 and 3 respectively. The abdominal pain and anemia were ongoing at the end of the study while the other AEs resolved.

Reviewer's comments: While the etiology of this patient's abnormal liver tests is unknown, it is possible that the ongoing abdominal pain and anemia could be related to pre-existing hepatomegaly and splenomegaly respectively.

2. Patient 7

Patient 7 was a 55 year old Caucasian female enrolled in A2401 with a history of bronchopneumonia, appendicitis and peritonitis with the following SAEs requiring hospitalization: blood bilirubin increased, transaminases increased, mental impairment, disease progression and vomiting. At baseline, her bilirubin was elevated at 33 umol/L (reference range 7-25 umol/L), as well as both SGOT and SGPT at 105 and 103 U/L (reference range 9-42 U/L). The subject received 1 dose of study drug on study day 1. On study day 2, SGOT and SGPT increased to 241 and 142 U/L respectively, with bilirubin 61 µmol/L. The patient received a 2nd dose of study drug but due to vomiting and mental impairment the patient received IV quinine (possibly for the SAE "disease progression", *i.e.*, cerebral malaria and the presence of *P. falciparum* asexual forms on day 2 sample). LFTs later that day continued to rise (SGOT 287 U/L, SGPT 161). LFTs were improving on study day 3 (SGOT 168 U/L, SGPT 118 U/L, bilirubin 40 umol/L). On day 4, mental impairment resolved and Coartem was restarted (3rd dose), and the patient completed the remaining doses according to schedule (received the 6 doses of Coartem over 6 days). When Coartem was reintroduced on day 4, no LFTs were done, but on day 7 LFTs were much improved although still abnormal (SGOT 70 U/L, SGPT 115 U/L) and were fully normal at follow up on day 32. The increased bilirubin and transaminases, mental impairment and vomiting were all coded as "suspected relationship to study drug" by the investigator. The patient also received paracetamol for fever but information regarding the number of doses she received was not recorded.

Reviewer's comment: Mental impairment, disease progression and vomiting were likely due to malaria. While the baseline increased bilirubin and transaminases were likely due to malaria, it is not possible to determine if the worsening of these lab parameters on day 2 were a result of study drug or ongoing malarial. Although no LFTs were drawn on days 4-6 when Coartem was restarted on day 4, the improved LFT levels on day 7 suggest the cause was likely malaria as rechallenge did not cause LFT elevation .

3. Patient 2

Patient 2 was a 62 year old Caucasian female enrolled in A2401. She received her last dose of Coartem on Dec 1, with onset of the following SAEs 19 days later on Dec 20: chills, pyrexia, headache and *Plasmodium falciparum* infection. She was hospitalized and received Malarone on (b) (6) and *P. falciparum* asexual forms were seen on a blood smear on Dec 22. She received Malarone for 3 days and made a complete recovery. These SAEs were resolved by Dec 24 and were malaria infection symptoms.

Reviewer's comment: This SAE is related to study medication (efficacy failure).

4. Patient 3

Patient 3 was a 37 year old Caucasian female enrolled in A2401 with hepatocellular damage requiring prolonged hospitalization. Review of the case report form showed no past medical

history. At baseline, SGPT was 25 U/L (range 10-35 U/L), SGOT 39 U/L (range 10-35U/L) and total bilirubin was 1 umol/L (range 0-1 umol/L). The following day, SGPT was 43 U/L and SGOT 81 U/L and on study day 8, SGPT was 239 U/L and SGOT 113 U/L. GGT was also elevated at 85 U/L (range <39 U/L). This SAE was reported to end on day 15 although there are no laboratory results available to substantiate this. However, her SGPT and total bilirubin were normal on day 28 at 22 U/L and 0.8 umol/L respectively. The patient received Novalgin (NSAID) on days 1-2, and paracetamol for fever on days 1-5, which could have contributed to the abnormal liver function tests.

Reviewer's comment: The SGOT was elevated at baseline and worsened with the addition of metamizole, paracetamol and Coartem. The abnormal liver function tests could be due to any or a combination of these medications. It is less likely due to malaria given the late temporal onset on day 8.

5. Patient 22

Patient 22 was a 55 year old black male enrolled in A2401 with the SAE endocarditis which started on study day 3. There was no past medical history available on this patient. A blood culture on study day 3 was positive for *Staphylococcus aureus* and the patient was diagnosed with endocarditis and hospitalized for vancomycin, gentamycin, rifampin and cefazolin therapy. He made a complete recovery 41 days later.

Reviewer's comment: This SAE is unlikely to be due to drug effect.

6. Patient 1

Patient 1 was a 54 year old Caucasian male enrolled in A2401 with the SAEs electrocardiogram abnormal and *Plasmodium falciparum* infection. Eighteen days after his last dose of Coartem, the patient was seen by his general practitioner for chest pain, and no action was recommended. Past medical history was significant for heavy smoking. On day 29, the patient presented to hospital with headache, nausea and vomiting, myalgias and a palpable spleen. He was diagnosed with relapsed *P. falciparum* malaria, hospitalized and treated with Malarone. The parasite density was 0.8% and PCR was positive for recrudescence. An EKG performed at the time of hospitalization showed abnormal T wave changes. Additional EKGs obtained on days 9 and 13 of hospitalization showed persistent negative T waves. Troponin levels remained within normal limits and the patient recovered "with sequelae".

With respect to the SAE *Plasmodium falciparum* infection, the expiration date on the Riamet medication the patient received was the same date the patient received his first dose. The investigator suspected the event was related to study medication (lack of efficacy).

Reviewer's comment: The history is suggestive of an acute coronary syndrome on study day 18 with EKG changes detected on day 29. Recrudescence was possibly related to expired study medication.

7. Patient 41

Patient 41 was a 20 year old male enrolled in A025 with the SAE typhoid fever. This was reported on study day 8 and resolved on day 19 with chloramphenicol and 1 dose of ceftriaxone. This SAE was assessed to be unrelated to study medication.

Reviewer's comment: This SAE is unlikely to be due to drug effect.

8. Patient 28

Patient 28 was a 28 year old male enrolled in A028 with the SAEs dyspnea and fluid overload. Onset of these SAEs was on day 2 with resolution on days 4 and 5 respectively. The patient received dextrose and sodium chloride the day prior at 100 mL/h for dehydration. Relationship to study drug was not suspected and review of the case report form stated the patient experienced pulmonary edema due to fluid overload. Furosemide was administered for management of the AE. The patient's past medical history included hepatomegaly (etiology unknown).

Reviewer's comment: This SAE is not due to drug effect.

9. Patient 259

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

Reviewer's comment: The etiology of the coma is unclear. Although cerebral malaria would be high on the differential, his parasite count (asexual forms) was negative. There are no CSF results or other laboratory tests which could provide this information. The ampicillin and metronidazole for aspiration pneumonia could have been concurrently treating a cerebral infection. Typhoid fever is another possibility due to high fever and would have been treated by ampicillin and chloramphenicol. Nonetheless, it is unlikely that Coartem was the cause of this SAE due to the late onset and multiple other explanations which cannot be ruled out.

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

In patients treated with the 4-dose regimen, seven SAEs were reported by 6 patients. Four of

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

6.1.3.2 Pediatric patients

SAEs in the FDA pediatric pooled safety population are presented in Table 16. Similar to the adult pooled population, there were few SAEs reported in the pediatric population, with 1.1 % and 1.3% of patients reporting SAEs in the 4-dose and 6-dose groups, respectively. There were 30 SAEs in 17 patients in the 6-dose group whereas the 7 SAEs in the 4-dose group were reported in 7 patients. There were no SAEs reported in the 78 patients who received MAS in the pediatric pooled safety population. The most frequently reported SAEs were anemia (4-dose) and *P. falciparum* infection (6-dose).

Table 16: SAEs in the FDA pediatric pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	SP N=143 (%)
Blood and lymphatic system disorders	Anaemia	3 (0.5)	2 (0.2)	0
	Iron deficiency anaemia	0	1 (0.1)	0
Eye disorders	Conjunctivitis	1 (0.2)	0	0
Gastrointestinal disorders	Diarrhoea	0	1 (0.1)	0
	Vomiting	1 (0.2)	1 (0.1)	0
General disorders and administration site conditions	Face oedema	0	1 (0.1)	0
	Pyrexia	0	3 (0.2)	1 (0.7)
Infections and infestations	Bronchitis	0	1 (0.1)	0
	Bronchopneumonia	1 (0.2)	0	0
	Gastroenteritis	0	1 (0.1)	0
	Hepatitis viral	0	1 (0.1)	0
	Infection	0	1 (0.1)	0
	Lower respiratory tract infection	0	1 (0.1)	0
	<i>Plasmodium falciparum</i> infection	0	7 (0.5)	0
	Pneumonia	1 (0.2)	1 (0.1)	0
Metabolism and nutrition disorders	Pneumonia primary atypical	0	1 (0.1)	0
	Haemoglobin decreased	0	1 (0.1)	0
	Dehydration	0	1 (0.1)	0

	Oral intake reduced	0	1 (0.1)	0
Nervous system disorders	Convulsion	0	3 (0.2)	0
	Hypotonia	0	1 (0.1)	1 (0.7)
	Lethargy	0	1 (0.1)	1 (0.7)
Renal and urinary disorders	Glomerulonephritis acute	0	1 (0.1)	1 (0.7)
Skin and subcutaneous tissue disorders	Urticaria	0	1 (0.1)	0
Vascular disorders	Haemorrhage	0	1 (0.1)	0
	Total number of patients	7 (1.1)	17 (1.3)	3 (2.1)

Table 17 summarizes the SAEs for the 6-dose standard tablet formulation, as the Applicant is not pursuing the other formulations of Coartem. Additional details are provided in the narratives below.

Table 17: SAE summary in the FDA pediatric pooled safety population receiving the 6-dose standard tablet regimen

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

Reviewer’s comments: Urticaria and other more serious skin reactions have been noted in post-marketing reports (please see Section 7.1.17 on Post-marketing experience) . While “hypersensitivity” is listed on the proposed label, this AE should be expanded to describe the types of serious skin reactions.

Pediatric SAE narratives for the 6-dose standard tablet formulation

1. Patient 204 (fatal SAE)

Patient 204 was a 4 year old black female enrolled in A2403. She received the full course of Coartem over 3 days and developed moderate diarrhea on study day 2 suspected to be related to study medication. She was treated with oral rehydration therapy and was clear of parasites on day 1. The diarrhea resolved after 1 day. On day 8 she had the AE cough, and the following day

(study day 9) she developed the SAE severe gastroenteritis and died the same day. The SAE was not felt to be related to study drug.

Reviewer's comment: There are no additional details regarding the gastroenteritis and death of this patient obtained from case report form review. However, given the occurrence of gastroenteritis 6 days after her last dose of study drug, it seems unlikely that the study drug was related to this SAE.

2. Patient 149

Patient 149 was a 1 year old black male enrolled in Study A2403. He had the SAE “hepatitis viral” recorded on study day 2 which was ongoing at the time of study termination. Relationship to study drug was not suspected since the patient’s baseline (Nov 4) liver enzymes were already elevated prior to initiation of study drug (total bilirubin 36 umol/L, SGPT 1250 U/L, SGOT 1670 U/L, gamma GT 118.8 U/L). On day 4 (Nov 7), the transaminases were coming down (SGPT 871.4 U/L, SGOT 977.1 U/L) although total bilirubin (145 umol/L) and gamma GT (132.5 U/L) increased. The patient was managed as a case of viral hepatitis despite a negative HBsAg test due to the presence of clinical jaundice, hepato- and splenomegaly on physical exam and elevated bilirubin and liver enzymes. It does not appear that other viral causes of hepatitis were investigated. The patient was discharged home fully active, feeding well with mild jaundice. His transaminases were still elevated but had reduced significantly (SGPT 236.7 U/L, SGOT 270 U/L; gamma GT 122.1 U/L)

Reviewer's comment: This SAE is unlikely to be related to study drug.

3. Patient 145

Patient 145 was an 8 month old black female enrolled in A2403. She received her last dose of Coartem on Oct 31 and was clear of parasites. On Nov 24 (study day 28), she presented with convulsion, ear pain and rash. Her parasite count was 19,775. The SAEs *Plasmodium falciparum* infection and convulsion were noted and she was treated with amodiaquine and recovered.

Reviewer's comment: This SAE is related to study drug (efficacy failure).

4. Patient 222

Patient 222 was a 4 year old black female enrolled in A2403. She had the SAEs pneumonia primary atypical and urticaria on study days 22 and 2 respectively. The urticaria was initially associated with fever with no mucosal or conjunctival involvement. The rash worsened on day 3 and study drug was discontinued that day after the patient only received 4 doses. Antihistamine and chlorpheniramine were given and the rash resolved on day 6. On day 22, the patient presented at an unplanned visit with an atypical pneumonia and was treated with erythromycin which resolved. From the case report form, it was revealed that the investigator suspected an underlying immune suppression, as the patient developed the severe AE otitis media with mastoiditis on day 8, and on study day 46 (period of extended follow-up) had malaria treated with amodiaquine.

Reviewer's comment: It is possible that the SAE urticaria was due to the study drug since the rash improved after discontinuing Coartem. The only other drug the patient received prior to the rash was paracetamol, which was discontinued on day 4. However, she received paracetamol again on days 7-9 without recurrence of the urticaria. The atypical pneumonia is unlikely related to study drug given the patient's history of other infections and the late onset of this SAE relative to drug.

Therefore, of the SAEs reported with the 6-dose standard tablet formulation, there were only 2 which were or possibly were related to study drug. Patient 145 had efficacy failure which was definitely related to study drug. Patient 222 had urticaria with onset after 2 doses of study drug and resolved after discontinuing study drug. While she was concurrently receiving paracetamol with study drug, she received paracetamol several days later with no recurrence of the urticaria.

Of all the SAEs reported with the 6-dose formulation, the most frequently reported was *Plasmodium falciparum* infection. This was reported as an SAE when danger signs of severe malaria developed early in the study (two cases), which led to discontinuation of study drug and treatment with rescue medication, or where new infections occurred late in the study in patients who had cleared their original infection (four cases). One further case of malaria also occurred late in the study (Day 29), but no PCR analysis was available so it is not known whether this was a new infection or a recrudescence of the original infection; the patient died as a result of this infection. Many of the other SAEs reported with the 6-dose formulation were likely complications of malaria (anemia and pyrexia) or were other infections that required patients to be hospitalized.

Pediatric SAEs for the 6-dose regimen (any formulation)

With respect to other significant SAEs reported with the 6-dose regimen (any formulation), there were 3 cases of convulsion. In 2 cases (patient 145 and 22), convulsion was likely secondary to cerebral malaria, while in the remaining patient (patient 46), convulsion was due to meningitis. In none of the cases was the study drug suspected to be the cause. Brief summaries of these cases are presented below:

1. Patient 145 (reported above) who likely had convulsion secondary to cerebral malaria.
 2. Patient 22 was a 2 year old black male enrolled in study B2303 who received Coartem (6 doses) in crushed tablet form. His last dose was Jan 13. On study day 42 (Feb 20), he had a convulsion and was diagnosed with malaria. His parasite count was 67,102. Both the convulsion and *P. falciparum* infection were coded as SAEs.
 3. Patient 46 was a 5 year old black male enrolled in Study B2303 who received the 6 dose Coartem treatment in dispersible tablet form. His last dose was Sept 7 and the SAE was reported on study day 29 (Oct 3) along with pyrexia. His parasite count was zero and he was diagnosed with meningitis and given benzylpenicillin.
- A diverse range of infections other than malaria were reported as SAEs. In two cases - one case of 'Infection', and one case of 'Gastroenteritis' - the infections were fatal (Section 7.1.1. Deaths). One case of viral hepatitis was ongoing at the end of the study, but all other infections

classified as SAEs were reported to have resolved following hospitalization and in some cases use of appropriate medication. One patient had diarrhea and vomiting, together with dehydration and 'oral intake reduced' (*i.e.*, refusal to feed) all reported as SAEs on Day 43, with no further information available. Only one SAE was suspected to be related to study medication. This was a case of severe urticarial rash reported on Day 1 in a 4-year-old patient taking the standard tablet in Study A2403. This resolved within 5 days following antihistamine treatment.

6.1.3.3 SAEs in ongoing studies

Narratives for all SAEs for ongoing studies that have been reported to Novartis as of 27-May-08 are reported below:

1. Initial report received 24 Nov 2007: This patient (centre number 1, patient number 157, randomisation number 5193) was enrolled in study CCOA566A24157, a phase IV, open-label, randomised, single centre, parallel study of the effects of artemether-lumefantrine (Coartem), atovaquone-proguanil (Malarone) and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *Plasmodium falciparum* malaria in patients 12 years of age or older. The patient did not have any relevant medical history. The patient commenced study medication (artesunate-mefloquine) on 20 Nov 2007. On (b) (6), the patient returned to hospital with vomiting. The patient was observed and administered intravenous fluids, normal saline and Metoclopramide. After 2 hours of observation, the patient displayed signs of respiratory difficulty. The dyspnoea became serious with a sensation of cramping of faeces and superior extremities. The picture presented by the patient was compatible with a '**secondary syndrome of respiratory difficulty to a extrapyramidal syndrome**'. The patient was diagnosed with respiratory distress syndrome. Additional treatment included Furosemide and Akineton. Hemoparasites were negative for malaria. On 24 Nov 2007, the patient was considered to have made a complete recovery. The investigator assessed that this event was not suspected to be related to study medication, stating that Metoclopramide is a medication that can trigger respiratory distress syndrome.

2. Initial report received on 18 Apr 2008: This patient (centre number 1, patient number 32) was enrolled in study CCOA566B2106, a randomized, open-label, single-dose, three-period, six-sequence crossover study of Coartem to evaluate the bioequivalence between the dispersible tablet manufactured at (b) (4), the dispersible tablet from a scale up batch (similar to the batch used in Novartis clinical studies) and the commercial tablet crushed for oral suspension, in sixty healthy volunteers. The patient commenced study medication (formulation unknown) on 02 Feb 2008. On (b) (6), the patient developed a **nasopharyngeal mass**. The patient was admitted to hospital due to the event. An excision biopsy of the mass was performed on (b) (6). The patient received treatment with Co-codamol, Dexamethasone, Paracetamol and Diclofenac. The patient had completely recovered by (b) (6) and was discharged from hospital the same day. In the absence of an investigators causality, the Novartis Medical Safety Physician, provided a provisional causality assessment of not suspected, based on the available information.

3. Initial report received on 03 May 2008: This patient was enrolled in study CCOA566A2422, a phase IV, prospective, community-based, longitudinal demographic surveillance study to assess the impact of Coartem when used as national policy first-line treatment on malaria morbidity and mortality in Tanzania. On (b) (4), the patient presented to the hospital with history of fevere, headache, convulsions, and vomiting. Upon examination, the patient was febrile, looking pale, jaundiced, and a splenomegally 4 cm was detected. The patient was diagnosed with malaria and was started on the study drug 2 tablets on (b) (4) at 10:32 am. Patient also received paracetamol therapy for the fever. Around 17:00 hours the patient returned with history of convulsions and drowsiness. The patient was hospitalised and treated with Quinine IV. The B/S revealed >9999 mp's/200wbcs (hyperparasitaemia). On (b) (4), the patient's condition worsened and she was transferred to another hospital for further management. the patient **died on the same day due to severe malaria**. Autopsy was not performed. The investigator assessed that this event was not suspected to be related to study medication but was due to progression of underlying illness.

4. Initial report received on 04 Mar 2008: : This patient was enrolled in study CCOA566A2422, a phase IV, prospective, community-based, longitudinal demographic surveillance study to assess the impact of Coartem when used as national policy first-line treatment on malaria morbidity and mortality in Tanzania. The patient commenced study medication on 27 Feb 2008. On 27 Feb, the patient was diagnosed with pneumonia. She was treated with X-pen, amoxycillin, and paractematol therapies. The patient died on (b) (6) due to **dyspnoea following severe diarrhoea, vomiting, and respiratory distress**. An autopsy was not performed. The investigator assessed that this event was not suspected to be related to study medication.

5. Initial report received 22 Nov 2007: This patient was enrolled in study CCOA566A2422, a phase IV, prospective, community-based, longitudinal demographic surveillance study to assess the impact of Coartem when used as national policy first-line treatment on malaria morbidity and mortality in Tanzania. The patient commenced study medication on 29 Oct 2007. On (b) (6), the patient experienced severe attacks (recurrent) with **difficulty breathing associated with shivering and temporary rigidity of the fingers**. The study medication was permanently discontinued due to this event. At the time of reporting, the patient's condition was still present and unchanged. This event involved or prolonged inpatient hospitalisation and the investigator assessed this event as life threatening. The investigator did suspect a relationship between this event and the study medication. Follow-up received on 13 Jun 2008: At the time of this report (04 Nov 2007), the patient had no complaints of difficulty in breathing or shivering. Finger rigidity was still slightly present. The patient was well oriented, healthy looking and extended her fingers normally. The patient reported that she had a serious condition from 30 Oct 2007 until 31 Oct 2007 but decided not to go to the hospital as instructed by the CO at the local medical facility. The patient was treated with chlorphenamine tablets (4mg b.i.d. x 3/7) and paracetamol for pyrexia. The patient was considered to have made a complete recovery by 02 Nov 2007. In the absence of a causality assessment from the investigator for the pyrexia, the Novartis Medical Safety Physician provisionally assessed the event as non-serious and suspected to be related to the study medication.

6.1.3.4 120 Day safety update

In the 120 day safety update, the Applicant reported 3 new SAEs reported in ongoing studies (all from Study A2422), and 8 new AEs reported from post-marketing experience. The latter is discussed in Section 7.1.17 Post-marketing Experience.

The SAEs were reported from Study A2422, a phase 4 prospective, longitudinal demographic surveillance study to assess the impact of malaria morbidity and mortality in Tanzania of Coartem when used as national policy first-line treatment. Brief narratives follow:

- A 26-month-old female patient experienced fever, vomiting, and asthenia one day after starting treatment. She was given an anti-emetic, quinine and paracetamol and completely recovered.
- A 6-year-old child experienced muscle twitching, pyrexia, asthenia and eating disorder. The treatment was changed to quinine. The patient recovered.
- A 38-year-old female patient experienced persisting pyrexia, vomiting and headache the day following treatment initiation. Coartem was continued and the patient was treated with an anti-emetic, quinine and paracetamol and she recovered.

Note: two additional cases were reported prior to the cut-off of the cumulative review provided with the submission of NDA 22-268. These were a possible allergic reaction in one patient and a fatal malaria in a 4-year-old female patient, which was not suspected to be related to study medication but was due to progression of underlying illness.

A literature review was also performed as part of the 120 day safety update. Three studies specifically examined the clinical safety of Coartem. Maiteki-Sebuguzi et al. compared the safety of amodiaquine and sulfadoxine-pyrimethamine, artesunate plus amodiaquine and Coartem in a longitudinal, single blind, randomized study of 382 children (1-12 years) in Uganda². The AE profile for Coartem was consistent with those previously described, and analysis out to 42 days did not change the nature of the AEs. SAEs were reported in 1.1% of Coartem patients.

Another study identified was a randomized trial comparing the efficacy and safety of artesunate/amodiaquine and Coartem when used to treat multiple episodes of malaria in children aged 6 months to 14 years in Ghana (Adjei et al., 2008³). Of interest in the current context is the collection of data on the safety of repeated treatments. 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. Both treatment groups had similar rates of malaria episodes (0.34 and 0.37, respectively) in the year following recruitment. The profiles of AEs and clinical laboratory evaluations were similar in the two treatment groups.

2 Maiteki-Sebuguzi C, Jagannathan P, Yau VM, et al. Safety and tolerability of combination antimalarial therapies for uncomplicated falciparum malaria in Ugandan children. *Malar J.* 2008 Jun 11;7:106

3 Adjei GO, Kurtzhals JA, Rodrigues OP, et al. Amodiaquine-artesunate vs. artemether –lumefantrine for uncomplicated malaria in Ghanaian children: a randomized efficacy and safety trial with one year follow-up. *Malar J.* 2008 Jul 11;7:127.

Many AEs were mild in intensity and overlapped with known malaria symptomatology. Audiological examinations in a subset of patients in each group revealed no evidence of hearing impairment. Similarly, neurological examinations showed that no abnormal neurological signs were observed during one year of follow-up. No adverse event exacerbation was observed in any of the patients who received multiple treatment courses with either regimen during the 1-year follow-up period. The remaining study is described in Section 7.1.5.4.4 Ear and auditory AEs, as it relates to assessing for possible ototoxicity associated with Coartem

6.1.4 Dropouts and Other Significant Adverse Events

6.1.4.1 Overall profile of dropouts

Patient disposition in the adult pooled population is shown in Table 18. “Discontinuation” refers to discontinuation at any point during the studies, and not just discontinuation of treatment. Most patients in all treatment groups completed the studies, as treatment periods were typically 2-3 days. The discontinuation rate was lower for the Coartem 6-dose regimen (17%) than the 4-dose regimen (28%); 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 15% of those treated with the 4-dose regimen). Unsatisfactory therapeutic effect most commonly referred to reappearance 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.

It should also be noted that in some early studies it was not possible to determine whether patients discontinued due to specific AEs, as the CRFs did not collect details of action taken in response to AEs, although the study completion pages did collect AEs as a reason for discontinuation.

Table 19 shows patient disposition for the FDA pediatric pooled safety population. The rate of premature discontinuation from the studies was higher in the 4-dose group (25%) than the 6-dose group (11%); this difference appeared to be mainly due to differences in rates of discontinuation due to unsatisfactory therapeutic effect (13% vs. 0.5%, respectively), and loss to follow-up (8% vs. 3%, respectively). ‘Unsatisfactory therapeutic effect’ referred to reappearance of parasites after clearance in all but one Coartem patient who took the 4-dose regimen, discontinued during treatment and received rescue medication.

6.1.4.2 Adverse events associated with dropouts

6.1.4.2.1 Adult patients

As shown in Table 18, one patient in the adult pooled safety population discontinued treatment prematurely due to an AE. Patient 7 was enrolled in Study A2401 and received the 6-dose Coartem regimen. This patient was a 58 year old black female who discontinued after the first dose after experiencing mild abdominal pain and mild diarrhea which resolved without intervention.

Table 18: Reasons for discontinuation, FDA adult pooled population

Discontinued reason	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)
Abnormal test procedure result(s)	0	2 (0.3)
Administrative problems	1 (0.1)	1 (0.2)
Adverse Event(s)	0	1 (0.2)
Death	3 (0.4)	0
Lost to follow-up	83 (10.6)	69 (10.7)
Non-compliance	8 (1.0)	1 (0.2)
<i>P. vivax</i> rescue medication	1 (0.1)	0
Protocol violation	3 (0.4)	7 (1.1)
Patient withdrew consent	2 (0.3)	2 (0.3)
Patient's condition no longer requires study drug	0	1 (0.2)
Unsatisfactory therapeutic effect	114 (14.6)	24 (3.7)
Total number of patients who discontinued study	215 (27.5)	108 (16.7)

6.1.4.2.2 Pediatric patients

Premature discontinuation for safety-related reasons was more common with the 6-dose regimen than the 4-dose regimen. Table 19 shows the reasons for discontinuation in the FDA pediatric population. In the 6-dose group, there were 71 discontinuations due to AEs (5.3%), of which 70 of the 71 patients came from Study B2303 (remaining patient from Study A2403). Of the 71 patients, 21 discontinued during the treatment period; 20 of these 21 cases came from Study B2303 and 17 of these 20 discontinued due to vomiting medication doses. This study specified that study drug was to be discontinued with severe nausea/vomiting, or vomiting more than 2 doses of study drug within 1 hour of administration or vomiting of the replacement dose within 2 hours. The remaining 50 patients who discontinued due to an AE after completing the treatment period most commonly did so following re-appearance of parasites (reported as *P. falciparum* infection). Study B2303 also had the following AEs which led to discontinuation: two patients discontinued due to anemia (both SAEs), two patients due to malaria (both SAEs), and one as a result of a lower respiratory tract infection. These were all from the dispersible tablet group. The one patient who discontinued treatment due to an AE in Study A2403 had urticaria. Table 20 details the 4 patients in the 4-dose group who discontinued due to an AE, and 1 in the 6-dose standard tablet group.

Table 19: Reasons for discontinuation, FDA pediatric pooled population

Discontinued reason	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)
Abnormal test procedure result(s)	0	1 (0.8)
Administrative problems	5 (0.8)	0
Adverse Event(s)	4 (0.6)	71 (5.3)
Death	0	4 (0.3)
Lost to follow-up	54 (8.2)	40 (3.0)
Non-compliance	2 (0.3)	0
Protocol violation	12 (1.8)	1 (0.8)
Patient withdrew consent	4 (0.6)	19 (1.4)
Unsatisfactory therapeutic effect	85 (12.9)	6 (0.5)
Total number of patients who discontinued study	166 (25.2)	142 (10.7)

Table 20: Discontinuations due to AEs in the 4- and 6-dose (standard tablet) Coartem groups

Study number/ patient ID	Demo- graphics	AEs at time of discontinuation	AEs coded as related to study drug	Interpretation
A010/157/ 4-dose	3 yo female	Mild abdominal pain, splenomegaly; moderate anemia; severe vomiting	No	Likely discontinued due to SAE vomiting; discontinued after 1 dose
A011/12 4-dose	2 yo female	Mild diarrhoea, dizziness, abdominal pain, vomiting; Moderate anaemia'	No	Likely discontinued due to vomiting, possibly diarrhea and abdominal pain
A011/162 4-dose	2 yo female	Mild cough, diarrhoea, fatigue, headache, chills, rhinorrhoea, vomiting	No	Likely discontinued due to vomiting
A011/176 4-dose	2 yo female	Severe anemia, anorexia, pyrexia; mild cough, fatigue, headache, hepatomegaly, abdominal pain, pneumonia, chills, sleep disorder, splenomegaly	No	Not clear which AE led to drug discontinuation, possibly anorexia?; abdominal pain, chills, headache and sleep disorder started on day -2, anemia, anorexia, pneumonia and pyrexia on study day 1
A2403/222/ 4-dose	4 yo	Mild pruritis, somnolence;	Yes	Likely discontinued

Study number/ patient ID	Demo- graphics	AEs at time of discontinuation	AEs coded as related to study drug	Interpretation
6-dose	female	severe urticaria	(urticaria), no for pruritis and somnolence	due to SAE urticaria

6.1.4.3 Other significant adverse events

None

6.1.4.4 Other Search Strategies

None

6.1.5 Common Adverse Events

6.1.5.1 Eliciting adverse events data in the development program

All AEs were obtained by questioning and /or examining the patient by the PI and recorded in the CRF.

6.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs in the two pooled population were coded using MedDRA version 10.1. The individual studies used different coding dictionaries and the Applicant cautioned that AEs presented in the studies may differ from those in the pooled analysis. The AEs for Study A2101 (healthy volunteer study) were coded using MedDRA version 9.1.

6.1.5.3 Common adverse event tables

6.1.5.3.1 Adult patients

Table 21 shows AEs by system organ class (SOC) for the FDA adult pooled safety population. The total rate of AEs was similar between groups for most SOCs, although all comparisons are made with caution. The frequency of AEs was greater with the 4-dose compared to the 6-dose

regimen for the majority of SOCs ('Blood and lymphatic system', 'Cardiac disorders', 'Gastrointestinal disorders', 'General disorders and administration site conditions', 'Hepatobiliary disorders', 'Metabolism and nutrition', 'Nervous system disorders' and 'Psychiatric disorders'). This is mostly likely due to between-study differences in methods of collecting AE data. Pre-printed AE case report forms (CRFs) were used in all the 4 dose regimen studies except for studies ABMO1 and ABMO2, while pre-printed CRFs were used only in three of the 6 dose regimen studies (A025, A026 and A028). These pages included tick boxes for specific AEs, including those related to malaria signs and symptoms, that resulted in some AEs appearing more frequently in the pooled safety analysis, e.g. headache, fatigue, dizziness, sleep disorder, anorexia. There were also a number of differences in entry criteria, such as the use of concomitant medications (notably antipyretics). The Applicant did point out that in study A025, the only study that compared the 4 dose to the 6 dose regimen, and in which pre-printed AE CRFs were used, no increase of either frequency or severity of the AEs was seen between the two dose regimen groups. Please refer to Section 7.1.4.5 Additional analyses and explorations for the FDA's analysis of Study A025.

The SOCs most frequently affected by AEs for the Coartem 6-dose regimen were 'General disorders and administrative site disorders'; 'Nervous system disorders'; 'Metabolism and nutrition disorders'; 'Gastrointestinal disorders' and 'Musculoskeletal and connective tissue disorders' (Table 21). SOCs which were higher for the Coartem 6 dose regimen compared to the 4-dose included: Ear and Labyrinth Disorders (4.5% vs 1.8% respectively, "Infections and infestations" (14.1% vs 7.2% respectively), and "Respiratory disorders" (7.9% vs. 5.7% respectively).

Table 21: Frequency of AEs by System Organ Class, FDA adult pooled safety population

MedDRA system organ class	Coartem 4 dose N=787 (%)	Coartem 6 dose n=647 (%)	Mefloquine Artesunate N=280 (%)
Blood and lymphatic system disorders	202 (25.7)	76 (11.8)	53 (18.9)
Cardiac disorders	195 (24.8)	120 (18.6)	126 (45.0)
Ear and labyrinth disorders	14 (1.8)	29 (4.5)	22 (7.9)
Endocrine disorders	0	1 (0.2)	0
Eye disorders	12 (1.5)	1 (0.2)	1 (0.4)
Gastrointestinal disorders	422 (53.6)	264 (40.8)	170 (60.7)
General disorders and administration site conditions	524 (66.6)	397 (61.4)	234 (83.6)
Hepatobiliary disorders	181 (23.0)	64 (9.9)	19 (6.8)
Infections and infestations	57 (7.2)	91 (14.1)	31 (11.1)
Injury, poisoning and procedural complications	0	1 (0.2)	3 (1.1)
Investigations	7 (0.9)	16 (2.5)	1 (0.4)
Metabolism and nutrition disorders	471 (59.9)	266 (41.1)	194 (69.3)
Musculoskeletal and connective tissue disorders	284 (36.1)	249 (38.5)	189 (67.5)
Nervous system disorders	563 (71.5)	386 (59.7)	228 (81.4)

MedDRA system organ class	Coartem 4 dose N=787 (%)	Coartem 6 dose n=647 (%)	Mefloquine Artesunate N=280 (%)
Psychiatric disorders	269 (34.2)	176 (27.2)	132 (47.1)
Renal and urinary disorders	9 (1.1)	6 (0.9)	0
Reproductive system and breast disorders	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	45 (5.7)	51 (7.9)	10 (3.6)
Skin and subcutaneous tissue disorders	57 (7.2)	50 (7.7)	20 (7.1)
Vascular disorders	5 (0.6)	6 (0.9)	0

Table 22 shows the most frequently-occurring AEs that were reported in at least 0.5% of patients in at least one treatment group in the FDA adult pooled safety population. The most frequent AEs reported in the 4-dose regimen were similar to those in the 6-dose group. Similar to the observation with SOCs, AEs were reported more frequently with the 4-dose than 6-dose regimen.

The most frequent AEs in the Coartem 6-dose regimen group were: headache (55.6%), anorexia (40.2%), dizziness (39.1%), asthenia (37.6%), arthralgia (33.8%), myalgia (31.8%), nausea (26.1%) and pyrexia (24.6%). Although these are treatment emergent AEs which are reported, it is still difficult to interpret these AEs independent from the natural history of malaria, since most AEs were reported on Days 1-3 but many were likely related to malaria infection.

The Applicant evaluated time of occurrence of AEs and found that nausea, abdominal pain, anorexia, headache, dizziness, asthenia, chills and fatigue (all of which are potentially signs or symptoms of malaria) appeared to be more common later in the studies with the 4-dose regimen than the 6-dose regimen.

Table 22: Most frequent AEs (0.5% or more in any group), FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Nervous system disorders	Headache	545 (69.3)	360 (55.6)	213 (76.1)
	Dizziness	418 (53.1)	253 (39.1)	203 (72.5)
	Clonus	5 (0.6)	16 (2.5)	0
	Tremor	23 (2.9)	16 (2.5)	13 (4.6)
	Nystagmus	8 (1.0)	5 (0.8)	16 (5.7)
	Hypoaesthesia	3 (0.4)	4 (0.6)	7 (2.5)
	Ataxia	11 (1.4)	3 (0.5)	14 (5.0)
	Somnolence	1 (0.1)	3 (0.5)	0
	Fine motor delay	0	2 (0.3)	2 (0.7)
	Paraesthesia	32 (4.1)	0	27 (9.6)
Metabolism and nutrition disorders	Anorexia	466 (59.2)	260 (40.2)	191 (68.2)
	Hypokalaemia	3 (0.4)	4 (0.6)	2 (0.7)

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
General disorders and administration site conditions	Asthenia	352 (44.7)	243 (37.6)	189 (67.5)
	Pyrexia	0	159 (24.6)	44 (15.7)
	Chills	320 (40.7)	147 (22.7)	90 (32.1)
	Fatigue	252 (32.0)	111 (17.2)	100 (35.7)
	Malaise	0	20 (3.1)	0
	Chest pain	0	3 (0.5)	1 (0.4)
	Gait disturbance	15 (1.9)	3 (0.5)	22 (7.9)
Musculoskeletal and connective tissue disorders	Arthralgia	250 (31.8)	219 (33.8)	184 (65.7)
	Myalgia	247 (31.4)	206 (31.8)	151 (53.9)
	Back pain	4 (0.5)	3 (0.5)	0
	Neck pain	1 (0.1)	3 (0.5)	0
Gastrointestinal disorders	Nausea	310 (39.4)	169 (26.1)	133 (47.5)
	Vomiting	216 (27.4)	113 (17.5)	72 (25.7)
	Abdominal pain	186 (23.6)	112 (17.3)	72 (25.7)
	Diarrhoea	59 (7.5)	46 (7.1)	16 (5.7)
	Dyspepsia	3 (0.4)	10 (1.5)	4 (1.4)
	Abdominal pain upper	3 (0.4)	3 (0.5)	0
	Peptic ulcer	6 (0.8)	3 (0.5)	0
	Toothache	4 (0.5)	3 (0.5)	1 (0.4)
	Constipation	6 (0.8)	2 (0.3)	0
Psychiatric disorders	Sleep disorder	261 (33.2)	144 (22.3)	128 (45.7)
	Insomnia	11 (1.4)	32 (4.9)	2 (0.7)
	Apathy	1 (0.1)	0	2 (0.7)
Cardiac disorders	Palpitations	193 (24.5)	115 (17.8)	126 (45.0)
Hepatobiliary disorders	Hepatomegaly	175 (22.2)	59 (9.1)	19 (6.8)
	Jaundice	1 (0.1)	3 (0.5)	0
Blood and lymphatic system disorders	Splenomegaly	172 (21.9)	57 (8.8)	41 (14.6)
	Anaemia	34 (4.3)	23 (3.6)	16 (5.7)
Respiratory, thoracic and mediastinal disorders	Cough	33 (4.2)	37 (5.7)	3 (1.1)
	Pharyngolaryngeal pain	9 (1.1)	15 (2.3)	4 (1.4)
	Dyspnoea	1 (0.1)	3 (0.5)	0
	Asthma	3 (0.4)	1 (0.2)	3 (1.1)
Skin and subcutaneous tissue disorders	Pruritus	36 (4.6)	24 (3.7)	17 (6.1)
	Rash	30 (3.8)	21 (3.2)	9 (3.2)
	Hyperhidrosis	4 (0.5)	10 (1.5)	0
	Urticaria	0	4 (0.6)	1 (0.4)
Ear and labyrinth disorders	Vertigo	0	21 (3.2)	0
	Tinnitus	3 (0.4)	4 (0.6)	1 (0.4)
	Hypoacusis	11 (1.4)	0	20 (7.1)
Infections and infestations	Malaria	0	18 (2.8)	3 (1.1)

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
	Nasopharyngitis	6 (0.8)	17 (2.6)	4 (1.4)
	Plasmodium falciparum infection	6 (0.8)	13 (2.0)	1 (0.4)
	Helminthic infection	5 (0.6)	10 (1.5)	1 (0.4)
	Urinary tract infection	4 (0.5)	5 (0.8)	4 (1.4)
	Hookworm infection	0	4 (0.6)	0
	Subcutaneous abscess	1 (0.1)	4 (0.6)	0
	Abscess	5 (0.6)	3 (0.5)	0
	Oral herpes	0	3 (0.5)	0
	Upper respiratory tract infection	7 (0.9)	3 (0.5)	1 (0.4)
	Pneumonia	7 (0.9)	1 (0.2)	9 (3.2)
	Respiratory tract infection	1 (0.1)	1 (0.2)	3 (1.1)
	Acarodermatitis	0	0	2 (0.7)
	Tonsillitis	1 (0.1)	0	2 (0.7)
Renal and urinary disorders	Proteinuria	1 (0.1)	5 (0.8)	0
	Haematuria	2 (0.3)	4 (0.6)	0
Investigations	Liver function test abnormal	0	3 (0.5)	0
Vascular disorders	Pallor	3 (0.4)	3 (0.5)	0
Eye disorders	Visual disturbance	6 (0.8)	0	0
Injury, poisoning and procedural complications	Overdose	0	0	3 (1.1)

Severity of AEs

All studies used severity gradings of ‘mild’, ‘moderate’ and ‘severe’, but studies A025, A026, A028, A2401, A005, A008, A011, A014 and A023 also included ‘life-threatening’ as a severity grade . There were only 2 AEs coded as “life-threatening” (1 report each of *P. falciparum* infection, and coma) and for the purposes of analysis, have been included in the tally. Table 23 shows the distribution of severe AEs in the FDA adult pooled population for Coartem and MAS.

Overall, most patients in the Coartem 4-dose and 6-dose regimen groups had only mild AEs with most of the remainder having moderate AEs. Severe AEs occurred in 3.7% of patients exposed to the 4-dose regimen, 5.3% of the 6-dose and 6.8% of MAS patients.

In the Coartem 6-dose regimen group, the most frequently reported severe AE was pyrexia (1.9%). In the 4-dose regimen, the most frequently reported severe AE was splenomegaly (1.4%). There were no obvious differences between the two Coartem groups and the MAS group in the overall distribution of severity of AEs. Most severe AEs were reported in at most

one patient in both Coartem groups with the exception of pyrexia, splenomegaly, *P. falciparum* infection, and headache in the 6-dose group, and splenomegaly, fatigue, hepatomegaly, *P. falciparum* infection and headache in the 4-dose group. For both groups, these AEs were likely to be signs and symptoms of malaria.

Table 23: Severe AEs for Coartem and MAS in the FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Blood and lymphatic system disorders	Anaemia	1 (0.1)	0	1 (0.4)
	Splenomegaly	11 (1.4)	8 (1.2)	10 (3.6)
Gastrointestinal disorders	Diarrhoea	0	0	1 (0.4)
	Nausea	0	1 (0.2)	1 (0.4)
	Toothache	1 (0.1)	0	0
	Vomiting	0	1 (0.2)	0
General disorders and administration site conditions	Asthenia	1 (0.1)	1 (0.2)	0
	Chills	1 (0.1)	0	0
	Disease progression	0	1 (0.2)	0
	Fatigue	3 (0.4)	0	0
	Pyrexia	0	12 (1.9)	3 (1.1)
Hepatobiliary disorders	Hepatitis	1 (0.1)	0	0
	Hepatomegaly	3 (0.4)	1 (0.2)	3 (1.1)
Infections and infestations	Hepatitis viral	1 (0.1)	0	0
	Plasmodium falciparum infection	2 (0.3)	2 (0.3)	0
	Urinary tract infection	0	0	1 (0.4)
Investigations	Electrocardiogram T wave abnormal	0	1 (0.2)	0
	Laboratory test abnormal	1 (0.1)	0	0
Metabolism and nutrition disorders	Anorexia	1 (0.1)	0	1 (0.4)
	Fluid overload	0	1 (0.2)	0
	Type 2 diabetes mellitus	1 (0.1)	0	0
Nervous system disorders	Headache	2 (0.3)	3 (0.5)	0
	Somnolence	0	1 (0.2)	0
	Syncope vasovagal	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0	1 (0.2)	0
Skin and subcutaneous tissue disorders	Hyperhidrosis	0	1 (0.2)	0

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
	Total number of patients	29 (3.7)	34 (5.3)	19 (6.8)

Of the severe AEs, the abnormal EKG and headaches were individually examined given the potential QT effects and nervous system effects of artemether:

1. “Electrocardiogram T-wave abnormal”: Patient 1 was a 54 year old Caucasian male enrolled in A2401 with the SAEs electrocardiogram abnormal and *Plasmodium falciparum* infection. Eighteen days after his last dose of Coartem, the patient was seen by his general practitioner for chest pain, and no action was recommended. Past medical history was significant for heavy smoking. On day 29, the patient presented to hospital with headache, nausea and vomiting, myalgias and a palpable spleen. He was diagnosed with relapsed *P. falciparum* malaria, hospitalized and treated with Malarone. The parasite density was 0.8% and PCR was positive for recrudescence. An EKG performed at the time of hospitalization showed abnormal T wave changes. Additional EKGs obtained on days 9 and 13 of hospitalization showed persistent negative T waves. Troponin levels remained within normal limits and the patient recovered “with sequelae”.

2. “Headache”: In 4 of the 6 cases, headache was either present before enrollment in the study (patient 11 in A014) or present at baseline and resolved between days 2-7. The two cases where headache was not present at baseline were Patients 3 and 9 from Study A2401. Patient 3 was a 32 year old male from South America who received the 6 dose Coartem regimen. He had onset of severe headache on study day 2 to day 3, and then mild headache on study day 4. He had concurrent mild malaise, pyrexia, and moderate vomiting on days 2 to 3 as well, and it is likely that his headache was due to malaria infection. Patient 9 was a 32 year old Caucasian male from France who received the 6 dose Coartem regimen. He had onset of both severe headache and hyperhidrosis on study day 3, which was the same day as his last dose of Coartem. Both AEs were of 1 day duration and no action was taken. Relationship to study drug was determined to be “unknown”. This patient did not report any other AEs and no data on concomitant medications was available.

6.1.5.3.2 Pediatric patients

Table 24 shows AEs by SOC for the FDA pediatric pooled safety population. Similar to the adult analysis, the frequency of AEs was greater with the 4-dose compared to the 6-dose regimen for the majority of SOCs, which is probably accounted for by between-study differences in methods of collecting AE data. The SOCs where AEs appeared to be more frequent with the 6-dose regimen were ‘Infections and infestations’, ‘Investigations’, and ‘Respiratory, thoracic and mediastinal disorders’.

The SOCs most commonly affected by AEs for the 6-dose group were ‘Infections and infestations’; ‘General disorders and administrative site disorders’; ‘Gastrointestinal disorders’; ‘Respiratory, thoracic and mediastinal disorders’; ‘Blood and lymphatic system disorders’ and ‘Nervous system disorders’.

Table 24: Frequency of AEs by MedDRA System Organ Class, FDA pediatric pooled safety population

MedDRA system organ class	Coartem 4 dose N=659	Coartem 6 dose N=1332	Mefloquine Artesunate N=150	SP N=143
Blood and lymphatic system disorders	280 (42.5)	235 (17.6)	56 (37.3)	89 (62.2)
Cardiac disorders	58 (8.8)	33 (2.5)	35 (23.3)	0
Congenital, familial and genetic disorders	0	0	0	1 (0.7)
Ear and labyrinth disorders	5 (0.8)	6 (0.5)	3 (2.0)	3 (2.1)
Eye disorders	27 (4.1)	23 (1.7)	1 (0.7)	4 (2.8)
Gastrointestinal disorders	318 (48.3)	410 (30.8)	91 (60.7)	52 (36.4)
General disorders and administration site conditions	328 (49.8)	458 (34.4)	117 (78.0)	39 (27.3)
Hepatobiliary disorders	148 (22.5)	78 (5.9)	33 (22.0)	21 (14.7)
Immune system disorders	0	1 (0.1)	0	0
Infections and infestations	120 (18.2)	492 (36.9)	11 (7.3)	35 (24.5)
Injury, poisoning and procedural complications	1 (0.2)	6 (0.5)	0	0
Investigations	2 (0.3)	113 (8.5)	0	0
Metabolism and nutrition disorders	263 (39.9)	179 (13.4)	107 (71.3)	25 (17.5)
Musculoskeletal and connective tissue disorders	77 (11.7)	50 (3.8)	74 (49.3)	1 (0.7)
Nervous system disorders	355 (53.9)	193 (14.5)	129 (86.0)	30 (21.0)
Psychiatric disorders	192 (29.1)	72 (5.4)	51 (34.0)	42 (29.4)
Renal and urinary disorders	3 (0.5)	3 (0.2)	0	1 (0.7)
Reproductive system and breast disorders	1 (0.2)	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	114 (17.3)	316 (23.7)	4 (2.7)	15 (10.5)
Skin and subcutaneous tissue disorders	40 (6.1)	62 (4.7)	8 (5.3)	9 (6.3)
Vascular disorders	1 (0.2)	6 (0.5)	0	1 (0.7)

Table 25 shows the most frequently-occurring AEs (those reported in at least 1%

of patients) in the FDA pediatric pooled safety population. AEs were reported more frequently with the 4-dose than 6-dose regimen. As in the adult pooled safety population, apparent between-group differences may be due to differences between studies in AE reporting.

The most frequently reported AEs for the 6-dose regimen were pyrexia, cough, vomiting, *P. falciparum* infection, anorexia and headache. The most frequent AEs in the 4-dose regimen group were similar to those in the 6-dose group, but also included abdominal pain, nausea, asthenia, chills, fatigue, dizziness and sleep disorder. These AEs were also commonly reported with MAS and SP and many are likely signs and symptoms of malaria.

AEs overall, and most specific AEs for all treatment groups were reported most frequently on Days 1-3, and the nature of many of these suggest they are signs and symptoms of malaria. The exception was *Plasmodium falciparum* infection, which was reported in most cases after Day 15, indicating late re-appearance of parasites or symptoms and efficacy failure. *Plasmodium falciparum* infection was reported much more frequently as an AE in the pediatric pooled safety population than in the adult pooled safety population (16.8% vs. 2.0%). The Applicant accounted for this difference as the result of the different regions in which studies contributing patients to the two populations were performed: studies in adults were performed in regions of low or no malaria endemicity (China, Thailand, Europe), whereas the studies in children and infants were predominantly performed in sub-Saharan African countries with high malaria transmission rates.

Table 25: Most frequent AEs (>1% or more in any group), pediatric pooled safety population

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
General disorders and administration site conditions	Pyrexia	36 (5.5)	381 (28.6)	19 (12.67)	6 (4.20)
	Chills	175 (26.6)	72 (5.4)	61 (40.67)	4 (2.80)
	Asthenia	133 (20.2)	63 (4.7)	84 (56.0)	33 (23.08)
	Fatigue	181 (27.5)	46 (3.5)	51 (34.0)	0
	Gait disturbance	7 (1.1)	0	9 (6.0)	0
Respiratory, thoracic and mediastinal disorders	Cough	106 (16.1)	302 (22.7)	1 (0.67)	14 (9.79)
	Rhinorrhoea	24 (3.6)	11 (0.8)	0	1 (0.70)
	Asthma	1 (0.2)	5 (0.4)	1 (0.67)	2 (1.40)
	Epistaxis	3 (0.5)	0	3 (2.0)	0
Gastrointestinal disorders	Vomiting	188 (28.5)	242 (18.2)	62 (41.33)	35 (24.48)
	Abdominal pain	162 (24.6)	112 (8.4)	40 (26.67)	25 (17.48)
	Diarrhoea	63 (9.6)	100 (7.5)	7 (4.67)	12 (8.39)
	Nausea	146 (22.2)	61 (4.6)	57 (38.0)	1 (0.70)
Infections and infestations	<i>Plasmodium falciparum</i> infection	0	224 (16.8)	0	0
	Rhinitis	0	51 (3.8)	0	0
	Upper respiratory tract infection	24 (3.6)	32 (2.4)	0	13 (9.09)

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
	Respiratory tract infection	2 (0.3)	28 (2.1)	0	1 (0.70)
	Bronchitis	1 (0.2)	26 (2.0)	1 (0.67)	0
	Helminthic infection	11 (1.7)	22 (1.7)	1 (0.67)	6 (4.20)
	Pneumonia	11 (1.7)	20 (1.5)	3 (2.0)	1 (0.70)
	Ear infection	0	17 (1.3)	0	0
	Acarodermatitis	6 (0.9)	15 (1.1)	0	1 (0.70)
	Lower respiratory tract infection	0	15 (1.1)	0	2 (1.40)
	Nasopharyngitis	10 (1.5)	14 (1.1)	2 (1.33)	0
	Otitis media	5 (0.8)	10 (0.8)	0	7 (4.90)
	Impetigo	7 (1.1)	8 (0.6)	0	4 (2.80)
	Urinary tract infection	7 (1.1)	2 (0.2)	0	0
Metabolism and nutrition disorders	Anorexia	246 (37.3)	175 (13.1)	107 (71.33)	0
	Feeding disorder	14 (2.1)	0	0	25 (17.48)
Nervous system disorders	Headache	281 (42.6)	168 (12.6)	126 (84.0)	27 (18.88)
	Dizziness	149 (22.6)	56 (4.2)	92 (61.33)	4 (2.80)
	Clonus	7 (1.1)	11 (0.8)	0	0
	Ataxia	3 (0.5)	1 (0.1)	5 (3.33)	0
	Dyskinesia	0	1 (0.1)	2 (1.33)	0
	Nystagmus	4 (0.6)	1 (0.1)	4 (2.67)	0
	Febrile convulsion	1 (0.2)	0	0	2 (1.40)
	Fine motor delay	8 (1.2)	0	0	0
	Hypokinesia	44 (6.7)	0	0	0
	Lethargy	34 (5.2)	0	0	1 (0.70)
	Paraesthesia	4 (0.6)	0	4 (2.67)	0
	Speech disorder	33 (5.0)	0	0	1 (0.70)
Blood and lymphatic system disorders	Splenomegaly	183 (27.8)	124 (9.3)	46 (30.67)	33 (23.08)
	Anaemia	145 (22.0)	115 (8.6)	15 (10.0)	76 (53.15)
	Eosinophilia	0	13 (1.0)	0	0
Hepatobiliary disorders	Hepatomegaly	147 (22.3)	75 (5.6)	33 (22.0)	21 (14.69)
Investigations	Aspartate aminotransferase increased	0	51 (3.8)	0	0
	Platelet count decreased	0	20 (1.5)	0	0
	White blood cell count decreased	0	13 (1.0)	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	59 (9.0)	39 (2.9)	60 (40.0)	1 (0.70)
	Myalgia	56 (8.5)	39 (2.9)	51 (34.0)	0
Skin and subcutaneous tissue disorders	Rash	17 (2.6)	38 (2.9)	2 (1.33)	5 (3.50)
	Pruritus	8 (1.2)	7 (0.5)	6 (4.0)	4 (2.80)

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
	Heat rash	7 (1.1)	5 (0.4)	0	0
	Skin ulcer	9 (1.4)	2 (0.2)	0	0
Psychiatric disorders	Sleep disorder	151 (22.9)	27 (2.0)	50 (33.33)	19 (13.29)
	Mood swings	13 (2.0)	15 (1.1)	0	0
	Insomnia	1 (0.2)	13 (1.0)	0	0
	Abnormal behaviour	6 (0.9)	0	0	15 (10.49)
	Social avoidant behaviour	58 (8.8)	0	0	16 (11.19)
Cardiac disorders	Palpitations	58 (8.8)	24 (1.8)	35 (23.33)	0
Eye disorders	Conjunctivitis	12 (1.8)	20 (1.5)	1 (0.67)	2 (1.40)

Cough was reported in 16% and 23% of pediatric patients compared to 4% and 6% of adult patients who received the 4- and 6-dose regimens of Coartem, respectively. This may be related to the higher incidence of upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, bronchitis and pneumonia in the pediatric patients compared to adults. The Applicant noted that cough, unlike most of the other common AEs, had a relatively even distribution throughout the duration of the studies, suggesting cough is probably related to neither malaria nor Coartem treatment. The Applicant pointed out that the pediatric pooled safety population were predominantly drawn from studies in very young children in the lowest body weight groups in sub-Saharan Africa, a population that might be expected to have a higher incidence of cough than the older children represented in most other treatment groups. It is also worth noting that respiratory infections are very common in African children presenting with malaria⁴.

AEs by Severity

Table 26 shows the distribution of severe AEs in the FDA pediatric pooled safety population for Coartem, MAS and SP. All studies used severity gradings of ‘mild’, ‘moderate’ and ‘severe’, but studies A025, A026, A028, A2401, A005, A008, A011, A014 and A023 also included ‘life-threatening’ as a severity grade. AEs graded as such were combined with AEs classified as severe for these analyses. The rate of severe AEs in Coartem patients receiving either the 4- or 6-dose regimen was similar (approximately 7.4%) compared to 12.7% of MAS patients and 4.9% of SP patients.

The rate of severe AEs for Coartem in the pediatric pooled population (6-dose 7.3%) is slightly higher than the 5.3% rate found in the adult pooled population. However, the rate of severe SAEs in the MAS pediatric population was also higher at 12.7% compared to the adult MAS rate of 6.8%.

⁴ O’Dempsey TJ, McArdle TF, Laurence BE, Lamont AC et al. Overlap in the clinical features of pneumonia and malaria in African children. *Trans R Soc Trop Med Hyg.* 1993;87(6):662-5.

In the Coartem group, the most frequently reported severe AEs (6-dose group) were pyrexia, splenomegaly, *P. falciparum* infection, anemia and cough. All other severe AEs reported were less than 0.25% (fewer than 5 cases). These were mostly symptoms and signs of malaria.

Table 26: Severe AEs in the FDA’s pediatric pooled population for Coartem, MAS and SP

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
Blood and lymphatic system disorders	Anaemia	17 (2.6)	5 (0.38)	0	5 (3.50)
	Iron deficiency anaemia	0	1 (0.1)	0	0
	Splenomegaly	16 (2.4)	12 (0.9)	15 (10.0)	0
Eye disorders	Conjunctivitis	1 (0.2)	0	0	0
Gastrointestinal disorders	Abdominal pain	1 (0.2)	0	0	0
	Diarrhoea	1 (0.2)	0	0	0
	Dysphagia	0	3 (0.2)	0	0
	Vomiting	5 (0.8)	0	0	0
General disorders and administration site conditions	Chills	1 (0.2)	0	0	0
	Face oedema	0	1 (0.1)	0	0
	Fatigue	1 (0.2)	0	0	0
	Pyrexia	3 (0.5)	53 (4.0)	2 (1.3)	1 (0.7)
Hepatobiliary disorders	Hepatomegaly	1 (0.2)	3 (0.2)	8 (5.3)	0
Infections and infestations	Acute tonsillitis	0	1 (0.1)	0	0
	Bronchitis	0	1 (0.1)	0	0
	Ear infection	0	1 (0.1)	0	0
	Gastroenteritis	0	1 (0.1)	0	0
	Hepatitis viral	0	1 (0.1)	0	0
	Infection	0	1 (0.1)	0	0
	Liver abscess	0	0	1 (0.7)	0
	Lower respiratory tract infection	0	1 (0.1)	0	0
	Plasmodium falciparum infection	0	9 (0.7)	0	0
	Pneumonia	0	1 (0.1)	0	0
	Typhoid fever	1 (0.2)	0	0	0
Investigations	Alanine aminotransferase increased	0	1 (0.1)	0	0
	Aspartate aminotransferase increased	0	1 (0.1)	0	0
	Hepatic enzyme increased	0	1 (0.1)	0	0
Metabolism and nutrition disorders	Anorexia	3 (0.5)	0	0	0
Nervous system disorders	Convulsion	0	1 (0.1)	0	0

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
	Headache	2 (0.3)	1 (0.1)	0	0
Psychiatric disorders	Sleep disorder	1 (0.2)	0	0	0
Renal and urinary disorders	Glomerulonephritis acute	0	0	0	1 (0.7)
	Haematuria	0	0	0	1 (0.7)
	Proteinuria	0	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	Cough	0	5 (0.4)	0	0
Skin and subcutaneous tissue disorders	Urticaria	0	1 (0.1)	0	0
Vascular disorders	Haemorrhage	0	1 (0.1)	0	0
	Total number of patients	49 (7.4)	97 (7.3)	19 (12.7)	7 (4.9)

Severe neurologic AEs are discussed in the following Section 7.1.5.4 Additional analyses and explorations. In all the cases, none of the severe AEs were related to study drug.

6.1.5.4 Additional analyses and explorations

The following additional analyses were performed:

- 1 – Safety of the Coartem 4-dose compared to 6-dose regimen
- 2 - Comparative studies A026 and A028
- 3 – Nervous system disorder AEs
- 4 – Ear and auditory AEs
- 5 – QT prolongation

6.1.5.4.1 Safety of the Coartem 4-dose compared to 6-dose regimens

Study A025 was the only study amongst the 8 key studies which compared the 4-dose and 6-dose Coartem regimens in the same study. Study A025 was a randomized, double-blind study of 359 patients administered 4-doses over 48 hours, 6 doses over 60 hours or 6 doses over 96 hours. AEs reported at $\geq 3\%$ for adults is shown in Table 27, and data for pediatric patients is shown in Table 28. Note that only the 6 dose over 60 hour patients have been included in the analysis, as this dosing regimen is most relevant to that sought by the Applicant. In both populations, AE rates were generally comparable between the 4- and 6-dose arms. The types of AEs most frequently reported were similar between the adult and pediatric populations.

Table 27: Most frequently reported AEs occurring in $\geq 3\%$ of adult patients in Study A025 by treatment group

MedDRA system organ class	Preferred term	Coartem 4 dose N=99 (%)	Coartem 6 dose N=88 (%)
Nervous system disorders	Headache	93 (93.9)	81 (92.1)
	Dizziness	73 (73.7)	69 (78.4)
	Clonus	5 (5.1)	8 (9.1)
	Tremor	9 (9.1)	8 (9.1)
Metabolism and nutrition disorders	Anorexia	84 (84.9)	76 (86.4)
General disorders and administration site conditions	Asthenia	83 (83.8)	67 (76.1)
	Chills	40 (40.4)	39 (44.3)
	Fatigue	30 (30.3)	38 (43.2)
Musculoskeletal and connective tissue disorders	Arthralgia	71 (71.7)	66 (75.0)
	Myalgia	76 (76.8)	66 (75.0)
Gastrointestinal disorders	Nausea	49 (49.5)	41 (46.6)
	Vomiting	31 (31.3)	33 (37.5)
	Abdominal pain	37 (37.4)	25 (28.4)
	Diarrhoea	6 (6.1)	4 (4.6)
Psychiatric disorders	Sleep disorder	44 (44.4)	39 (44.3)
Cardiac disorders	Palpitations	43 (43.4)	34 (38.6)
Blood and lymphatic system disorders	Splenomegaly	22 (22.2)	14 (15.9)
	Anaemia	6 (6.1)	6 (6.8)
Hepatobiliary disorders	Hepatomegaly	19 (19.2)	13 (14.8)
Skin and subcutaneous tissue disorders	Rash	13 (13.1)	7 (8.0)
	Pruritus	13 (13.1)	7 (8.0)
Infections and infestations	Helminthic infection	3 (3.0)	6 (6.8)
	Nasopharyngitis	2 (2.0)	5 (5.7)
	Abscess	5 (5.1)	3 (3.4)
	Pneumonia	3 (3.0)	0
Respiratory, thoracic and mediastinal disorders	Cough	3 (3.0)	2 (2.3)
	Pharyngolaryngeal pain	4 (4.0)	3 (3.4)

Table 28: Most frequently reported AEs occurring in $\geq 3\%$ of pediatric patients in Study A025 by treatment group

MedDRA system organ class	Preferred Term	Coartem 4 dose N=21 (%)	Coartem 6 dose N=30 (%)
Nervous system disorders	Headache	20 (95.2)	27 (90)
	Dizziness	8 (38.1)	14 (46.7)
Metabolism and nutrition	Anorexia	18 (85.7)	25 (83.3)

MedDRA system organ class	Preferred Term	Coartem 4 dose N=21 (%)	Coartem 6 dose N=30 (%)
disorders			
General disorders and administration site conditions	Asthenia	10 (47.6)	17 (56.7)
	Chills	7 (33.3)	11 (36.7)
	Fatigue	4 (19.1)	5 (16.7)
Musculoskeletal and connective tissue disorders	Myalgia	11 (52.4)	15 (50.0)
	Arthralgia	6 (28.6)	10 (33.3)
Gastrointestinal disorders	Nausea	7 (33.3)	12 (40.0)
	Vomiting	9 (42.9)	9 (30.0)
	Abdominal pain	3 (14.3)	7 (23.3)
	Diarrhoea	1 (4.8)	3 (5.1)
Blood and lymphatic system disorders	Splenomegaly	7 (33.3)	10 (33.3)
	Anaemia	4 (19.1)	3 (10.0)
Hepatobiliary disorders	Hepatomegaly	3 (14.3)	9 (30.0)
Psychiatric disorders	Sleep disorder	5 (23.8)	6 (20.0)
Cardiac disorders	Palpitations	4 (19.1)	5 (16.7)
Infections and infestations	Parasitic gastroenteritis	3 (14.3)	6 (20.0)
	Pneumonia	1 (4.8)	3 (10.0)
	Helminthic infection	1 (4.8)	2 (6.7)
	Ascariasis	1 (4.8)	2 (6.7)
Skin and subcutaneous tissue disorders	Pruritus	0	2 (3.4)
Investigations	Blood potassium decreased	0	1 (3.3)
Gastrointestinal disorders	Dyspepsia	0	1 (3.3)
Renal and urinary disorders	Oliguria	0	1 (3.3)

6.1.5.4.2 Comparative studies A026 and A028

Comparative studies A026 and A028 were examined separately, as these were the only studies among the 8 key studies selected which compared Coartem with another malaria drug. Both studies were randomized, open label parallel group studies comparing Coartem with MAS. While the open label aspect of the studies may have affected the quality of the safety data collected, it was still relevant to know the safety profile of Coartem relative to MAS, and to determine if the profile, distribution, severity and seriousness of AEs differed from the FDA adult pooled safety populations. Note that these latter populations also consisted of studies which were single arm, non-comparative studies, or compared Coartem with its components.

The inclusion criteria for both studies allowed the enrollment of pediatric patients. Study A026 enrolled patients aged 2 years or greater, and A028 enrolled patients >12 years. There were 57

and 27 patients in studies A026 and A028 respectively, for a total of 84 pediatric patients 16 years or younger. Pediatric patients represented 20% (84/419) of patients from these combined studies. There was only 1 patient from A028 who met the geriatric age criteria of greater than 65 years of age.

The results of the comparison between the A026/A028 and FDA pooled adult population is presented first, followed by the pediatric pooled populations.

6.1.5.4.2.1 Adult patients

Table 29 below shows AEs by SOC in the A026/A028 pooled adult population. The SOC most frequently reported by both groups in descending order were “General disorders and administrative site conditions” followed by “Nervous system disorders” and “Gastrointestinal disorders”. These SOC categories, and their respective rates are similar to those reported for the FDA adult pooled safety population (Coartem 6-dose regimen). In general, the rate of AEs was higher in the MAS group compared to the Coartem group with the exception of “Hepatobiliary disorders”, “Musculoskeletal disorders”, “Nervous system disorders” and “Vascular disorders”. Other than hepatobiliary disorders, these rates were only slightly higher in the Coartem group.

Table 29: AEs by SOC in Studies A026 and A028, Adult pooled safety population

MedDRA system organ class	Coartem 6 dose (tablet) N=258 (%)	Mefloquine Artesunate N=77 (%)
Blood and lymphatic system disorders	26 (10.1)	10 (13.0)
Cardiac disorders	45 (17.4)	15 (19.5)
Ear and labyrinth disorders	1 (0.4)	1 (1.3)
Eye disorders	0	1 (1.3)
Gastrointestinal disorders	92 (35.7)	35 (45.5)
General disorders and administration site conditions	180 (69.8)	54 (70.1)
Hepatobiliary disorders	33 (12.8)	4 (5.2)
Infections and infestations	26 (10.1)	8 (10.4)
Injury, poisoning and procedural complications	0	3 (3.9)
Investigations	2 (0.8)	0
Metabolism and nutrition disorders	84 (32.6)	29 (37.7)
Musculoskeletal and connective tissue disorders	87 (33.7)	24 (31.2)
Nervous system disorders	140 (54.3)	36 (46.8)
Psychiatric disorders	58 (22.5)	23 (29.9)
Respiratory, thoracic and mediastinal disorders	17 (6.6)	7 (9.1)
Skin and subcutaneous tissue disorders	12 (4.7)	4 (5.2)
Vascular disorders	4 (1.6)	0

AEs according to PTs greater than 3% for Coartem and MAS groups are shown in Table 30. While AE rates for Coartem in the A026/A028 adult population was similar to those in the FDA pooled adult population, AE rates for MAS were lower in the A026/A028 population compared with the FDA pooled adult population. The reason for this observation is unclear; while relatively few subjects received MAS (n=77), the comparative nature of the design is suggestive that the safety profile of Coartem is probably more similar to MAS than the data in the FDA pooled population would suggest, where MAS tended to have higher overall AE rates. Again, this highlights the caution in comparing Coartem and MAS data in the FDA pooled populations.

The most frequently reported AEs in both Coartem and MAS A026/A028 groups were pyrexia (Coartem 58%, MAS 57%), headache (Coartem 50%, MAS 42%), dizziness (Coartem 39%, MAS 36%), asthenia (Coartem 32%, MAS 33%) and anorexia (Coartem 30%, MAS 34%). These AEs were likely symptoms and signs of malaria. Rates for the other PTs were also comparable between groups. One exception was cough (Coartem 4.7%, MAS 1.3%). This was similarly observed in the FDA adult pooled safety population, where the rate of cough was 5.7% in the 6-dose group, 4.2% in the 4-dose group and 1.1% in the MAS group. This may be due to the higher incidence of upper respiratory tract infection, lung infection and nasopharyngitis in the Coartem group compared to MAS.

Table 30 : Most frequently reported AEs (>3%) in adult patients treated with Coartem or MAS (Studies A026 and A028)

System Organ Class	Preferred Term	Coartem Tablets N=258 (%)	Mefloquine Artesunate N=77 (%)
General disorders and administration site conditions	Pyrexia	149 (57.8)	44 (57.1)
	Asthenia	83 (32.2)	25 (32.5)
	Chills	48 (18.6)	16 (20.8)
	Fatigue	29 (11.2)	8 (10.4)
Nervous system disorders	Headache	129 (50.0)	32 (41.6)
	Dizziness	100 (38.8)	28 (36.4)
Musculoskeletal and connective tissue disorders	Arthralgia	82 (31.8)	24 (31.2)
	Myalgia	65 (25.2)	14 (18.2)
Metabolism and nutrition disorders	Anorexia	78 (30.2)	26 (33.8)
	Hypokalaemia	4 (1.6)	2 (2.6)
Gastrointestinal disorders	Nausea	64 (24.8)	25 (32.5)
	Abdominal pain	44 (17.1)	11 (14.3)
	Vomiting	27 (10.5)	10 (13.0)
	Diarrhoea	11 (4.3)	2 (2.6)
	Dyspepsia	10 (3.9)	4 (5.2)
Psychiatric disorders	Sleep disorder	58 (22.5)	23 (29.9)
Cardiac disorders	Palpitations	45 (17.4)	15 (19.5)
Hepatobiliary disorders	Hepatomegaly	31 (12.0)	4 (5.2)
Blood and lymphatic system disorders	Splenomegaly	22 (8.5)	8 (10.4)
	Anemia	6 (2.3)	2 (2.6)

System Organ Class	Preferred Term	Coartem Tablets N=258 (%)	Mefloquine Artesunate N=77 (%)
Respiratory, thoracic and mediastinal disorders	Cough	12 (4.7)	1 (1.3)
	Pharyngolaryngeal pain	7 (2.7)	4 (5.2)
	Asthma	0	2 (2.6)
Skin and subcutaneous tissue disorders	Pruritus	8 (3.1)	4 (5.2)
	Rash	5 (1.9)	3 (3.9)
Infections and infestations	Nasopharyngitis	7 (2.7)	2 (2.6)
Injury, poisoning and procedural complications	Overdose	0	3 (3.9)

Studies A026 and A028 both included “life-threatening” as a severity grade along with the standard gradings of mild, moderate and severe, although in the end there was only one AE coded as life-threatening (coma). This was included in the tally for severe AEs. Table 31 shows the severe AEs in the two studies. The incidence of severe AEs was 8.9% in Coartem patients compared to 9.1% of MAS patients, and 5.3% of 6-dose regimen patients in the FDA adult pooled population.

Table 31: Severe AEs in Studies A026 and A028, pooled adult population

MedDRA system organ class	Preferred Term	Coartem N=258 (%)	MAS N=77 (%)
Blood and lymphatic system disorders	Anaemia	1 (0.4)	1 (1.3)
	Splenomegaly	5 (1.9)	2 (2.6)
General disorders and administration site conditions	Pyrexia	14 (5.4)	4 (5.2)
Hepatobiliary disorders	Hepatomegaly	1 (0.4)	0
Infections and infestations	Urinary tract infection	0	1 (1.3)
Metabolism and nutrition disorders	Fluid overload	1 (0.4)	0
Nervous system disorders	Coma*	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1 (0.4)	0
	Total number of patients	23 (8.9)	7 (9.1)

* Coded as life-threatening

The one life-threatening SAE (coma) was reported in Patient 259 enrolled in Study A026. The narrative for this patient was presented in the SAE section (Section 7.1.3 Other Serious Adverse Events). Coartem was unlikely the cause of this SAE due to the late onset of the SAE relative to the last dose of drug, and multiple other explanations which could not be ruled out as the cause of the SAE.

There were 24 severe AEs in 23 patients treated with Coartem. The majority of these were signs and symptoms of malaria, with pyrexia (5.4%) and splenomegaly (1.9%) as the most frequently

reported. Severe AEs which occurred with greater frequency in the Coartem group compared to the MAS group were pyrexia, hepatomegaly, fluid overload and dyspnoea. The latter two severe AEs were iatrogenic and reported in patient 28 enrolled in A028. The patient narrative for this was described in Section 7.1.3 Other Serious Adverse Events. The differences in pyrexia and hepatomegaly between groups were small.

There were few SAEs in these studies (Table 32). SAEs occurred in 0.8% of patients in the Coartem group compared to 1.3% in the MAS group and 1.4% in the FDA adult pooled population (6-dose regimen). There were no deaths in these studies and none of the SAEs were likely to be related to study drug. Narratives for these SAEs are presented below.

Table 32: SAEs in Studies A026 and A028, pooled adult population

MedDRA system organ class	Preferred Term	Coartem N=258 (%)	MAS N=77 (%)
Metabolism and nutrition disorders	Fluid overload	1 (0.4)	0
Nervous system disorders	Coma	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1 (0.4)	0
Skin and subcutaneous tissue disorders	Urticaria	0	1 (1.3)
	Total number of patients	2 (0.8)	1 (1.3)

Narratives for SAES from Studies A026/A028

Coartem group

1. Patient 28 -This was a 28 year old male enrolled in A028 with the SAEs dyspnea and fluid overload. This patient presented with the common malaria symptoms and received his first dose of trial medication on 26-Nov-98. At baseline already the following laboratory abnormalities were noted: hypokalemia, thrombocytopenia (grade 3), raised liver enzymes (grade 3) and marked hyperbilirubinemia (grade 4). He received dextrose and sodium chloride at 100 mL/h for dehydration and vomiting. On the next day ^{(b) (6)}, the patient was admitted to hospital with dyspnea, the cause of which was determined to be pulmonary edema, possibly due to fluid overload. Chest X-ray showed pulmonary congestion. The patient was treated with furosemide 20 mg i.v. on 27-Nov-98 and 40 mg i.v. for the next four days. By Day 8 hypokalemia and thrombocytopenia normalised, while the liver function tests improved significantly. This patient was lost to follow-up after the first week.

Reviewer's comment: The SAEs are unlikely to be related to study drug.

2. Patient 259 – this was a 17 year old male in Study A026 with the SAE coma. He presented at baseline with anorexia, dizziness, fever, chills, headache, nausea, vomiting, arthralgia, myalgia, asthenia and sleep disorder. All of these AEs resolved by study day 8. Coma was recorded on study day 14. His baseline *P. falciparum* asexual form count was 10 826 and was cleared in 3 days although gametocytes did not clear until day 15. Two days prior to the onset of coma, the patient had experienced fever, chills and feeling unwell (according to patient's sister). He then "became unconscious with fever and vomiting". His temperature on day 15 was 40.5C. He

received phenobarbital, quinine, paracetamol and glucose, and later received chloramphenicol for possible meningitis and diazepam for convulsions. A lumbar puncture was attempted but was not successful. No parasites were found in his blood smear. The patient received ampicillin and metronidazole for aspiration pneumonia for the duration of the SAE. The case report form coded the SAE as “febrile coma, reason unknown”. The patient made a complete recovery on day 24, regaining consciousness. He experienced mild hallucinations with mild agitation but was eating and drinking. Information regarding follow up was not available.

Reviewer’s comment: Although the etiology of the SAE coma was unknown, it is unlikely to be related to study drug since onset of this SAE was 12 days after his last dose of study drug with no renal or hepatic dysfunction.

MAS group

1. Patient 160 was a 27 year old male in Study A026 with the SAE urticaria. The patient was randomized to MAS and started trial treatment on 10-Feb-98. He received an overdose of artesunate due to a miscalculation (5 tablets = 4.6 mg/kg).

There were no acute signs or symptoms associated with this overdose on this day. On 11-Feb-98 again 5 tablets of artesunate were given at 9:00, as well as 3 tablets of mefloquine (= 13 mg/kg). The patient developed a urticarial rash all over his body after this first dose of mefloquine.

Treatment with artesunate was continued but mefloquine was stopped and the patient made a complete recovery by 13-Feb-98. Relationship to drug was considered possible given that the patient received a higher than usual dose of artesunate although mefloquine was suspected to be the most likely cause. The patient was prematurely discontinued (lost to follow-up).

Reviewer’s comment: The temporal onset and resolution of the urticaria with discontinuation of mefloquine appears to suggest mefloquine as the cause of urticaria.

6.1.5.4.2.2 Pediatric patients

Table 33 below shows AEs by SOC for the pediatric pooled population from Studies A026 and A028. The SOC most frequently reported by the Coartem group was “General disorders and administrative site conditions” followed by “Nervous system disorders” and “Gastrointestinal disorders”. In the MAS group, the same SOCs were the most common although the rank order was different, with “Gastrointestinal disorders” more frequent than “Nervous system disorders”. In contrast to the adult A026/A028 analysis where AE rates (by SOC) for MAS were generally higher than SOC AE rates for Coartem, the reverse pattern is observed with the pediatric A026/A028 population. While it is noted that the numbers of pediatric patients in the A026/A028 pooled studies are small, this observation was also seen at the PT level (Table 34).

Table 33: AEs by SOC in Studies A026 and A028, pediatric pooled population

MedDRA system organ class	Coartem 6 dose N=56 (%)	Mefloquine Artesunate N=28 (%)
Blood and lymphatic system disorders	19 (33.9)	6 (21.4)

MedDRA system organ class	Coartem 6 dose N=56 (%)	Mefloquine Artesunate N=28 (%)
Cardiac disorders	10 (17.9)	2 (7.1)
Eye disorders	1 (1.8)	0
Gastrointestinal disorders	31 (55.4)	15 (53.6)
General disorders and administration site conditions	39 (69.6)	21 (75.0)
Hepatobiliary disorders	17 (30.4)	4 (14.3)
Infections and infestations	8 (14.3)	4 (14.3)
Metabolism and nutrition disorders	30 (53.6)	11 (39.3)
Musculoskeletal and connective tissue disorders	17 (30.4)	7 (25.0)
Nervous system disorders	37 (66.1)	14 (50.0)
Psychiatric disorders	12 (21.4)	7 (25.0)
Respiratory, thoracic and mediastinal disorders	2 (3.6)	3 (10.7)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (3.6)

AEs according to PTs (>2%) are shown in Table 34. The most frequently reported in both groups was headache (Coartem 66%, MAS 50%) and pyrexia (Coartem 61%, MAS 68%). For Coartem, other frequently reported AEs were anorexia, asthenia and dizziness while for MAS, vomiting, anorexia and nausea were common. Similar to the pattern observed with SOC, AE rates according to PT for the more commonly reported AEs were slightly higher for Coartem compared to MAS.

In addition, Coartem AE rates were significantly higher in the pediatric A026/A028 population compared to the 6-dose rates observed in the FDA pooled pediatric population. This is likely due to the fact that pediatric patients in A026 were 2 years and older, and in A028 were 12 years and older, whereas a large percentage of the FDA pooled pediatric population were very young infants (particularly Study B2303) unable to verbalize symptoms.

Table 34: Most frequently reported AEs by Preferred Term (>3%), pediatric pooled safety population

System Organ Class	Preferred Term	Coartem Tablets N=56 (%)	Mefloquine Artesunate N=28 (%)
Nervous system disorders	Headache	37 (66.1)	14 (50.0)
	Dizziness	23 (41.1)	9 (32.1)
General disorders and administration site conditions	Pyrexia	34 (60.7)	19 (67.9)
	Asthenia	25 (44.6)	8 (28.6)
	Chills	19 (33.9)	4 (14.3)
	Fatigue	5 (8.9)	0
Metabolism and nutrition disorders	Anorexia	30 (53.6)	11 (39.3)
Gastrointestinal disorders	Vomiting	23 (41.1)	12 (42.9)

	Nausea	18 (32.1)	9 (32.1)
	Abdominal pain	17 (30.4)	9 (32.1)
	Dyspepsia	0	1 (3.6)
Blood and lymphatic system disorders	Splenomegaly	18 (32.1)	4 (14.3)
	Anaemia	4 (7.1)	2 (7.1)
Hepatobiliary disorders	Hepatomegaly	17 (30.4)	4 (14.3)
Musculoskeletal and connective tissue disorders	Arthralgia	17 (30.4)	7 (25.0)
	Myalgia	9 (16.1)	5 (17.9)
Psychiatric disorders	Sleep disorder	12 (21.4)	7 (25.0)
Cardiac disorders	Palpitations	10 (17.9)	2 (7.1)
Infections and infestations	Respiratory tract infection	2 (3.6)	0
	Nasopharyngitis	1 (1.8)	2 (7.1)
	Bronchitis	0	1 (3.6)
	Parasitic gastroenteritis	0	1 (3.6)
	Subcutaneous abscess	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	2 (3.6)	0
	Cough	0	1 (3.6)
	Epistaxis	0	3 (10.7)
Skin and subcutaneous tissue disorders	Urticaria	0	1 (3.6)

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

In conclusion, comparator studies A026 and A028 did not show any safety findings which were significantly different than the FDA adult and pediatric pooled populations. In adults, Coartem AE rates for the most common AEs and severe AEs were generally similar between the A026/A028 and FDA pooled population. In pediatrics, higher Coartem AE rates in the A026/A028 population compared to the FDA pooled population are likely due to demographic differences, as the pediatric population in A026 was 2 years and older, and in A028 were 12 years and older, whereas a large percentage of the FDA pooled pediatric population were very young infants (particularly Study B2303) who were likely unable to express symptoms.

6.1.5.4.3 Nervous system AEs

AEs related to the nervous system (balance and auditory) were examined in detail given previous known toxicities of the artemisinin derivatives.

In animal models, artemisinin derivatives such as artemether, have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. In dogs, microscopic lesions mainly in the brainstem and cerebellum roof nuclei were observed in dogs administered 20

mg/kg/day IM doses following 30 days of treatment, and clinical data showed tremors in one animal and convulsions in another animal after > 27 days of treatment. Additional studies at doses ranging from 10 to 80 mg/kg/day for 5 to 8 days of treatment have confirmed that brain lesions are observed following IM doses in the dog when animals are treated for 8 or more days at high doses. Daily 10 mg/kg/day IM dosing for 8 days did not cause brain lesions (NOEL).

Oral doses in the general toxicity program showed no brain lesions and no clinical evidence of neurotoxicity (e.g., no seizures or tremors) in the dog at up to 300 mg/kg/day of artemether for 13 weeks. 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 IM 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 for 8 days 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 (artemether AUC values were 100-fold the clinical exposure), and sporadic vomiting was noted at the 300 mg/kg/day dose thereafter. Hearing tests revealed minimal hearing loss at 20 dB, which would not impair the hearing of a dog, and this change was not accompanied by any histopathologic changes in the brain. The Coartem animals showed no changes in any parameter. These results suggest artemether plasma AUC at the 10 mg/kg IM dose (NOEL) on Day 8 was equivalent to the AUC values from the Day 1, 600 mg/kg oral dose.

Reviewer's comment: Although it is not known what degree of hearing loss humans may develop with an equivalent degree of exposure, 20 dB in humans is considered clinically significant. In children, this could result in difficulties in understanding language and speech.

Thus the neurotoxic effects appear to occur with high doses of liposoluble compounds administered parenterally, while oral administration and water-soluble compounds appear to be far less toxic. Repeat oral dosing with artemether resulted in a reduction of both C_{max} and AUC values between day 1 and 8. This reduction in systemic exposure to artemether over time was not seen in the repeat dose IM studies. This suggests that artemether induces its own metabolism when given orally, unlike IM administration which does not have a hepatic first pass effect.

Neurotoxicity of this type has not been seen in humans^{5,6}, even following repeated exposure to artemisinin derivatives⁷ and no evidence of such neuropathology was observed in a series of autopsies carried out on patients who died due to severe malaria despite treatment with high-dose

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

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

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

intramuscular artemether⁸. However, concerns have been expressed regarding the possibility of neurological effects in humans⁹. There have been case reports of neurological problems (including ataxia, nystagmus, tremor and slurred speech), occurring after administration of herbal artemisinin¹⁰ or artesunate monotherapy^{11,12}, in one case following five 10-day courses of the drug, but in each case the attribution of neurotoxicity to artemisinin treatment was questionable^{13,14,15}.

In the development of Coartem, no significant neurotoxicity associated with treatment was observed, with either the 6-dose or 4-dose regimens.

In summary, while IM dosing of artemether was shown to cause neurotoxic effects in multiple regions of the brain in dogs, systemic plasma concentrations of artemether following oral administration to beagle dogs were lower and did not achieve concentrations sufficient to cause brain histopathology. Therefore, the neurotoxicity with IM artemether in dogs may not be relevant to the oral use of Coartem in patients.

6.1.5.4.3.1 Neurologic examinations

Neurological examinations were performed only selected studies: Studies A2403, B2303 and at one site only in both studies A025 and A026. In studies ABMO2, A023, A028, A2401, neurological findings were recorded as AEs only. It is recognized that the absence of systematic exams may have affected Nervous system disorder rates.

In studies A025, A026 and A2403, 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

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

9 Johann-Liang R, Albrecht R. Safety evaluations of drugs containing artemisinin derivatives for the treatment of malaria. *Clin Infect Dis* 2003;36(12):1626-7.

10 Panossian LA, Garga NI, Pelletier D. Toxic brainstem encephalopathy after artemisinin treatment for breast cancer. *Ann Neurol*. 2005;58(5):812-3.

11 Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Eng J Med* 1997;336(18):1328.

12 Franco-Paredes C, Dismukes R, Nicolls D et al. Neurotoxicity due to antimalarial therapy associated with misdiagnosis of malaria. *Clin Infect Dis* 2005;40(11):1710-11.

13 White NJ, Ashley EA, Nosten F. Toxic brainstem encephalopathy after artemisinin treatment for breast cancer. *Ann Neurol*. 2005;59(4):725-6.

14 Davis RM, Edwards GO, McCarthy JS. Artesunate and cerebellar dysfunction in falciparum malaria. *N Eng J Med* 1997;337(11):792.

15 Newton PN, Day NP, White NJ. Isattribution of central nervous system dysfunction to artesunate. *Clin Infect Dis*. 2005;41(11):1687-8.

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, (Subjects 229 and 313 described under “Clonus” in 7.1.5.4.3.3 Pediatric patients). Results of neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any postbaseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

A consult to the Division of Neurology was pending at the time of this review.

6.1.5.4.3.2 Adult patients

Nervous system AEs (affecting the SOC ‘Nervous system disorders’) in the FDA adult pooled safety population are shown in Table 35. By far, the most frequently reported AEs in all treatment groups were headache followed by dizziness. These were likely symptoms of malaria. With respect to Coartem 4- and 6-dose groups, AE rates tended to be higher with the 4-dose for those AEs where there was more than 1 report. The exception was clonus (2.5% compared to Coartem 4 dose 0.6% and MAS 0%). The cases of clonus occurred in patients enrolled in Studies A025 and A026 and were originally reported as “involuntary muscle contraction” in the clinical study reports, and were recoded in MedDRA as “clonus”. All but 1 case of clonus were reported on days 1-3 and all but 1 were of mild intensity. All were not thought to be related to study medication by the Investigator. AEs representing balance (PTs ataxia, coordination abnormal, dizziness, nystagmus and tremor) were generally higher in the 4-dose regimen, and may have been a result of differences in reporting methods between studies.

Table 35: Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Headache	545 (69.3)	360 (55.6)	213 (76.1)
Dizziness	418 (53.1)	253 (39.1)	203 (72.5)
Clonus	5 (0.6)	16 (2.5)	0
Tremor	23 (2.9)	16 (2.5)	13 (4.6)
Nystagmus	8 (1.0)	5 (0.8)	16 (5.7)
Hypoaesthesia	3 (0.4)	4 (0.6)	7 (2.5)
Ataxia	11 (1.4)	3 (0.5)	14 (5.0)
Somnolence	1 (0.1)	3 (0.5)	0
Fine motor delay	0	2 (0.3)	2 (0.7)
Coma	0	1 (0.2)	0
Mental impairment	0	1 (0.2)	0
Convulsion	1 (0.1)	0	0

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Coordination abnormal	0	0	1 (0.4)
Dysgeusia	1 (0.1)	0	0
Hypersomnia	1 (0.1)	0	0
Lethargy	1 (0.1)	0	0
Paraesthesia	32 (4.1)	0	27 (9.6)
Syncope vasovagal	1 (0.1)	0	0

Nervous system disorder AEs of severe intensity

Table 36 shows the severe AEs in the nervous system disorders SOC. Nervous system AEs of severe intensity were reported in 0.5% and 0.8% of patients in the 4- and 6-dose Coartem groups respectively. There were no severe AEs in adult subjects who received MAS.

Table 36: Nervous system disorder AEs of severe intensity, FDA adult pooled safety population

MedDRA preferred term	Coartem		Related to study drug?
	4-dose N=787 (%)	6-dose N=647 (%)	
Coma*	0	1 (0.2)	Unlikely
Headache	3 (0.4)	3 (0.5)	Unlikely
Somnolence	0	1 (0.2)	Possible
Syncope vasovagal	1 (0.1)	0	Unlikely

* coded as life-threatening

Narratives for the severe AEs in the SOC Nervous system disorders follow:

1. Coma

The narrative for this subject was presented in Section 7.1.2 Other Serious Adverse Events.

2. Somnolence

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

Reviewer's comment: The temporal onset and resolution of the severe AE somnolence suggest it could have been related to study drug. There are inadequate details to attribute this AE to domperidone.

3. Syncope vasovagal

Subject 11 was a 33 year old Caucasian male enrolled in A014 who received the Coartem 4-dose regimen. Prior to the start of the study, he reported the severe AE headache as well as chills, nausea, sleep disorder, and hyperhidrosis. His baseline parasite count was 197 200, rapidly dropped to 45 on day 2, but did not drop to 0 until day 8. On study day 2, the severe AEs syncope vasovagal and fatigue were recorded, both of 1 day's duration. His blood pressure was 85/50 with a pulse of 76 on this day, both decreased from a baseline blood pressure of 120/80 and pulse 80. All AEs resolved by study day 4. On study day 14, severe asthenia, as well as moderate headache and insomnia were recorded. None of his AEs were felt to be related to study drug. No additional information was available about the subject's past medical history or concomitant medications.

Reviewer's comment: The severe headache was likely a symptom of malaria and resolved as his parasite count dropped. There are no details regarding the syncope, such as cardiac history or situation before the event, although the drop in both blood pressure and pulse suggest this was vasovagal in nature.

4. Headache

The 6 subjects with severe headache were reviewed and are presented in Table 37. The 6 subjects (3 male, 3 female) were equally divided with respect to receipt of 4 or 6-dose Coartem. Three of the subjects were enrolled in Study A025. Four of the subjects had onset of headache either before or on the same day as receipt of study drug, which makes it less likely to be related to study drug. Most headaches resolved shortly after completing the course of Coartem, with only 1 case of headache lasting out to study day 8 (Subject 103).

There were 2 subjects with onset of severe headache after initiating Coartem on study day 1. Both were not felt to be related to the study drug by the reviewer. Subject 3 was a 32 year old male enrolled in A2401 who also had no AEs at baseline, but had typical malaria symptoms reported on day 2 and 3 including chills, malaise, pyrexia and vomiting in addition to the severe AE headache. His parasite count at baseline was 108 and dropped to 0 by day 2. The headache resolved with medications on day 4 while all other AEs resolved on day 3. While it is possible that the headache was related to Coartem, the clustering of other typical malaria symptoms at the same time the headache was reported makes it less likely. Subject 9 was also a 32 year old male enrolled in A2401 who received the 6-dose Coartem regimen. He had no AEs recorded other than both severe headache and severe hyperhidrosis on day 3 which resolved in 1 day with no therapy or action. These occurred off study drug. His parasite count dropped to 0 on study day 3 from a baseline of 3980.

Table 37: Headaches of severe intensity, FDA adult pooled safety population

Subject/ Study/Coartem dose	Subject demogra- phics	Study day headache onset recorded	Study day headache ended	Related to study drug	Comments
11/A014/4 dose	33 yo Caucasian male	-4	5	Unlikely	Also experienced severe AE “vasovagal syncope”
35/A025/4 dose	30 yo female	1	3	Unlikely	Anorexia, arthralgia, asthenia, chills, dizziness, fatigue, myalgia, nausea, vomiting all resolved on study day 3
103/A025/4 dose	35 yo female	1	8	Unlikely	Present at baseline
85/A025/6 dose	19 yo female	1	3	Unlikely	Abdominal pain, anorexia, arthralgia, asthenia, chills, clonus, diarrhea, dizziness, fatigue, myalgia, nausea, palpitations, pruritus, rash, sleep disorder, tremor and vomiting all started on study day 1 and resolved on day 3
3/A2401/6 dose	32 yo male	2	4	Unlikely	No AEs reported at baseline (day 1), chills, headache on day 2, malaise, pyrexia and vomiting on day 3. Subject received ibuprofen and paracetamol for headache
9/A2401/6 dose	32 yo Caucasian male	3	3	Unlikely	Last dose of study drug on day 2, onset of severe headache and hyperhidrosis, both 1 day’s duration on day 3; no action taken, no information on medications

Nervous system disorder SAEs

All SAEs within the Nervous system disorders SOC were reported in the 6-dose group. There were 3 cases in total, 1 case each of coma, headache and mental impairment. The narratives for these SAEs were presented in Section 7.1.3 Other Serious Adverse Events. The cases of headache and mental impairment were related to malaria recrudescence in 2 subjects. The AE coma was unlikely to be related to study drug.

6.1.5.4.3.3 Pediatric patients

Table 38 shows the most common nervous system AEs observed in the FDA pediatric pooled safety population, and Table 39 shows nervous system AEs for the 6-dose regimen by age group.

Nearly all nervous system AE rates were lower with the pediatric population compared to adults, and may be due to the fact that infants and small children cannot report symptoms. Table 39 confirms that subjective symptoms that smaller children may have been less able to report, such as dizziness and headache, occurred at lower rates in children ≤ 2 years of age, and increased in frequency with age. Objective neurologic findings were generally similar between age categories.

Most AEs were reported on study days 1-3. The most frequently reported nervous system AEs for all treatment groups were headache and dizziness. While the frequency of headache was

similar between adults and pediatrics for the MAS groups (76% and 84% respectively), the rate of headache was significantly higher in adults compared to pediatrics for the 6-dose Coartem group (56% vs. 13%).

In general, nervous system AEs were generally higher for the 4-dose compared to 6-dose Coartem regimens and is likely attributed to differences in collecting AEs and study design.

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

Table 38: Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric pooled safety population

Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6-dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
Aphasia	1 (0.2)	0	0	0
Ataxia	3 (0.5)	1 (0.1)	5 (3.3)	0
Clonus	7 (1.1)	11 (0.8)	0	0
Convulsion	6 (0.9)	4 (0.3)	0	0
Coordination abnormal	2 (0.3)	0	0	0
Dizziness	149 (22.6)	56 (4.2)	92 (61.3)	4 (2.8)
Dyskinesia	0	1 (0.1)	2 (1.3)	0
Epilepsy	0	1 (0.1)	0	0
Facial palsy	1 (0.2)	0	0	0
Febrile convulsion	1 (0.2)	0	0	2 (1.4)
Fine motor delay	8 (1.2)	0	0	0
Headache	281 (42.6)	168 (12.6)	126 (84.0)	27 (18.9)
Hyperreflexia	2 (0.3)	6 (0.5)	0	0
Hypersomnia	1 (0.2)	0	0	0
Hypokinesia	44 (6.7)	0	0	0
Hypotonia	0	0	0	1 (0.7)
Lethargy	34 (5.2)	0	0	1 (0.7)
Myoclonus	0	3 (0.2)	0	0
Nystagmus	4 (0.6)	1 (0.1)	4 (2.7)	0
Paraesthesia	4 (0.6)	0	4 (2.7)	0
Somnolence	2 (0.3)	4 (0.3)	0	1 (0.7)
Speech disorder	33 (5.0)	0	0	1 (0.7)
Tremor	3 (0.5)	2 (0.2)	1 (0.7)	0

Table 39: Nervous system disorders in the 6-dose FDA pediatric pooled safety population by age group

MedDRA preferred term	Age group (years)			
	≤ 2 N=587 (%)	>2 to ≤ 6 N=473 (%)	>6 to ≤ 12 n=207 (%)	>12 to ≤16 N=66 (%)
Ataxia	0	0	0	1 (1.5)
Clonus	9 (1.5)	1 (0.2)	0	1 (1.5)
Convulsion	2 (0.3)	2 (0.4)	0	0
Dizziness	1 (0.2)	2 (0.4)	17 (8.2)	36 (55.4)
Dyskinesia	0	1 (0.2)	0	0
Epilepsy	0	1 (0.2)	0	0
Headache	4 (0.7)	46 (9.7)	71 (34.3)	47 (72.3)
Hyperreflexia	5 (0.9)	1 (0.2)	0	0
Myoclonus	1 (0.2)	2 (0.4)	0	0
Nystagmus	0	0	0	1 (1.5)
Somnolence	0	3 (0.6)	1 (0.5)	0
Tremor	0	1 (0.2)	0	1 (1.5)

Narratives for Nervous system AEs of severe intensity

There were 4 nervous system disorder AEs coded as severe in the FDA pediatric population: 3 were headaches and 1 was convulsion. All occurred in Coartem treatment groups, with none in the MAS or SP groups. Narratives for these severe AEs follow. In all the cases, none of the severe AEs were related to study drug.

Convulsion

Subject 46 was a 5 year old black male enrolled in Study B2303 who received Coartem 6-dose as a dispersible tablet. His last dose was Sept 7 and convulsion (severe intensity as well as SAE) was reported on study day 29 (Oct 3) along with mild pyrexia. His parasite count was zero at presentation, he was diagnosed with meningitis and treated with benzylpenicillin.

Headache:

- Subject 90 was a 12 year old female enrolled in A003 who received Coartem 4-dose. Severe headache in addition to moderate fatigue, dizziness, nausea, vomiting and chills were noted on study day 1. The headache resolved on day 4, and her parasite count was 0 by day 2. There is no information on concomitant medications.

Reviewer's comment: This subject's headache was likely due to malaria.

- Subject 140 was a 12 year old female enrolled in A003 who received Coartem 4-dose. Severe headache in addition to moderate fatigue, dizziness, and mild anorexia and chills were present on study day 1 and all resolved by day 2-4 (headache resolved on day 3).

Reviewer's comment: This subject's headache was likely due to malaria.

- Subject 74 was a 6 year old female enrolled in B2303 who received Coartem 6-dose. She developed severe headache and pyrexia on study day 35 and was diagnosed with *Plasmodium falciparum* infection.

Reviewer's comment: This subject's headache was due to malaria recrudescence.

Nervous system disorder SAEs

All SAEs within the Nervous system disorders SOC were reported in the 6-dose group. There were 3 cases of convulsion, 1 case each with the crushed tablet, dispersible tablet and standard tablet forms. The narratives for these SAEs were presented in Section 7.1.3 Other Serious Adverse Events. In none of the cases was the study drug suspected to be the cause - two of the convulsions were related to cerebral malaria, and the remaining case was due to meningitis. There was 1 case of hypotonia and 1 case of lethargy reported in subjects receiving SP.

Clonus

Clonus was observed in both adults and pediatrics with both the 4- and 6-dose Coartem regimens, with no cases reported with MAS or SP.

In the adult population, this can be accounted for by recoding. All cases of clonus reported in the 6-dose group occurred in patients enrolled in Studies A025 and A026 and were originally reported as "involuntary muscle contraction" in the clinical study reports, and were recoded in MedDRA as "clonus". All but 1 case of clonus were reported on days 1-3 and all but 1 were of mild intensity. All were not thought to be related to study medication by the Investigator. This may account for the higher rate of clonus in the 6-dose group (2.5%) compared to the rate in the 4-dose group.(0.6%)

The possible explanation for the finding of clonus in the pediatric population is that of a center effect - of the 11 cases of clonus observed in the 6-dose group, ten of the cases were reported in Study A2403, and all from 1 center. Nine of the 10 cases were detected during routine neurological examinations (predefined in the study protocol) in which specified signs and symptoms were evaluated. Six cases were reported between Day 1 and 3, four between Day 4 and 8. In all cases, the investigator described the clonus as suspected to be related to study medication. The intensity of clonus was mild in all but one case which was of moderate intensity (Subject 231). No action was taken in any of the cases and none of the cases were further documented beyond the clinical observation. In 8 of the 10 cases of clonus, no other nervous system disorder AEs were reported. The remaining 2 subjects (Subjects 122 and 313) had clonus reported with mild hyperreflexia; in the former subject, the AEs were not concurrent and it may be that hyperreflexia was actually clonus in resolution, and with the latter subject, clonus started before hyperreflexia but no end dates were available on these AEs. It is possible that these represented the same resolving phenomenon. There was one case of a 2 year old female (Subject 229) with mild hyperreflexia reported from study day 8 to 30, and mild myoclonus from days 15 to 30. Her parasite count was 0 on day 8 and 15, but was 35,337 on day 30. Both nervous system AEs were suspected by the investigator to be related to study drug. The remaining 3 reports of hyperreflexia were reported with no other neurological AEs.

The one case of clonus that was not reported from A2403 was subject 74 from study A025. This was a 14 year old male from Thailand with the nervous system AEs clonus, ataxia, headache, nystagmus and tremor reported on study day 1. All were of mild intensity and resolved by day 2 or 3. He also experienced anorexia, diarrhea, dizziness, fatigue, hepatomegaly, pruritis, nausea, nystagmus, abdominal pain, arthralgia, myalgia, palpitations, chills, sleep disorder, vomiting and asthenia on day 1. The neurologic symptoms were not felt to be related to study drug and no action was taken.

No cases of clonus or hyperreflexia occurred at the other two centers in Study A2403, or in Study B2303, which was the largest study performed with the 6-dose regimen (899 patients).

Overall, the significance of these cases of clonus is not clear. The Applicant pointed out the difficulties in excluding a possible subclinical cerebral involvement in malaria, and in distinguishing clonus from, for example, muscle contractions due to electrolyte disturbances that might occur in febrile patients. If such a phenomenon is real, the cases are mild, transient, and occur at a rate of approximately 1% with both 4- and 6-dose regimens in both adults and pediatrics.

Summary of Nervous system disorder findings

In adult patients, the vast majority of nervous system disorder AEs are headache and dizziness, which are non-specific and may be related to malaria infection itself. AEs relating to balance, such as ataxia, and nystagmus were of low frequency. Of note, there were no cases of “coordination abnormal” or “speech abnormal” (approximating slurred speech) in either the 4- or 6-dose groups. AE rates were higher for the 4-dose group compared to the 6-dose group, which relates to study design differences and different methods in collecting AEs. Of note, most AEs were of mild intensity. Of the AEs of severe intensity, most of these cases were headaches, which were unlikely to be related to study drug. None of the SAEs were felt to be related to study drug by the reviewer.

Similar findings were observed in pediatric patients. In the younger patients, objective findings such as clonus and hyperreflexia were more frequent (approximately 1-1.5%), whereas subjective symptoms including headache and dizziness predominated as the age groups got older. AEs relating to balance were reported more frequently with the 4-dose regimen than 6-dose. There were reports of ataxia in both groups (0.4% and 0.1%) but cases of “coordination abnormal”, “aphasia” and “speech disorder” in the 4-dose group only. None of the SAEs were related to study drug.

The significance of clonus/ hyperreflexia is not clear. The Applicant has questioned the accuracy in capturing and coding these events. The cases occur at low frequency, are mild and transient. The clinical significance of these events is not yet known.

6.1.5.4.4 Ear and auditory AEs

The neurotoxicity observed in animals when given large parenteral doses of some artemisinin derivatives is focused on lesions in specific brain nuclei involving the auditory and vestibular pathways. Clinical and pathological studies^{16,17,18,19} have found no evidence to date of similar lesions in human malaria patients.

In 2004, however, the results of an audiometry study of workers at a construction site in Mozambique was published.²⁰ This retrospective case-control study found that workers who developed malaria and were treated with Coartem had significantly greater increases in pure-tone thresholds (although the changes were subclinical) than matched control patients who had not had malaria and were not treated with Coartem. The methodology of this study has been criticized^{21,22} 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^{23,24} or in patients treated with Coartem²⁵. A study in volunteers with experimental malaria treated with Coartem also found no evidence of drug-related damage to hearing²⁶.

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

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

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

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

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

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

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

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

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

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

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

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

6.1.5.4.4.1 Adult Patients

Table 40 shows AEs affecting the auditory system, including relevant preferred terms from the SOC ‘Infections and infestations’, *i.e.* infections affecting the ear, as well the SOC ‘Ear and labyrinth disorders’ in the FDA adult pooled safety population. Overall, few AEs affecting the auditory system occurred in this population. For the Coartem 6-dose regimen group, the most frequent AE affecting the ear was vertigo, with no cases reported in the 4-dose group. In the 6-dose regimen group, 20/21 cases of vertigo were reported as mild and only one case was considered related to study drug. Fifteen cases of vertigo were reported between Days 1 and 3, 5 between Days 4 and 8 and 2 between Days 16 and 29.

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

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

One patient in the Coartem 6-dose regimen group had the AE deafness. This was a patient from Study A2401 who reported mild worsening of hearing loss that was present at baseline, following the first dose of Coartem; this was reported to have resolved by Day 3. There were no AEs of severe intensity, and no SAEs reported in the SOC Ear and labyrinth disorders.

Table 40: Adverse events affecting the auditory system, FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Ear and labyrinth disorders	Deafness	0	1 (0.2)	0
	Ear pruritus	0	0	1 (0.4)
	Hypoacusis	11 (1.4)	0	20 (7.1)
	Middle ear inflammation	0	1 (0.2)	0
	Motion sickness	0	2 (0.3)	0
	Tinnitus	3 (0.4)	4 (0.6)	1 (0.4)
	Vertigo	0	21 (3.3)	0
Infections & infestations	Otitis media	0	1 (0.2)	0

6.1.5.4.4.2 Pediatric patients

Table 41 shows AEs affecting the auditory system in the FDA pediatric pooled safety population. Table 42 shows the same AEs for the Coartem 6-dose regimen by age group.

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

Table 41: Adverse events affecting the auditory system, FDA pediatric pooled safety population

MedDRA system organ class	MedDRA Preferred Term	Coartem 4 dose N=659	Coartem 6 dose N=1332	Mefloquine Artesunate N=150	SP N=143
Ear and labyrinth disorders	Cerumen impaction	0	1 (0.1)	0	0
	Ear disorder	0	0	0	2 (1.4)
	Ear pain	0	3 (0.2)	0	0
	Ear pruritus	0	1 (0.1)	0	0
	Hypoacusis	5 (0.8)	0	3 (2.0)	0

MedDRA system organ class	MedDRA Preferred Term	Coartem 4 dose N=659	Coartem 6 dose N=1332	Mefloquine Artesunate N=150	SP N=143
	Otorrhoea	0	1 (0.1)	0	1 (0.7)
Infections & infestations	Otitis media	5 (0.8)	10 (0.8)	0	8 (5.6)
	Otitis externa	6 (0.9)	3 (0.2)	0	0

Table 42: Ear and labyrinth disorders in the 6-dose FDA pediatric pooled safety population by age group

MedDRA system organ class	MedDRA preferred term	Age group	
		0-2 N=587 (%)	>2 to ≤6 N=473 (%)
Ear and labyrinth disorders	Cerumen impaction	1 (0.2)	0
	Ear pain	2 (0.3)	1 (0.2)
	Ear pruritus	1 (0.2)	0
	Otorrhoea	1 (0.2)	0

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

6.1.5.4.4.3 Literature

In the 120 day safety report, the Applicant identified 2 new studies in the literature which specifically assessed for ototoxicity. Gurkov et al. performed a randomized, open-label study comparing the ototoxicity, tolerability, and efficacy of Coartem, quinine or atovaquone/proguanil in 97 patients (at least 5 years of age) with falciparum malaria in south-west Ethiopia (Gurkov et al., 2008²⁷). Patients were followed up for 90 days after initiating treatment. Comprehensive audiovestibular testing by pure tone audiometry (PTA), transitory evoked (TE) and distortion product (DP) otoacoustic emissions (OAE) and brain stem-evoked response audiometry (BERA) was performed before enrollment and after 7, 28 and 90 days. Pure-tone audiometry and DP-OAE levels revealed transient significant cochlear hearing loss in patients treated with quinine but not in those treated with Coartem or atovaquone/proguanil. TE-OAE could be elicited in all examinations, except for three patients in the quinine group on day 7, who suffered a transient hearing loss greater than 30 dB. BERA measurements revealed no evidence of drug induced brain stem lesions. The authors concluded that there was no detrimental effect of a standard oral regimen of Coartem on peripheral hearing or brainstem auditory pathways in patients with uncomplicated falciparum malaria.

Another study identified was a randomized trial comparing the efficacy and safety of artesunate/amodiaquine and Coartem when used to treat multiple episodes of malaria in children aged 6 months to 14 years in Ghana (Adjei et al., 2008²⁸). Audiological examinations in a subset

27 Gurkov R, Eshetu T, Miranda IB et al. Ototoxicity of artemether/lumefantrine in the treatment of falciparum malaria: a randomized trial. *Marla J.* 2008 Sept 16;7:179.

28 Adjei GO, Kurtzhals JA, Rodrigues OP, et al. Amodiaquine-artesunate vs. artemether –lumefantrine for

of patients in each group revealed no evidence of hearing impairment. Similarly, neurological examinations showed that no abnormal neurological signs were observed during one year of follow-up. No adverse event exacerbation was observed in any of the patients who received multiple treatment courses with either regimen during the 1-year follow-up period.

Summary of Ear and Labyrinth Findings

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

6.1.5.4.5 QTc interval prolongation

6.1.5.4.5.1 Study A2101: Definitive QTc study in healthy volunteers

Study A2101 was reviewed by the FDA Interdisciplinary Review Team for QT studies (QT-IRT), and their complete analysis can be found in DFS. The following is a summary of their findings:

Study A2101 was a definitive QTc study (following the ICH E14 guideline) performed in a healthy adult volunteer group. It is noted that the ICH E14 guidance refers to a “thorough QT study” as one that uses escalating doses of study drug and a positive control (moxifloxacin). While study A2101 did use a positive control, therapeutic doses of Coartem were studied. QTcF prolongation was observed when Coartem was administered orally as a 6-dose regimen of 80/480 mg Coartem over 3 days in this randomized, placebo-controlled parallel study in 126 healthy subjects. Table 43 summarizes the study results for QTcF. At the therapeutic dosing regimen, Coartem was associated with a mean maximum increase in QTcF relative to placebo of 7.45 msec, with the upper 90% CI for the maximum mean change in baseline- and placebo-adjusted QTcF ($\Delta\Delta\text{QTcF}$) exceeding 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. Moxifloxacin was used as the positive control to establish assay sensitivity. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, indicating that the study was adequately designed and conducted to detect a small effect on the QT interval. There were no clinically significant effects on the PR and QRS intervals (maximum upper bound of 90% CI 3.6 and 2.8 ms respectively).

Table 43: Largest Time-Matched Increase in QTcF by Treatment Group

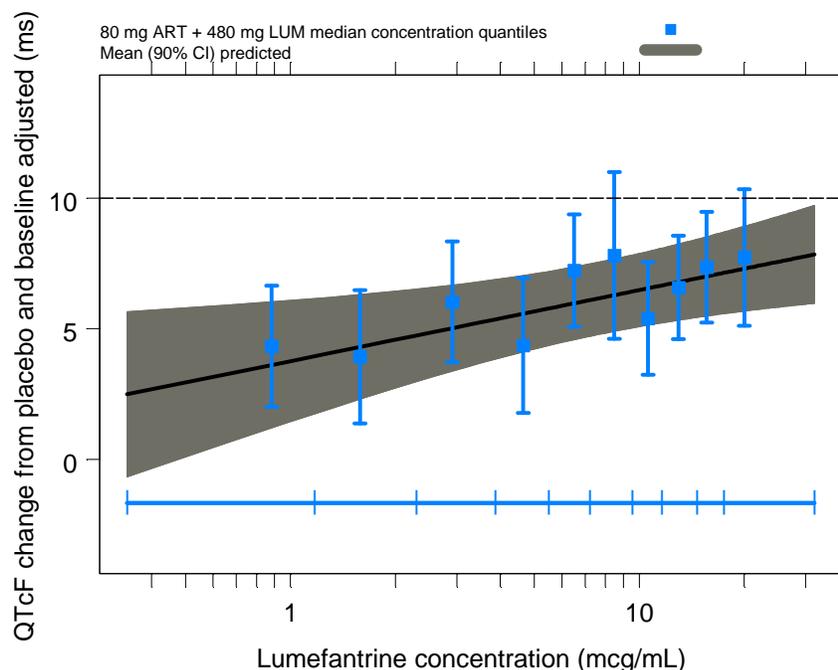
Treatment	Time, hr	$\Delta\Delta\text{QTcF}$, ms	90% CI, ms
Coartem	72	7.29	(3.6, 11.0)
Moxifloxacin	61*	14.1	(8.9, 19.4)

* Moxifloxacin was administered at time 60 hours

Source: QT-IRT review

Significant positive lumefantrine concentration- $\Delta\Delta\text{QTcF}$ relationship was identified (Figure 1). Based on a linear relationship, the predicted mean (90% confidence interval) $\Delta\Delta\text{QTcF}$ for the mean C_{max} of 480 mg lumefantrine dose was 7.0 (5.5, 8.5) ms. These findings are consistent with the primary statistical analysis.

Figure 1: Mean (90% CI) predicted $\Delta\Delta\text{QTc}$ vs. Lumefantrine Concentration (black line and shaded grey area) and observed median-quantile concentrations and associated mean $\Delta\Delta\text{QTcF}$ (90% CI)



Source: QT-IRT review

Only the therapeutic dosing regimen of Coartem was tested in the TQT study. No specific pharmacokinetic studies have been performed in subjects with hepatic and renal impairment or in elderly patients to determine the highest expected clinical exposure. In four studies in adult or child malaria patients using the 6-dose regimen of Coartem (A025, A2401, A2403, and A2303), the lumefantrine exposure (mean AUC_{∞} ranged from 335 to 1260 $\mu\text{g}\cdot\text{h}/\text{ml}$) did not exceed the exposure level in healthy subjects (mean AUC_{∞} was 1320 $\mu\text{g}\cdot\text{h}/\text{ml}$).

Drugs that are found to prolong the QT interval greater than the 10 ms threshold at clinically relevant exposures, ICH E14 specifies that an expanded ECG safety evaluation during later stages of drug development might be appropriate to describe the QT effect of the drug in the target population. In the Coartem development program, ECG evaluations were performed in most studies (20) and were included in the pooled safety population (the exceptions were A008, A010, A011 and A2412). Over 6 % of adults had a QTcF increase of 60 ms from baseline. QTcF prolongation of >500 ms was reported in 3 (0.3%) patients. Over 5% of children had an increase in QTcF of over 60 ms. No child had QTcF >500 ms. The main cardiac adverse event reported was palpitation which is consistent with fever and anemia associated with the disease state.

6.1.5.4.5.2 ECG findings

There were few AEs reported related to ECG changes and findings (Table 44). All were reported with the 6-dose Coartem group, with no reports in the 4-dose Coartem or MAS groups. In the adult population, one subject with vasovagal syncope had a QTcB of 290 msec on the same day as the AE. The two subjects with “Electrocardiogram QT prolonged” had a QTcB of 450 msec and a QTcF 436 msec for one, a QTcB of 428 msec and a QTcF of 411 msec for the other, both on the same day as the AE. There were no reports of AE outcomes related to QT prolongation such as sudden cardiac death, seizure and significant ventricular arrhythmias.

In the pediatric pooled safety population, there was only one subject in the Coartem crushed tablet 6-dose regimen who had QTc prolongation reported as an AE (QTcB was 485 msec and QTcF was 423 msec).

Table 44: Adverse events potentially related to QT prolongation, FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)
Investigations	Electrocardiogram abnormal	0	2 (0.3)
	Electrocardiogram change	0	1 (0.2)
	Electrocardiogram QT prolonged	0	2 (0.3)
	Electrocardiogram T wave abnormal	0	1 (0.2)
Nervous system disorders	Syncope vasovagal	1 (0.1)	0

In conclusion, Coartem treatment is associated with a small increase in QTc interval. In the QT-IRT consult, there were changes suggested in labeling, which included moving sections regarding QT prolongation to the “Warning and Precautions” section from “Contraindications” given the short duration of Coartem therapy, severity of disease, relatively small size of QT prolongation and absence of any confirmed AEs related to QT prolongation.

6.1.6 Less Common Adverse Events

None

6.1.7 Laboratory Findings

6.1.7.1 Overview of laboratory testing in the development program

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

Hematology parameters assessed were: hemoglobin, hematocrit, erythrocyte count, platelet count, reticulocyte count, total leukocyte count, absolute neutrophil count and counts of eosinophils, basophils, lymphocytes and monocytes as % of total leukocytes.

Clinical chemistry parameters assessed were: random blood glucose, creatinine clearance, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ -glutamyl transferase (GGT), alkaline phosphatase, and total bilirubin.

6.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

6.1.7.2.1 Hematology AEs

6.1.7.2.1.1 Adult subjects

Hematology AEs are shown for the FDA adult pooled safety population in Table 45. Anemia was reported far above any other PT, and occurred at similar rates in each group. There were only 2 cases of severe anemia, 1 from each Coartem treatment regimen. The other anemia cases, and all other hematology AEs were of either mild or moderate severity.

Table 45: Hematology AEs, FDA adult pooled safety population

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Anaemia	33 (4.2)	26 (4.0)	17 (6.1)
Microcytic anaemia	0	1 (0.2)	0
Neutropenia	1 (0.1)	1 (0.2)	0
Thrombocytopenia	0	1 (0.2)	0

There were small changes in hemoglobin from baseline in the earlier time windows, followed by small increases in baseline value at the Day 27-40 window in all the Coartem groups. The changes are consistent with the successful treatment and resolution of malaria. The comparator antimalarials group also had similar patterns of changes but it is noted that in some cases relatively few patients had assessments. In the Applicant's shift table analysis from baseline to each time window (data not shown), Coartem-treated patients had shifts to higher toxicity Grades most commonly at the Day 2-4 time window. Apart from baseline, where Grade 3 or 4 were most commonly observed, the highest incidence for Grade 3 or 4 for hemoglobin were observed during the window day 2-4, mainly in patients who already presented with a Grade 2, 3 or 4 at baseline. Overall, most patients either shifted to normal values or to lower Grade during the study consistent with malaria recovery.

Hematocrit and erythrocyte counts followed a similar pattern to hemoglobin.

6.1.7.2.1.2 Pediatric subjects

Table 46 shows AEs related to hematology in the FDA pediatric pooled safety population. As in the adult population, anemia was by far the most common such AE. Anemia was commonly reported in the Day 1-3 time window for the Coartem 4-dose regimen, and in the Day 4-8 window for the 6-dose regimen. Increased reticulocyte count, which could represent hemolysis, was observed in three patients treated with the Coartem 6-dose regimen. These patients were all from Study B2303 (2 treated with the standard tablet, 1 with the dispersible tablet). The reticulocyte increases were reported as mild, and hemoglobin levels increased during the study in all patients, and all showed increases in leukocyte and platelet counts concomitantly with the reticulocyte count increases. None of the patients with reticulocyte increases had severe anemia.

Table 46: Hematology adverse events, FDA pediatric pooled safety population

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
Blood and lymphatic system disorders	Anaemia	146 (22.2)	116 (8.7)	15 (10.0)	77 (53.9)
	Eosinophilia	0	13 (1.0)	0	0
	Iron deficiency anaemia	0	1 (0.1)	0	0
	Leukocytosis	0	4 (0.3)	0	0
	Leukopenia	0	0	0	1 (0.7)
	Lymphadenitis	0	1 (0.1)	0	0
	Monocytosis	0	3 (0.2)	0	0
	Neutropenia	0	2 (0.2)	0	0
	Splenomegaly	183 (27.8)	133 (10.0)	56 (37.3)	33 (23.1)
	Thrombocytopenia	0	3 (0.2)	0	0
Investigations	Eosinophil count decreased	0	1 (0.1)	0	0
	Eosinophil count increased	0	4 (0.3)	0	0

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
	Haematocrit decreased	0	12 (1.0)	0	0
	Haemoglobin decreased	0	10 (0.8)	0	0
	Haemoglobin increased	0	1 (0.1)	0	0
	Lymphocyte count decreased	0	1 (0.1)	0	0
	Lymphocyte count increased	0	2 (0.2)	0	0
	Lymphocyte morphology abnormal	0	9 (0.7)	0	0
	Monocyte morphology abnormal	0	1 (0.1)	0	0
	Neutrophil count decreased	0	3 (0.2)	0	0
	Platelet count decreased	0	20 (1.5)	0	0
	Platelet count increased	0	5 (0.4)	0	0
	Red blood cell count decreased	0	2 (0.2)	0	0
	Reticulocyte count decreased	0	3 (0.2)	0	0
	Reticulocyte count increased	0	4 (0.3)	0	0
	White blood cell count decreased	0	13 (1.0)	0	0
	White blood cell count increased	0	7 (0.5)	0	0

Hemoglobin levels in pediatrics was similar to the adult population, with decreases from baseline in mean and median hemoglobin in the earlier time window up to Day 5-12 with increases from baseline at subsequent time windows. Shift table analysis was also similar (data not shown), with shifts to higher toxicity Grades most commonly at the Day 2-4 time window. The highest incidence for Grade 3 or 4 for hemoglobin were observed during the window day 2-4, mainly in patients who already presented with a Grade 3 or Grade 4 at baseline.

Similar patterns were seen for comparator antimalarials, although only limited data were available on these. Hematocrit and erythrocyte counts showed a similar pattern to hemoglobin, as would be expected.

6.1.7.2.2 Hepatic AEs

6.1.7.2.2.1 Adult subjects

AEs affecting the liver are shown for the FDA adult pooled safety population in Table 47. Hepatomegaly was the most frequently reported PT for all treatment groups, and was highest in the Coartem 4-dose regimen group. Hepatomegaly is a common sign of malaria, and most cases were reported between Days 1 and 3. Other hepatic system AEs were reported in very few patients.

Table 47: Liver adverse events, FDA Adult pooled safety population

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Blood alkaline phosphatase increased	0	1	0
Blood bilirubin increased	0	1 (0.2)	0
Chronic hepatitis	1 (0.1)	0	0
Cytolytic hepatitis	1 (0.1)	0	0
Hepatic enzyme abnormal	0	2 (0.3)	0
Hepatic enzyme increased	0	1 (0.2)	0
Hepatitis	3 (0.4)	1 (0.2)	0
Hepatocellular damage	0	1 (0.2)	0
Hepatomegaly	179 (22.9)	106 (16.4)	36 (12.9)
Hyperbilirubinaemia	0	1 (0.2)	0
Jaundice	1 (0.1)	3 (0.5)	0
Liver function test abnormal	0	3 (0.5)	0
Ocular icterus	0	1 (0.2)	0
Transaminases increased	0	1 (0.2)	0

The Coartem treatment groups showed decreases from baseline at all time windows in aspartate aminotransferase (ASAT), and decreases from baseline in alanine aminotransferase (ALAT) at most time windows (4-dose group showed increases at the Day 5-12 and Day 27-40 time window; 6-dose regimen at the Day 5-12 window). Shift table analysis from baseline to each time window showed only very few patients shifted to grade 3 or 4 (data not shown). Most patients who were not normal (Grade 0) at baseline tended to show shifts to lower grades particularly in later time windows. No patient in the 6 dose regimen had a Grade 3 or 4 toxicity that had not shifted to lower than Grade 3 or 4 by their last visit.

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

The adult and adolescent pooled safety population was searched for cases potentially qualifying for Hy's Law cases, i.e. cases of elevated total bilirubin > 2 x ULN with ALAT/ASAT elevations >3 x ULN, in a context of pure hepatocellular injury, without cholestasis (i.e. with normal

alkaline phosphatase), and for which no other reason can be found to explain the combination of increased ALAT/ASAT and total bilirubin. There were three such patients receiving the 6-dose regimen, all from Study A028, and ten patients treated with the 4-dose regimen who had post-baseline values of ALAT or ASAT $\geq 3 \times$ ULN in association with total bilirubin $\geq 2 \times$ ULN. In twelve of these patients, alkaline phosphatase levels were also elevated. All patients but one had abnormal values at baseline. In nine cases, the values improved during the study.

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

6.1.7.2.2.2 Pediatric subjects

For the pediatric pooled safety population, hepatic system AEs are presented in Table 48. Similar to adults, the only frequent AE reported in all treatment groups was hepatomegaly. Other AEs related to hepatic disorders were less common, although elevated serum transaminases (aspartate aminotransferase) were reported more commonly in the Coartem 6-dose regimen groups, particularly the dispersible tablet group. Most of these AEs were reported in the Day 1-3 time window.

Table 48: Hepatic disorder adverse events, FDA pediatric pooled safety population

Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
Alanine aminotransferase increased	0	11 (0.8)	0	0
Aspartate aminotransferase increased	0	51 (3.8)	0	0
Gamma-glutamyltransferase increased	0	8 (0.6)	0	0
Hepatic enzyme increased	0	1 (0.1)	0	0
Hepatitis	0	1 (0.1)	0	0
Hepatomegaly	147 (22.3)	85 (6.4)	38 (25.3)	21 (14.7)
Hepatosplenomegaly	0	2 (0.2)	0	0
Jaundice	2 (0.3)	2 (0.2)	0	0
Ocular icterus	1 (0.2)	0	0	0
Transaminases increased	0	1 (0.1)	0	0

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

The pediatric pooled safety population was also searched for patients with baseline transaminase values of Grade 0, 1 or 2 who experienced an increase by 2 Grades, and at least up to Grade 3 (corresponding to 5.1 to 10 x ULN). Four patients with normal transaminases levels at baseline,

had an increase between 5 and 10 x ULN, which normalized at last visit (day 42/43) and two patients experienced delayed increases above 10 x ULN, one of which normalized while the other was detected at the last study visit.

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

6.1.8 Vital Signs

6.1.8.1 Overview of vital signs testing in the development program

Vital signs data were not collected in all studies. No vital signs data are available from studies A003, A010, and A011 and in A2403 no blood pressure data were collected, although pulse was reported.

6.1.8.2 Standard analyses and explorations of vital signs data

Fewer than 2% of subjects met the clinically notable criteria of a pulse rate <40 bpm or >150 bpm; systolic blood pressure <80 mmHg or >180 mmHg; diastolic blood pressure <30 mmHg or >110 mmHg (data not shown).

For the pediatric pooled safety population, the following limits were used to determine clinically notable vital sign results: pulse rate <80 bpm (≤ 2 years) or <50 bpm (>2 and ≤ 12 years), or >180 bpm (≤ 2 years) or >160 bpm (>2 and ≤ 12 years); systolic blood pressure <60 mmHg (≤ 2 years) or <70 mmHg (>2 and ≤ 12 years), or >100 mmHg (0 to ≤ 1 month) or >120 mmHg (>1 month and ≤ 2 years) or >150 mmHg (>2 and ≤ 12 years); diastolic blood pressure <30 mmHg or >70 mmHg (0 to ≤ 1 month), >90 mmHg (>1 month and ≤ 2 years) or >100 mmHg (>2 and ≤ 12 years). High systolic blood pressure was the most commonly observed vital signs abnormality, and occurred in ~10% of subjects (data not shown).

6.1.9 Electrocardiograms (ECGs)

6.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Lumefantrine is chemically related to another antimalarial, halofantrine. Halofantrine is known to be associated with significant prolongation of the QTc interval. In *in vitro* electrophysiology studies, lumefantrine and desbutyl-lumefantrine inhibited the hERG tail current with a higher IC₅₀ value than mefloquine, chloroquine and halofantrine. This, together with calculated cardiac safety indices, suggested that lumefantrine and desbutyl-lumefantrine have weaker proarrhythmic potential than their comparator compounds.

Malaria and anemia secondary to malaria appear to lengthen the QT interval, which make it difficult to assess the effects of antimalarials treatment on cardiac conduction. This is compounded 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. Furthermore, healthy small children typically have heart rates above 60 beats/minute, making the assessment in pediatric malaria patients even more difficult.

A definitive QTc study was performed in healthy volunteers and is discussed in Section 7.1.8.4. ECG evaluations have been included in most studies of Coartem treatment.

Reviewer's comments: The Guidance for Industry 'E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs' states: "Bazett's correction is frequently used in clinical practice and in the medical literature. In general, however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute (bpm) and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates." The following discussion will focus only on QTc.

6.1.9.2 Standard analyses and explorations of ECG data

6.1.9.2.1 Analyses focused on measures of central tendency

ECG evaluations were performed in most studies included in the pooled safety populations (the exceptions were A008, A010, A011 and A2412), with particular emphasis on analysis of the QTc interval. The time points at which ECGs were performed, the method of reading ECGs, and the number of assessments made varied between studies. In some studies, ECGs were analyzed independently by a specialist CRC^{(b) (4)}. In other studies, some ECGs (typically those with QTc > 450 msec, or if there were other concerns) were peer reviewed by an independent cardiologist as well as being analyzed by the

investigators. In other studies, ECGs were read only by the investigators. The pooled analyses presented here include eRT-analyzed data where these were available, and investigator-analyzed data where ^{(b) (4)} data were not available. Peer reviewed ECG data were not included in these pooled analyses.

6.1.9.2.1.1 Adult Patients

For the Applicant's adult and adolescent pooled safety population (*i.e.*, patients \geq 12 years of age), changes in ECG parameters over time are summarized in Table 49.

The QTcF showed greater mean increases from baseline for all treatment groups and were similar for the 4-dose and 6-dose groups.

For the total Coartem group, approximately 4% of patients who had normal QTcF at baseline shifted to either borderline or prolonged categories respectively. There appeared to be no major differences between the 4-dose and 6-dose regimens. Very few patients had QTcF values of $>$ 500 msec.

Appears This Way On Original

Table 49: Summary statistics of changes from baseline in ECG parameters, Applicant's adult and adolescent pooled safety population

Parameter	Co-artemether		Total
	4-dose	6-dose	
QTc (Bazett) (msec)			
Day 1-4			
N	419	465	884
Baseline	408.6	409.0	408.8
Change from baseline	2.4	1.5	1.9
Day 5-9			
N	417	348	765
Baseline	409.2	410.9	410.0
Change from baseline	-3.2	1.8	-0.9
Day >9-44			
N	262	313	575
Baseline	406.1	411.1	408.8
Change from baseline	-4.0	-0.4	-2.0
QTc (Fridericia) (msec)			
Day 1-4			
N	303	465	768
Baseline	388.1	386.5	387.1
Change from baseline	16.7	10.4	12.9
Day 5-9			
N	304	348	652
Baseline	389.0	388.2	388.5
Change from baseline	10.4	11.2	10.8
Day >9-44			
N	177	313	490
Baseline	388.8	388.5	388.6
Change from baseline	2.3	7.5	5.6
Uncorrected QT interval (msec)			
Day 1-4			
N	304	465	769
Baseline	340.6	346.4	344.1
Change from baseline	42.9	25.9	32.6
Day 5-9			
N	305	348	653
Baseline	341.5	347.5	344.7
Change from baseline	36.9	27.2	31.8
Day >9-44			
N	178	313	491
Baseline	342.2	348.0	345.9
Change from baseline	16.8	20.8	19.3

Bazett's formula: $QTc = QT/(RR^{*0.5})$

Fridericia's formula: $QTc = QT/(RR^{*1/3})$

A patient must have both baseline and post-baseline value to be included.

If a patient had more than one ECG within the given time interval the mean was used.

Source: Novartis Clinical Overview

6.1.9.2.1.2 Pediatric Subjects

For the Applicant's pediatric pooled safety population (*i.e.*, children < 12 years of age), changes in ECG parameters over time are summarized in Table 50. Only approximately 10% of the total Coartem group had ECG assessments after Day 4, and relatively few patients treated with the 4-dose regimen had ECG assessments. The total Coartem group thus primarily consisted of patients treated with the 6 dose regimen, either of the standard tablet or the dispersible tablet.

Almost all patients had normal QTcF at baseline and remained normal.

There were no Coartem-treated patients with post-baseline QTcF values > 500 msec, although a higher proportion of patients had increases from baseline of > 60 msec and 30-60 msec, and fewer had decreases from baseline, than was the case for QTcB. As with the similar situation in the adult and adolescent pooled safety population, this difference is probably related to the way that the two formulae for correcting the QT interval deal with changes in heart rate, as seen in this population group as their malaria resolved.

Appears This Way On Original

Table 50: Summary statistics of changes from baseline in ECG parameters, Applicant's pediatric pooled safety population (Source: Novartis Clinical Overview)

Parameter	Co-artemether		
	4-dose	Total 6-dose	Total
QTc (Bazett) (msec)			
Day 1-4			
N	87	1153	1240
Baseline	405.6	420.4	419.4
Change from baseline	10.1	8.0	8.1
Day 5-9			
N	85	34	119
Baseline	406.0	417.6	409.3
Change from baseline	3.2	5.8	3.9
Day >9-44			
N	79	44	123
Baseline	405.5	423.4	411.9
Change from baseline	0.7	-2.6	-0.5
QTc (Fridericia) (msec)			
Day 1-4			
N	27	1153	1180
Baseline	365.0	368.9	368.8
Change from baseline	17.4	18.6	18.6
Day 5-9			
N	27	34	61
Baseline	365.0	374.5	370.3
Change from baseline	18.5	14.7	16.3
Day >9-44			
N	21	44	65
Baseline	360.9	378.7	373.0
Change from baseline	22.8	9.7	13.9
Uncorrected QT interval (msec)			
Day 1-4			
N	27	1153	1180
Baseline	295.5	285.1	285.3
Change from baseline	32.9	33.4	33.4
Day 5-9			
N	27	34	61
Baseline	295.5	302.7	299.5
Change from baseline	39.1	27.6	32.7
Day >9-44			
N	21	44	65
Baseline	290.7	304.4	299.9
Change from baseline	44.3	28.7	33.7

Bazett's formula: $QTc = QT / (RR^{*0.5})$

Friderica's formula: $QTc = QT / (RR^{*1/3})$

A patient must have both baseline and post-baseline value to be included.

If a patient had more than one ECG within the given time interval, the mean was used

QTc values > 500 msec

Applicant's Adult and adolescent patients

A total of three adult patients treated with the Coartem 6-dose regimen had QTc values (Bazett and/or Fridericia) of > 500 msec. Two of these patients were from Study A025, and the values were reported on Day 8 (QTc Fridericia values of 534 and 473 msec). However, for both of these patients, a peer review of the ECGs judged these values to be less than 500 msec. The third patient was from Study A028, and the QTc value of > 500 msec (QTc Fridericia 454 msec) was reported at Day 29; this patient's ECG was not peer reviewed.

Five adult patients treated with the 4-dose regimen were also reported as having QTc values (Bazett and/or Fridericia) of > 500 msec; ECGs were not peer reviewed for any of these patients. In two of these patients, the QTc values were reported at Days 29 and 30; one patient was reported at Day 2 and the investigator commented that there was possible evidence of an old anteroseptal infarct; and two patients from Study AB/MO2 with the values on Days 2 and 3.

Applicant's pediatric patients

No pediatric patient had a QTcF of > 500 msec.

QTc data across both adult and pediatric populations, key studies

At FDA's request, further summaries of QTc data were prepared by the Applicant. In line with the request, data for patients (both adult and pediatric) from the 6 key studies with the 6-dose regimen, plus the 4-dose studies ABMO2 and A023, were pooled. The proportions of patients with absolute QTc values > 450 msec, > 480 msec, and > 500 msec were summarized, as were the proportions of patients with increases from baseline in QTc of > 30 msec and > 60 msec. These data are summarized in Table 51. In these tables, the proportions of patients with QTc changes from baseline for the time interval up to or on Day 4, and for any time post-baseline are summarized. Changes from baseline to either highest value prior to or on Day 4, or to highest value at any time, in QTcF showed that most Coartem-treated patients had decreases from baseline or increases of < 30 msec. A higher incidence of changes from baseline of >30 msec, 30-60 msec and >60 msec was observed for QTcF than for QTcB; this was also seen for the Applicant's adult and pediatric pooled safety populations and probably relates to differences in the way the two formulae respond to decreases in ventricular rate, such as those typically observed during the resolution of malaria.

With respect to prolonged QTcF, up to or on Day 4, approximately 2% of Coartem-treated patients had QTc (Fridericia) >450 msec, with 0.2% of patients having values >480 msec and 0.1% (two patients) with values of > 500 msec. The proportions of patients with these values at any time post-baseline was slightly higher, indicating that some patients had QTc (Fridericia) values above these thresholds later in the studies.

Table 51: Proportion of patients with QTcF signal values, or signal increases in QTcF, pooled population of studies ABMO2, A023, A025, A026, A028, A2401, A2403 and B2303

	Co-artemether regimen			
	4-dose N = 225	6-dose N = 1480	Total 6-dose N = 1927	Total N = 2152
QTc (Fridericia) increases between baseline and highest value prior to or on Day 4				
n/M (%) patients				
≤0 msec	24/134 (17.9)	235/1234 (19.0)	336/1663 (20.2)	360/1797 (20.0)
>0 - <30 msec	49/134 (36.6)	577/1234 (46.8)	767/1663 (46.1)	816/1797 (45.4)
30 - 60 msec	43/134 (32.1)	315/1234 (25.5)	436/1663 (26.2)	479/1797 (26.7)
>30 msec	55/134 (41.0)	361/1234 (29.3)	488/1663 (29.3)	543/1797 (30.2)
>60 msec	13/134 (9.7)	64/1234 (5.2)	79/1663 (4.8)	92/1797 (5.1)
Baseline missing	5/134 (3.7)	43/1234 (3.5)	45/1663 (2.7)	50/1797 (2.8)
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)
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)
>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)

	Co-artemether regimen			
	4-dose N = 225	6-dose N = 1480	Total 6-dose N = 1927	Total N = 2152
Any post-baseline QTc (Fridericia):				
>450 msec	15/135 (11.1)	35/1270 (2.8)	36/1699 (2.1)	51/1834 (2.8)
>480 msec	4/135 (3.0)	3/1270 (0.2)	3/1699 (0.2)	7/1834 (0.4)
>500 msec	2/135 (1.5)	1/1270 (0.1)	1/1699 (0.1)	3/1834 (0.2)

Fridericia's correction: $QTc = QT / (RR^{1/3})$

n = number of patients with a value in the respective category.

M = number of patients with a post-baseline ECG in the given interval.

M is used as the denominator for the calculation of percentages.

Source: [CO Appendix-Table 5.4-26](#)

Data is available for comparison with other antimalarials. For the 105 patients treated with MAS, the majority (58%) had changes from baseline of either < 0 msec or 0 to < 30 msec, and only 7% had increases of > 60 msec from baseline to the highest value up to or on Day 4. There were 7% of patients with absolute values > 450 msec, but no patients with QTcF of > 480 msec or > 500 msec. For the 52 patients with artemether monotherapy, the proportions of patients with signal changes from baseline, either to the highest value up to or on Day 4, or at any time during the study, of 30-60 msec, >30 msec or > 60 msec appeared to be higher than those in the total Coartem group, but these differences need to be interpreted with caution, for the reasons described previously. However, there were no artemether-treated patients with QTcF of > 500

msec. The lumefantrine tablet group (N = 103) appeared to show somewhat higher rates of changes from baseline of 30 to 60 msec, > 30 msec, > 60 msec; and absolute QTcF of > 450 msec, > 480 msec and > 500 msec than the total Coartem group, although this comparison within the pooled population should be interpreted cautiously.

Subgroup analysis by Sex and Age

Analyses of QTc interval by sex and age were also undertaken. No major differences between male and female patients were observed; age also did not appear to have a major influence on QTc findings, although there were very few patients aged > 65 years.

6.1.9.3 Additional analyses and explorations

6.1.9.3.1 Adult Subgroup Analyses

6.1.9.3.1.1 Sex

Table 52 shows AEs by SOC stratified by sex for the 4- and 6-dose regimens in the adult pooled populations. The frequency of most AEs by SOC was higher for females compared to males in the 4-dose regimen, but this was not as strongly observed for the 6-dose regimen. There were some differences in AEs between the sexes: there were more blood and lymphatic disorders for male patients mainly due to higher incidence of splenomegaly, although there were more female patients with anemia. There were also more cardiac disorders in female patients, mainly due to a higher incidence of palpitations, and more gastrointestinal disorders, with higher rates of nausea and abdominal pain. Sleep disorders and asthenia were also more common in females. The most frequently reported AEs for both sexes in both the 4- and 6-dose groups were general disorders and nervous system disorders. Nervous system disorders were slightly higher for females compared to males for both the 4- and 6-dose regimens.

Overall, there were no apparent differences in AEs based on sex.

Table 52: AEs by SOC for the FDA adult pooled safety population stratified by dose and sex

MedDRA system organ class	Coartem 4 dose N=787 (%)		Coartem 6 dose N=647 (%)	
	Female N=201 (%)	Male N=581(%)	Female N=174 (%)	Male N=471 (%)
Blood and lymphatic system disorders	51 (25.4)	157 (27.0)	21 (12.1)	103 (21.9)
Cardiac disorders	77 (38.3)	119 (20.5)	42 (24.1)	88 (18.7)
Ear and labyrinth disorders	3 (1.5)	11 (1.9)	11 (6.3)	18 (3.8)
Endocrine disorders	0	0	1 (0.6)	0
Eye disorders	4 (2.0)	8 (1.4)	1 (0.6)	0
Gastrointestinal disorders	131 (65.2)	311 (53.5)	106 (60.9)	243 (51.6)
General disorders and administration site conditions	189 (94.0)	510 (87.8)	141 (81.0)	382 (81.1)

MedDRA system organ class	Coartem 4 dose N=787 (%)		Coartem 6 dose N=647 (%)	
	Hepatobiliary disorders	54 (26.9)	131 (22.6)	26 (14.9)
Infections and infestations	16 (8.0)	43 (7.4)	26 (14.9)	66 (14.0)
Injury, poisoning and procedural complications	0	0	1 (0.6)	0
Investigations	3 (1.5)	5 (0.9)	5 (2.9)	11 (2.3)
Metabolism and nutrition disorders	143 (71.1)	340 (58.5)	102 (58.6)	255 (54.1)
Musculoskeletal and connective tissue disorders	86 (42.8)	215 (37.0)	84 (48.3)	266 (56.5)
Nervous system disorders	168 (83.6)	436 (75.0)	138 (79.3)	359 (76.2)
Psychiatric disorders	90 (44.8)	183 (31.5)	61 (35.1)	146 (31.0)
Renal and urinary disorders	2 (1.0)	8 (1.4)	1 (0.6)	5 (1.1)
Reproductive system and breast disorders	0	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	11 (5.5)	39 (6.7)	16 (9.2)	36 (7.6)
Skin and subcutaneous tissue disorders	18 (9.0)	49 (8.4)	17 (9.8)	33 (7.0)
Vascular disorders	3 (1.5)	2 (0.3)	0	6 (1.3)

Sex appeared to have no effect on laboratory parameters apart from lower baseline hemoglobin levels in female patients (data not shown).

6.1.9.3.1.2 Age

Patient age did not appear to affect the safety profile as assessed by AE rates in subgroups of patients (pediatrics ≤ 16 years; adults > 16 years). Of note, there were only 7 subjects in the geriatric subgroup (> 65 years), where the most frequently reported AE in the 4-dose Coartem group was anorexia (3 subjects), while the 6-dose group had single reports of asthenia, chills, fatigue, pyrexia, hepatomegaly, anorexia, arthralgia, myalgia, dizziness and headache. There were no SAEs or deaths in this subpopulation. There were 2 discontinuations in the 4-dose group, 1 due to a protocol violation, and 1 due to unsatisfactory therapeutic effect.

The only effect of age on laboratory parameters seemed to slightly lower hemoglobin levels at baseline in patients aged $>12\text{-}\leq 16$ years than in those aged $>16\text{-}<65$ years or ≥ 65 years, although there were few patients in the latter subgroup.

6.1.9.3.1.3 Race

Information on race was collected in few studies and is shown for the 3 subpopulations in Table 53. Table 54 shows AEs by SOC reported for 4 and 6-dose Coartem regimens in the FDA adult pooled safety population.

For most patients in the FDA adult pooled safety population, race was not reported (81%). Race was most frequently collected in studies performed in Europe (A005, A014, and A2401).

Differences between studies contributing patients to different race subgroups probably influenced the outcomes of the analyses. Therefore, analysis of race subgroups showed apparently higher AE rates in Caucasian than Black patients for both the 4- and 6-dose regimens. The differences were in AEs such as vertigo, diarrhea, vomiting, malaise, headache, insomnia, and hyperhidrosis, as well as a higher rate of infections, mainly malaria. For both Black and Caucasian populations, the most commonly reported AEs for the 4-dose regimen were nervous system disorders and general disorders, while the 6-dose regimen had general disorders and gastrointestinal disorders reported most frequently. In Oriental patients (6-dose), infections were the most frequently reported SOC, followed by nervous system disorders. Oriental patients showed higher total rates of AEs than either Caucasian or Black patients, with notably higher rates of malaria as an AE, probably because most Oriental patients were living in endemic countries, unlike the Caucasian or Black patients. Those patients with race recorded as ‘Other’, almost entirely Hispanic patients from Colombia in Study A2401, showed a similar AE profile to Caucasian patients. The patients for whom race was not reported showed higher AE rates than those for whom race was categorized. The AEs that were more common were mainly malaria symptoms such as splenomegaly, palpitations, nausea, abdominal pain, fever, asthenia, chills, fever, hepatomegaly, arthralgia and myalgia., sleep disorder. Pruritus tended also to be more frequent. In the adult pooled safety population, as most of the studies were performed in China or Thailand, patients who did not have race reported were likely to be Oriental, and to be resident in endemic areas.

Overall, there did not appear to be any particular safety signal associated with race.

Table 53: Study subject race stratified by age group

Race	Pediatrics ≤ 16 years N=1991 (%)	Adult > 16 years* N=1434 (%)
Black	1209 (60.7)	80 (5.6)
Caucasian	0	101 (7.0)
Oriental	9 (0.5)	44 (3.1)
Other (Hispanic)	0	47 (3.3)
Not collected	774 (38.9)	1162 (81.0)

* Includes 7 patients greater than 65 years of age: 1 Caucasian, 2 Other, 4 Not collected

Table 54: AE by SOC for the FDA adult* pooled safety population stratified by dose and race

MedDRA system organ class	Coartem 4 dose			Coartem 6 dose				
	Black N=40 (%)	Caucasian N=21 (%)	Not collected N=721 (%)	Black N=40 (%)	Caucasian N=79 (%)	Not collected N=437 (%)	Oriental N=44 (%)	Other N=45 (%)
Blood and lymphatic system disorders	8 (20.0)	3 (14.3)	197 (27.3)	1 (2.5)	1 (1.3)	113 (25.9)	6 (13.6)	3 (6.7)
Cardiac disorders	1 (2.5)	3 (14.3)	192 (26.6)	1 (2.5)	4 (5.1)	125 (28.6)	0	0

MedDRA system organ class	Coartem 4 dose			Coartem 6 dose				
	Black N=40 (%)	Caucasian N=21 (%)	Not collected N=721 (%)	Black N=40 (%)	Caucasian N=79 (%)	Not collected N=437 (%)	Oriental N=44 (%)	Other N=45 (%)
Ear and labyrinth disorders	1 (2.5)	3 (14.3)	10 (1.4)	3 (7.5)	12 (15.2)	1 (0.2)	3 (6.8)	10 (22.2)
Endocrine disorders	0	0	0	0	0	1 (0.2)	0	0
Eye disorders	0	0	12 (1.7)	0	0	0	0	1 (2.2)
Gastrointestinal disorders	22 (55.0)	14 (66.7)	406 (56.3)	6 (15.0)	25 (31.7)	292 (66.8)	9 (20.5)	17 (37.8)
General disorders and administration site conditions	29 (72.5)	16 (76.2)	654 (90.7)	20 (50.0)	40 (50.6)	421 (96.3)	15 (34.1)	27 (60.0)
Hepatobiliary disorders	5 (12.5)	4 (19.1)	176 (24.4)	0	3 (3.8)	107 (24.5)	0	0
Infections and infestations	5 (12.5)	6 (28.6)	48 (6.7)	1 (2.5)	11 (13.9)	50 (11.4)	27 (61.4)	3 (6.7)
Injury, poisoning and procedural complications	0	0	0	0	1 (1.3)	0	0	0
Investigations	3 (7.5)	1 (4.8)	4 (0.6)	1 (2.5)	10 (12.7)	3 (0.7)	0	2 (4.4)
Metabolism and nutrition disorders	12 (30.0)	2 (9.5)	469 (65.1)	5 (12.5)	10 (12.7)	330 (75.5)	10 (22.7)	2 (4.4)
Musculoskeletal and connective tissue disorders	24 (60.0)	7 (33.3)	270 (37.5)	1 (2.5)	9 (11.4)	338 (77.4)	1 (2.3)	1 (2.2)
Nervous system disorders	34 (85.0)	18 (85.7)	552 (76.6)	9 (22.5)	14 (17.7)	429 (98.2)	18 (40.9)	27 (60.0)
Psychiatric disorders	6 (15.0)	7 (33.3)	260 (36.1)	5 (12.5)	17 (21.5)	174 (39.8)	8 (18.2)	3 (6.7)
Renal and urinary disorders	1 (2.5)	0	9 (1.3)	0	0	5 (1.1)	0	1 (2.2)
Reproductive system and breast disorders	0	0	0	0	1 (1.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (7.5)	1 (4.8)	46 (6.4)	3 (7.5)	12 (15.2)	28 (6.4)	2 (4.6)	7 (15.6)
Skin and subcutaneous tissue disorders	9 (22.5)	7 (33.3)	51 (7.1)	1 (2.5)	11 (13.9)	30 (6.9)	1 (2.3)	7 (15.6)
Vascular disorders	2 (5.0)	0	3 (0.4)	0	2 (2.5)	4 (0.9)	0	0

* for this analysis, adult was defined as >16 but ≤ 65 years of age

Subgroup analysis of the geriatric population according to race was not performed given the small numbers of subjects in this group.

Analysis of laboratory parameters by race was difficult because race was not reported for many patients. Hemoglobin levels at baseline appeared to be higher in Caucasian than Black patients at baseline, but no other effects of race were apparent, although it was impossible to draw meaningful conclusions in many cases.

6.1.9.3.1.4 Geographic Region

The Applicant also summarized AEs by region. The studies in adults were performed in South-East Asia, India, Europe and Colombia, but not in Africa. The overall rate of AEs was higher in patients from Asia as compared with Europe, mainly due to higher rates of gastrointestinal disorders (nausea, vomiting and abdominal pain); splenomegaly; asthenia and fatigue; tachycardia; and hepatobiliary disorders (hepatomegaly). Some AEs reported in Asia were not reported in patients in Europe (clonus and tremor, for example), although some of these differences could be due to the use of specific neurological examinations in some of the studies in South-East Asia. Cough and vertigo were reported more frequently in Europe than in Asia.

Subgroup analysis of laboratory parameters by region was limited by lack of data in some regions, but the only differences appeared to be between baseline levels for hemoglobin and ALAT.

6.1.9.3.1.5 Hepatic and Renal Impairment

Hepatic

Patients with hepatic impairment at baseline differed from those with normal hepatic function in that their ASAT, ALAT and bilirubin decreased from baseline, with no notable changes in the patients with normal hepatic function. γ -GT levels showed no differences between patients with normal and impaired hepatic function.

Patients with mild, moderate and severe hepatic impairment tended to report more frequently splenomegaly, palpitations, nausea, vomiting, abdominal pain, asthenia, hepatomegaly, anorexia, arthralgia and myalgia, headache and dizziness, clonus, tremor, pruritus and rash than those with normal hepatic function (Table 55). Except for pruritus and rash, all others can be considered as signs and symptoms of malaria. Baseline hepatic impairment may simply be a reflection of more severe disease.

Table 55: Most frequently reported AEs ($\geq 2\%$ in any group) in adult patients receiving the 6-dose Coartem regimen with hepatic impairment at baseline (Source: Novartis fax dated 19-Nov-2008)

Preferred term	Patients, n (%)				
	Normal n=167	Mild n = 121	Moderate n = 60	Severe n = 17	Missing n = 282
Headache	58 (34.7)	43 (35.5)	23 (38.3)	10 (58.8)	226 (80.1)
Pyrexia	39 (23.4)	34 (28.1)	16 (26.7)	7 (41.2)	63 (22.3)
Nausea	23 (13.8)	31 (25.6)	18 (30.0)	7 (41.2)	90 (31.9)
Asthenia	21 (12.6)	23 (19.0)	17 (28.3)	9 (52.9)	173 (61.3)
Cough	17 (10.2)	10 (8.3)	4 (6.7)	2 (11.8)	4 (1.4)

Preferred term	Patients, n (%)				
	Normal n=167	Mild n = 121	Moderate n = 60	Severe n = 17	Missing n = 282
Vomiting	15 (9.0)	25 (20.7)	16 (26.7)	7 (41.2)	50 (17.7)
Diarrhea	14 (8.4)	9 (7.4)	6 (10.0)	3 (17.6)	14 (5.0)
Dizziness	14 (8.4)	28 (23.1)	15 (25.0)	8 (47.1)	188 (66.7)
Anorexia	13 (7.8)	31 (25.6)	15 (25.0)	7 (41.2)	194 (68.8)
Chills	12 (7.2)	15 (12.4)	15 (25.0)	6 (35.3)	99 (35.1)
Fatigue	11 (6.6)	26 (21.5)	16 (26.7)	6 (35.3)	52 (18.4)
Abdominal pain	10 (6.0)	20 (16.5)	9 (15.0)	6 (35.3)	67 (23.8)
Myalgia	10 (6.0)	21 (17.4)	8 (13.3)	7 (41.2)	160 (56.7)
Insomnia	10 (6.0)	7 (5.8)	4 (6.7)	1 (5.9)	10 (3.5)
Malaise	9 (5.4)	4 (3.3)	3 (5.0)	1 (5.9)	3 (1.1)
Vertigo	9 (5.4)	6 (5.0)	2 (3.3)	0 (0.0)	4 (1.4)
Arthralgia	8 (4.8)	12 (9.9)	6 (10.0)	6 (35.3)	187 (66.3)
Pharyngolaryngeal pain	8 (4.8)	3 (2.5)	1 (1.7)	1 (5.9)	2 (0.7)
Sleep disorder	7 (4.2)	13 (10.7)	10 (16.7)	4 (23.5)	110 (39.0)
Nasopharyngitis	7 (4.2)	4 (3.3)	4 (6.7)	0 (0.0)	2 (0.7)
Palpitations	6 (3.6)	13 (10.7)	9 (15.0)	7 (41.2)	80 (28.4)
Pruritus	4 (2.4)	8 (6.6)	7 (11.7)	2 (11.8)	3 (1.1)
Clonus	4 (2.4)	7 (5.8)	2 (3.3)	2 (11.8)	1 (0.4)
Hyperhidrosis	4 (2.4)	1 (0.8)	2 (3.3)	0 (0.0)	3 (1.1)
Rash	3 (1.8)	5 (4.1)	7 (11.7)	2 (11.8)	4 (1.4)
Hepatomegaly	3 (1.8)	11 (9.1)	7 (11.7)	3 (17.6)	35 (12.4)
Anemia	3 (1.8)	2 (1.7)	0 (0.0)	2 (11.8)	16 (5.7)
Tremor	3 (1.8)	7 (5.8)	2 (3.3)	2 (11.8)	2 (0.7)
Dyspepsia	2 (1.2)	5 (4.1)	2 (3.3)	1 (5.9)	0 (0.0)
Splenomegaly	2 (1.2)	10 (8.3)	4 (6.7)	3 (17.6)	38 (13.5)
Urticaria	1 (0.6)	0 (0.0)	2 (3.3)	0 (0.0)	1 (0.4)
Helminthic infection	1 (0.6)	7 (5.8)	2 (3.3)	0 (0.0)	0 (0.0)
P falciparum infection	0 (0.0)	3 (2.5)	1 (1.7)	0 (0.0)	9 (3.2)
Hypokalaemia	1 (0.6)	0 (0.0)	3 (5.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	1 (0.4)
Nystagmus	1 (0.6)	1 (0.8)	0 (0.0)	2 (11.8)	1 (0.4)
Microcytic anaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Jaundice	0 (0.0)	0 (0.0)	2 (3.3)	1 (5.9)	0 (0.0)
Eye abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Liver function test abnormal	1 (0.6)	1 (0.8)	0 (0.0)	1 (5.9)	0 (0.0)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Fluid overload	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Haematuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	3 (1.1)
Malaria	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	17 (6.0)

Source: Appendix 3- Table 34

Renal

In patients with impaired renal function at baseline, creatinine clearance improved over the course of the studies, but remained stable in patients with normal renal function at baseline.

Subgroup analysis by renal function (Table 56) showed no differences in the overall incidence of AEs between patients with mild or moderate renal impairment and normal renal function. However, there was a trend for higher rates of splenomegaly, asthenia, fatigue, chills, pyrexia, hepatomegaly, myalgia and arthralgia in renally- impaired patients.

Table 56: Most frequently reported AEs ($\geq 2\%$ in any group) in adult patients receiving the 6-dose Coartem regimen with renal impairment at baseline (Source: Novartis fax dated 19-Nov-2008)

Preferred term	Patients, n (%)				
	Normal n = 225	Mild n = 143	Moderate n = 10	Severe n = 0	Missing n = 269
Splenomegaly	9 (4.0)	10 (7.0)	0 (0.0)	0 (0.0)	38 (14.1)
Palpitations	15 (6.7)	19 (13.3)	1 (10.0)	0 (0.0)	80 (29.7)
Vertigo	15 (6.7)	6 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	45 (20.0)	34 (23.8)	2 (20.0)	0 (0.0)	88 (32.7)
Vomiting	32 (14.2)	29 (20.3)	3 (30.0)	0 (0.0)	49 (18.2)
Diarrhea	24 (10.7)	9 (6.3)	3 (30.0)	0 (0.0)	10 (3.7)
Abdominal pain	21 (9.3)	23 (16.1)	2 (20.0)	0 (0.0)	66 (24.5)
Pyrexia	41 (18.2)	49 (34.3)	6 (60.0)	0 (0.0)	63 (23.4)
Asthenia	39 (17.3)	30 (21.0)	2 (20.0)	0 (0.0)	172 (63.9)
Fatigue	34 (15.1)	26 (18.2)	2 (20.0)	0 (0.0)	49 (18.2)
Chills	24 (10.7)	23 (16.1)	1 (10.0)	0 (0.0)	99 (36.8)
Malaise	15 (6.7)	4 (2.8)	0 (0.0)	0 (0.0)	1 (0.4)
Hepatomegaly	10 (4.4)	12 (8.4)	2 (20.0)	0 (0.0)	35 (13.0)
Nasopharyngitis	8 (3.6)	6 (4.2)	1 (10.0)	0 (0.0)	2 (0.7)
Anorexia	40 (17.8)	27 (18.9)	2 (20.0)	0 (0.0)	191 (71.0)
Myalgia	22 (9.8)	24 (16.8)	3 (30.0)	0 (0.0)	157 (58.4)
Arthralgia	16 (7.1)	15 (10.5)	1 (10.0)	0 (0.0)	187 (69.5)
Headache	82 (36.4)	53 (37.1)	4 (40.0)	0 (0.0)	221 (82.2)
Dizziness	29 (12.9)	34 (23.8)	2 (20.0)	0 (0.0)	188 (69.9)
Clonus	6 (2.7)	8 (5.6)	1 (10.0)	0 (0.0)	1 (0.4)
Tremor	5 (2.2)	8 (5.6)	1 (10.0)	0 (0.0)	2 (0.7)
Insomnia	18 (8.0)	6 (4.2)	0 (0.0)	0 (0.0)	8 (3.0)
Sleep Disorder	16 (7.1)	18 (12.6)	0 (0.0)	0 (0.0)	110 (40.9)
Cough	23 (10.2)	11 (7.7)	1 (10.0)	0 (0.0)	2 (0.7)
Pharyngolaryngeal pain	6 (2.7)	9 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	10 (4.4)	9 (6.3)	1 (10.0)	0 (0.0)	4 (1.5)
Hyperhidrosis	9 (4.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	6 (2.7)	8 (5.6)	2 (20.0)	0 (0.0)	5 (1.9)
Anaemia	4 (1.8)	3 (2.1)	0 (0.0)	0 (0.0)	16 (5.9)
Dyspepsia	4 (1.8)	6 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Helminthic infection	3 (1.3)	7 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred term	Patients, n (%)				
	Normal n = 225	Mild n = 143	Moderate n = 10	Severe n = 0	Missing n = 269
Hookworm infection	0 (0.0)	2 (1.4)	1 (10.0)	0 (0.0)	1 (0.4)
Hypokalaemia	2 (0.9)	1 (0.7)	1 (10.0)	0 (0.0)	0 (0.0)
Nystagmus	1 (0.4)	2 (1.4)	1 (10.0)	0 (0.0)	1 (0.4)
Pallor	2 (0.9)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Malaria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	17 (6.3)
Plasmodium falciparum	3 (1.3)	1 (0.7)	0 (0.0)	0 (0.0)	9 (3.3)

6.1.9.3.2 Pediatric patients

6.1.9.3.2.1 Sex

In the pediatric population, the frequency of most AEs by SOC was slightly higher for females compared to males in the 4-dose regimen, but this was more balanced between sex for the 6-dose regimen (Table 57). The most frequently reported AEs for both sexes in the 4-dose group were general disorders and nervous system disorders, while in the 6-dose group both sexes reported general disorders and infections and infestations most frequently. Nervous system disorders were higher for females compared to males for only the 4-dose regimen. Overall, sex did not appear to influence the AE profile in children.

Table 57: AEs by SOC for the FDA pediatric pooled safety population stratified by dose and sex

MedDRA system organ class	Coartem 4 dose N=659		Coartem 6 dose N=1332	
	Female n=257 (%)	Male n=402 (%)	Female n=622 (%)	Male n=711 (%)
Blood and lymphatic system disorders	111 (43.2)	170 (42.3)	107 (17.2)	138 (19.4)
Cardiac disorders	21 (8.2)	38 (9.5)	17 (2.7)	17 (2.4)
Ear and labyrinth disorders	2 (0.8)	3 (0.8)	4 (0.6)	2 (0.3)
Eye disorders	12 (4.7)	17 (4.2)	16 (2.6)	7 (1)
Gastrointestinal disorders	173 (67.3)	248 (61.7)	189 (30.4)	230 (32.3)
General disorders and administration site conditions	194 (75.5)	301 (74.9)	385 (61.9)	452 (63.6)
Hepatobiliary disorders	54 (21.0)	94 (23.4)	37 (5.9)	51 (7.2)
Immune system disorders	0	0	0	1 (0.1)
Infections and infestations	51 (19.8)	73 (18.2)	241 (38.7)	251 (35.3)
Injury, poisoning and procedural complications	0	1 (0.3)	2 (0.3)	4 (0.6)
Investigations	0	2 (0.5)	52 (8.4)	61 (8.6)
Metabolism and nutrition disorders	148 (57.6)	207 (51.5)	81 (13)	111 (15.6)
Musculoskeletal and connective tissue disorders	35 (13.6)	50 (12.4)	20 (3.9)	34 (4.8)

	Coartem 4 dose N=659		Coartem 6 dose N=1332	
Nervous system disorders	183 (71.2)	258 (64.2)	88 (14.1)	119 (16.7)
Psychiatric disorders	115 (44.8)	163 (40.6)	35 (5.6)	40 (5.6)
Renal and urinary disorders	0	3 (0.8)	2 (0.3)	1 (0.1)
Reproductive system and breast disorders	1 (0.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	66 (25.7)	79 (19.7)	139 (22.3)	177 (24.9)
Skin and subcutaneous tissue disorders	16 (6.2)	27 (6.7)	29 (4.7)	33 (4.6)
Vascular disorders	1 (0.4)	0	3 (0.5)	3 (0.4)

6.1.9.3.2.2 Age

The overall incidence of AEs in patients of ≤ 2 years of age was similar to that in the >2 to ≤ 12 years age group. The infants ≤ 2 years of age had higher rates of anemia, vomiting, diarrhea and cough than older children, as well as more cases of clonus and rash. Lower rates of pyrexia and chills were observed in infants (possibly because patients with high baseline parasitemia were excluded from the main study that recruited very small children, A2403). Other AEs that occurred at lower rates in children ≤ 2 years of age were those such as headache, nausea and palpitations that were subjective symptoms that smaller children may have been less able to report than older patients.

As Coartem is dosed according to body weight, AE data was also summarized by body weight for pediatric patients. In general, all body weight groups had similar AE profiles, although anemia was more common in the 5- <10 kg group, as were vomiting and diarrhea. Splenomegaly was more common with increasing body weight, as were subjective symptoms such as headache and nausea, which may reflect the ability of patients to report such symptoms. The general similarity of the AE profile across body weight groups is noteworthy, particularly for the Coartem 6-dose group, drawn primarily from studies A2403 and B2303 (which included small infants of body weight as low as 5 kg). In these studies, because of the dose adjustment by body weight, a patient of body weight 14 kg received the same absolute dose as a 5 kg patient (1 standard tablet, 20 mg artemether and 120 mg lumefantrine, at each dose). On a mg/kg basis, a 5 kg patient would receive almost three times the doses of artemether and lumefantrine as a 14 kg patient, but this does not appear to result in any major difference in safety profile.

6.1.9.3.2.3 Race

AEs were also summarized by race (Table 58). Given that the two studies performed in Africa in which race was collected had 100% Black patients, it is reasonable to assume that patients in the other studies in Africa were also Black, and that the other patients (from studies in SE Asia, in which race was not recorded) were not Black. There was no information collected on race for the 4-dose regimen. Given the small number of patients in the latter group, it is impossible to draw any firm conclusions regarding the effects of race on AEs in this population. However, the black patients did not appear to have a different profile from the non-black patients. In particular, the

incidence of anemia was not higher in black patients despite a potentially higher risk for glucose-6-phosphate dehydrogenase deficiency.

Table 58: AE by SOC for the FDA pediatric pooled safety population stratified by dose and race

MedDRA system organ class	Coartem 6 dose N=1332		
	Black N=1209 (%)	Not collected N=115 (%)	Oriental N=9 (%)
Blood and lymphatic system disorders	191 (15.8)	52 (45.2)	2 (22.2)
Cardiac disorders	9 (0.7)	25 (21.7)	0
Ear and labyrinth disorders	6 (0.5)	0	0
Eye disorders	22 (1.8)	1 (0.9)	0
Gastrointestinal disorders	337 (27.9)	80 (69.6)	2 (22.2)
General disorders and administration site conditions	724 (59.9)	108 (93.9)	5 (55.6)
Hepatobiliary disorders	42 (3.5)	45 (39.1)	1 (11.1)
Immune system disorders	1 (0.1)	0	0
Infections and infestations	457 (37.8)	30 (26.1)	5 (55.6)
Injury, poisoning and procedural complications	6 (0.5)	0	0
Investigations	112 (9.3)	1 (0.9)	0
Metabolism and nutrition disorders	99 (8.2)	91 (79.1)	2 (22.2)
Musculoskeletal and connective tissue disorders	0	54 (47.0)	0
Nervous system disorders	98 (8.1)	107 (93.0)	2 (22.2)
Psychiatric disorders	44 (3.6)	30 (26.1)	1 (11.1)
Renal and urinary disorders	2 (0.2)	1 (0.9)	0
Reproductive system and breast disorders	0	0	0
Respiratory, thoracic and mediastinal disorders	311 (25.7)	4 (3.5)	1 (11.1)
Skin and subcutaneous tissue disorders	59 (48.8)	3 (2.6)	0
Vascular disorders	6 (0.5)	0	0

6.1.9.3.2.4 Geographic Region

Analysis by region should be interpreted with caution, as most of the safety data in children, particularly for the 6-dose regimen, comes from studies in Africa. A lower overall rate of AEs was observed in Africa than in Asia; the differences being mainly in rates of nausea, vomiting, anorexia, headache, splenomegaly, hepatomegaly, sleep disorder. Convulsions were observed in more African children, but the African patients included a greater proportion of young infants, who would be more likely to have febrile convulsions than older patients. There was also a higher rate of *Plasmodium falciparum* reported as an AE in African children, which was almost certainly related to the much higher malaria endemicity in Africa as compared with Thailand. Cough was also more common in African children, possibly reflecting a higher rate of respiratory infections or the fact that there were more very young children in African studies (cough was more common in patients ≤ 2 years of age).

Analysis of laboratory parameters by region compared African patients with those from South-East Asia. Hemoglobin levels were lower at baseline and throughout the studies in African compared with Asian patients, but relatively few data were available for the latter subgroup. African patients also had lower ASAT and bilirubin. No effects on other parameters were observed.

6.1.9.3.2.5 Hepatic and Renal Impairment

Hepatic

Analyses of AEs by hepatic function found that pediatric patients receiving the 6-dose regimen with mild or moderate hepatic impairment tended to report more AEs than those with normal renal function (Table 59). This may be because hepatic impairment may be associated with disease severity in malaria. AEs that were more frequent in patients with hepatic impairment were anemia, and cutaneous rash in patients with mild hepatic impairment. The incidence of neurological disorders was not different between hepatic function subgroups. Due to the small numbers of patients with moderate or severe hepatic impairment (these were exclusion criteria in most of the studies), no definitive conclusions can be made regarding AEs in these subgroups.

Patients with hepatic impairment at baseline differed from those with normal hepatic function in that their ASAT, ALAT and bilirubin decreased from baseline, with no notable changes in the patients with normal hepatic function. γ -GT levels showed no differences between patients with normal and impaired hepatic function.

Table 59: Most frequently reported AEs ($\geq 2\%$ in any group) in pediatric patients receiving the 6-dose Coartem regimen with hepatic impairment at baseline

Preferred term	Patients, n (%)				
	Normal n= 144	Mild n = 170	Moderate n = 24	Severe n = 2	Missing n = 992
Cough	29 (20.1)	40 (23.5)	8 (33.3)	0 (0.0)	225 (22.7)
Anaemia	24 (16.7)	43 (25.3)	5 (20.8)	1 (50.0)	42 (4.2)
Diarrhea	16 (11.1)	17 (10.0)	2 (8.3)	0 (0.0)	65 (6.6)
Vomiting	14 (9.7)	29 (17.1)	9 (37.5)	0 (0.0)	190 (19.2)
P falciparum infection	14 (9.7)	17 (10.0)	3 (12.5)	0 (0.0)	190 (19.2)
Splenomegaly	12 (8.3)	16 (9.4)	1 (4.2)	0 (0.0)	95 (9.6)
Anorexia	11 (7.6)	26 (15.3)	8 (33.3)	1 (50.0)	129 (13.0)
Hepatomegaly	11 (7.6)	18 (10.6)	4 (16.7)	2 (100)	40 (4.0)
Pyrexia	9 (6.3)	7 (4.1)	2 (8.3)	1 (50.0)	362 (36.5)
Headache	8 (5.6)	10 (5.9)	2 (8.3)	2 (100)	146 (14.7)
Eosinophilia	7 (4.9)	6 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

Preferred term	Patients, n (%)				
	Normal n = 144	Mild n = 170	Moderate n = 24	Severe n = 2	Missing n = 992
Respiratory Tract infection	7 (4.9)	18 (10.6)	0 (0.0)	0 (0.0)	3 (0.3)
Upper Respiratory Tract infection	7 (4.9)	8 (4.7)	0 (0.0)	0 (0.0)	17 (1.7)
Nasopharyngitis	6 (4.2)	4 (2.4)	1 (4.2)	0 (0.0)	3 (0.3)
Rash	6 (4.2)	12 (7.1)	1 (4.2)	0 (0.0)	19 (1.9)
Abdominal pain	5 (3.5)	7 (4.1)	1 (4.2)	2 (100)	97 (9.8)
Acarodermatitis	5 (3.5)	7 (4.1)	0 (0.0)	0 (0.0)	3 (0.3)
Rhinitis	5 (3.5)	10 (5.9)	4 (16.7)	0 (0.0)	32 (3.2)
Nausea	4 (2.8)	7 (4.1)	3 (12.5)	1 (50.0)	46 (4.6)
Constipation	4 (2.8)	6 (3.5)	1 (4.2)	0 (0.0)	0 (0.0)
Clonus	3 (2.1)	7 (4.1)	1 (4.2)	0 (0.0)	0 (0.0)
Hyperreflexia	3 (2.1)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Myoclonus	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Monocytosis	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	3 (2.1)	7 (4.1)	2 (8.3)	0 (0.0)	3 (0.3)
Insomnia	1 (0.7)	10 (5.9)	0 (0.0)	0 (0.0)	2 (0.2)
Asthenia	2 (1.4)	7 (4.1)	2 (8.3)	1 (50.0)	51 (5.1)
Irritability	0 (0.0)	6 (3.5)	1 (4.2)	0 (0.0)	0 (0.0)
Chills	2 (1.4)	5 (2.9)	2 (8.3)	0 (0.0)	63 (6.4)
Helminthic infection	2 (1.4)	5 (2.9)	1 (4.2)	0 (0.0)	14 (1.4)
Conjunctivitis	2 (1.4)	4 (2.4)	1 (4.2)	0 (0.0)	13 (1.3)
Fatigue	2 (1.4)	4 (2.4)	2 (8.3)	1 (50.0)	37 (3.7)
Hypothermia	1 (0.7)	4 (2.4)	1 (4.2)	0 (0.0)	
Gastroenteritis	2 (1.4)	4 (2.4)	0 (0.0)	0 (0.0)	5 (0.5)
Otitis media	0 (0.0)	4 (2.4)	0 (0.0)	0 (0.0)	6 (0.6)
Palpitations	0 (0.0)	2 (1.2)	2 (8.3)	0 (0.0)	20 (2.0)
Arthralgia	1 (0.7)	2 (1.2)	2 (8.3)	0 (0.0)	34 (3.4)
Myalgia	1 (0.7)	3 (1.8)	2 (8.3)	0 (0.0)	33 (3.3)
Dizziness	1 (0.7)	3 (1.8)	2 (8.3)	1 (50.0)	49 (4.9)
Sleep Disorder	2 (1.4)	1 (0.6)	2 (8.3)	0 (0.0)	22 (2.2)
Ear pain	0 (0.0)	1 (0.6)	1 (4.2)	0 (0.0)	1 (0.1)
Ear pruritus	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Abdominal distension	0 (0.0)	3 (1.8)	1 (4.2)	0 (0.0)	1 (0.1)
Dental caries	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Jaundice	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (0.1)
Ascariasis	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	2 (0.2)
Furuncle	1 (0.7)	2 (1.2)	1 (4.2)	0 (0.0)	2 (0.2)
Hepatitis viral	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Oral herpes	1 (0.7)	1 (0.6)	1 (4.2)	0 (0.0)	0 (0.0)
Otitis externa	1 (0.7)	1 (0.6)	1 (4.2)	0 (0.0)	0 (0.0)
Tinea versicolour	0 (0.0)	1 (0.6)	1 (4.2)	0 (0.0)	1 (0.1)
Varicella	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	3 (0.3)

Preferred term	Patients, n (%)				
	Normal n = 144	Mild n = 170	Moderate n = 24	Severe n = 2	Missing n = 992
Haemoglobin decreased	1 (0.7)	1 (0.6)	1 (4.2)	0 (0.0)	7 (0.7)
Ataxia	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	3 (0.3)
Nystagmus	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (0.1)
Chromaturia	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Pharyngolaryngeal pain	1 (0.7)	1 (0.6)	1 (4.2)	0 (0.0)	0 (0.0)
Heat rash	1 (0.7)	2 (1.2)	1 (4.2)	0 (0.0)	1 (0.1)
Pruritus	0 (0.0)	3 (1.8)	1 (4.2)	0 (0.0)	3 (0.3)
Skin ulcer	1 (0.7)	0 (0.0)	1 (4.2)	0 (0.0)	
Pallor	0 (0.0)	2 (1.2)	1 (4.2)	0 (0.0)	2 (0.2)
Aspartate aminotransferase increase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	51 (5.1)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (2.6)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (2.0)

Source: Novartis fax dated 19-Nov-2008

Renal

Analyses of AEs by renal function showed that pediatric patients receiving the 6 dose regimen with mild, moderate or severe renal impairment at baseline tended to report more AEs than those without renal impairment (Table 60). These were mainly anemia, splenomegaly, vomiting, abdominal pain, diarrhea, pyrexia, hepatomegaly, headache, cough, rhinitis, respiratory tract infection, anorexia, and mood swings. All these could be considered as signs and symptoms of malaria reflecting slightly more severe disease that could be the cause of the renal impairment at baseline. Except for few cases of arrhythmia (tachycardia) in patients with mild or moderate renal impairment (3 cases each), the cardiac safety profile was similar to that in patients with normal renal function. Except for headache and a few cases of clonus and hyperreflexia in patients with severe renal impairment, there was no difference in terms of neurological safety profile compared to patients with normal renal function. Patients with severe renal impairment also tended to report more rash than those with normal function.

Pediatric patients with impaired renal function at baseline showed improvement in creatinine clearance over the course of the studies, and creatinine clearance remained stable in patients with normal renal function at baseline. There were no clinically relevant differences in clinical laboratory findings in different body weight groups.

Table 60: Most frequently reported AEs ($\geq 2\%$ in any group) in pediatric patients receiving the 6-dose Coartem regimen with renal impairment at baseline

Preferred term	Patients, n (%)				
	Normal n = 326	Mild n = 510	Moderate n = 292	Severe n = 102	Missing n = 102
Pyrexia	66 (20.2)	153 (30.0)	113 (38.7)	19 (18.6)	30 (29.4)

Preferred term	Patients, n (%)				
	Normal n = 326	Mild n = 510	Moderate n = 292	Severe n = 102	Missing n = 102
Plasmodium Falciparum	54 (16.6)	109 (21.4)	47 (16.1)	11 (10.8)	3 (2.9)
Cough	40 (12.3)	129 (25.3)	96 (32.9)	33 (32.4)	4(3.9)
Vomiting	34 (10.4)	80 (15.7)	66 (22.6)	20 (19.6)	42 (41.2)
Aspartate aminotransferase increased	24 (7.4)	23 (4.5)	3 (1.0)	0 (0.0)	1 (1.0)
Anorexia	21 (6.4)	39 (7.6)	33 (11.3)	11 (10.8)	71 (69.6)
Headache	19 (5.8)	42 (8.2)	27 (9.2)	1 (1.0)	79 (77.5)
Abdominal pain	13 (4.0)	38 (7.5)	31 (10.6)	2 (2.0)	28 (27.5)
Platelet count decreased	12 (3.7)	7 (1.4)	1 (0.3)	0 (0.0)	0 (0.0)
White blood cell count decreased	10 (3.1)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	10 (3.1)	24 (4.7)	37 (12.7)	26 (25.5)	3 (2.9)
Splenomegaly	10 (3.1)	33 (6.5)	32 (11.0)	16 (15.7)	33(32.4)
Upper Respiratory Tract infection	8 (2.5)	13 (2.5)	4 (1.4)	7 (6.9)	0 (0.0)
Rhinitis	7 (2.1)	18 (3.5)	24 (8.2)	2 (2.0)	0 (0.0)
Conjunctivitis	7 (2.1)	6 (1.2)	5 (1.7)	2 (2.0)	0 (0.0)
Rash	7 (2.1)	11 (2.2)	10 (3.4)	9 (8.8)	1 (1.0)
Anaemia	5 (1.5)	30 (5.9)	24 (8.2)	41 (40.2)	15 (14.7)
Fatigue	4 (1.2)	13 (2.5)	17 (5.8)	1 (1.0)	11 (10.8)
Hepatomegaly	4 (1.2)	12 (2.4)	14 (4.8)	17 (16.7)	28 (27.5)
Bronchitis	1 (0.3)	15 (2.9)	9 (3.1)	1 (1.0)	0 (0.0)
Nausea	2 (0.6)	11 (2.2)	10 (3.4)	2 (2.0)	36 (35.3)
Chills	5 (1.5)	11 (2.2)	14 (4.8)	2 (2.0)	40 (39.2)
Dysphagia	0 (0.0)	4 (0.8)	8 (2.7)	0 (0.0)	0 (0.0)
Helminthic infection	3 (0.9)	9 (1.8)	10 (3.4)	0 (0.0)	0 (0.0)
Ear infection	1 (0.3)	7 (1.4)	6 (2.1)	2 (2.0)	1 (1.0)
Pneumonia	3 (0.9)	5 (1.0)	6 (2.1)	1 (1.0)	5 (4.9)
Tonsillitis	1 (0.3)	2 (0.4)	6 (2.1)	0 (0.0)	0 (0.0)
Mood swings	0 (0.0)	8 (1.6)	7 (2.4)	0 (0.0)	0 (0.0)
Hypothermia	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.9)	0 (0.0)
Respiratory tract infection	2 (0.6)	4 (0.8)	3 (1.0)	17 (16.7)	2 (2.0)

Clinical Review
 {Insert Reviewer Name}
 {Insert Application and Submission Number}
 {Insert Product Trade and Generic Name}

Nasopharyngitis	3 (0.9)	0 (0.0)	3 (1.0)	6 (5.9)	2 (2.0)
Furuncle	0 (0.0)	1 (0.2)	1 (0.3)	4 (3.9)	0 (0.0)
Gastroenteritis	1 (0.3)	3 (0.6)	4 (1.4)	3 (2.9)	0 (0.0)
Clonus	0 (0.0)	1 (0.2)	1 (0.3)	9 (8.8)	0 (0.0)
Hyperreflexia	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.9)	0 (0.0)
Myoclonus	0 (0.0)	0 (0.0)	1 (0.3)	2 (2.0)	0 (0.0)
Insomnia	0 (0.0)	1 (0.2)	3 (1.0)	8 (7.8)	1 (1.0)
Agitation	3 (0.9)	2 (0.4)	4 (1.4)	2 (2.0)	0 (0.0)
Palpitations	0 (0.0)	2 (0.4)	2 (0.7)	0 (0.0)	20 (19.6)

Preferred term	Patients, n (%)				
	Normal n = 326	Mild n = 510	Moderate n = 292	Severe n = 102	Missing n = 102
Asthenia	5 (1.5)	5 (1.0)	3 (1.0)	0 (0.0)	50 (49.0)
Parasitic gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (11.8)
Malaria	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	5 (4.9)
Ascariasis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (2.0)
Arthralgia	1 (0.3)	2 (0.4)	2 (0.7)	0 (0.0)	34 (33.3)
Myalgia	2 (0.6)	2 (0.4)	2 (0.7)	0 (0.0)	33 (32.4)
Sleep disorder	1 (0.3)	1 (0.2)	3 (1.0)	0 (0.0)	22 (21.6)
Dizziness	2 (0.6)	4 (0.8)	2 (0.7)	0 (0.0)	48 (47.1)

Source: Novartis fax dated 19-Nov-2008

6.1.9.3.2.6 ECG evaluations

ECG evaluations were analysed by body weight subgroups in the pediatric pooled safety population. There was a slight trend towards greater increase in QTc, particularly QTc (Bazett), in the lowest body weight group (5 - < 10 kg) as compared to other body weight groups, but it should be noted that this may be related to changes in ventricular rate in this subgroup: ventricular rate was higher at baseline in this subgroup than other body weight subgroups.

6.1.10 Immunogenicity

Not applicable.

6.1.11 Human Carcinogenicity

Not applicable due to the short duration of treatment.

6.1.12 Special Safety Studies

Adverse events in healthy volunteers

Nine studies have been performed with Coartem in healthy volunteers. Most of these studies used single doses and/or had small treatment groups. The exception was Study A2101, a thorough QTc study in healthy volunteers. This was a randomized, parallel group, single-blind study in healthy volunteers and included a placebo and moxifloxacin control group (n=42 per group) which evaluated the 6-dose regimen of Coartem. Patients were followed up for 18 days after the end of treatment. All subjects received the full course of assigned treatment.

AEs reported in Study A2101 are presented in Table 61. No deaths, serious AEs or AEs leading to study discontinuation occurred. The total AE rate for the Coartem group was similar to that in the placebo group. The most common AE in the co-artemether group was sciatica, reported in two patients. The profile of AEs observed in this population of healthy adult volunteers is quite different from that seen in adult malaria patients treated with the co-artemether 6-dose regimen, with the exception of headache and chills, and both of which occurred far more frequently in malaria patients than the healthy volunteers. This supports the idea that many of the AEs commonly observed in malaria patients treated with co-artemether are primarily related to malaria signs and symptoms, rather than to treatment.

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Table 61: Summary of adverse events in healthy volunteers, Study A2101

System Organ Class Preferred Term	Co-artemether 6-dose regimen N = 42	Placebo N = 42	Placebo plus moxifloxacin N = 42
Any Body System –Total	7 (16.7)	10 (23.8)	8 (19.0)
Cardiac disorders			
Total	1 (2.4)	0 (-)	3 (7.1)
Extrasystoles	1 (2.4)	0 (-)	0 (-)
Palpitations	0 (-)	0 (-)	3 (7.1)
Gastrointestinal disorders			
Total	1 (2.4)	1 (2.4)	4 (9.5)
Abdominal pain	0 (-)	0 (-)	1 (2.4)
Diarrhea	0 (-)	1 (2.4)	3 (7.1)
Dyspepsia	1 (2.4)	0 (-)	1 (2.4)
Flatulence	0 (-)	0 (-)	1 (2.4)
General disorders and administration site conditions			
Total	1 (2.4)	0 (-)	0 (-)
Chills	1 (2.4)	0 (-)	0 (-)
Infections and infestations			
Total	2 (4.8)	4 (9.5)	1 (2.4)
Bronchitis	1 (2.4)	0 (-)	0 (-)
Gastroenteritis	0 (-)	0 (-)	1 (2.4)
Herpes simplex	1 (2.4)	0 (-)	0 (-)
Nasopharyngitis	0 (-)	2 (4.8)	0 (-)
Rhinitis	1 (2.4)	2 (4.8)	0 (-)
Musculoskeletal and connective tissue disorders			
Total	1 (2.4)	3 (7.1)	2 (4.8)
Back pain	1 (2.4)	0 (-)	1 (2.4)
Myalgia	0 (-)	1 (2.4)	0 (-)
Pain in extremity	0 (-)	0 (-)	1 (2.4)
Sense of heaviness	0 (-)	2 (4.8)	0 (-)
Nervous system disorders			
Total	3 (7.1)	3 (7.1)	1 (2.4)
Headache	1 (7.1)	3 (7.1)	0 (-)
Sciatica	2 (4.8)	0 (-)	0 (-)
Tremor	0 (-)	0 (-)	1 (2.4)
Vascular disorders			
Total	0 (-)	2 (4.8)	0 (-)
Hot flush	0 (-)	1 (2.4)	0 (-)
Venous thrombosis limb	0 (-)	1 (2.4)	0 (-)

Source: Novartis Clinical Overview

6.1.13 Withdrawal Phenomena and/or Abuse Potential

Drug abuse is unlikely, because Coartem is given as a short treatment course, as a prescription drug and is not known to have any euphoric effects. Patients should be warned

that dizziness or fatigue/asthenia might occur, in which case they should not drive or use machines while taking Coartem.

6.1.14 Human Reproduction and Pregnancy Data

6.1.14.1 Maternal Health Team consult

The Maternal Health Team (MHT) was consulted with respect to labeling, the appropriate risk classification regarding use of Coartem in pregnancy, and review of the submitted pregnancy registry data. This review is available in DFS. A summary of the consult can be found in the CDTL memo and briefly in this review:

The MHT recommended that ^{(b) (4)}

 Based on regulatory definitions of the pregnancy categories, Coartem should be assigned a Pregnancy Category C due to the increase in embryo-fetal loss in animal studies”.

There were also recommendations regarding the establishment of an international antimalarial pregnancy exposure registry, and post-marketing requirements of lactation and pharmacokinetic studies in pregnant women which are still under consideration by the Review Division.

6.1.14.2 Pregnancy observational study

The safety of Coartem in pregnancy is being evaluated in a multicenter, prospective observational study set up in collaboration with the WHO in Zambia where Coartem is used as first-line treatment for acute uncomplicated *P. falciparum* malaria. Study A2407 enrolled women who had used Coartem or SP to treat symptomatic malaria during pregnancy and assigned subjects to exposure groups (1:1 enrollment ratio) based on the antimalarial treatment they had received for the treatment of the most recent malaria episode prior to registry entry (index episode). The primary objective is to evaluate the safety of Coartem through measuring the incidence of perinatal mortality (defined as stillbirth [> 28 weeks of gestation] and early neonatal death within 7 days of birth) following symptomatic malaria. Secondary objectives include the assessment of gestational age, birth weight as well as other exploratory objectives (e.g. spontaneous abortion, preterm delivery, neonatal mortality, maternal mortality and birth defects). Mothers were followed up until 6 weeks after birth, and newborns until 12 months after birth.

At the time of NDA submission, the study was still ongoing but a preliminary report based on outcomes up to 6 weeks after birth was available. A total of 1001 pregnant women (Coartem 495; SP 506) entered the registry. Approximately 85% of the enrolled pregnant women

completed the registry to 6 weeks after delivery. Over 90% of the pregnant women had live births, with approximately 2% having stillbirth and around 1% having spontaneous abortion.

Table 62 shows the pregnancy outcomes evaluated in this observational study. The primary analysis showed no difference between exposure groups in rates of perinatal mortality (4.2% with co-artemether and 5.0% with SP). No between-group differences were observed in neonatal mortality (death within 28 days after birth: 3.0% of each exposure group); rates of abortion (1.4% in the co-artemether exposure group, 1.6% in the SP group); stillbirth (1.8% in the co-artemether group, 2.5% in the SP group); preterm delivery (14.1% in the co-artemether group, 17.4% in the SP group); or low birth weight (9.0% in the Coartem group, 7.7% in the SP group). 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; umbilical hernia (common in African newborns and of no clinical significance) was more common in the co-artemether exposure group (3.7% versus 1.5% in the SP group) but other birth defects showed no differences between groups, most occurred only in single infants. Other infant outcomes (length, gestational age, birth weight, head circumference) were also similar in the two exposure groups, as was maternal mortality. One patient in the co-artemether exposure group died (this patient was immunosuppressed, probably due to HIV infection, and died due to anemia following a spontaneous abortion). Five patients in the SP group died, one due to Kaposi's sarcoma, three due to infections and one of unknown causes. The most frequent non-fatal SAEs were complications of pregnancy or birth, notably premature delivery, stillbirth and abortion. Other SAEs were infrequent – the most common were infections, reported in 0.6% of the co-artemether group and 0.8% of the SP group. Relatively few other AEs were reported. Lack of efficacy was not reported as an AE. It should be noted that due to the design of the study, patients had received treatment before entering the study, and only AEs reported after registry entry were reported.

Table 62: Pregnancy outcomes in subjects treated with Coartem and Sulfadoxine-pyrimethamine (SP)

Pregnancy outcome - n (%)	Coartem [®] (N=504)	SP (N=516)
Abortion(< 28 weeks of gestation)	7(1.4)	*8 (1.6)
Stillbirth (> 28 weeks of gestation)	9 (1.8)	13 (2.5)
Preterm delivery (< 37 completed weeks of gestation)	71 (14.1)	90 (17.4)
Full term delivery (> 37 completed weeks of gestation)	394 (78.2)	376 (72.9)
Unknown (mother withdrawn prior to delivery)	23 (4.6)	29 (5.6)

*5 abortions: one woman with triplets, one with twins

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

Exposure to Coartem in the first trimester of pregnancy

In Study A2407, 144 (33%) patients were inadvertently exposed to co-artemether and 127 (26%) received SP during the first trimester. In most cases, the treatment was for the index episode. Exploratory analyses suggested that exposure to co-artemether in the first trimester was not associated with an increased risk of neonatal death or stillbirth. Birth weight and birth weight

adjusted for gestational age showed no notable differences between the use and non-use of treatment in the first trimester. However, most cases of abortion (defined as <28 weeks) in the co-artemether exposure group occurred in patients who had received treatment during the first trimester; this finding would merit further investigation. Evaluation of cases of abortion showed that there were 6 abortions in the 142 women who received co-artemether (4 cases) or co-artemether and SP (2 cases) in the first trimester, giving a rate of 4.2%, and 1 abortion in the 305 women who did not receive co-artemether in the first trimester (0.3%). In the SP group none of the 124 women who received treatment in the first trimester had abortion, compared with 5 of 320 women (1.6%) who did not receive treatment in the first trimester.

The incidence of malformations in babies born to mothers who received co-artemether in the first trimester was 9/142, 7.7%; in all but one case, these were umbilical hernias – the remaining baby was reported as having small labia and a small nose. In the SP group, four babies born to the 124 women who received treatment in the first trimester had birth defects: these were umbilical hernias in two babies, malformed ears in one baby, and polydactyly in the remaining baby. Co-artem treatment is contraindicated during the first trimester of pregnancy in situations where other effective anti-malarials are available. However, it should not be withheld in lifethreatening situations where no other effective anti-malarials are available. During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

6.1.14.3 Postmarketing experience: Drug exposure during pregnancy

Table 63 summarizes the information regarding 62 prospective and 118 retrospective pregnancy cases reported with exposure to Coartem during gestation.

Table 63: Summary table of pregnancy outcome

Pregnancy outcome	Prospective cases (number)				Retrospective cases (number)			
	Timing of exposure in pregnancy (trimester)				Timing of exposure in pregnancy (trimester)			
	Sub-total prospective	1 st	After 1 st	Unk	Sub-total retrospective	1 st	After 1 st	Unk
Ectopic pregnancy					1	1		
Spontaneous abortion					8	8		
Induced abortion (intrauterine death)					1	1		
*Stillbirth	1		1		8	2	6	
*Live birth with congenital anomaly	1	1			25	6	16	3

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

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Live birth without congenital anomaly	12	2	9	1	73	18	51	4
Outcome unknown	48	8		41	2		1	1
Total	62	11	10	42	118	36	74	8

* These cases are summarized in Table 64 (below)

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

A summary of 26 reports of live birth with congenital abnormalities and 9 reports of stillbirth were received are shown in Table 64. The majority were retrospective cases of umbilical hernia, which is common and of no clinical significance.

Table 64: Cumulative reports of stillbirth and live birth with abnormalities

Case IDs	Pregnancy outcome	Exposure trimester	Abnormality	Comment
Prospective cases				
PHHO2006TH10435-B PHHO2006TH05924-M	Initial LB-CA; on follow-up reported as normal	2 nd	Deep dimple in natal cleft, spina bifida occulta	Assessed as unrelated to Coartem [®] . On follow up the deep natal cleft was considered to be within normal limits
PHRM2008FR01310-B PHRM2007FR01862-M	LB-CA	1 st	Atrial septal defect	Assessed as unrelated to Coartem [®]
PHHO2005ZM15448-M	Stillbirth	2 nd	Stillbirth. No abnormalities	Mother died one day after delivery due to Kaposi's sarcoma. Assessed as unrelated to Coartem [®]
Retrospective cases				
PHHO2006ZM01103-B PHHO2006ZM01023-M	LB-CA	1 st	Polydactyly	Assessed as unrelated to Coartem [®]
PHHO2006ZM02266-B PHHO2006ZM02056-M	LB-CA	2 nd	Down's syndrome	Assessed as unrelated to Coartem [®]
PHHO2006ZM03190-B PHHO2006ZM02929-M	LB-CA	3 rd	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM03192-B PHHO2006ZM02936-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM07358-B PHHO2006ZM07256-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM11150-B PHHO2006ZM10860-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM11193-B PHHO2006ZM07350-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM16062-B PHHO2006ZM15957-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem [®]
PHHO2006ZM16403-B PHHO2006ZM16283-M	LB-CA	3 rd	Umbilical hernia	Assessed as unrelated to Coartem [®]

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Case IDs	Pregnancy outcome	Exposure trimester	Abnormality	Comment
PHHO2006ZM16496-B PHHO2006ZM16494-M	LB-CA	3 rd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2006ZM17096-B PHHO2006ZM16997-M	LB-CA	3 rd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2006ZM21761-B PHHO2006ZM20462-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2006ZM21118-B PHHO2006ZM21117-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2006ZM02485-B *PHHO2006ZM02483-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2007ZM07506-B PHHO2007ZM07367-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2006ZM02484-B *PHHO2006ZM02483-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2008ZM02623-B PHHO2008ZM02400-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2008ZM02592-B PHHO2008ZM02404-M	LB-CA	1 st	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2008ZM026024 -B PHHO2008ZM02401-M	LB-CA	2 nd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2008ZM02625-B PHHO2008ZM02410-M	LB-CA	3 rd	Umbilical hernia	Assessed as unrelated to Coartem®
PHHO2005TH11739-B PHHO2005TH11581-M	LB-CA	Unk	Head circumference abnormal (35cm/increased to 38cm), abnormal brain, cerebral ventricle dilatation, cerebral cyst	Assessed as unrelated to Coartem®
PHHO2005TH18484-B PHHO2005TH18482-M	LB-CA	Unk	Head circumference abnormal (35cm/increased to 38cm), abnormal brain, cerebral ventricle dilatation, cerebral cyst	Assessed as unrelated to Coartem®
PHHO2006TH05957-B PHHO2006TH05956-M	LB-CA	2 nd	Inverted left nipple with a smaller areola than the right.	Assessed as unrelated to Coartem®
PHHO2006TH21938 B PHHO2006TH10425 M	LB-CA	Unk	Lissencephaly	Assessed as unrelated to Coartem®
PHHO2007ZM05491 B PHHO2007ZM05489 M	LB-CA	2 nd	Trisomy 18 , Hirschsprung disease	Assessed as unrelated to Coartem®
PHHO2006ZM13318-M	Stillbirth	3 rd	Macerated stillbirth. No abnormalities reported.	Assessed as unrelated to Coartem®
PHHO2006ZM14101-M	Stillbirth	2 nd	Macerated stillbirth. No abnormalities reported.	Assessed as unrelated to Coartem®.
PHHO2006ZM15071-M	Stillbirth	2 nd	Stillbirth. The fetus had died due to a cord around the neck.	An ultrasound revealed a single normal fetus, but there were two gestational sacs, one of which was close to the fundus appearing anembryonic. Stillbirth assessed as unrelated to Coartem®.
PHHO2006ZM17448-M	Stillbirth	2 nd	Stillbirth due to fetal distress. Postmature.	Assessed as unrelated to Coartem®.

Case IDs	Pregnancy outcome	Exposure trimester	Abnormality	Comment
PHHO2006ZM11732-M	Stillbirth	2 nd	Stillbirth following prolonged difficult labor	Assessed as unrelated to Coartem [®] .
PHHO2005ZM20773-M	Stillbirth	1 st	Stillbirth, 3 rd trimester. No abnormalities reported.	Assessed as unrelated to Coartem [®] .
PHHO2006ZM21105-M	Stillbirth	3 rd	Stillbirth, 3 rd trimester. No abnormalities reported.	Assessed as unrelated to Coartem [®] .
PHHO2006ZM02027-M	Stillbirth	2 nd	Stillbirth, 2 nd trimester. No abnormalities reported.	Assessed as unrelated to Coartem [®] .

*Mother of twins; M = mother case; B = baby case; LB-CA=Life birth with congenital anomaly

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

Additional information regarding exposure to Coartem and outcomes in pregnancy comes from Study A2415. This was a randomized controlled trial which examined the safety, tolerability and efficacy of artesunate monotherapy (AS7) with co-artemether in pregnancy in an area of multi-drug resistance. Patients in the second and third trimesters of pregnancy with uncomplicated falciparum malaria were randomized to three days AL (n=125), or seven days of artesunate (AS7; n=128).

Interim results showed that both regimens were well tolerated. There were no significant differences in the major birth indicators between the groups, including estimated gestational age, proportion premature, proportion stillbirths, proportion male infants and congenital abnormality. There was no difference in the neurological optimality score of neonates whose mothers were treated with AS7 or AL. The only symptom that differed significantly between the groups in follow-up, when it was not present on admission, was tinnitus, which was more frequent in the AS7 group 8.9% (7/79) compared to 0% (0/85) in co-artemether group, P=0.005 (Fisher's exact).

Lastly, there was 1 report of a congenital defect in the 120 day Safety Update supplied by the Applicant. A female baby of a patient treated with Coartem during an investigator-initiated trial (study CCOA566A2415, a single-blind, randomized study of Coartem and artesunate in the treatment of drug-resistant falciparum malaria in pregnancy) was born lacking nails on two fingers and six of her toes. She was born approximately 4.5 months after her mother completed treatment with Coartem. Her mother had also been hospitalized due to fever with headache approximately 2.5 months prior to the birth. The reporting physician did not make an assessment of causality, but the Novartis medical safety physician provisionally assessed the baby's absent nails as suspected to be related to Coartem.

Summary of pregnancy data

Based on animal data, Coartem is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation.

Pregnancy data to date, which includes 495 subjects exposed to Coartem in Zambia, Study A2415 and postmarketing data suggest no significant differences in congenital abnormalities and birth indicators between Coartem, SP and artesunate monotherapy. As malaria is a life-threatening disease particularly in pregnant women, use of Coartem in any trimester should be based on a risk-benefit consideration, *i.e.* if the expected benefit to the mother outweighs the risk to the fetus.

6.1.14.4 Lactation

Animal data suggest excretion into breast milk but no data are available in humans and therefore breastfeeding women should not take co-artemether. The MHT consult referred to the WHO guidelines for the treatment of malaria, which recommends that only tetracycline and dapsone be withheld during lactation and not artemisinin drugs, and argued that breastfeeding is particularly important in underdeveloped countries where malaria is endemic. A lactation study was recommended.

6.1.15 Assessment of Effect on Growth

Not applicable due to the short duration of treatment.

6.1.16 Overdose Experience

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG parameters and blood electrolyte levels should be monitored.

There is no information in patients who overdosed on Coartem.

6.1.17 Postmarketing Experience

Postmarketing safety data is collected from a variety of sources including (but not limited to) published literature, Health Authority notifications, post-marketing studies, clinical trials and spontaneous reports from both healthcare professionals and the general public.

A total number of 123 spontaneous cases, and 15 suspected cases from PMS studies were reported since 14 October 1998; date of first worldwide approval, and up to 30 June 2008. Cumulatively, 64 suspected serious AEs from clinical trials have been recorded in the global safety database.

Table 65 shows details on the distribution of the cases. The majority (56%) of spontaneous reports originated in 3 countries, Cameroon, Cote d'Ivoire and South Africa. The remainder of

the reports also came from mostly African countries and fewer from Europe and other countries. Of note, France reported 14% of cases.

Table 65: Overview of AEs by report type and source

Type of Report	Serious		Non-serious		Total
	HCP	Non-HCP	HCP	Non-HCP	
Spontaneous	60	4	50	9	123
PMS	15				15
Suspected CT	64				64
Total	141	4	48	9	202

HCP = Health Care Professional

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

Table 66 shows the cases by age group. Among the 25 spontaneous and PMS cases reported in children up to 16 years of age, 18 occurred in children ≤ 12 years. Four of these cases were reported in neonates whose mother and are discussed later in the pregnancy section (2 premature babies, one atrial septal defect and one umbilical hernia). Therefore, while 70% of the product distributed is used for treatment of children, the number of spontaneous reports in this population represents only 11.6% of the spontaneous reports.

Table 66: Overview of reported cases by age group

Age	≤ 16 years		17-64 years		≥ 65 years		Age not specified		Total	
	Type of report	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious		Non-serious
Spontaneous		11	7	44	31		3	9	18	123
PMS		7		5				3		15
CT SARs		13		29		0		22		64
Total		31	7	78	31	0	3	37	18	202

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

The distribution of cases by MedDRA SOC of the primary event is shown in Table 67. The SOCs most represented in the reports are “General Disorders and administration site conditions” in adults and “Infections and infestations” in the pediatric population. Most of the cases classified in these SOCs were SAEs from clinical trials reporting lack of efficacy or malaria.

Table 67: Distribution of cases by MedDRA SOC of the primary event

MedDRA System Organ Class	Age	≤16 years		17-64 years		≥65 years		Not specified	
		Total	S	NS	S	NS	S	NS	S
Blood and lymphatic system disorders	10	3		6				1	
Cardiac disorders	3			3					
Congenital, familial and genetic disorders	2	1						1	
Eye	2	1		1					
Gastrointestinal disorders	9	1	3		3				2
General disorders and administration site conditions	51	2	2	18	7			15	7
Hepatobiliary disorders	8	2	1	5					
Immune system disorders	3	2			1				
Infections and infestations	34	9		18				7	
Injury, poisoning and procedural complications	14	1		2	4			2	5
Investigations	4	1		2	1				
Metabolism	1			1					
Musculoskeletal and connective tissue disorders	3	1	1				1		
Nervous system disorders	9			4	2			1	2
Pregnancy, puerperium and perinatal conditions	11	4		4	1			2	
Psychiatric disorders	2							2	
Renal and urinary disorders	8	2		4	1				1
Skin	22	1		5	11		2	2	1
Surgical	3			3					
Total	202	31	7	78	31	0	3	33	18

Source: Novartis Cumulative Postmarketing Safety Experience fax, submitted 29 Aug 2008

There were 6 cases with a fatal outcome described in the post-marketing database and are summarized in Table 68.

Of all the reports, anemia and hemolysis were the most frequently reported, with 57 related reports. There were 22 cases of hemolytic anemia/hemolysis/hemoglobinuria, 30 reports of malaria reappearance, and 5 cases of anemia which were present prior to treatment with co-artemether (2 cases), associated with epidermolysis bullosa (1 case), or related to malaria (2 cases). The Applicant noted that anemia, hemolysis and hemoglobinuria are common findings in malaria and dissociation from a drug effect is difficult. The majority of the reports had alternative explanations such as concomitant blackwater fever, known to result in hemolysis with hemoglobinuria and anemia, baseline anemia, G6PD deficiency and/or concomitant medications.

Table 68: Fatal cases from post-marketing data

Subject	AEs	Investigator's assessment of relationship to drug	Comments
55 yo F	Comatose state, weak, severe jaundice, hematuria, colored urine	Unlikely	"a case of cardiovascular disease and a typical case of hemolytic jaundice without direct link to Coartem"
45 yo F	Lyell's syndrome	Possible	2 hours after second intake on day 2, developed burning sensation in throat and conjunctival irritation; Other drugs may be implicated but Coartem was the last drug she took
Newborn with mother in A2407 (pregnancy registry)	Premature	-	Coartem on 29 Apr 06, EDC 23 Jul 06, infant born (b) (6) weighing 2kg
Newborn with mother in A2407 (pregnancy registry)	Premature	-	Coartem on 28 Sept 05, EDC 19 May 06, infant born (b) (6), breech presentation, mother delivered baby herself
Newborn with mother in A2407 (pregnancy registry)	Death	Unlikely	Coartem 9 Dec 05, EDC 19 Feb 06, infant born (b) (6), normal neonate. Died (b) (6), cause of death unknown
Newborn with mother in A2407 (pregnancy registry)	Death	-	Coartem 22 Jul 06, infant born (b) (6) apparently normal. Infant died 2 weeks later on (b) (6), cause of death unknown

Four reports were identified when searched for Torsades de pointes/QT prolongation. One was a report of dizziness (cardiac disorders is the secondary SOC in MedDRA), and another was a case of palpitations. The other two cases were identified in non-suspected solicited reports: a fatal case of cardiorespiratory arrest attributed to cerebral malaria, and a fatal case of Alagille syndrome in a 16 day old male newborn. There were no reports of QTc prolongation.

Ear disorders were investigated through a search for cases of hypoacusis using MedDRA (version 10.1) PTs "hypoacusis, hearing impaired, sudden hearing loss, conductive deafness, deafness, deafness neurosensory, deafness bilateral, deafness unilateral, deafness transitory, deafness permanent" with no cases retrieved.

Six nervous system SAEs were reported in addition to few non serious cases of headache or dizziness:

- 8-year-old female subject experienced flaccid paralysis of the lower limbs 3 days after being treated with Coartem. The reporter could not assess the causality due to lack of information
- 30-year-old female experienced facial paralysis and spasmodic movements of one arm. She had no history of seizures. Outcome is unknown
- 30-year-old female patient experienced an extrapyramidal syndrome and tetany with trismus, formication, skin hyperesthesia two days after starting Coartem. No investigation was performed and she recovered within 2 days after a treatment with diazepam and magnesium pidolate.
- 37-year-old male patient receiving multiple drug therapy and with a history of asthma and dust allergy was treated with Coartem and developed abnormal behavior, euphoric mood, vertigo, dysarthria and an abnormal coordination 2 days after the last Coartem® dose. MRI and blood tests were normal. On follow-up, the patient additionally reported elevated liver enzymes (not stated by the physician), which were treated with natural medicine. The subject improved, speech was normal and vertigo had disappeared although minor memory loss remained
- male patient was diagnosed with malaria on 21 Nov 2004 and received Coartem and quinine sulphate. The patient had some clonic jerking and has been taking Coartem that has expired six months ago. The outcome was not reported
- Clinical trial case: a patient commenced study medication on 27 Apr 2004. On (b) (6) the patient suffered from mental aberration with increased transaminase and bilirubin and was hospitalized. Coartem® was discontinued and quinine was administered as treatment. The patient made a complete recovery on an unspecified date, and when study medication was reintroduced the patient's liver tests remained in normal range.

One additional nervous system SAE reported in the 120 day Safety Update was a 54-year-old male patient, treated with Fansidar as well as Coartem, experienced, after the treatment course, cerebellar symptoms with ataxia, abasia, dyskinesia, gait disturbance, tremor, photophobia, saccadic eye movement, malaise, hypertension. Brain MRI was normal. According to the reporting neurologist, it was thought likely to be a drug-induced reaction due to Coartem or a "post malaria neurological syndrome" (PMNS). The results of investigations and the outcome of this event were not reported.

There were 5 psychiatric disorders SAEs reported in adult subjects. One subject attempted suicide and was diagnosed with a psychotic reaction with acute persecutory delusion and hallucinations. The psychiatrist felt this could be an underlying psychotic disorder revealed by the malarial infection. The remaining subjects reported hallucinations (2 cases) and anxiety (1 case) and abnormal behavior and euphoric mood (1 case, also described in Nervous system disorders section).

The UK Health Authority has requested monitoring for the following: severe skin disorders, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), hepatic disorders and blurred vision. The Applicant reported no new emerging signal for hepatic disorders and only 2 cases of blurred vision.

There were 30 reports of hypersensitivity, including the case of Lyell's syndrome described in Table 60. The other reports included 4 cases of hypersensitivity with systemic involvement (facial swelling, eyelid edema), 4 cases of urticaria, 1 case of angioedema with laryngeal compression and urticaria, 10 cases of rash (all adults) and 4 cases of facial edema (although 2 cases occurred in subjects with nephritic syndrome and asthma).

Reviewer's comments: Hypersensitivity is listed as part of the proposed Postmarketing Experience section on the label without any descriptors. It is suggested that specific examples of hypersensitivity, including "serious skin reactions" and "facial edema" be included to accurately describe the nature of hypersensitivity reactions observed with Coartem.

There were 28 reports of hepatic disorders, the majority in adult subjects. There were 5 cases of hepatitis, 2 of which had insufficient information, 2 cases of alternative explanations and 1 case of a past history of hepatitis B. There were 9 reports of abnormal liver function tests with alternative explanations or insufficient information including past history of hepatitis, concomitant medications known to cause liver disorders and negative rechallenge. Hepatic disorders also included one fatal case of liver failure in a dysmorphic baby with Alagille syndrome.

Two eye disorder SAE cases were reported: a 15 year old male with "left strabismus, blurred vision, diplopia and reduced visual acuity" in the left eye 8 days after the last dose of Coartem with no data on the outcome; a 30 year old female experienced cephalgia and asthenia that worsened after the second intake. On follow-up, blurred vision, intense asthenia, stomach upset, nausea and vomiting were also reported. Coartem was discontinued and the patient recovered.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The database used for the FDA's analysis of clinical safety included all subjects who had received either the 4-dose (4 tablets over 2 days) or 6-dose (4 tablets over 3 days) Coartem regimens. This included 8 key studies selected for efficacy in addition to 8 additional studies which used these dosing regimens. Pediatric subjects who received either crushed or dispersible tablet formulations were also included. Alternate dosing regimens, including 3-dose, and a 4-dose regimen where only half the dose (2 tablets) were administered at each dosing interval instead of 4 tablets, were not included as these represented lower exposures to Coartem.

Two safety populations were defined: Adults (>16 and ≤65 years of age) and pediatrics (≤16 years of age). A total of 1427 adult subjects and 1992 pediatric subjects were exposed to Coartem (Table 63). The pediatric population was further subdivided into the following age categories for nervous system disorder analysis: age ≤ 2 years (587 subjects), age > 2 to ≤ 6

years (473 subjects), age > 6 to ≤ 12 years (207 subjects), and age > 12 to ≤ 16 years (66 subjects).

Table 63: Subjects included the FDA adult and pediatric pooled safety populations

Population	Number of Coartem 4-dose patients	Number of Coartem 6-dose patients	Population total
Adult	787	647	1434
Pediatrics	659	1331	1991
Coartem (dose) total	1446	1979	3425

6.2.1.1 Study type and design/patient enumeration

The 16 studies pooled for efficacy included a variety of designs (comparative and noncomparative; blinded and unblinded; randomized and unrandomized). The total number of subjects enrolled into each safety population is shown in table 63.

6.2.1.2 Demographics

Demographic data is shown in Table 64.

Table 64: Demographic characteristics at baseline, adult pooled safety population

	Adults N=1427		Pediatrics N=1992	
	4-dose N=787 (%)	6-dose N=647 (%)	4-dose N=659 (%)	6-dose N=1332 (%)
Male gender	581 (74.3)	471 (73.0)	402 (61.0)	711 (53.3)
Race				
Black	40 (5.1)	40 (6.2)	-	1209 (90.7)
Caucasian	21 (2.7)	79 (12.2)	-	-
Not collected	721 (92.2)	437 (67.8)	-	115 (8.6)
Oriental	0	44 (6.8)	-	9 (0.7)
Other	0	45 (7.0)	-	-
Mean body weight (kg)*	50.8	55.6	15.8	14.0

* Calculated by Novartis for their original populations (adults and adolescents >12 years of age, pediatrics ≤12 years of age)

6.2.1.2.1 Adult subjects

The majority of subjects were male. Information on race was not collected in most studies, but most adult studies were performed in Asia. Mean and median age were similar across the

treatment groups and for most comparator antimalarials (data not shown), and mean and median body weights were similar for the Coartem groups and the MAS group. Body weight was relatively low in these treatment groups (median approximately 50 kg), because most of the studies contributing patients to these populations were conducted in Thailand. The slightly higher mean and median in the Coartem 6-dose regimen group may reflect the inclusion of Study 2401 in the pooled population, which enrolled subjects residing in Europe or non-endemic regions of Colombia and was non-comparative, so it did not contribute patients to any other treatment group.

With respect to disease characteristics, the mean and median asexual baseline *P. falciparum* parasitemia were higher in the Coartem 4-dose group than in the 6-dose regimen and MAS groups (Applicant’s data, Table 65). Similarly, a lower proportion of the co-artemether 4-dose regimen was afebrile (<37.5C) at baseline than the 6-dose regimen and MAS groups.

Table 65: Disease characteristics at baseline, Applicant’s* adult and adolescent pooled safety population

Variable Statistic/category	Co-artemether			MAS N= 352
	4-dose N=1098	Total 6-dose N=713	Total N= 1811	
Parasite count of <i>P. falciparum</i> (asexual forms / μ L)				
N	1095	608	1703	352
Mean	31424	27751	30113	24663
SD	50134.0	53481.1	51368.5	40829.3
Minimum	0	0	0	0
Median	12040	5455	9630	4332
Maximum	730000	464880	730000	235688
<i>P. falciparum</i> asexual forms category, n (%)				
< 2,000 / μ L	188 (17.1)	195 (27.3)	383 (21.1)	132 (37.5)
2,000-<5,000 / μ L	157 (14.3)	99 (13.9)	256 (14.1)	52 (14.8)
5,000-<15,000 / μ L	241 (21.9)	87 (12.2)	328 (18.1)	44 (12.5)
15,000-<50,000 / μ L	296 (27.0)	119 (16.7)	415 (22.9)	64 (18.2)
50,000-<100,000 / μ L	129 (11.7)	62 (8.7)	191 (10.5)	34 (9.7)
100,000-200,000 / μ L	75 (6.8)	36 (5.0)	111 (6.1)	21 (6.0)
> 200,000// μ L	8 (0.7)	9 (1.3)	17 (0.9)	4 (1.1)
Missing slide/other unit	3 (0.3)	102 (14.3)	105 (5.8)	0 (-)
None	1 (0.1)	4 (0.6)	5 (0.3)	1 (0.3)

Body Temperature (°C)				
N	1098	712	1810	352
Mean	38.1	37.8	38.0	37.8
SD	1.07	1.10	1.09	1.04
Minimum	35.4	35.1	35.1	36.0
Median	38.0	37.7	37.9	37.6
Maximum	41.0	41.5	41.5	40.5
Body Temperature category, n (%)				
<37.5°C	349 (31.8)	291 (40.8)	640 (35.3)	157 (44.6)
37.5- <39.0°C	500 (45.5)	286 (40.1)	786 (43.4)	133 (37.8)
≥ 39.0°C	249 (22.7)	135 (18.9)	384 (21.2)	62 (17.6)
Missing	0	1 (0.1)	1 (0.1)	0

* Adults in the original Applicant's submission were defined as ≥ 12 years of age
 Source: Novartis Clinical Overview

Reviewer's comments: The difference in disease characteristics at baseline may account for why most of the more common AEs were seen more frequently with the 4-dose Coartem regimen compared to the 6-dose (see Table 65). It may be that the 4-dose population had more severe or advanced malaria and the AEs reported were those seen with malaria infection.

6.2.1.2.2 Pediatric subjects

As shown in Table 64, the majority of subjects were male. There was no information on race for the 4-dose studies, but the majority of 6-dose studies were performed in Black subjects in Africa. There were some differences between groups in age. The co-artemether total 6-dose group had a lower mean and median age than other treatment groups, apart from the SP and chloroquine groups, with the co-artemether 6-dose standard tablet group with still lower mean and median age. This difference probably results from the inclusion of Study A2403 in the 6-dose standard tablet group, where there was a higher proportion of patients ≤ 2 years of age than in any other treatment group with the exception of the chloroquine group. Body weight data showed a similar pattern to the age data, with the co-artemether 6-dose regimen groups and particularly the standard tablet 6-dose regimen group, the SP and chloroquine groups tending to have lower body weights. The body weight distribution also reflects this: patients weighing 5- < 10 kg were only represented in co-artemether treatment groups that included patients taking the 6-dose regimen, and in the SP and chloroquine groups.

Mean and median baseline *P.falciparum* asexual parasite counts were higher in the co-artemether 4-dose and SP groups than in the other treatment groups, with higher proportions of patients in both of these groups with baseline parasite counts over 100 000 asexual forms/μL. This is due to differences in the entry criteria of the studies that contributed patients to the different patient groups. The entry criteria for Study A010 specified patients should have parasitemia between 5 000 and 250 000/μL. This study provided all of the SP group and more than a quarter of the co-artemether 4-dose group. Study A011 provided a further quarter of the 4-dose regimen group and all of the chloroquine group, and included in its entry criteria a lower limit of parasitemia of

20 000/μL but specified no upper limit. The co-artemether 6- dose regimen group, however, primarily included patients from Study A2403 and Study B2303, and the former excluded patients with baseline parasitemia of > 100 000/μL and the upper limit for participation in Study B2303 was 200 000/μL.

Mean and median baseline body temperature were similar across the treatment groups.

Table 66: Disease characteristics at baseline, Applicant’s* pediatric pooled safety population

Variable Statistic/category	Co-artemether			MAS N= 78	SP N= 143
	4-dose N=521	Total 6-dose N=1267	Total N= 1788		
Parasite count of <i>P. falciparum</i> asexual forms (μL)					
N	520	1266	1786	77	143
Mean	126637	42611	67076	42457	243374
SD	172688.1	46951.5	108124.5	55185.0	256505.9
Minimum	0	0	0	0	5000
Median	72328	24702	33371	7600	168000
Maximum	1872000	628571	1872000	177988	1820000
<i>P. falciparum</i> asexual forms category, n (%)					
< 2,000 /μL	31 (6.0)	31 (2.4)	62 (3.5)	24 (30.8)	0 (-)
2,000-< 5,000 /μL	16 (3.1)	158 (12.5)	174 (9.7)	9 (11.5)	0 (-)
5,000-< 15,000 / μL	42 (8.1)	265 (20.9)	307 (17.2)	8 (10.3)	6 (4.2)
15,000-< 50,000 / μL	114 (21.9)	431 (34.0)	545 (30.5)	10 (12.8)	22 (15.4)
50,000-< 100,000/ μL	94 (18.0)	241 (19.0)	335 (18.7)	9 (11.5)	15 (10.5)
100,000-200,000/ μL	120 (23.0)	137 (10.8)	257 (14.4)	16 (20.5)	41 (28.7)
> 200,000/ μL	95 (18.2)	2 (0.2)	97 (5.4)	0 (-)	59 (41.3)
Missing slide/other unit	1 (0.2)	1 (0.1)	2 (0.1)	1 (1.3)	0 (-)
None	8 (1.5)	1 (0.1)	9 (0.5)	1 (1.3)	0 (-)
Body Temperature (°C)					
N	521	1264	1785	78	143
Mean	38.6	38.2	38.3	37.9	38.6
SD	1.09	1.06	1.09	0.94	1.07
Minimum	35.8	35.6	35.6	36.1	36.2
Median	38.6	38.0	38.2	37.8	38.7
Maximum	41.9	41.5	41.9	40.3	40.7
Body Temperature category, n (%)					
< 37.5°C	68 (13.1)	277 (21.9)	345 (19.3)	26 (33.3)	22 (15.4)
37.5-< 39.0°C	234 (44.9)	678 (53.5)	912 (51.0)	40 (51.3)	62 (43.4)
≥ 39.0°C	219 (42.0)	309 (24.4)	528 (29.5)	12 (15.4)	59 (41.3)
Missing	0	3 (0.2)	3 (0.2)	0	0

Source: [CO Appendix-Table 5.1-8](#)

* Pediatrics in the original Applicant’s submission were defined as < 12 years of age

Reviewer’s comments: Similar to the adult population, the 4-dose Coartem studies may have enrolled subjects with more advanced/severe malaria infection compared to the other treatment groups. This may partially account for the higher AE rates reported with the 4-dose regimen compared to the 6-dose, since the AEs may have been reflective of malaria symptoms.

6.2.1.3 Extent of exposure (dose/duration)

The primary exposures analyzed in this review were the 4-dose (4 tablets over 2 days) or 6-dose (4 tablets over 3 days) regimens with the specific dose based on body weight.

6.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

6.2.2.1 Other studies

6.2.2.2 Postmarketing experience

This was fully described in Section 7.1.17 Postmarketing experience.

6.2.2.3 Literature

Literature reports, particularly those describing neurotoxicity and ototoxicity, and the Riamet label were used to further evaluate the safety of Coartem.

6.2.3 Adequacy of Overall Clinical Experience

There were 1434 adult subjects and 1991 pediatric subjects included in the pooled safety analysis. In addition, a large postmarketing safety database exists since Coartem was first approved for clinical use in 1998. Since that time, it is estimated that approximately ^{(b) (4)} patients have been treated with Coartem.

6.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Applicant has adequately investigated Coartem in preclinical animal models, especially with regard to neurotoxicity (in dogs), cardiac effects (HERG assay), and auditory effects (in dogs). With respect to neurotoxicity, the effects appear related to concentrations of artemether which are only achieved with IM administration, and not with oral administration due to the large first pass effect which effectively reduces plasma concentrations of artemether. Please refer to the Pharmacology/Toxicology review for further details.

6.2.5 Adequacy of Routine Clinical Testing

Neurological examinations were performed only selected studies: Studies A2403, B2303 and at one site only in both studies A025 and A026. In studies ABMO2, A023, A028, A2401, neurological findings were recorded as AEs only.

In studies A025, A026 and A2403, 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, (Subjects 229 and 313 described previously). Results of neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any postbaseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

6.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Applicant has adequately worked up the metabolism and interaction potential of Coartem. No additional studies will be requested. Please refer to the Clinical Pharmacology review for further details.

6.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

AEs were captured adequately in the 8 key studies through questioning patients and recording signs and symptoms on case report forms. All AEs present at baseline were captured as AEs, with any new AEs or worsening of baseline AEs recorded as treatment emergent AEs. Follow-up was for at least 28 days. Studies ABMO1 and ABMO2 had far fewer AEs recorded compared to other studies for no known reason. A DSI inspection has not found anything of concern although the complete inspection report was pending at the time of this review.

6.2.8 Assessment of Quality and Completeness of Data

The quality of the data was acceptable, and data was complete.

6.2.9 Additional Submissions, Including Safety Update

The Applicant submitted a 120 day safety update which has been included in this review.

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Safety issues of specific concern were identified and reviewed in detail. These included neurotoxicity, ototoxicity and QT prolongation.

6.3.1 Pooling Data Across Studies to Estimate and Compare Incidence

6.3.1.1 Pooled data vs. individual study data

Individual study data was analyzed for quality and pooled for review of the safety issues of specific concern.

6.3.2 Explorations for Predictive Factors

6.3.2.1 Explorations for dose dependency for adverse findings

Safety data for co-artemether included both 4-dose and 6-dose data to look specifically for dose dependant AEs. No relationship between dose and AEs was identified.

6.3.2.2 Explorations for drug-demographic interactions

Subgroup analysis by age, sex and race did not show any drug-demographic interactions.

6.3.3 Causality Determination

AEs were attributed to the study drug if there was a temporal association, no other causative agents and no other explanations could account for the occurrence of the AE.

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

In the drug development plan of co-artemether, several dosing regimens were investigated. All were through the oral route. After several Phase 2 studies, the 6-dose regimen was chosen for further development as the efficacy of this regimen was superior to the 4-dose regimen and had comparable safety.

Administration

Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

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

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

Dosage in Adult Patients (> 16 years of age)

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

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

Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended.

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

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

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

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

Dosage in Patients with Renal or Hepatic Impairment

No specific studies have been carried out in patients with renal or hepatic impairment. Most patients with acute malaria present with some degree of related hepatic impairment. In clinical studies, the adverse event profile did not differ in patients with or without mild or moderate hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with Coartem Tablets. Therefore, no specific dose adjustments are needed for patients with mild or moderate hepatic insufficiency.

In clinical studies, the adverse event profile did not differ in patients with or without mild or moderate renal impairment. There were no patients with severe renal impairment in the clinical studies. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe renal or severe hepatic impairment.

7.2 Drug-Drug Interactions

Artemether induces CYP3A4 and both artemether and lumefantrine are metabolized by CYP3A4. Lumefantrine inhibits CYP2D6. Coartem Tablets should be used with caution when administered with agents that induce, inhibit, or are metabolized by CYP3A4 and those that are metabolized by CYP2D6 because of the potential for QT prolongation, or altered concentrations of the interacting drug (i.e., increased concentrations with the potential to increase the risk of an adverse reaction or decreased concentrations resulting in loss of efficacy).

Halofantrine, an antimalarial related to lumefantrine, is associated with prolongation of the QT interval on the electrocardiogram and rare cases of torsade de pointes. Lumefantrine has also been shown to prolong the QT interval. Therefore, Coartem is not recommended in patients:

- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolides, fluoroquinolones, imidazole, and triazole antifungal agents); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride.
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).

In patients previously treated with halofantrine, Coartem Tablets should not be administered earlier than one month after the last halofantrine dose, also due to the potential additive effects on the QT interval.

In patients previously treated with quinine, ECG monitoring should be performed due to the potential additive effects of quinine and Coartem Tablets on the QT interval.

Patients previously treated with mefloquine may have a decreased exposure to lumefantrine upon administration of Coartem Tablets. Patients should be monitored for lack of efficacy and food consumption should be encouraged.

Data on safety and efficacy of use of Coartem with other antimalarials are limited. Concurrent administration of Coartem with other antimalarial drugs is not recommended.

The long elimination half-life (3-6 days) of lumefantrine must be taken into account when administering quinine in patients previously treated with Coartem. Artemether concentrations in humans were shown to decrease with administration of a single dose of IV quinine. Monitoring of the ECG is recommended.

Caution is recommended when combining Coartem Tablets with substrates, inhibitors, or inducers of CYP3A4, especially anti-retroviral drugs and those that have an effect on the QT interval due to the potential to increase lumefantrine concentrations and potentiate QT prolongation or result in decreased concentrations and loss of efficacy of the concomitant drug.

Lumefantrine inhibits the activity of the cytochrome enzyme CYP2D6 *in vitro*. Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

Please refer to the Clinical Pharmacology review for further details.

7.3 Special Populations

There were only 8 subjects greater than 65 years of age in the pooled safety population, and therefore analysis of the efficacy and safety of co-artemether in this population remains unknown.

The safety of co-artemether in pregnancy was discussed in Section 7.1.13 Human Reproduction and Pregnancy Data and 7.1.16 Postmarketing Experience.

The immune status of subjects was considered unlikely to influence safety and tolerability of the drug and was therefore not analyzed as a separate population.

Hepatic and renal impairment was discussed in Section 7.1.9.3.15 Hepatic and renal impairment. Patients with mild moderate and severe hepatic impairment tended to report more AEs which were

mostly related to malaria infection, suggesting that patients with hepatic impairment had more severe disease at baseline. Similarly, patients with renal impairment also tended to have higher rates of AEs, although no patients with severe renal impairment were included in the studies.

7.4 Pediatrics

Pediatric subjects were fully analyzed as a separate safety population in this Application.

7.5 Advisory Committee Meeting

As Coartem is a new molecular entity, the drug will be presented at an Advisory Committee Meeting on December 3, 2008.

7.6 Literature Review

Literature reports, particularly those describing neurotoxicity and ototoxicity, and the Riamet label were used to further evaluate the safety of Coartem.

7.7 Postmarketing Risk Management Plan

To be determined based on discussions at the Advisory Committee meeting.

7.8 Other Relevant Materials

Not applicable.

8 OVERALL ASSESSMENT

8.1 Conclusions

Pooled safety analyses was conducted on over 3400 subjects (1427 adult subjects, 1992 pediatric subjects) exposed to either a 4- or 6-dose regimen of Coartem for the treatment of acute, uncomplicated malaria due to infections with *Plasmodium falciparum* or mixed infections including *P. falciparum*. Based on these analyses, the proposed 6-dose regimen of Coartem appears safe for the treatment of malaria.

In both adults and pediatrics, symptoms present at baseline were recorded as AEs, and therefore it is difficult to distinguish drug effect from the natural history of malaria infection. In adults, the most frequently reported AEs for the Coartem 6-dose regimen were headache, asthenia, dizziness and anorexia. The majority of AEs were of mild or moderate intensity, with severe AEs reported in 5.4% of subjects. Deaths (0.2%) and SAEs (6-dose group 1.4%) were similarly infrequently reported, with the majority of SAEs likely related to malaria infection or recrudescence (efficacy failure). In pediatric subjects, the most frequently reported AEs for the Coartem 6-dose regimen were pyrexia, vomiting, *P. falciparum* infection and anorexia. Severe AEs were reported in 7.3% of 6-dose regimen subjects. Deaths (0.2%) were primarily due to infection. SAEs in the 6-dose group (1.3%) were mostly cases of serious *P. falciparum* infection.

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

No safety concerns could be found with respect to ear and labyrinth disorders in the pooled analysis.

A definitive QTc study, Study A2101, showed that Coartem was associated with a mean maximum increase in QTcF relative to placebo of 7.29 msec (3.6, 11.0).

Pregnancy registry and postmarketing data suggest no increase in teratogenic effects or spontaneous abortions in women who received co-artemether during pregnancy.

8.2 Recommendation on Regulatory Action

Based upon this safety review, Coartem is recommended for approval of Coartem for treatment of malaria in patients of 5 kg body weight and above with acute uncomplicated *P. falciparum* infection.

For Coartem efficacy conclusions and recommendations, please see the review by Dr. Elizabeth O'Shaughnessey.

8.3 Recommendation on Postmarketing Actions

To be determined.

8.3.1 Risk Management Activity

To be determined.

8.3.2 Required Phase 4 Commitments

To be determined.

8.3.3 Other Phase 4 Requests

8.4 Labeling Review

Revision to the label is ongoing at the time of writing of this review. The following groups were consulted and their recommendations will be incorporated into the label:

- QT-IRT
- SEALD
- MHT
- OSE/DRISK
- OSE/DMEPA
- Division of Neurology

Section 6 (Adverse Reactions) was revised according to the “Guidance on Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products”. Focus was placed on describing the data supporting the 6-dose regimen for which the Applicant was seeking approval although the safety database also consisted of 4-dose data. The numbers of patients and types of studies (mostly non-comparative) from which these patients were obtained were described to provide the context on which AE data was evaluated. The most frequently reported AEs in the pooled adult and pediatric populations were included, as well as the most frequently reported AEs obtained from comparative studies A026/A028.

8.5 Comments to Applicant

Pending at the time of this review.

9 APPENDICES

9.1 Review of Individual Study Reports

The 8 key studies were individually reviewed by several reviewers:

- The 4 dose studies A023 and ABM02 were completed by Dr. Joette Meyer
- Study reports A025 and A026 were completed by Dr. Regina Alivasatos
- Study reports A028 and A2401 were completed by Dr. Sue Lim
- For the pediatric studies A2403 and B2303, please refer to the separate review by Dr. Ozlem Belen

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SAFETY REVIEW: STUDY A023

No serious AEs were seen during the trial and none of the AEs was assessed as being related to any of the three trial treatments. No patient discontinued due to an AE or laboratory abnormality.

All AEs recorded during the trial were summarized using the maximum severity grade for each patient and experience. At baseline (Day 1) all symptoms experienced by the patients were recorded as AEs, even if they were related to malaria. The most frequently reported symptoms in all treatment groups were the typical malaria symptoms: headache (>84%), fatigue (>76%), anorexia (>62%), rigors (>50%), dizziness (>34%), nausea (>32%), and sleep disorder (>30%).

The AEs that started after baseline are shown in Tables 1-3 for the three treatment groups. One or more AE starting after baseline were recorded for 25 patients (7 on Coartem (Coartem), 9 on lumefantrine (B) tablets and 9 on B capsules). Anorexia, abdominal pain and headache were each seen in two patients (3.8%) on Coartem. All other AEs starting after baseline were reported for one patient each in this treatment group. In both single treatment groups headache starting after baseline was reported in more than 5% of the patients: 5 patients (9.8%) in the B tablets group, and 3 patients (6%) in the B capsules group. Nausea was reported for 3 patients (5.9%) in the B tablets group. All other AEs occurred only in one or two patients. AEs were all mild severity, with the exception of moderate headache in 2 patients in the B capsules group.

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Table 1: Summary of patients in the Coartem group with AEs which started after baseline

TREATMENT CGP 56697

		TREATMENT			
		CGP 56697			
		SEVERITY OF ADVERSE EXPERIENCE		ALL	
		MILD			
		N	%	N	%
BODY SYSTEM	PREFERRED TERM				
--ALL--	WITH EXPERIENCES	7	13.5	7	13.5
BODY AS A WHOLE	--TOTAL--	1	1.9	1	1.9
	FATIGUE	1	1.9	1	1.9
DIGESTIVE SYSTEM	--TOTAL--	3	5.8	3	5.8
	ANOREXIA	2	3.8	2	3.8
	NAUSEA	1	1.9	1	1.9
	PAIN ABDOMINAL	2	3.8	2	3.8
	VOMITING	1	1.9	1	1.9
HEMIC AND LYMPHATIC SYSTEM	--TOTAL--	1	1.9	1	1.9
	SPLENOMEGALY	1	1.9	1	1.9
NERVOUS SYSTEM	--TOTAL--	3	5.8	3	5.8
	DIZZINESS	1	1.9	1	1.9
	HEADACHE	2	3.8	2	3.8
	SLEEP DISORDER	1	1.9	1	1.9
RESPIRATORY SYSTEM	--TOTAL--	1	1.9	1	1.9
	EPISTAXIS	1	1.9	1	1.9
SPECIAL SENSES	--TOTAL--	1	1.9	1	1.9
	CONJUNCTIVITIS	1	1.9	1	1.9

(CONTINUED)

TREATMENT CGP 56697

		TREATMENT			
		CGP 56697			
		SEVERITY OF ADVERSE EXPERIENCE		ALL	
		MILD			
		N	%	N	%
BODY SYSTEM	PREFERRED TERM				
UROGENITAL SYSTEM	--TOTAL--	1	1.9	1	1.9
	DYSURIA	1	1.9	1	1.9

Source: Table 9.1-3 applicant's study report for Study 023

Table 2: Summary of patients in the lumefantrine tablet group with AEs which started after baseline

TREATMENT B tablets

		TREATMENT			
		B tablets			
		SEVERITY OF ADVERSE EXPERIENCE		ALL	
		MILD			
		N	%	N	%
BODY SYSTEM	PREFERRED TERM				
--ALL--	WITH EXPERIENCES	9	17.6	9	17.6
BODY AS A WHOLE	--TOTAL--	4	7.8	4	7.8
	ASTHENIA	1	2.0	1	2.0
	FATIGUE	2	3.9	2	3.9
	FEVER	1	2.0	1	2.0
CARDIOVASCULAR SYSTEM	RIGORS	2	3.9	2	3.9
	--TOTAL--	1	2.0	1	2.0
DIGESTIVE SYSTEM	PALPITATION	1	2.0	1	2.0
	--TOTAL--	5	9.8	5	9.8
NERVOUS SYSTEM	ANOREXIA	2	3.9	2	3.9
	DIARRHEA	1	2.0	1	2.0
	NAUSEA	3	5.9	3	5.9
	PAIN ABDOMINAL	1	2.0	1	2.0
RESPIRATORY SYSTEM	--TOTAL--	5	9.8	5	9.8
	HEADACHE	5	9.8	5	9.8

Source: Table 9.1-3 applicant's study report for Study 023

Table 3: Summary of patients in the lumefantrine capsule group with AEs which started after baseline

TREATMENT B capsules

		TREATMENT					
		B capsules					
		SEVERITY OF ADVERSE EXPERIENCE				ALL	
		MILD		MODERATE			
		N	%	N	%	N	%
BODY SYSTEM	PREFERRED TERM						
--ALL--	WITH EXPERIENCES	7	14.0	2	4.0	9	18.0
BODY AS A WHOLE	--TOTAL--	1	2.0			1	2.0
	FATIGUE	1	2.0			1	2.0
DIGESTIVE SYSTEM	--TOTAL--	3	6.0			3	6.0
	ANOREXIA	1	2.0			1	2.0
	PAIN ABDOMINAL	2	4.0			2	4.0
NERVOUS SYSTEM	--TOTAL--	2	4.0	2	4.0	4	8.0
	HEADACHE	1	2.0	2	4.0	3	6.0
	SLEEP DISORDER	1	2.0			1	2.0
RESPIRATORY SYSTEM	--TOTAL--	1	2.0			1	2.0
	PHARYNGITIS	1	2.0			1	2.0
UROGENITAL SYSTEM	--TOTAL--	1	2.0			1	2.0
	STRANGURY	1	2.0			1	2.0

Source: Table 9.1-3 applicant's study report for Study 023

ECGs

ECG monitoring was performed on Days 1 (pre-treatment), 2, 4, 8 and 29. The electrocardiograph recorded the tracings and automatically classified them as "normal"; "borderline" (this included for example tachycardia, early transition patterns, non-specific T wave and ST segment abnormalities); and "abnormal" (including 2 or more changes, mostly non-specific T wave and non-specific ST segment abnormalities, long QT or short PR interval).

At baseline, 42% of patients' ECG's were classified as "normal" in the Coartem group and 49% and 50% respectively in the other two groups. On Day 2 most of ECGs were classified as "normal". The tracings of the majority of patients showed some small variations during the trial. These variations were similar in the treatment groups and no clinically relevant pattern was identified. All these variations were assessed as normal and not clinically relevant by the investigators in the context of malaria.

The heart rate was high at baseline, probably due to pyrexia, but decreased after baseline, reflecting resolution of the initial fever-induced tachycardia. Compared to baseline, the QT interval was prolonged slightly on Days 2, 4 and 8 but returned to baseline by Day 29. When the QT interval was corrected for heart rate (QTc), using the Bazett formula ($QTc = QT / \sqrt{RR}$) the difference between the baseline and Day 2, 4 and 8 values disappeared. The median change from baseline on Day 2 negative (-0.7%) for patients on Coartem and a 0.4% increase or no increase for patients in the lumefantrine groups.

Only two patients showed more than a 20% increase in QTc: patient No. 110 (Coartem) had an increase from 328 to 420 msec (28%) on Day 2, and patient No. 109 (B capsules) from 443 to 555 msec (25.3%) on Day 2 and normalized thereafter.

No new symptoms relating to the cardiovascular system (other than palpitation in one case) were recorded as an adverse experience after baseline.

Clinical Labs

Several laboratory parameters were below normal at baseline as a consequence of the disease status at presentation (e.g. decreased hemoglobin/hematocrit, WBC count, and platelet count) but increased to the normal range in many patients during the trial.

- At baseline, 16% of the patients had hemoglobin below the normal range, and hematocrit was below the normal range in about 62% of the patients. The values further decreased during the first days but improved by Day 29.
- WBC count was below the normal range at baseline in about 18% of the patients in all groups; these values also tended to improve during the trial.
- Absolute neutrophil count decreased slightly on Days 2 and 4 in all treatment groups and returned to normal on Day 29.

- The number of circulating lymphocytes was below normal at baseline in all three treatment groups and returned to normal over the course of the therapy, with a tendency toward an increase above normal range.
- There was also an increase in absolute eosinophils recorded on Day 29.
- About 21% of the patients had a platelet count below the normal range at baseline, but by Day 8 more than 95% of the patients had normal values.

Total bilirubin values were high (NIH Grade 3-4) in about 30% of patients at baseline in all groups; by Day 8 most patients had returned to normal values, as shown in Table 4 below.

Table 4: Bilirubin levels for patients in Study A023

Laboratory test=Bilirubin (total)

Treatment	Baseline	ALL (Day 1)	Day 2					Day 4					Day 8					Day 29			
			NIH grade					NIH grade					NIH grade					NIH grade			
			N	0	2	3	4	N	0	2	3	4	N	0	2	3	N	0	2	3	
CGP 56697	Baseline	30		29	1			1	28	1				1	27	2			1	28	1
	NIH grade 0	5		5				4	1					3	2				5		
	NIH grade 2	9		6	3			9						9					7	1	1
	NIH grade 3	8		4	1	2	1		6		1	1		8					7	1	
	NIH grade 4	52		44	5	2	1	1	47	2	1	1	1	47	4				1	47	2
B tablets	Baseline																				
	NIH grade 0	26	1	25				1	24		1		1	24	1			1	23	1	1
	NIH grade 2	8		3	4	1			8					7	1				8		
	NIH grade 3	9		3	3		3		7	1	1			9					7		2
	NIH grade 4	8		5	1		2		7			1		8					7	1	
	ALL (Day>1)	51	1	36	8	1	5	1	46	1	2	1	1	48	2				1	45	2
B capsules	Baseline																				
	NIH grade 0	27	1	24	2			1	25			1	1	24		2	1	24	2		
	NIH grade 2	10		9	1				10					10					9	1	
	NIH grade 3	5		1	3	1			4			1		5					5		
	NIH grade 4	8		6	1	1			7			1		6	2				7	1	
	ALL (Day>1)	50	1	40	7	2		1	46			3	1	45	2	2	1	45	4		

Source: Table 9.6-1 in the applicant's study report for Study 023

SGPT (ALT) and SGOT (AST) showed slight variations in most patients and by Day 29 only one patient had a value above NIH grade 1.

Safety Summary

The safety profile was similar between the treatment arms. There were no deaths or serious AEs and no patient discontinued from the study due to an AE. Only a small percentage of patients experienced AEs, mostly mild severity, which started or worsened after baseline. Headache and anorexia occurred in ≥ 2 patients in all treatment groups. Other AEs occurring in ≥ 2 patients after baseline included abdominal pain in the Coartem and B capsules group, nausea and rigors (in the B tablet group, and fatigue in both lumefantrine groups. The low, abnormal laboratory values that were reported most likely reflected changes due to malaria rather than effects of the treatments, since they mostly improved over the course of the study.

SAFETY REVIEW: STUDY ABMO2

In the following discussion, A refers to artemether, B to lumefantrine, and A+B is Coartem.

Five patients were excluded from the safety analysis. Patients #71 (A+B), #223 (A) and #230 (A+B) had no visit with a completed laboratory test and ECG measurement after baseline, and patients #159 (A+B) and #169 (A) had no laboratory test after Day 4. Therefore, there were 102 patients included in the safety population (50/53 randomized to A+B, 50/52 randomized to A, and 52/52 randomized to B).

None of the patients died or has a serious adverse event (SAE) or discontinued to an adverse event (AE) and/or abnormal laboratory abnormalities.

The patients were asked about presenting symptoms and complaints at the screening visit. All 157 patients were recorded as having fever, 153 patients were recorded as having chills, 32 patients had headache, 22 dizziness, 18 rigors, 14 general aching, 3 backache, 1 abdominal pain and 1 patient stomach ache. All of these symptoms were recorded as "still present" at the start of the trial (except chills for 22 patients, fever for 2 patients and rigors for 13 of the 18 patients), but were not recorded again during the trial. The incidence of these presenting symptoms at the start of the trial was the same in the three treatment groups.

Three patients had "signs and symptoms of complicated/severe malaria" at the start of the trial. Patient #91 (A) had enlarged spleen from baseline until Day 8 (3 cm palpable below ribs at baseline, 2 cm on Days 2-7 and 1 cm on Day 8). Patient #59 (A+B) had enlarged liver from baseline until Day 8 (2 cm below costal margin) and patient #79 (B) had enlarged liver during the whole trial period (2 cm below costal margin).

"Other signs/physical findings not related to malaria" were recorded during the trial for 5 patients treated with A (#76 had tonsillitis; #112 caught a cold; for #91, #216 and #226 the specific symptom was not recorded but occurred while receiving rescue medication) and 6 patients treated with B (#88, #107, #126 and #160 caught a cold; #214 had recorded diarrhea and bloody stool; and #154 caught a cold, sore throat, tonsillitis between Days 16-21 and had also had unknown signs/findings while receiving rescue medication after Day 25). No patient treated with A+B reported any other signs/physical findings not related to malaria.

In total 30 patients were recorded as having a cold (11 treated with A+B, 9 treated with A and 10 treated with B). Tonsillitis was reported for 4 patients (2 treated with A and 2 treated with B).

During the trial only 2 AEs were recorded in on patient. Patient #214 (B) had diarrhea on Days 3, 4 and 5 and purulent and bloody stool on Days 4 and 5.

For Patient #228 (A) "Possible malarial hepatitis" was recorded before he had recrudescence at Day 12.

ECGs

The heart rate decreased for patients from a median of 88 bpm at baseline to 66 bpm on Day 2 for patients treated with A+B, from 83.5 bpm to 61 bpm for patients treated with A and from 86.5 bpm to 72 bpm for the patients treated with B, as would be expected in patients being treated for acute malaria.

Forty-six patients had "Nonspecific T wave abnormality" recorded on the ECG machine print-out: 15 treated with A+B (8 of those had the abnormality present or only recorded at baseline), 14 treated with A (11 of those had the abnormality present or only recorded at baseline) and 17 treated with B (6 of those had the abnormality present or only recorded at baseline).

After initiation of treatment, 8 patients (4 treated with A+B, 2 treated with A and 2 treated with B) developed "First degree AV block." The comment "RSR(QR) in lead V1N2 consistently with right ventricular conduction abnormality" or "nonspecific intraventricular conduction delay" was made for 20 patients: 6 treated with A+B (in 2/6 it was present at baseline), 5 treated with A and 9 treated with B (in 2/9 it was present at baseline).

A comment about "Voltage criteria for LVH" was recorded for 22 patients after initiation of treatment (4 treated with A+B, 9 treated with A and 9 treated with B).

After initiation of treatment 7 patients had the comment "sinus rhythm with supraventricular premature complexes" recorded (4 treated with A+B, 1 treated with A and 2 treated with B). An additional 8 patients had a comment recorded about "atrial rhythm" (3 treated with A+B, 2 treated with A and 3 treated with B). One patient treated with A+B had both of these comments recorded.

QTc

ECGs were recorded using a portable ^{(b) (4)} machine with automatic print-out and analysis. The QTc was calculated by the ECG machine using the formula: $QTc = QT + (1000 - RR \text{ interval})/7$. In some of the ECGs the QT interval was difficult to define due to T-wave abnormalities and/or superimposed U-waves. Therefore, the sponsor acknowledges that some of the QT intervals might have been overestimated by the computer program.

QTc was also calculated by using Bazett's formula ($QTc = QT / \sqrt{RR}$, where RR was given in seconds (=60/heart rate)). In general, the baseline values using Bazett's formula were higher and the interval longer than those reported using the ECG machine's values.

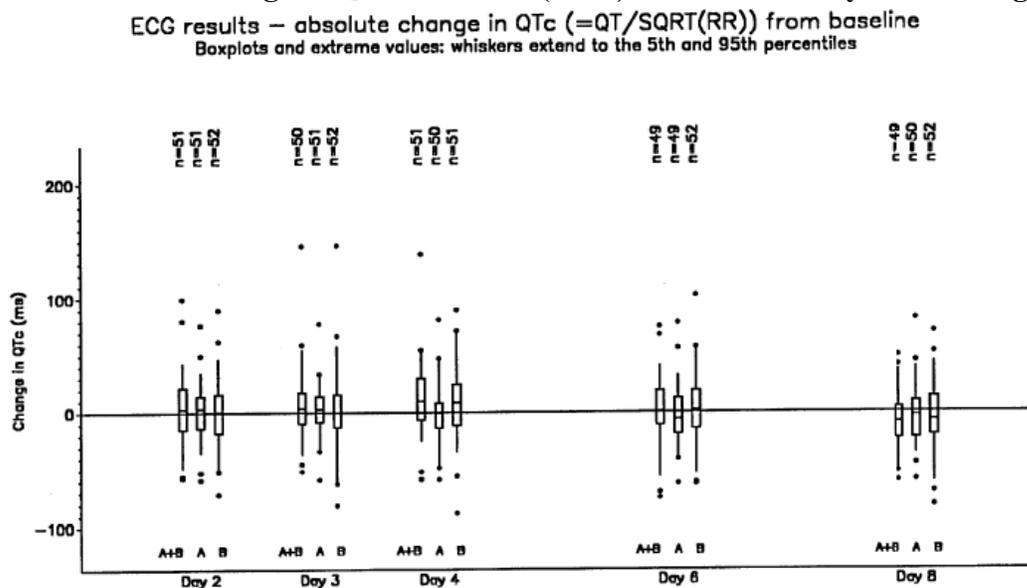
Using Bazett's formula, 12 patients had a QTc of more than 500 msec recorded during the study (3 treated with A+B, 1 treated with A, and 8 treated with B). Patient #139 (B) had a QTc value of 558 msec recorded on Day 3 and Patient #142 (B) 547 msec on Day 4.

Four patients had a >25% percentage increase in QTcB interval (Patients #159 (A+B), #133 (A), #139 (B) and #154 (B)).

Nineteen patients (8 treated with A+B, 2 treated with A and 9 treated with B) had a QTcB value >50 msec recorded during the study.

Figure 1 shows the absolute change in QTc interval from baseline using Bazett's formula by treatment group and appears to be similar between the groups.

Figure 1: Absolute change in QTcB interval (msec) from baseline by treatment group



Source: Figure 9.5-12 in the sponsor's study report ABMO2

Clinical Laboratory

Hemoglobin, hematocrit, and RBC count were below the normal range for the majority of patients at baseline and did not resolve by the follow-up visit. Whereas the platelet count was below baseline in many patients, it increased for nearly all patients by the follow-up visit.

At baseline, creatinine was above the normal range and equal to NIH grade 2 in two patients (1 treated with A and 1 treated with B), but there were no patients during the study who had an elevation in creatinine above grade 1. Patients with values equal to NIH grade 1 were 9 (baseline), 7 (Day 4) and 10 (follow-up) patients treated with A+B; 13, 8 and 9 patients treated with A; and 12, 2 and 11 patients treated with B.

Total bilirubin was above normal range at baseline for 18 patients treated with A+B (15 grade 2, two grade 3, and 1 grade 4). By Day 4, all but 3 patients had a return to baseline; however, at follow-up 15 patients had a grade 2 value and one patient had a grade 3 value. In the group treated with A, seventeen patients had a grade 2 bilirubin value and 7 had a grade 3 value at baseline. At Day 4 and follow-up, the number of patients with grade 2 or grade 3 values was 5 and 25, respectively. Finally, in those patients treated with B, there were 29 (baseline), 13 (Day 4), and 28 (follow-up) patients with grade 2 or 3 abnormalities. One patient treated with B had a grade 4 bilirubin value at baseline and continued to have a grade 3 elevation at follow-up

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

SGOT values above the normal range (NIH grades 1) were seen for 2 (baseline), 3 (Day 4) and 12 (follow-up) patients treated with A+B; for 4, 5 and 12 patients treated with A; and for 6, 6 and 12 patients treated with B. NIH grade 2 values were reported at follow-up for 4 patients (1 treated with A+B, 2 treated with A, and 1 treated with B).

SGPT values above the normal range (NIH grade 1) were seen for 2, 1 and 5 patients treated with A+B; for 0, 4, and 5 patients treated with A; and for 1,1 and 5 patients treated with B.

Appears This Way On Original

SAFETY REVIEW: STUDY A025

Title: A randomized, double-blind, parallel group trial comparing efficacy, safety and pharmacokinetics of the standard schedule (4x4 tablets over 48 hours) with two higher dose schedules of Coartem in the treatment of acute *Plasmodium falciparum* malaria in adults and children in Thailand

Study dates: September 1996-March 1997

This was a randomized, double-blind, parallel group, 2 center, 4 week trial to compare the efficacy, safety and pharmacokinetics of the standard 4 dose regimen over 48 hours to two other dose regimens of Coartem, given in 6 doses over 60 hours and 6 doses over 96 hours, in adults and children > 2 years with acute, uncomplicated *P. falciparum* malaria.

Suitable patients who presented to the following hospitals were randomly allocated to one of the three trial treatments

- Centre 1: Hospital for Tropical Diseases, Faculty of Tropical Diseases, Mahidol University, Bangkok, Thailand (Inpatients)
- Centre 3: MaeLa Camp, SMRU, Mae Sot, Thailand (Outpatients)

The patient population included male and female children (>2 years) and non-pregnant adults with acute, uncomplicated *P. falciparum* malaria.

The sample size of 366 patients (120 in Bangkok, 246 in MaeLa) was planned in order to demonstrate superiority of either of the two higher dose regimens over the 4 dose regimen in terms of the 28 day cure rate.

Patients who met the inclusion criteria were allocated in equal numbers to one of the three treatment groups, receiving Coartem, formulation F4 (Final Market Image). Each tablet contained 20 mg artemether and 120 mg lumefantrine:

- 48 hours regimen: 4 doses of 1, 2, 3 or 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)
- 60 hours regimen: 6 doses of 1, 2, 3 or 4 tablets over 60 hours (plus placebos at 2 time points) = (total dose: 480 mg artemether and 2,880 mg lumefantrine)
- 96 hours regimen: 6 doses of 1, 2, 3 or 4 tablets over 96 hours (plus placebos at 2 time points) = (total dose: 480 mg artemether and 2,880 mg lumefantrine)

All patients received 4 tablets (active or placebo) at each of the 8 dosing points from the individual patient medication pack. In MaeLa, the number of tablets per dose was adjusted according to patient body weight as follows:

- >35 kg: 4 tablets per dose`

- 25-35 kg: 3 tablets per dose
- 15-25 kg: 2 tablets per dose
- ≤ 15 kg: 1 tablet per dose

All malaria related symptoms at baseline were recorded in the CRF as adverse experiences (AEs) and not as medical history. The day the patient was first seen was also the day treatment started and therefore this date was mostly used as the start date for any malaria symptoms. All AEs were obtained by questioning and/or examining the patient. Any worsening of a medical condition that was present at the initial visit was reported as a new AE.

Severity of an AE was defined by the qualitative assessment of the intensity as determined by the investigator or reported by the patient. The severity was assessed irrespective of drug relationship or seriousness of the experience and was evaluated according to the following scale:

- 1 = Mild (=NIH Grade 1)
- 2 = Moderate (=NIH Grade 2)
- 3 = Severe (=NIH Grade 3)
- 4 = Life Threatening (=NIH Grade 4)

Safety monitoring and tolerability evaluations included physical examinations, vital signs, ECGs and neurological examinations. All ECG tracings were evaluated by an independent cardiologist focusing on QTc prolongation and compared with the automatic ECG printouts. Patients also underwent clinical laboratory evaluations for hematological, biochemical, and urine parameters.

Safety and tolerability were evaluated by:

- ECG changes in QTc from baseline on Days 3,4, 5, 8 and 29 (based on findings evaluated by an independent Peer Reviewer);
- Clinically significant laboratory changes (in terms of NIH/NCI Common Toxicity Criteria);
- Neurological changes from baseline and on Days 5, 8, and 29;
- The incidence, severity, and relationship of new AEs.

Safety and tolerability assessments were summarized for the ITT patient population, defined as all patients allocated to randomized treatment who received at least one dose of trial medication.

Reviewer's comments: ECGs and clinical laboratory evaluations were only performed in the Bangkok site, while neurological examinations were performed at MaeLa only.

Statistical methodology

Adverse experiences were originally summarized by IMN preferred terms and COSTART body system. In the datasets submitted to the Agency MedDRA terms were used.

Disposition of Patients: As can be seen in the following table, AEs were assessed in 359 patients. EKG and PK data was obtained in progressively fewer patients as the study duration increased.

Table 1: Distribution of patients by treatment group

Number of patients	4 doses 48 hours	6 doses 60 hours	6 doses 96 hours	Total	
Enrolled / Randomised	120	118	121	359	
Centre 1 (Bangkok) / Centre 3 (MaeLa)	34 / 86	32 / 86	34 / 87	100 / 259	
Incomplete treatment course	2	1	7	10	
Discontinued prematurely					
Total	35	23	18	76	
For "Unsatisfactory therapeutic response"	20	4	2	26	
For "Death"	2	-	-	2	
For "Lost to follow-up"	11	19	15	45	
For "Administrative problems"	-	-	1	1	
For "Does not meet protocol criteria"	1	-	-	1	
For "Non-compliance"	1	-	-	1	
Efficacy analyses					
ITT (28 day cure rate, PCT)	120	118	121	359	
Evaluable patients (28 day cure rate)	104	96	106	306	
Evaluable patients (FCT)	61	59	80	200	
Safety analyses					
Adverse experiences	120	118	121	359	
Laboratory tests					
Day 1	113	115	120	348	
Day 4	114	114	116	344	
(Bangkok only) Day 6)	(34)	(31)	(33)	(98)	
Day 8	112	107	107	326	
Day 29	85	88	96	269	
ECG (Bangkok only)					
Day 1	34	32	34	100	
Day 3	33	29	34	96	
Day 4	33	31	33	97	
Day 5	32	30	34	96	
Day 8	32	32	34	98	
Day 29	20	26	28	74	
Pharmacokinetics					
Complete pharmacokinetic profile	Bangkok	17	18	17	52
Population kinetics	MaeLa	75	75	75	225

Extent of Exposure

16 patients did not receive all doses, including 10 patients who did not receive the full course of active trial treatment (2 on the 48 hours regimen, 1 on the 60 hours regimen and 7 patients on the 96 hours regimen) as well as 6 patients who received placebo.

Of the 359 patients, 14 (3.9%) had a body weight below 15 kg and received one tablet at each dosing point, 19 (5.3%) weighed between 15 and 25 kg and received two tablets, and 15 (4.2%) who weighed between 25 and 35 kg received three tablets. The other 311 (86.6%) who weighed

more than 35 kg received 4 tablets per dose. In the 48, 60 and 96 hour regimens, 13, 20, and 14 patients, respectively weighed less than 35 kg and received less than 4 tablets per dose.

Patients on the 48 hours regimen received a median of 6.4 mg/kg total dose of artemether per kg body weight (25-75th percentiles (5.8, 7.1) and a median of 38.4 mg/kg (34.9, 42.7) total lumefantrine dose. Patients on the two higher doses (i.e. 150% of the standard dose) had a median of 9.6 mg/kg (8.7, 10.7) and 9.8 mg/kg (8.9, 10.9) for artemether and 57.9 mg/kg/(52.4, 64) and 58.8 mg/kg (53.3, 65.5) for lumefantrine

Results: Safety and tolerability

60% of the patients in all three treatment groups presented with malaria symptoms including headache (> 80%), anorexia (> 75%), asthenia (> 66%), arthralgia (> 60%), myalgia (> 59%), and dizziness (>58%). Other malaria symptoms recorded in about 30 to 45% of the patients at baseline were nausea, rigors, sleep disorder, vomiting and palpitation; about 20 to 30% of the patients presented with fatigue, abdominal pain, splenomegaly and hepatomegaly. Malaria symptoms which were present at baseline disappeared rapidly with treatment in all groups. Resolution of rigors, nausea, fatigue and sleep disorder was faster than resolution of headache, anorexia, and dizziness. Fatigue, anorexia, dizziness and sleep disorder persisted in a few patients on the 60 hours regimen, despite resolution of acute malaria.

Overall, about two thirds of the patients in each treatment group presented with AEs after baseline but before reappearance of parasites. Only a few patients (4 who received the 48 hours regimen, 3 and 1 patient in the higher doses respectively) had AEs recorded after reappearance of parasites.

In all three treatment groups headache was the most frequent AE recorded after baseline. Dizziness, as a new occurrence or worsening, was recorded in twice as many patients on the 48 and 60 hour regimens (20% and 19.5% respectively) as in those on the 96 hours regimen (10.7%). Asthenia and anorexia were reported in more patients on the 48 hours regimen than in patients treated with the higher doses, although the differences between the groups are small. Symptoms of the digestive system started, or worsened after baseline, in 29.2%, 21.2% and 33.9% of patients in the three treatment groups respectively. The biggest differences were for abdominal pain, nausea and vomiting which were recorded for more patients on the 96 hours regimen than for the other doses.

Eight patients (6.7%) on the 48 hours regimen had one or more severe AEs recorded. These included splenomegaly in 5 patients, headache in 2 patients, and vomiting and abnormal laboratory values in one patient each. Malaria recrudescence was recorded in the CRF as "life threatening parasitic infestation", and was also reported as SAE (Patient No. 46). In the 60 hour regimen, 6 patients (5.1%) presented with severe AEs: 5 patients with splenomegaly and one patient with anorexia. In the 96 hour regimen, 7 patients (5.8%) presented with at least one severe AE: 5 patients with splenomegaly, one patient each with asthenia and headache, and one patient with both nausea and vomiting.

Percentage of patients with related adverse experiences

A similar percentage of patients in each treatment group presented with treatment-related AEs: 16.7% (20 patients), 16.1% (19 patients), and 14.9% (18 patients) respectively. All these AEs were mild in severity with the exception of one moderate urticaria and one moderate abdominal pain, which both occurred in a patient treated with the 60 hours regimen.

The treatment-related AEs which occurred in more than 3% of the patients on the 48 hours regimen were: 7 cases (5.8%) of anorexia, 5 cases (4.2%) each of arthralgia, myalgia and dizziness, and 4 cases (3.3%) of asthenia. For the 60 hour regimen, the AEs assessed to be related to treatment were: 6 cases (5.1%) of anorexia, 5 cases (4.2%) each of asthenia and palpitation, 4 cases (3.4%) of dizziness. For the 96 hour regimen, these AEs were: 6 cases (5.0%) of asthenia, 5 cases (4.1%) each of nausea and myalgia, 4 cases (3.3%) each of palpitation and dizziness.

Serious adverse experiences and premature discontinuations

Serious AEs were reported for 4 patients on the 48 hour regimen and for one patient who received the 96 hour regimen. Two of these patients died due to the SAE - one patient was shot by a military group (patient No. 197) and one patient was killed when he stepped on a mine (patient No. 420). The other SAEs were: chronic hepatitis (patient No. 21 who received the 48 hours regimen), severe malaria (patient No. 46 who was on the 48 hours regimen), typhoid fever (patient No. 41 on the 96 hours regimen).

Patient No. 46 who presented with severe malaria was discontinued from the study. None of the other patients discontinued prematurely due to an AE or laboratory abnormalities.

Patient narratives of serious adverse experiences and premature discontinuations

Center/Patient number: 1 / 21

Treatment group: Coartem 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 20 years Sex: Male Weight: 45 kg

Adverse experience: Chronic hepatitis

Relationship to trial treatment: Not related

Prematurely discontinued: No

Discussion: The patient was randomized to the standard 4 dose regimen and was admitted to the hospital ward for the 28 day trial period. He started the trial treatment on ^{(b) (6)}. He received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, and 48 h plus placebo at 36 h and 60 h, 72 h and 96 h to match the other treatment groups. No previous relevant medical history and medication were recorded. Since admission to the hospital at trial start persistent elevated levels of liver enzymes AST (SGOT: 88 UL on 14-Nov-97) and ALT (SGPT: 141 on 14-Nov-96) were recorded. On day 29 an increase of AST (SGOT: 900 UL on 12-Dec-96) and ALT (SGPT: 795 on 12-Dec-96) was measured. Four days later, on 16-Dec-96 the liver enzyme values were still high (SGOT: 826 UL, SGPT: 750 U/L). On 23-Dec-96 the values had dropped (SGOT: 290 UL, SGPT: 437 UL). The liver enzyme tests together with the ELISA tests confirmed the diagnosis of chronic hepatitis

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

and the patient had no clinical signs of acute hepatitis. On 12- Dec-96 treatment with lipochol was initiated. The patient's condition improved, the liver enzyme values decreased. On the (b) (6) the patient was discharged from the hospital. He did not return for the follow-up visit, no other laboratory test values are available.

Center/patient number: 1/141

Treatment group: CGP Coartem 6 x 4 tablets over 96 hours (plus placebos at 2 time points) = (total dose: 480 mg artemether and 2,880 mg lumefantrine)

Age: 20 years Sex: Male Weight: 53 kg

Adverse experience: Typhoid fever

Relationship to trial treatment: Not related

Prematurely discontinued: No

Discussion: The patient was randomized to the 96 hours regimen, and was admitted to the hospital ward for the 28 day trial period. He started trial treatment on (b) (6) and received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, 48 h, 72 h and 96 h plus placebo at 36 h and 60 h to match the other treatment groups. He recovered from malaria within 72 h. On 30-Dec-96, a Widal test for typhoid fever was performed and a titer of 1:40 was measured. Two days later, on 01- Jan-97 the patient's temperature rose to 40.6 OC and typhoid fever was suspected. The patient was treated with IM cephalosporin (from 02-Jan-97 to 11-Jan-97), oral metronidazole (from 02-Jan-97 to 12-Jan-97), IM chloramphenicol (from 03-Jan-97 to 13-Jan-97) and with oral indomethacin (from 03-Jan-97 to 12-Jan-97). On 03-Jan-97 the diagnosis of HIV was made. On 09-Jan-97 his temperature had dropped to 37.8 °C. One week later, on 15-Jan-97 the patient's temperature was 37.3 OC and the Widal titer had increased to 1:80. The patient's condition was diagnosed as likely typhoid fever by the investigator. Due to the SAE the patient's hospitalization was prolonged until the (b) (6) when the patient had completely recovered from the typhoid fever and was discharged.

Center/patient number: 1/146

Treatment group: Coartem 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 28 years Sex: Male Weight: 55 kg

Adverse experience: Severe malaria

Relationship to trial treatment: Not related

Prematurely discontinued: Yes

Discussion: The patient was randomized to the standard 4 dose regimen, and was admitted to the hospital ward for the 28 day trial period. He started the trial treatment on (b) (6) and received the first two doses, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) at 0 and 8 h. Despite treatment the patient's condition deteriorated to severe malaria within 12 hours and high levels of bilirubin, creatinine and urea were measured. He was discontinued from the trial and transferred to the ICU for rescue medication (artesunate IV 60 bid from 13-Jan-97 to 17-Jan-97). The patient completely recovered and was discharged from the hospital on (b) (6).

Center/Patient number: 3/197

Treatment group: Coartem, 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 37 years Sex: Male Weight: 54 kg

Adverse experience: Shot by military group

Relationship to trial treatment: Not related

Prematurely discontinued: Yes

Discussion: The patient was randomized to the standard 4 dose regimen and started the trial treatment on 17-Oct-96. He received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, and 48 h plus placebo at 36 h and 60 h, 72 h and 96 h to match the other treatment groups. The malaria smear was negative on 18-Oct-96. When the patient did not come back for a follow-up visit it was found that he had been shot by a military group and died on (b) (6).

Center/patient number: 3/420

Treatment group: Coartem 4 x 4 tablets over 48 hours (plus placebos at 4 time points) = (total dose: 320 mg artemether and 1,920 mg lumefantrine)

Age: 36 years Sex: Male Weight: 42 kg

Adverse experience: Injury by foreign body

Relationship to trial treatment: Not related

Prematurely discontinued: Yes

Discussion: The patient was randomized to the standard 4 dose regimen and started the trial treatment on 20-Jan-97. He received the full treatment course, i.e. 4 tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) each at 0, 8 h, 24 h, and 48 h plus placebo at 36 h and 60 h, 72 h and 96 h to match the other treatment groups. He recovered from malaria within 48 hours. On (b) (6) the patient stepped on a mine while walking in the fields and died immediately.

Deaths

Two patients died during the trial for reasons totally unrelated to either the disease or the treatment - one patient was shot by a military group (patient No. 197) and one patient was killed when he stepped on a land mine (patient No. 420).

Safety monitoring and tolerability evaluations

Electrocardiographic monitoring of the patients in Bangkok was performed at baseline, on Days 3, 4, 5 (normally about 4 to 6 hours after dosing), and Days 8 and 29. A comprehensive, blinded review of all the tracings (focusing on QTc) was performed by an independent cardiologist.

The mean and median QTc values were not affected by any of the treatments. No patient had an absolute QTc value measured by Peer Review above 500 msec after baseline. The three patients (patient Nos. 1, 6 and 19) who had a baseline QTc of 566, 582 and 512 msec (peer review) had normal values after baseline. Two patients (patient Nos. 58 and 75) with QTc above 500 msec on Day 8 were both evaluated as normal (with values of 385 and 413 respectively) by the peer review.

Five patients had an increase of more than 60 msec after baseline (patient No. 79 on the 60 hours regimen, patient Nos. 34, 39, 85, and 110 on the 96 hours regimen), but only in 2 of those cases, did the QTc exceed the normal limit of 430 msec (male) or 450 msec (female) respectively (patient Nos. 79 and 110). Another 11 patients had an increase of more than 30 msec which led to a QTc value of higher than 430/450 msec (patient Nos. 4, 24, 73, 78, 82, 108 on the 48 hours regimen, patient No. 25 on the 60 hours regimen, and patient Nos. 32, 44, 83 and 92 on the 96 hours regimen). The Peer Reviewer examined individual patients with the largest increases in QTc or a high QTc value. The review took into account the patient's electrolyte imbalances, general status (*i.e.*, dehydration) and concomitant medication.

Neurological examinations were performed at MaeLa only, at baseline and on Days 5, 8, 29 and 63. At baseline, abnormal neurological findings were recorded for 4 patients and were due to malaria (*e.g.* gait abnormal, tremor, Romberg test positive). During the trial, two of these patients still had abnormal findings on Days 5 and 8, and patient No. 184 had "hearing decreased" reported after the neurological test on Day 8, which resolved at the 4 week follow-up visit. There were no abnormal neurological findings thereafter. All the symptoms detected were recorded as AEs.

Clinical laboratory evaluations

Data are from about 30 patients in each treatment group who were treated in Bangkok. At baseline, a few patients in all three groups presented with severe anaemia. On Day 4, there was a worsening of anaemia in all treatment groups, but by Day 8 there was an improvement, and by Day 29 most patients had NIH Grade 0 or 1 hemoglobin values

A few patients in each treatment group had severe thrombocytopenia at presentation, which improved rapidly; on Day 8, more than 90% of the patients had NIH grade 0 values. However, on Day 29 a few patients showed a minimal decrease in platelets count, presenting with NIH grade 1 values (17%, 14.8%, and 9.5% in the three treatment groups respectively. These small shifts were of no clinical significance.

All the values concerning white blood cells over the course of the trial showed changes typical of malaria in all three treatment groups. The leukopenia at presentation was not very pronounced in any of the groups, and improved slightly over time.

Reticulocytes increased on Day 8 in all three treatment groups, reflecting increased hematopoiesis in the setting of anemia.

Liver function tests (LFTs) did not show any significant changes, other than those related to disease resolution: all parameters normalized over the course of treatment. One patient (No. 21) had a chronic hepatitis, reported as an SAE. One patient (No. 106) had abnormal bilirubin, alkaline phosphatase, SGOT and SGPT at baseline, and a further small increase of these liver enzyme values on Day 4. All LFTs decreased thereafter, and were normal on Day 29. One patient (No. 93) had minimal alterations of all liver function tests at baseline, and an additional small increase of SGOT and alkaline phosphatase on Day 4 and 6 and of SGPT on Day 4,

whereas bilirubin started to decrease already on Day 4. All values had returned to normal by the end of the trial.

Kidney function, as measured by creatinine and BUN, did not show any pronounced change over the course of the trial. One patient (No. 46), presented with abnormal values at entry, which persisted over the course of the trial. He was discontinued from the trial due to disease progression.

The results of the other laboratory tests performed (serum electrolytes, total serum protein, serum albumin), were very similar in all treatment groups and did not show any change after baseline, other than a tendency toward normalization.

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SAFETY REVIEW: STUDY 026

Title: A randomized trial confirming efficacy and safety of the high dose regimen of Coartem (in comparison with mefloquine + artesunate) in the treatment of acute *Plasmodium falciparum* malaria in adults and children in Thailand

Trial period: 12-Nov-97 to 9-Mar-98

Summary: This was a randomized, open-label, comparative, parallel group, 2 centre, 4 week trial to confirm the efficacy and safety of Coartem, given in 6 doses over 3 days in adults and children ≥ 2 years with acute, uncomplicated *P. falciparum* malaria. For comparison with historical data, a control arm (MAS) was included in this trial. The trial was conducted at two centers:

- Centre 1: Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Centre 2: MaeLa Camp, SMRU, Mae Sot, Thailand

Patients in Centre 1 were admitted for in-patient observation for the 28 day trial period, whereas patients in Centre 2 were treated as outpatients and seen daily for the first week, thereafter weekly until Day 29. Some patients in this centre also attended a long-term follow-up on Days 36 and 43, according to this hospital's practice.

As 28 day cure rates with the two 6-dose regimens given over 3 or 5 days were similar in trial 025, the shorter regimen which was expected to have better compliance was chosen. The number of tablets per dose was adjusted according to body weight as in the previous trial 025.

The aim of the trial was to confirm the safety and efficacy of the 6-dose regimen of Coartem given over 3 days. Efficacy was assessed by the 28 day cure rate, parasite reduction and proportion of patients with negative slide on Days 2, 3 and 4, and anti-gametocyte activity. Safety and tolerability were assessed by standard haematological and biochemical parameters, QTc measurements and adverse experiences (AEs) reported spontaneously by the patients or obtained from direct questioning of the patient. Plasma samples were collected to explore any relationship between any change in QTc measurements and lumefantrine plasma levels.

Patients allocated to Coartem received tablets at 0 and 8 hours, and twice daily in the following 2 days. Each tablet contained 20 mg artemether and 120 mg lumefantrine. The number of tablets per dose given was adjusted by body weight:

- ≥ 35 kg: 4 tablets per dose
- ≥ 25 and < 35 kg: 3 tablets per dose
- ≥ 15 and < 25 kg: 2 tablets per dose
- < 15 kg: 1 tablet per dose

Patients allocated to MAS received artesunate 4 mg/kg/day once daily for 3 days, plus mefloquine 25 mg/kg given as a split dose of 15 mg/kg plus 10 mg/kg on Days 2 and 3. For both

artesunate (50 mg tablets) and mefloquine (250 mg tablets), the exact dosage per kg body weight was determined and calculated to the nearest quarter tablet at trial entry.

The main safety evaluation was based on the proportion of patients with AEs after baseline but before reappearance of parasites (TESS), as malaria related symptoms at baseline were recorded in the CRF as adverse experiences (AEs) and not as medical history. All AEs were obtained by questioning and/or examining the patient. Any worsening of a medical condition that was present at the initial visit was reported as a new AE. Any abnormality detected by the neurological examination was recorded as an AE.

Severity of an AE was defined by the qualitative assessment of the intensity as determined by the investigator or reported to him/her by the patient. The severity was assessed irrespective of drug relationship or seriousness of the experience and was evaluated according to the following scale:

- 1 = Mild (=NIH Grade 1)
- 2 = Moderate (=NIH Grade 2)
- 3 = Severe (=NIH Grade 3)
- 4 = Life Threatening (=NIH Grade 4)

The investigator was instructed to report any serious adverse experiences (SAEs) to the Novartis monitor immediately and to take appropriate follow-up action.

Safety and tolerability were evaluated by:

- ECG changes in QTc from baseline;
- clinically significant laboratory changes (in terms of NIH/NCI Common Toxicity criteria grades and deviations from laboratory normal ranges);
- neurological changes from baseline;
- incidence, severity, and relationship of new AEs.

Safety and tolerability assessments were summarized for the ITT population, defined as all patients allocated to randomized treatment who received at least one dose of trial medication.

Adverse experiences were originally summarized by IMN preferred terms and COSTART body system but were reallocated by MedDRA coding for the purposes of this submission.

The incidence of all AEs and malaria symptoms was tabulated by highest severity for each patient, each body system category and as well as each preferred term. The denominator for the incidence rates in all tables represented all patients treated in the respective treatment group. AEs were also classified as "possible", "probable" or "highly probable" treatment-related by the investigator.

A 12 lead ECG was taken at baseline, and the time points of the first 5 measurements after baseline had to be coordinated with the PK blood sampling for each patient so that the drug level at the time of the ECG could be determined. V2 tracings were used to evaluate QTc, and therefore at least 4-6 continuous complexes were required, which allowed detailed and accurate review of any abnormalities.

ECG tracings from 41 patients with a prolongation of QTc by more than 30 msec which yielded to an abnormal value, *i.e.*, QTc > 430 msec for males, > 450 msec for females, within the first week after start of treatment were evaluated by an independent cardiologist who was blinded to the treatment code

Comment: all patients enrolled at center 1 had a full laboratory assessment, however only selected patients at center 2 underwent selected laboratory tests. It should be noted that approximately 805 of patients were enrolled at center 2.

All patients with clinically significant abnormal laboratory values were followed regularly until the values returned to normal or until a valid reason for the abnormality was identified.

Extent of Exposure

150 patients were randomized to receive Coartem and 50 to receive MAS. There were 34 children (≤ 12) enrolled.

Table 1: Baseline characteristics by age group

	CGP 56597	MAS	All patients
Children ≤ 12 years			
N	25	9	34
Mean	8.2	7.4	8.0
Std	3.6	3.4	3.5
Median	9.0	7.0	8.0
Q1-Q3	6.0-11.0	6.0-10.0	6.0-11.0
Range	2.0-12.0	3.0-12.0	2.0-12.0
Patients > 12 years			
N	125	41	166
Mean	26.7	27.2	26.8
Std	10.7	10.8	10.7
Median	23.0	25.0	24.5
Q1-Q3	18.0-32.0	19.0-32.0	18.0-32.0
Range	13.0-63.0	13.0-61.0	13.0-63.0
ALL			
N	150	50	200
Mean	23.6	23.6	23.6
Std	12.1	12.5	12.2
Median	22.0	24.5	22.0
Q1-Q3	16.0-30.0	14.0-30.0	15.5-30.0
Range	2.0-63.0	3.0-61.0	2.0-63.0

None of the patients on Coartem (Coartem in the above table) had to stop treatment because of an AE or any other safety reason. Two patients did not receive the full treatment of 6 doses: patient No. 38 only received one dose of Coartem, as malaria infection with *P. falciparum* was not confirmed, and patient No. 233 did not receive the second dose by mistake. Four patients did

not receive the number of tablets as planned in the protocol: patient No. 8 with 20 kg who should have received 2 tablets per dose only received 6x1 tablets, patient No. 45 with a weight of 15 kg received only 6x1 tablets and patient No. 260 with a weight of 25 kg was planned to receive 6x3 tablets but took only 6x2 tablets. Further, patient No. 77 only had 3 rather than 4 tablets at dose 4 by mistake. All four patients were cured despite suboptimal dosing.

Of the 150 patients on Coartem, 6 (4%) patients received 6x1 tablets, 11 (7.3%) patients received 6x2 tablets, 9 (6%) patients received 6x3 tablets, and the other 124 (82.7%) patients who weighed ≥ 35 kg received 4 tablets at each of the six dosing points. Overall in all weight categories, patients received a median of 9.6 mg/kg total dose of artemether per kg body weight (25-75th percentiles (8.7-10.7) and a median of 57.6 mg/kg (52.4-64.0) total lumefantrine dose. The highest total dose of lumefantrine given was 90 mg/kg for a two year old girl who weighed 8 kg and received 6x1 tablets. All other children weighed more than 10 kg. Further, two boys (patient Nos. 191 and 197 who were 5 and 7 years old) weighed 16 kg and received 6x2 tablets which also gives a total dose of 90 mg/kg. No safety problems were identified for these three children.

Patient No. 160 did not receive the complete treatment with mefloquine and artesunate, as severe urticaria was seen after the first dose of mefloquine. Overall, the patients on MAS received a median of 4 mg/kg artesunate and 25 mg/kg mefloquine as planned in the protocol.

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Table 2: Distribution of patients by treatment group

Pharmacokinetics (CGP 56697)	5 samples together with the ECGs **	148	.	148
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* For patients on MAS the second ECG was taken after the first dose of mefloquine (Day 2), the third ECG after the second dose of mefloquine (Day 3) and the fourth ECG about 24 hours after this dose (Day 4). For patients on CGP 56697 another ECG was taken before dose 6 (Day 3).

Deaths

There were no deaths in this trial.

SAEs

Two SAEs were reported during the trial. Coma and fever in patient No. 259 on Coartem and generalized pruritic urticaria in patient No. 160 on MAS. The latter patient was discontinued from the trial. Both patients completely recovered. No other patients were discontinued from the trial due to adverse experiences or abnormal laboratory values.

Case Narratives of SAEs:

Center/Patient number: Age: 17 years Sex: Male Weight: .46 kg

AE: Coma, fever

Relationship to trial treatment: Not related

Prematurely discontinued: No

Discussion: The patient presented with *P. falciparum* and was randomized to Coartem on 26-Jan-98; he received 4 tablets bid for 3 days. He cleared his parasites in three days, but he carried on having gametocytes until 10-Feb-98. No reappearance of parasites was seen during the trial period.

On 02-Feb-98 the patient returned for the follow-up visit and was feeling well. Laboratory values were unremarkable and no AEs were recorded on that day.

On 08-Feb-98, the patient experienced fever, chills and did not feel well. The next day, the patient became unconscious with fever and vomiting. He was brought to the clinic where he was treated with phenobarbitone to prevent convulsions, paracetamol and quinine. No parasites were found in his blood smear. Haemoglobin value was 12.7 g/dL. Urine dipstick glucose measurement led the investigator to suspect hypoglycemia. The patient was given a dextrose 5% solution.

On 10-Feb-98, the patient was still febrile and unconscious. A short convulsive episode was controlled with diazepam. The patient was transferred to another clinic. On arrival, the coma score was 2, no symptoms of meningismus, blood pressure was 120/80 mmHg, body temperature 39.4°C, pulse 128 beats/minute, respiratory rate 28. The ECG showed no abnormalities; lumbar puncture was attempted without success. Malaria smear was 2 Gametocytes/500 WBC, blood tests showed a WBC count of 16.6 (86% neutrophils, 14% lymphocytes), glucose value was normal (5.4 mmol/L). The patient was then started on chloramphenicol IV because meningitis was suspected. The coma score was 3.

On 11-Feb-98, febrile coma of unknown origin was diagnosed. Ampicillin and metronidazole were started for aspiration pneumonia. On 13-Feb-98 the patient regained consciousness. He experienced mild hallucinations with mild agitation but was eating and drinking. The patient was discharged from hospital on (b) (6), having made a complete recovery.

T-Number: T98HQ00136

Center/Patient number: 1 / 160, MAS

Age: 27 years Sex: Male Weight: 54.5 kg

Adverse experience: Urticaria pruritic generalized

Relationship to trial treatment: Possible

Prematurely discontinued: Yes (due to lost to follow-up)

Discussion: The patient was randomized to MAS and started trial treatment on 10-Feb-98. He received an overdose of artesunate due to a miscalculation (5 tablets = 4.6 mg/kg). There were no acute signs or symptoms associated with this overdose on this day.

On 11-Feb-98 again 5 tablets of artesunate were given at 9:00, as well as 3 tablets of

mefloquine (= 13 mg/kg). The patient developed a urticarial rash all over his body. Treatment with artesunate was continued but mefloquine was stopped due to hypersensitivity which precluded full trial treatment. The patient had made a complete recovery by 13-Feb-98 but was lost to follow-up one week after he started treatment.

AEs

At baseline (Day 1) all symptoms experienced by the patients were recorded as AEs, even if they were related to malaria. As expected the most common symptoms in patients in both treatment groups at presentation were headache (> 86%), asthenia (> 66%), arthralgia (> 62%), fever (> 60%), dizziness (>58%) and anorexia (> 54%). Other malaria symptoms such as nausea, rigors, myalgia, sleep disorders, vomiting, splenomegaly, abdominal pain and palpitation were present in a percentage of patients varying between 20 and 47% in both treatment groups. As anticipated, the malaria symptoms tended to disappear rapidly with treatment in both groups. The percentage of patients with AEs starting or worsening after baseline but before reappearance of malaria were assessed as the most reliable indication of the number of patient who experienced AEs related to trial treatment.

Overall, 102/150 (68%) patients in the Coartem treatment group and 44/50 (88%) patients in the MAS group presented with AEs during this time period. The majority of AEs recorded were symptoms typical of malaria. Symptoms belonging to the digestive system were reported in 36.7% of the patients in the Coartem group but in 62.0% of the patients in the MAS group; nervous system symptoms were reported in 42.7% of the patients in the Coartem group and 54% in the MAS group.

Skin reactions were reported for a small percentage of patients in both treatment groups. Pruritus and/or rash were reported for 3 (2.0%) patients on Coartem and for 2 (4.0%) patients on MAS, urticaria was reported for one patient (2.0%) on MAS.

Table 3: FDA analysis of treatment emergent AEs

	Coartem N=150 (%)	MAS N=50 (%)
All patients with any AE	150 (100)	50 (100)
Body as a Whole	138 (92)	46 (92)
Asthenia	115 (76.7)	36 (72)
Fatigue	39(26)	12 (24)
Fever	102 (68)	37 (74)
Overdose	-	3 (6)
Fungal Infection	1(0.7)	-
Chest Pain	-	1 (2)
Rigors	70 (46.7)	21 (42)
Cardiovascular system	57 (38)	18 (36)
Aortic Stenosis	1(0.7)	-
Heart Murmur	1(0.7)	-
Palpitations	56 (37.3)	18 (36)

Clinical Review
 {Insert Reviewer Name}
 {Insert Application and Submission Number}
 {Insert Product Trade and Generic Name}

Digestive system	135 (90)	47 (94)
Anorexia	119 (79.3)	39 (78)
Diarrhea	6 (4)	-
Hepatomegaly	52 (34.7)	10 (20)
Nausea	79 (52.7)	29 (58)
Abdominal Pain	48 (32)	20 (44)
Toothache	1 (0.7)	-
Vomiting	53 (35.3)	22 (44)
Heme and Lymphatic system	46 (30.7)	17 (34)
Anemia	9 (6)	4 (8)
Splenomegaly	42 (28)	13 (26)
Infections and Infestations	1 (0.7)	1 (2)
Viral Infection	1 (0.7)	-
Parasitic Infection	-	1 (2)
Musculoskeletal system	104 (69.3)	36 (72)
Arthralgia	100 (66.7)	34 (68)
Myalgia	77 (51.3)	24 (48)
Back Pain	1 (0.7)	-
Nervous system	144 (96)	48 (96)
Ataxia	1 (0.7)	-
Coma	1 (0.7)	-
Coordination abnormal	2 (1.3)	-
Dizziness	122 (81.3)	38 (76)
Gait abnormal	1 (0.7)	1 (2)
Headache	140 (93.3)	45 (90)
Hypoaesthesia	2 (1.3)	-
Muscle Contractions Involuntary	2 (1.3)	1 (2)
Sleep disorder	72 (48)	29 (58)
Tremor	2 (1.3)	1 (2)
Nystagmus	1 (0.7)	-
Respiratory system	5 (3.3)	4 (8)
Coughing	1 (0.7)	-
Chest Infection	3 (2)	-
Pharyngitis	1 (0.7)	-
Respiratory Disorder	1 (0.7)	-
Asthma	-	2 (4)
Bronchitis	-	1 (2)
URI	-	1 (2)
Skin and Appendages	3 (2)	5 (10)
Pruritus	3 (2)	4 (8)
Rash	3 (2)	4 (8)
Urticaria	-	1 (2)
Special Senses	1 (0.7)	1 (2)

Conjunctivitis	1 (0.7)	-
Strabismus		1 (2)

The Applicant provided a number of analyses of AEs as a function over time, including AEs that occurred after baseline and AEs after baseline but before reappearance of malaria. These analyses was prespecified in the protocol.

In this analysis, the percentages of patients with sleep disorder, dizziness, vomiting, nausea, abdominal pain, and anorexia were higher in the MAS group (> 10% difference between treatment groups). Palpitation was experienced by slightly more patients in the MAS group. Other symptoms occurred in similar percentages in both treatment groups, i.e., with a difference less than 5%.

Table 4: AEs that occurred after baseline but before malaria reappearance

	Coartem N=150 (%)	MAS N=50 (%)
All patients with any AE	102 (67)	44 (8)
Body as a Whole	47 (31.3)	16 (32)
Asthenia	35 (23.3)	9 (18)
Fatigue	2 (1.3)	6 (12)
Fever	17 (11.3)	6 (12)
Overdose	-	2 (4)
Rigors	6 (4)	-
Cardiovascular system	22 (14.7)	10 (20)
Palpitations	22 (14.7)	10 (20)
Digestive system	55 (36.7)	31 (62)
Anorexia	32 (21.3)	16 (32)
Diarrhea	2 (1.3)	-
Hepatomegaly	4 (2.7)	1 (2)
Nausea	11 (7.5)	11 (22)
Abdominal Pain	21 (14)	13 (26)
Tooth Acne	1 (0.7)	
Vomiting	6 (4)	8 (16)
Heme and Lymphatic system	9 (6)	4 (8)
Anemia	5 (3.3)	3 (6)
Splenomegaly	4 (2.7)	1 (2)
Infections and Infestations	1 (0.7)	1 (2)
Viral Infection	1 (0.7)	-
Parasitic Infection	-	1 (2)
Musculoskeletal system	26 (17.3)	8 (16)
Arthralgia	21 (14)	5 (10)
Myalgia	19 (12.7)	7 (14)
Back Pain	1 (0.7)	-
Nervous system	64 (42.7)	48 (96)

Coma	1 (0.7)	-
Dizziness	35 (23.3)	18 (36)
Headache	36 (24)	11 (22)
Hypoaesthesia	2 (1.3)	-
Sleep disorder	22 (14.7)	13 (26)
Tremor	2 (1.3)	-
Respiratory system	3 (2)	-
Chest Infection	3 (2)	-
Skin and Appendages	2 (1.3)	2 (4)
Pruritus	3 (2)	2 (4)
Rash	3 (2)	2 (4)
Urticaria	-	1 (2)
Special Senses	1 (0.7)	-
Conjunctivitis	1 (0.7)	-

AEs by Severity

Most AEs which occurred during the trial were rated as of mild or moderate severity. There were more SAEs in the Coartem treatment group (20 AEs (in 19 patients, 12.7%) primarily attributable to the underlying malaria. "severe";. Two of these AEs started after baseline: one case of fever and one splenomegaly. Further, the SAE (febrile coma for patient No. 259) two weeks after start of Coartem was rated as "life-threatening".

In the MAS group 5 AEs (in 4 patients, 8.0%) were rated as "severe". These were all present at baseline (fever and hepatosplenomegaly). After baseline, all AEs occurring in patients on MAS were rated as of mild or moderate severity. In both groups, the great majority of events recorded after baseline were rated as mild.

Table 5: AEs of severe intensity

	Coartem N=150 (%)	MAS N=50 (%)
All patients	150	50
All patients with SAE	19 (12.7)	4 (8)
Body as a Whole	7 (4.7)	1 (2)
Fever	7 (4.7)	1 (2)
Digestive system	3 (2)	1 (2)
Hepatomegaly	3 (2)	1 (2)
Heme and Lymphatic system	10 (6.7)	3 (6)
Splenomegaly	10 (6.7)	3 (6)
Nervous system		
Coma	1 (0.7)	-

All AEs for which the relationship to trial treatment was assessed by the Investigator as possible, probable or highly probable were grouped under the heading "related".

33 patients Coartem (22%) had AEs assessed as being related to treatment. The most

frequent were: anorexia (9, 6%), dizziness (8, 5.3%), asthenia (4, 2.7%), nausea (4, 2.7%) and abdominal pain (4, 2.7%). In the MAS group, 23 patients (46%) had AEs assessed as being related. The most frequent were: dizziness (13 (26%), anorexia (8), sleep disorder (8), palpitation (7), nausea (6), asthenia (3) and headache (2).

AEs by age group for both treatments (≤ 12 years vs. > 12 years):

A higher percentage of children in both treatment groups as compared to adult patients presented with anemia, hepatosplenomegaly, fever and vomiting.

A higher percentage of adult patients at baseline had asthenia, fatigue, palpitation, arthralgia, myalgia, headache and dizziness, as compared to the children of the same treatment group. After baseline, the symptoms that showed an age-related difference in the Coartem group were palpitation, arthralgia, myalgia, headache, dizziness and asthenia (more frequent in the adults); and vomiting (more frequent in the children). The same was seen for patients on MAS, and likely relates to the ability to verbalize symptoms. There were no differences between the treatment arms in either group.

In a by-center analysis of AEs (Bangkok N = 28 and MaeLa N = 172) provided by the sponsor, the percentage number for AEs is distinctly higher in MaeLa than in Bangkok, where only very few AEs were reported and only one AE (urticaria in a patient on MAS) was considered by the investigator as related to trial medication.

ECGs

Electrocardiographic monitoring was performed at baseline, Day 8 and Day 29 for all the patients in both treatment groups. For patients on Coartem, a further 4 ECGs were taken within the first week according to either of the two PK schedules, *i.e.*, prior to dose 2 (or 3), prior to dose 4 (or 5), prior to dose 6, and 8-16 hours after dose 6.

For patients on MAS, only a further 3 ECGs were taken: about 1 hour after the first and second dose of mefloquine and again about 24 hours after the second dose of mefloquine. The ECG recorded the tracings and automatically performed measurements of the main parameters.

Overall, the QRS duration did not change during treatment for patients on Coartem, but a slight increase in QRS by a median of about 3 to 4 msec was seen for patients after mefloquine was given.

The PR interval slightly increased for both treatment groups after baseline by a median of up to 10 msec

At baseline, the median QTc was 412 msec, with a range between 354 and 484 msec and 25th to 75th percentiles of 397 and 427 msec respectively. After baseline, QTc values increased slightly in both treatment groups although the overall median percentage increase compared to baseline was not clinically relevant. For patients on Coartem, the highest increase was seen before and after dose 6 when a median increase by 7 and 8 msec (1.7 and 1.9%) respectively was seen. On MAS, an increase in QTc (by a median of 1.5%, *i.e.*, 6 msec) was seen after the first

dose of mefloquine was taken. One day later, after the second dose of mefloquine was taken; QTc values were higher than at baseline in 70% of the patients (by a median of 1.4% or 5.5 msec). About 24 hours after the second dose of mefloquine, more than 75% of the patients had an increase (by a median of 3.9% or 17 msec).

Table 6: Increase in QTc within the first week after start of treatment

	Number of patients with QTc at baseline and at least once within first week	QTc increase >60 msec N (%)	QTc increase >30 msec and QTc >430/450 N (%)	QTc increase >30 msec and QTc >450/470 N (%)
CGP 56697	149	7 (4.7%)	32 (21.5%)	18 (12.1%)
MAS	49	3 (6.1%)	9 (18.4%)	6 (12.2%)

All the tracings for the 41 patients (32 on Coartem and 9 on MAS) who showed an increase > 30 msec in QTc values which yielded a QTc value above 430 and 450 for males and females patients respectively were evaluated by an independent cardiologist who was blinded to the treatment. This Peer Review confirmed that the QTc measurements derived from the ECG machine measurements could be used for analysis and no large differences were seen when measured by hand.

No patient had an absolute QTc value above 550 msec which is recognized to be associated with an increased risk of ventricular arrhythmia. No symptoms relating to the cardiovascular system (except palpitations) were recorded as an AE after baseline. An attempt to correlate the changes of the QTc interval with actual plasma levels of lumefantrine, showed no relationship between lumefantrine and ECG changes.

Clinical Laboratory changes

Limited testing was performed on 21 patients in the Coartem and 7 patients in the MAS treatment groups which were recruited in the hospital in Bangkok. Anemia was found a baseline in 30% of the patients in both groups. On Day 4, there was a worsening of anemia in both treatment groups. Anemia corrected by the end of the study in most patients. 5 patients in the Coartem group and 1 in the MAS group had severe thrombocytopenia at presentation, which improved rapidly; WBC values did not change markedly over the course of the trial. Eosinophils increased above the normal range in more than 50% of the patients in both groups on Day 8 and 29.

Liver function tests were only slightly abnormal at baseline and did not show any significant changes, other than those related to the disease resolution. All parameters normalized over the course of treatment.

Kidney function, as measured by creatinine and BUN, was not affected at baseline, and it did

Clinical Review

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{Insert Application and Submission Number}

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not show any change over the course of the trial. The results of the other laboratory tests performed (serum electrolytes, glucose, total serum protein, serum albumin, urine tests), were very similar in the two groups and did not show any relevant change after baseline

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