CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-268

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	22-268
Drug	Artemether 20 mg/Lumefantrine 120 mg
Date of Submission	06/27/08
Trade Name	Coartem Tablets
OCP Reviewer	Dakshina M. Chilukuri, Ph.D.
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OND division	OAP; DSPTP
Applicant	Novartis
Date	12/22/08

Subject: Assessment of the potential interaction between Coartem and primaquine and addition of wording in the Coartem Tablets label related to grapefruit juice interaction

1. Based on the review of a paper by Bangchang et.al., entitled "*Primaquine metabolism by human liver microsomes: effect of other antimalarial drugs*" (*Biochemical Pharmacology. Vol. 44, No. 3. pp. 587-590. 1992*), it appears that artemether has no appreciable effect on the *in vitro* CYP3A4 mediated metabolism of primaquine, with a reported IC_{50} value of >500 μM. Therefore, no additional *in vivo* drug-drug interaction study is needed between Coartem tablets and primaquine. Furthermore, although not studied in this paper, no interaction is expected to occur between lumefantrine, an inhibitor of CYP2D6, and primaquine, a substrate of CYP3A4.

2. Based on the WHO Guidelines for Coartem, the label for Coartem Tablets is being revised to add wording related to the potential interaction between Coartem and grapefruit juice. Besides the WHO Guidelines, two literature references were also identified, both of which reported an increase in the oral bioavailability (Cmax and AUC) of artemether following co-administration of 350 mL of double strength grapefruit juice with either single or repeat dose administration of artemether tablets (2 x 50 mg) to healthy volunteers (Eur. J. Clin Pharmacol. 1999 Jul; 55(5): 405-410; Clin. Pharmacol, Ther. 1999; 66: 408-416). There was no evaluation of the effect of grapefruit juice on lumefantrine pharmacokinetics in these papers. The proposed wording in the label is given below in double underline:

   5.4 Drug Interactions with CYP3A4

   When Coartem Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Coartem Tablets are co-administered with an inhibitor of CYP3A4**, including grapefruit juice,** it may result in increased concentrations of artemether and/or lumefantrine and potentiate QT prolongation. When Coartem Tablets are co-

administered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Dakshina M. Chilukuri, Ph.D.
Reviewer, DCP4/OCP

Concurrence

Philip M. Colangelo, Pharm.D., Ph.D.
Team Leader, DCP4/OCP

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/s/

Dakshina Chilukuri
12/22/2008 01:48:12 PM
BIOPHARMACEUTICS

Phil Colangelo
12/22/2008 02:00:41 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA	22-268
Drug	Artemether 20 mg/Lumefantrine 120 mg
Date of Submission	06/27/08
Trade Name	Coartem
OCP Reviewers	Dakshina M. Chilukuri Gerlie Gieser (In vitro metabolism studies) Christoffer Tornoe (QT review) Christine Garnett (Secondary QT review)
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OND division	ODE IV; DSPTP
Applicant	Novartis
Submission Type	New Drug Application
Formulation	Oral, tablets
Indication	Treatment of malaria
Date of Review	11/24/08

Table of Contents

1. Executive Summary

The applicant is seeking approval of Coartem, a fixed combination tablet comprising of artemether and lumefantrine. Both components of Coartem are anti-malarial agents intended for administration in adults and pediatric patients greater than 5 kg body weight. The applicant has sought to approve Coartem for the treatment of malaria caused by *Plasmodium falciparum*.

Coartem (co-artemether; artemether-lumefantrine; also marketed as Riamet®), 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 have

dissimilar modes of action providing synergistic activity against *Plasmodium falciparum*. Co-artemether is currently approved in >80 countries including Switzerland (1999) and EU. It is the first fixed dose artemisinin-based combination therapy (ACT) for acute uncomplicated *Plasmodium falciparum* malaria that has been pre-qualified by the World Health Organization (WHO) since 2004 and that is widely available internationally. Artemether and lumefantrine have been included on the WHO model list of Essential Medicines since March 2002 and on the 1st WHO model List of Essential Medicines for Children since October 2007.

Upon administration of Coartem, artemether is presumed to have a rapid onset of action and rapid elimination, whereas lumefantrine has a slower onset of action and is eliminated more slowly and is expected to provide long-term cure rate after a short treatment course. The combination thus provides rapid clearance of parasitemia and most malaria-related symptoms, coupled with prevention of recrudescence. In addition, co-artemether provides an ACT with a fixed ratio of components in a single tablet. This potentially allows a more convenient treatment than combinations of loose tablets.

The current NDA is (b) (4) 6-dose regimen of co-artemether in the treatment of acute uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Approval is being sought for the co-artemether tablet, as marketed in other countries and distributed in endemic countries.

The following 6-dose regimen of Coartem was administered to adult and pediatric malaria patients in the key clinical trials reviewed in this NDA:

- Children and adults with BW ≥35 kg: 6 x 4 tablets, i.e. four tablets at the time of diagnosis, again four tablets 8 h later, and then four tablets twice-daily on each of the following 2 days (total course comprises 24 tablets, i.e. 480 mg artemether/2880 mg lumefantrine)
- Children 25 kg to <35 kg BW: 6 x 3 tablets, i.e. three tablets (as a single dose) at the time of diagnosis, again three tablets 8 h later, and then three tablets twice-daily on each of the following 2 days (total course comprises 18 tablets, i.e. 360 mg artemether/2160 mg lumefantrine)
- Children 15 kg to <25 kg BW: 6 x 2 tablets, i.e. two tablets (as a single dose) at the time of diagnosis, again two tablets 8 h later, and then two tablets twice-daily on each of the following 2 days (total course comprises 12 tablets, i.e. 240 mg artemether/1440 mg lumefantrine)
- Children 5 kg to <15 kg BW: 6 x 1 tablet, i.e. one tablet at the time of diagnosis, again one tablet 8 h later, and then twice-daily on each of the following 2 days (total course comprises 6 tablets, i.e. 120 mg artemether/720 mg lumefantrine)

For pediatric patients who cannot swallow the intact tablets, the tablets may be crushed and mixed with water for administration. This was how co-artemether was given to pediatric patients in the clinical trials submitted in this NDA.

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

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

Food intake significantly increases the bioavailability of co-artemether. In healthy volunteers, the relative bioavailability of artemether was increased more than 2-fold, and that of lumefantrine 16-fold after a standard FDA breakfast compared to fasting conditions. Given the pronounced increase in systemic concentrations when administered with food, malaria patients studied in all subsequent Phase I/II studies and the Phase III clinical efficacy and safety trials were encouraged to take co-artemether with food, in particular fat-containing meals, as soon as food was tolerated. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately 2-fold), probably due to the lower fat content of the food ingested by acutely ill patients. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated

Artemether and lumefantrine are metabolized mainly through CYP3A4 enzymes. Modest changes (<2.5-fold increase) in systemic exposure were observed with inhibitors or substrates of CYP3A4 including ketoconazole, mefloquine or quinine. These changes (2.5-fold increase as a maximum) were not considered to be of clinical importance particularly in light of the substantial increase in the bioavailability of both drugs when co-artemether is given with food. Moreover, the concentrations seen in the ketoconazole drug interaction study were within the range of systemic concentrations of Coartem seen in malaria patients in Phase III efficacy and safety studies.

The effectiveness and safety of the 6-dose regimen were evaluated in 7 clinical studies in adults and pediatric malaria patients. Based on the review of the data, it was determined by the clinical review team that Coartem is safe and effective.

No outstanding clinical pharmacology issues were identified with Coartem in this current NDA submission.

1.1. Recommendation

The clinical pharmacology and biopharmaceutics information submitted to NDA 22-268 for Coartem is acceptable from the perspective of the Office of Clinical Pharmacology (OCP).

1.2. Phase 4 Commitments

Not applicable

1.3. Labeling Comments / Revisions

Labeling changes will be addressed separately.

1.4. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Absorption
Artemether is absorbed fairly rapidly with peak plasma concentrations (C_{max}) reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after administration. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than 2-fold and that of lumefantrine 16-fold compared with fasted conditions when co-artemether was taken after a high-fat meal. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately 2-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution
Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47%- 76%).

Biotransformation
Artemether is rapidly and extensively metabolized by the liver and undergoes substantial first-pass metabolism. Human liver microsomes metabolize artemether to the biologically active main metabolite, dihydroartemisinin (DHA), predominantly through the enzyme CYP3A4/5 (via demethylation). The *in vivo* pharmacokinetics of this metabolite has also been described in humans. Following repeated administration of co-artemether (alone or in combination with mefloquine), plasma artemether concentrations decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. This suggests that there is induction of the enzyme(s) responsible for the metabolism of artemether.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In *in vivo* studies in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. The kinetic profile of the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5- to 8-fold higher than lumefantrine, has been documented in malaria patients, and was shown to represent less than 1% (in terms of AUC) of the parent exposure. *In vitro*, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations and so the concurrent administration of Coartem and substrates of CYP2D6 (e.g., several tricyclic antidepressants) is to be avoided.

Elimination
Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated slowly with a terminal half-life of

2-3 days in healthy volunteers and 4-6 days in patients with *P. falciparum* malaria. Demographic characteristics such as gender and weight appear to have no clinically relevant effects on the pharmacokinetics of co-artemether.

No urinary excretion data are available for humans. In rats and dogs, unchanged artemether has not been detected in feces and urine due to its rapid and high first-pass metabolism, but several metabolites (unidentified) have been detected in both feces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the feces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and feces was relatively low, most of the dose being recovered as parent drug.

Pharmacokinetics in special patient populations
No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or elderly patients.

Two studies have been conducted in infants and children with malaria, i.e. Study CCOA566A2403 and Study CCOA566B2303. Crushed tablets of co-artemether were used in both studies. Artemether and DHA concentrations were determined after the first dose in Study CCOA566B2303, and lumefantrine was determined at various time-points up to 14 days after the first dose in both studies

Artemether and DHA concentrations and exposure estimates observed in Study CCOA566B2303 were comparable to those observed previously in adult malaria patients in Thailand (Study CCOA566A028) treated with the 6-dose regimen of co-artemether. The children were treated with the 6-dose regimen based on body weight, i.e. 6 x 1 tablet for children 5-<15 kg, 6 x 2 tablets for children 15-<25 kg and 6 x 3 tablets for children 25-<35 kg.

Interaction with other medicinal products and other forms of interaction
Three specific pharmacokinetic and pharmacodynamic drug-drug interaction studies with ketoconazole (a potent CYP3A4 inhibitor), mefloquine, and quinine have been conducted in healthy volunteers.

Interaction with other anti-malarials – mefloquine and quinine
The combined (sequential) oral administration of mefloquine (administered as three doses, 500 mg, 250 mg and 250 mg) prior to co-artemether (6 doses of 4 tablets of Coartem, 20/120 mg) had no effect on plasma concentrations of artemether or the artemether/DHA ratio but there was a 32% reduction in plasma exposure (C_{max} and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. This reduction in exposure is not considered to be clinically relevant, but patients should be encouraged to eat at dosing times to compensate for this decrease in bioavailability of lumefantrine. However, in the clinical setting concurrent use of Coartem and mefloquine is not anticipated. If malaria therapy due to Coartem

fails then patients will be switched to mefloquine. Thus, there is no clinical implication of the interaction between the two drugs.

The combined (sequential) intravenous administration of quinine (10 mg/kg BW) with co-artemether had no effect on plasma concentrations of DHA, lumefantrine or quinine. Plasma concentrations of artemether were 46% lower when administered with quinine compared to Coartem alone. In this study, administration of co-artemether to 14 subjects had no effect on the QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of the QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but not significantly, greater when quinine was infused after co-artemether in 14 additional subjects. In a clinical trial in Thailand some patients received co-artemether following treatment failures with mefloquine or quinine. In total, 34 and 9 patients had measurable quinine and mefloquine concentrations, respectively, at enrolment. These patients showed similar safety and pharmacokinetic profiles of co-artemether to patients who had no detectable concentrations of other anti-malarials.

Interaction with ketoconazole (potent CYP450 3A4 inhibitor)
The concurrent oral administration of ketoconazole (400 mg on Day 1 followed by 200 mg on days 2,3, 4 and 5) with co-artemether (single dose of 4 tablets of 20/120 mg) led to a modest increase in artemether (2.3-fold), dihydroartemisinin (1.5 fold), and lumefantrine (1.6-fold) exposure in healthy subjects. This increase in exposure to the anti-malarial combination was not associated with increased side effects or changes in ECG parameters. Based on this study, dose adjustment of co-artemether is considered unnecessary in *P. falciparum* malaria patients when administered in association with ketoconazole or other CYP3A4 inhibitors.

Interaction with CYP450 enzymes in general
Though *in vitro* metabolism studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisinins generally have some capacity to induce CYP450 enzymes. The results of repeated dose studies in healthy volunteers and patients indicated that repeat administration of Coartem (eg., Day 3) results in lower exposure of artemether compared to single administration (i.e., Day 1).

Lumefantrine was found to inhibit CYP2D6 *in vitro*. Co-administration of co-artemether with drugs that are metabolized by this isoenzyme (e.g., neuroleptics and tricyclic antidepressants) are to be avoided.

_____.
Dakshina M. Chilukuri, Ph.D.
Reviewer, DCP4/OCP

Concurrence _____.
Philip M. Colangelo, Pharm.D., Ph.D.
Team Leader, DCP4/OCP

2. Question Based Review

2.1. General Attributes of the Drug

2.1.1. What are the proposed dosage(s) for various indications?

The proposed dosage regimen for Coartem is given below:

Dosage in children with BW ≥35 kg, and in adults:

- 6 x 4 tablets, i.e. four tablets at the time of diagnosis, again four tablets 8 h later, and then four tablets twice-daily on each of the following 2 days (total course comprises 24 tablets, i.e. 480 mg artemether/2880 mg lumefantrine)

Dosage in infants and children with body weight (BW) between 5 kg and less than 35 kg

- 5 kg to <15 kg BW: 6 x 1 tablet, i.e. one tablet at the time of diagnosis, again one tablet 8 h later, and then twice-daily on each of the following 2 days (total course comprises 6 tablets, i.e. 120 mg artemether/720 mg lumefantrine)
- 15 kg to <25 kg BW: 6 x 2 tablets, i.e. two tablets (as a single dose) at the time of diagnosis, again two tablets 8 h later, and then two tablets twice-daily on each of the following 2 days (total course comprises 12 tablets, i.e. 240 mg artemether/1440 mg lumefantrine)
- 25 kg to <35 kg BW: 6 x 3 tablets, i.e. three tablets (as a single dose) at the time of diagnosis, again three tablets 8 h later, and then three tablets twice-daily on each of the following 2 days (total course comprises 18 tablets, i.e. 360 mg artemether/2160 mg lumefantrine)

2.1.2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Artemether is a white (b) (4) crystalline, (b) (4) powder; freely soluble (b) (4) in acetone, (b) (4) (b) (4), methanol and in ethanol, and practically insoluble (b) (4) in water. Partition coefficient between (b) (4) (logP) is (b) (4)

Lumefantrine is a yellow crystalline, (b) (4) powder, freely soluble (b) (4) in N,N-dimethylformamide and ethyl acetate, soluble in dichloromethane (b) (4) slightly soluble (b) (4) in ethanol and methanol, and insoluble in water. Its estimated logP is (b) (4)

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Artemether and lumefantrine are blood schizonticidal antimalarials displaying activity against chloroquine-resistant strains of *P. falciparum in vitro*. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of hem, a toxic intermediate produced during hemoglobin breakdown, to non-toxic hemozoin. Lumefantrine is thought to interfere with the polymerisation process, while

artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and hem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite. A high susceptibility of *P. falciparum* to artemether and lumefantrine has been demonstrated as well as a clear synergy between artemether and lumefantrine over a broad range of concentrations and ratios in chloroquine-resistant *P. falciparum* strains *in vitro*.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 8 key studies were conducted by the applicant to demonstrate the effectiveness of Coartem in the treatment of malaria. All of the clinical studies were conducted outside the U.S. and FDA did not have any input on the design and conduct of the studies. Of these 8 studies, Study AB/M02 (a four-dose regimen) was conducted to compare the PK, safety and effectiveness of Coartem compared to the individual components, artemether and lumefantrine. The studies conducted to demonstrate the safety and efficacy of Coartem are given below:

Table 1. Clinical studies conducted in support of approval of Coartem

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

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies

The primary clinical efficacy end point in the clinical studies was the '28-day cure rate'. Other secondary endpoints were 'time to fever resolution and 'parasite reduction at 24 hours'. Time to fever resolution is often confounded with antipyretic usage and so was not considered important by the medical review team from an effectiveness perspective.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties, artemether, lumefantrine and DHA (active metabolite of artemether) were measured using HPLC with UV detection.

2.2.4. Exposure-response relationships

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy?*

The exposure-response response relationship of co-artemether has been evaluated in malaria patients based on two studies conducted in Thailand (studies CCOA56A012 and CCOA566A025). Study CCOA566A012 (260 patients) tested three different dose regimens over 2 days, i.e. either 3x4 tablets, 4x2 tablets or 4x4 tablets. Study CCOA566A025 (359 patients) compared the 4-dose regimen (2 days) with the 6-dose regimen given over 3 or 5 days.

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

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

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

The pooled results of efficacy in adult and pediatric patients are given below in Table 2 and 3, respectively.

Table 2. Efficacy results in all adult patients (>16 years of age)

Efficacy parameter	Coartem 4-dose n = 784	Coartem 6-dose n = 599	p value[1]
28-day cure rate, n/M (%) (mITT)			
Uncorrected	593/784 (75.6)	497/599 (83.0)	0.0009
Corrected	331/450 (73.6)	499/598 (83.4)	0.0001
28-day cure rate, n/M (%) (evaluable)			
Uncorrected	588/693 (84.8)	494/511 (96.7)	< 0.0001
Corrected	328/383 (85.6)	495/510 (97.1)	< 0.0001
Median PCT, hours (95% CI) (mITT)	36.0 (33.5, 36.0)	42.3 (41.5, 43.2)	
Median FCT, hours (95% CI) (mITT)	24.0 (24.0, 29.0)	28.5 (22.3, 34.0)	

mITT = modified intent to treat population; PCT = parasite clearance time; FCT = fever clearance time
[1]Fisher's exact test.

Table 3. Efficacy results in all pediatric patients (<16 years of age)

Efficacy parameter	Coartem 4-dose n = 650	Coartem 6-dose n = 877	*p* value[1]
28-day cure rate, n/M (%) (mITT)			
Uncorrected	331/507 (65.3)	743/863 (86.1)	< 0.0001
Corrected	295/431 (68.4)	798/854 (93.4)	< 0.0001
28-day cure rate, n/M (%) (evaluable)			
Uncorrected	324/446 (72.6)	737/823 (89.6)	< 0.0001
Corrected	288/370 (77.8)	792/814 (97.3)	< 0.0001
Median PCT, hours (95% CI) (mITT)	45.0 (42.0, 48.0)	35.3 (31.7, 35.7)	
Median FCT, hours (95% CI) (mITT)	24.3 (24.0, 26.0)	7.9 (7.9, 8.0)	

mITT = modified intent to treat population; PCT = parasite clearance time; FCT = fever clearance time
[1]Fisher's exact test.

2.2.4.2.What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*?

The applicant indicated that no relationship was established between the systemic exposure of artemether and lumefantrine and occurrence of adverse events. No safety concerns with either of the two drugs were identified during review by the clinical review team and so no further analyses were conducted by the clinical pharmacology team.

2.2.4.3.Does this drug prolong the QT or QTc interval?

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 4 summarizes the study results for QTcF. 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 4. Primary results of the QTc Study

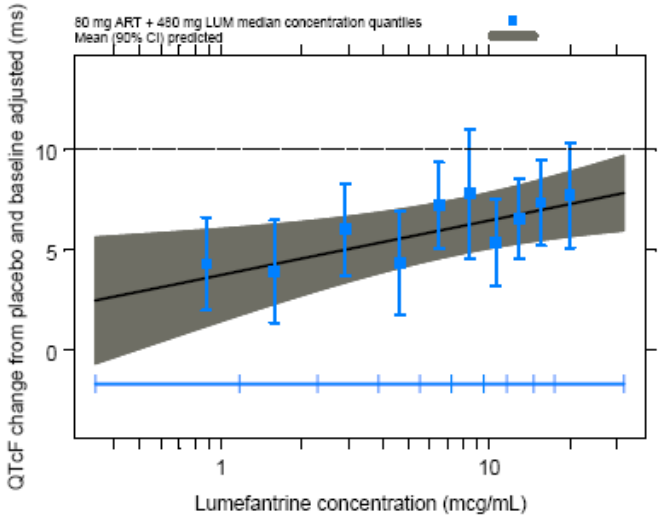
Treatment	Time, hr	ΔΔQTcF, ms	90% CI, ms
Coartem	72	7.29	(3.6, 11.0)
Moxifloxacin	61*	14.1	(8.9, 19.4)

* Moxifloxacin was administered at time 60 hours

Significant positive lumefantrine concentration-QTcF relationship was identified. Based on a linear relationship, the predicted mean (90% confidence interval) ΔΔQTcF for the mean C_{max} of 480 mg lumefantrine dose was 7.0 (5.5, 8.5) ms. These findings are consistent with the primary statistical analyses. Only the therapeutic dosing regimen of Coartem was tested. 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 (CCOA566A025, CCOA566A2401, CCOA566A2403, and CCOA566A2303), the lumefantrine exposure (mean AUC∞ ranged from 335 to 1260 µg.h/ml) did not exceed the exposure level in healthy subjects (mean AUC∞ was 1320 µg.h/ml).

The C_{max} ranged between 5.72 ±2.91 µg/mL to 10.5 ±6.39 µg/mL in malaria patients and between 5.09 ±1.9 µg/mL to 28.3±13.6 µg/mL in healthy volunteers. Though the highest Cmax observed in healthy volunteers exceeds that seen in the QT study (~16 µg/mL) it is unlikely to result in clinically significant QT prolongation, given that the concentration-QT relationship predicts that the mean QT prolongation at an exposure of ~30 µg/mL would be <10 msec. Also, the inter-subject variability was high (~50%) in both healthy volunteers and patients

Figure 1. ΔΔQTcF vs. lumefantrine concentrations



2.2.4.4. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The results of the 7 key clinical trials have shown that the effectiveness of Coartem when administered as a 6-dose regimen is highly effective (28-day cure rate of >95%). The 4-dose regimen displayed variable effectiveness rates in different studies, but overall, it was demonstrated that the 6-dose regimen is more effective that the 4-dose regimen (Study 025). No major safety issues were identified by the applicant and this was confirmed by the medical reviewer for safety, Dr. Sue Lim. Overall there are no unresolved dosing or administration issues with Coartem.

Given the high rate of cure seen in the pivotal clinical trials, it is evident that the systemic concentrations of Coartem are likely at the asymptotic region of the dose (or exposure) response curve. The applicant did not perform any systematic dose-response evaluations during their drug development program.

2.2.5. What are the PK characteristics of the drug and its major metabolites

2.2.5.1. What are the single dose and multiple dose PK parameters?

The PK estimates following single and multiple dose administration of Coartem in healthy subjects and patients are given below:

Table 5a. Summary of PK parameters of artemether, DHA and lumefantrine, in healthy subjects (Study 027). In the following 3 tables, CGP 56697 stands for Coartem.

Artemether

		CGP 56697 alone		
		After first dose	After last dose	Ratio
C_{max}	[ng/mL]	72.2 ± 33.2	27.4 ± 30.9	0.4
t_{max}	[h, median]	2.0	1.5	
$AUC_{(0-t)}$	[ng·h/mL]	204 ± 107	63.6 ± 72.5	0.3
$t_{½}$	[h]	1.4 ± 0.4	1.6	

DHA

		CGP 56697 alone		
		After first dose	After last dose	Ratio
C_{max}	[ng/mL]	57.5 ± 28.1	74.9 ± 41.7	1.6
t_{max}	[h, median]	1.5	1.5	
$AUC_{(0-t)}$	[ng·h/mL]	181 ± 74.9	191 ± 93.1	1.1
$t_{½}$	[h]	2.1 ± 1.0	1.5 ± 0.6	

Lumefantrine:

		CGP 56697 alone
C_{max}	[µg/mL]	28.3 ± 13.6
t_{max}	[h, median]	64
$AUC_{(0-816h)}$	[µg·h/mL]	2290 ± 1450
AUC	[µg·h/mL]	2730 ± 1710
$t_{½}$	[h]	275 ± 176

Note: Lumefantrine AUC was measured over 0 to 816 hours (6-dose regimen). Tmax is reported as the time at which the highest concentration was observed. Following single doses, however, the Tmax ranged between 6-8 hours.

Table 5b. Summary of PK parameters of lumefantrine, desbutyl-lumefantrine, artemether and DHA in adult and pediatric malaria patients

Study	Location/Year/Dose/Objective	Analyte	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	t_{max} (h)	$t_{½}$ (h)
Adult patients						
A025	Thailand/1996-97/ 4- & 6-dose regimens Double-blind, randomized (1/1), parallel group, comparative efficacy/safety trial of 3 dose regimens of co-artemether (4-dose over 2 days, and 6-dose over 3 or 5 days)	Lumefantrine (results for 6-dose regimen over 3 days)	10.5 ± 8.39 (n=18)	758 ± 65[1] (n=18)	60.0[2] (n=18)	na
A028	Thailand/1998-99/6-dose regimen Open-label, randomized (3/1), parallel group, confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine-artesunate	Lumefantrine	25.7 ± 16.3[3] (n=25)	na	na	na
A2401[4]	Europe + Colombia/2001-05/6-dose regimen Open-label, non-comparative, efficacy/safety trial in non-immune patients	Lumefantrine	5.72 ± 2.91 (n=15)	272 ± 159[5] (n=15)	62.42[2] (n=15)	na
		Desbutyl-lumefantrine	0.019 ± 0.008 (n=15)	0.905 ± 0.738[5] (n=15)	62.67[2] (n=15)	na
Pediatric patients						
A2403	Africa/2002-03/6-dose regimen Open-label, non-comparative, efficacy/safety trial in children (5-25 kg bodyweight)	Lumefantrine				
		5 to <15 kg (n=156)[6]	4.71	372[7]	6.0[8]	58.0
		15 to <25 kg (n=25)[6]	12.6	655[7]	6.0[9]	82.0

Study	Location/Year/Dose/Objective	Analyte	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	t_{max} (h)	$t_{½}$ (h)
B2303[10]	Africa/2006-07/6-dose regimen Investigator-blind, randomized, parallel group, efficacy/safety trial in infants and children (5-35 kg bodyweight)	Lumefantrine				
		5 to <15 kg (n=194)[6]	6.13	577[7]	6.0[8]	na
		15 to <25 kg (n=102)[6]	9.37	699[7]	6.0[8]	na
		25 to <35 kg (n=19)[6]	21.9[11]	1150[7]	6.0[12]	na

[1] AUC_{last} = $AUC_{0\text{-}240h}$ ("0" is time of first dose of Coartem)
[2] post first dose of Coartem
[3] value observed after last (sixth) dose of Coartem on Day 3
[4] shown is rich PK (i.e. patients in Colombia)
[5] AUC_{last} = $AUC_{0\text{-}168h}$ ("0" is time of first dose of Coartem)
[6] n represents the number of values (one sample was taken per patient) used in the re-constitution of the population mean plasma concentration-time profile; AUC_{last} was calculated from mean concentration-time profile by non-compartmental method; C_{max} and t_{max} were taken from the mean concentration-time profile
[7] AUC_{last} = $AUC_{0\text{-}14\ days}$ ("0" is time of first dose of Coartem)
[8] post dose 6
[9] post dose 3
[10] shown are values for crushed commercial tablet
[11] n = 1
[12] post dose 5
na = not available

Study	Location/Year/Dose/Objective	Analyte	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	t_{max} (h)	$t_{½}$ (h)
Adult patients						
A028	Thailand/1998-99/6-dose regimen Open-label, randomized (3/1), parallel group, confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine-artesunate	Artemether[1]				
		Day 1	186 ± 125 (n=25)	535 ± 272 (n=25)[2]	2.0 (n=25)	1.6 ± 0.3 (n=12)
		Day 3	66.2 ± 54.3 (n=25)	211 ± 109 (n=22)[2]	2.0 (n=25)	2.2 ± 1.0 (n=7)
		DHA[1]				
		Day 1	101 ± 58.0 (n=25)	320 ± 159 (n=25)[2]	3.0 (n=25)	1.5 ± 0.5 (n=7)
		Day 3	205 ± 102 (n=25)	604 ± 259 (n=25)[2]	2.0 (n=25)	1.6 ± 0.4 (n=12)
Pediatric patients						
B2303[3]	Africa/2006-07/6-dose regimen Investigator-blind, randomized, parallel group, efficacy/safety trial in infants and children (5-35 kg bodyweight)	Artemether				
		5 to <15 kg	223 ± 309 (n=55)[4]	na	na	na
		15 to <25 kg	198 ± 179 (n=29)[4]	na	na	na
		25 to <35 kg	174 ± 145 (n=8)[4]	na	na	na
		DHA				
		5 to <15 kg	54.7 ± 58.9 (n=56)[4]	na	na	na
		15 to <25 kg	79.8 ± 80.5 (n=29)[4]	na	na	na
		25 to <35 kg	65.3 ± 23.6 (n=8)[4]	na	na	na

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

[2] AUC_{last} = AUC_{0-6h}

[3] shown are values for crushed commercial tablet

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

na = not available

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The vast majority of the studies in healthy volunteers were done under fed conditions to maximize exposure, while patients had variable food intake as they had malaria, and most often took no or little food, especially at start of treatment. Artemether and lumefantrine also have highly variable, and time dependent PK (artemether). Due to the very different PK profiles of artemether and lumefantrine, each requiring specific blood PK sampling schedules, the PK of artemether and lumefantrine was not necessarily both evaluated in every study, in particular in malaria patients who are usually anemic and therefore could ill afford additional blood sampling. Malaria studies are also usually conducted in developing countries with limited resources for sample preparation and storage. All of these factors make comparison of exposure values between the two populations complex and difficult. In both populations, however, the same active metabolites are observed in similar ratios to the parent compounds with similar though variable exposure.

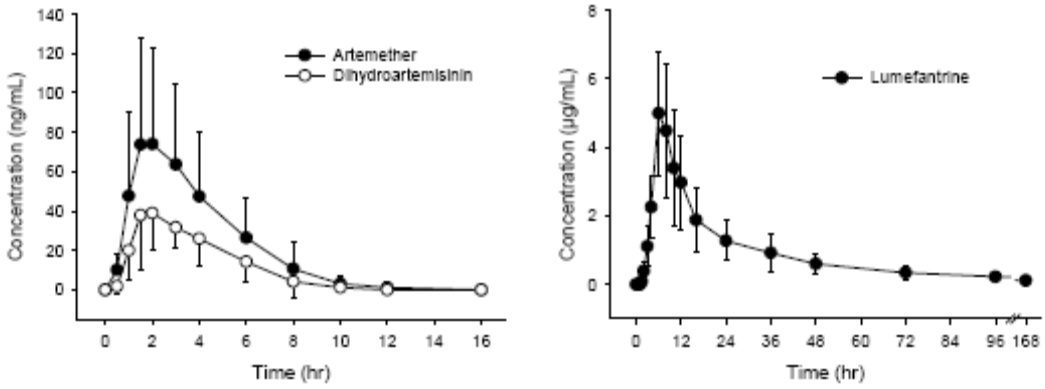
There were four studies in adult (CCOA566A025 and CCOA566A2401) or pediatric (CCOA566A2403 and CCOA566B2303) malaria patients using the 6-dose regimen of co-artemether, in which lumefantrine exposure was measured. In all these patient studies, lumefantrine exposure (mean AUC_∞ ranged from 335 to 1260 µg·h/mL) did not exceed the exposure level observed in healthy subjects and in particular in the thorough QT/QTc CP Study CCOA566A2101 (mean lumefantrine AUC_∞ was 1320 µg·h/mL).
The C_{max} ranged between 5.72 ±2.91 µg/mL to 10.5 ±6.39 µg/mL in malaria patients and between 5.09 ±1.9 µg/mL to 28.3±13.6 µg/mL in healthy

volunteers. Also, the inter-subject variability was high (>50%) in both healthy volunteers and patients.

2.2.5.3. What are the characteristics of drug absorption?

The absolute bioavailability of artemether and lumefantrine after oral administration of co-artemether has not been investigated as there is no intravenous formulation. After oral administration of co-artemether, artemether is absorbed fairly rapidly with peak plasma concentrations (C_{max}) reached about 1-2 hours after dosing (Figure 2). Its major metabolite DHA appears rapidly in plasma with C_{max} (≥50% of parent after single dose) reached at t_{max} around 1-2 hours post-dose. Absorption of lumefantrine, a highly lipophilic compound, is slower and starts after a lag-time of up to 2 hours. Peak plasma concentrations occurred at about 6-8 hours after administration.

Figure 2. Typical artemether, dihydroartemisinin and lumefantrine plasma profiles (mean ± SD, n = 16) in healthy volunteers (fed) given a single dose of co-artemether (80/480 mg)



2.2.5.4. What are the characteristics of drug distribution?

The *in vitro* binding to human serum is approximately 95% for artemether and 99.7% for lumefantrine.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass-balance study was conducted as part of drug development and so the contribution of the renal and hepatic pathways are unknown.

2.2.5.6. What are the characteristics of drug metabolism?

Findings of *in vitro* studies using human liver microsomes and recombinant CYP450 enzymes indicate that the metabolism of artemether and lumefantrine are catalyzed mainly by CYP3A4. The metabolism of artemether is also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19.

2.2.5.7. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

No standard evaluation of the dose-proportionality or dose-linearity of the pharmacokinetics of co-artemether has been performed using traditional dose-escalating studies in healthy subjects. However, the pharmacokinetics of co-artemether was compared in malaria patients (studies CCOA566A012 and CCOA566A025) following administration of several dose regimens of co-artemether using different total doses of artemether/lumefantrine.

Study CCOA566A012 was conducted in Thailand and aimed to compare three dose regimens: 4 x 2 tablets over 2 days (160 mg artemether/960 mg lumefantrine), 3 x 4 tablets over 1 day (240 mg artemether/1440 mg lumefantrine), and 4 x 4 tablets over 2 days (total dose 320 mg artemether/1920 mg lumefantrine). Plasma exposure to artemether, DHA and lumefantrine increased with rising total doses of co-artemether, and lumefantrine AUC values increased almost 2-fold (from 168 to 290 µg·h/mL) when the dose was doubled (from 4 x 2 to 4 x 4 tablets over 2 days), suggesting a dose-proportional increase.

Study CCOA566A025 was also conducted in Thailand and aimed to compare the 4-dose regimen (given over 2 days, total dose 320 mg artemether/1920 mg lumefantrine) with the 6- dose regimen given over 3 or 5 days (total dose 480 mg artemether/2880 mg lumefantrine). In total, 359 adult male and female patients and children were enrolled in this study and were randomized to one of the three treatments. Rich PK data for lumefantrine were obtained for 51 hospitalized patients, and sparse data were collected for 215 patients. Based on a compartmental analysis, the two higher dose regimens (6 doses over 3 or 5 days) gave 60% (561 µg·h/mL) and 100% (712 µg·h/mL) higher AUC values, respectively, than the 4-dose regimen (356 µg·h/mL). The noncompartmental analysis showed an average 38% (758 µg·h/mL) and 105% (1132 µg·h/mL) higher AUC, respectively, than the 4-dose regimen (551 µg·h/mL).

Comparable dose-dependency was observed for artemether and DHA concentrations. However, due to the high inter-subject variability of the pharmacokinetic variables (overall CVs approximately 110%), no conclusive assessment of dose-proportionality or dose-linearity of artemether was given.

2.2.5.8. How do the PK parameters change with time following chronic dosing?

Artemether is rapidly metabolized to DHA with a half-life of around 2 hours. DHA is also rapidly metabolized with a half-life of around 2 hours. Repeat administration results in a lowering of artemether concentrations compared to single-dose administration in both healthy subjects and patients. Artemether is presumed to induce its own metabolism**,** however,

the applicant has not conducted any *in vitro* or *in vivo* studies to confirm the induction potential of artemether**.** Lumefantrine is eliminated slowly with a half-life of around 3-5 days. Steady-state concentrations are not reached within the 3-day dosing interval.

Table 6. Artemether and DHA PK parameters in Study 028 (n = 25**)**

		Artemether			DHA		
		After first dose	After last dose	Ratio	After first dose	After last dose	Ratio
C_{max}	[ng/mL]	186 ± 125	66.2 ± 54.3	0.42	101 ± 58	205 ± 102	2.9
t_{max}	[h, median]	2.0	2.0		3.0	2.0	
AUC_{last}	[ng·h/mL]	535 ± 272	211 ± 109 [1]	0.44	320 ± 159	604 ± 259	2.5
$t_{½}$	[h]	1.6 ± 0.3 [2]	2.2 ± 1.0 [3]		1.5 ± 0.5 [3]	1.6 ± 0.4 [2]	

[1] n = 22, [2] n = 12, [3] n = 7.

2.2.5.9. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter- and intra-individual variability in C_{max} and AUC values of artemether, DHA and lumefantrine from Clinical Pharmacology studies conducted in healthy volunteers are summarized in Tables 7 and 8.

There were four crossover studies where the same subject was treated with co-artemether tablets in all periods, allowing the calculation of intra-subject variability. They were CP Study CCOA566A006, CP Study CCOA566A020, [CP Study CCOA566A2301 and CP Study CCOA566B2104. However none of these were ideal for assessing the intra-subject variability due to study design factors which could also have contributed to the intra-subject variability. Study A006 compared two different tablet formulations, study A020 compared fed versus fasted, study A2301 involved co-administration of quinine and study B2104 compared the tablet formulation with crushed tablet and dispersible tablet. On the whole, the intra-subject variability accounts for the majority of the variability measured between subjects. Inter-subject variability for the AUC values in the above studies (Table 7) of artemether and lumefantrine ranged from 34% to 155%, with the median variability for given studies of 52% to 53%. Intra-subject variability in Table 8 ranged from 28% to 103%, with a median value of 41% to 42%.

Table 7. Inter-subject variability (CV%) of artemether, DHA and lumefantrine pharmacokinetic parameters

Parameter	Study		Artemether	DHA	Lumefantrine
AUC_{0-t}	A006	Formulation F2	80	72	155
	A020	Fasted	77	55	55
		Fed	52	34	34
	A024		49	30	53
	A027	First dose	52	41	63
		Last dose	114	49	N/A
	A2101	Day 1	45	31	43
		Day 3	102	35	N/A
	A2301		45	36	61
	A2302		143[2]	40[2]	79[2]
	B2102		49	30	44
	B2104		58	34	48
C_{max}	A006	Formulation F2	78	57	148
	A020	Fasted	86	64	64
		Fed	51	47	47
	A024		59	31	40
	A027	First dose	46	49	48
		Last dose	113	56	N/A
	A2101	Day 1	58	47	42
		Day 3	104	50	N/A
	A2301		38	43	44
	A2302		82	31	55
	B2102		54	34	43
	B2104		71	54	43

[1] CV% calculated from arithmetic mean and standard deviation; [2] $AUC_{(t2-last)}$; Bold = studies used FMI

Table 8. Intra-subject variability (CV%) of artemether, DHA and lumefantrine pharmacokinetic parameters

Parameter	Study	Artemether	DHA	Lumefantrine
AUC_{0-t}	A006	55	58	103
	A020	44	35	46
	A2301	28	22	44
	B2104	27	33	27
C_{max}	A006	56	35	99
	A020	45	37	38
	A2301	34	26	39
	B2104	37	35	29

[1] CV% calculated from residual mean square error from statistical analysis of log-transformed data

2.3. *Intrinsic Factors*

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Please see below for a discussion of the PK in special populations and the impact on dosing recommendations.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1. Elderly

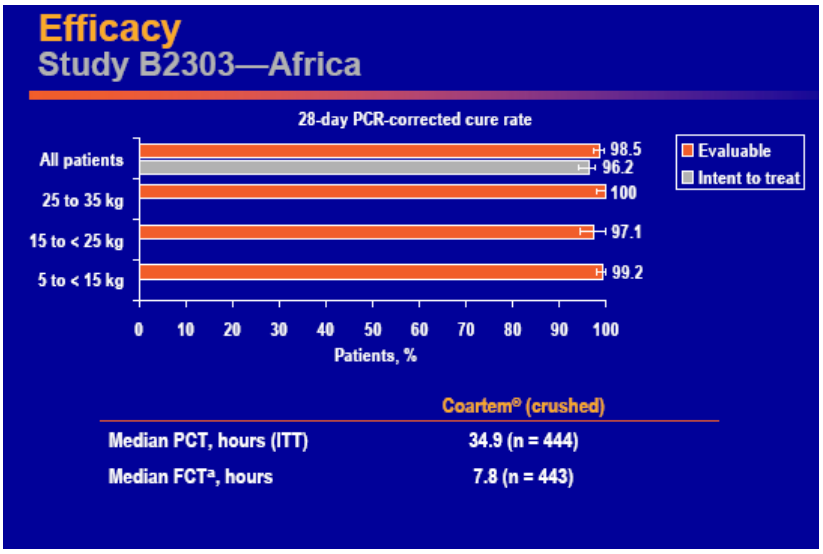
No specific pharmacokinetic studies have been performed in elderly subjects.

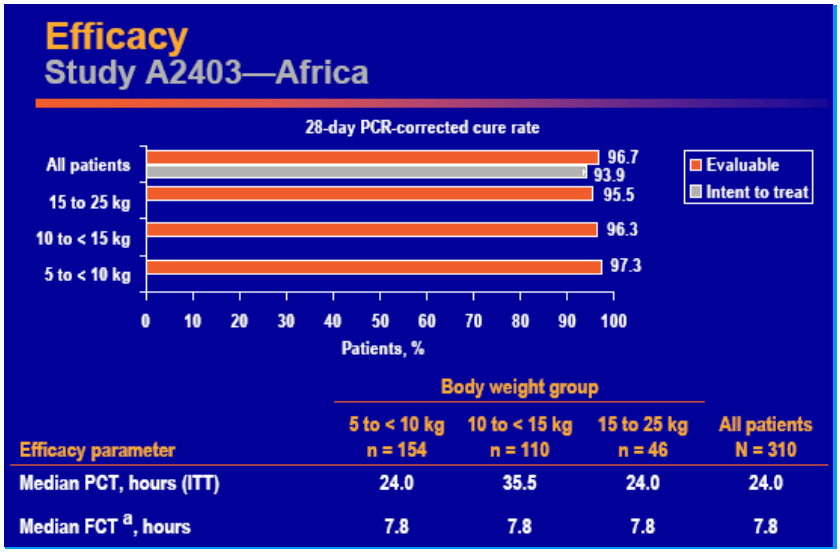
2.3.2.2. Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

In addition to adults, co-artemether is also indicated for use in pediatric malaria patients with bodyweight as low as 5 kg, but the currently available tablets usually need to be crushed and mixed with water prior to administration, especially for small children and infants who cannot swallow the intact tablets and/or in whom swallowing the tablets is associated with the risk of choking.

Two studies have been conducted in infants and children with malaria, i.e. Study CCOA566A2403 and Study CCOA566B2303. Crushed standard tablets of co-artemether were used in both studies. Artemether and DHA concentrations were determined after the first dose in Study CCOA566B2303, and lumefantrine was determined at various time-points up to 14 days after the first dose in both studies.

The effectiveness of Coartem was high in both studies as seen below in the two plots.





Artemether and DHA concentrations observed in Study CCOA566B2303 were in line with those observed previously in adult malaria patients in Thailand (Study CCOA566A028) treated with the 6-dose regimen of co-artemether. The children were treated with the 6-dose regimen based on body weight, i.e. 6 x 1 tablet for children 5-<15 kg, 6 x 2 tablets for children 15-<25 kg and 6 x 3 tablets for children 25-<35 kg.

	Body weight group (Dosing regimen)		
	5-<15 kg (6 x 1 tablet)	15-<25 kg (6 x 2 tablets)	25-<35kg (6 x 3 tablets)
Crushed tablet (N=93)	N=55	N=29	N=8
C_{max} artemether (ng/mL)	223 ± 309 (CV 139%)	198 ± 179 (CV 90%)	174 ± 145 (CV 83%)
C_{max} DHA (ng/mL)	54.7 ± 58.9 (CV 108%)*	79.8 ± 80.5 (CV 101%)	65.3 ± 23.6 (CV 36%)
Total dose artemether (mg/kg BW)	11.1 ± 3.54 (n=56)	13.4 ± 1.76	13.2 ± 1.02
Dispersible tablet (N=91)	N=52	N=30	N=9
C_{max} artemether (ng/mL)	196 ± 204 (CV 104%)	150± 106 (CV 71%)	134 ± 56.7 (CV 42%)
C_{max} DHA (ng/mL)	67.8 ± 74.7 (CV 110%)	66.5 ± 49.0 (CV 74%)	73.9 ± 48.7 (CV 66%)
Total dose artemether (mg/kg BW)	11.6 ± 2.87 (n=53)	13.4 ± 2.05	12.7 ± 1.21

* N (number of patients)=56
BW = body weight

Lumefantrine exposure in pediatric patients of Study CCOA566B2303 (crushed and dispersible tablets) is given in Table 9a. Note that the dispersible tablets are not marketed or being sought for approval in this NDA. They were included in the study for comparative purposes in anticipation for a future application.

Table 9a. Lumefantrine PK estimates following co-artemether crushed or dispersible tablet in pediatric patient

	Body weight group (Dosing regimen)		
	5-<15 kg (6 x 1 tablet)	**15-<25 kg (6 x 2 tablets)**	**25-<35 kg (6 x 3 tablets)**
Crushed tablet (N=315)	N=194	N=102	N=19
Lumefantrine dose (mg/kg BW)	66.7 ± 15.3	82.9 ± 11.0	75.9 ± 7.21
C_{max} (µg/mL)	6.13 (n=101)	9.37 (n=53)	21.9 (n=1)[1]
$AUC_{0\text{-}last}$ (µg·h/mL)	577	699	1150
Dispersible tablet (N=310)	N=191	N=102	N=17
Lumefantrine dose (mg/kg BW)	68.6 ± 16.9	80.6 ± 11.5	77.8 ± 8.57
C_{max} (µg/mL)	5.16 (n=14)	8.03 (n=48)	12.3 (n=3)
$AUC_{0\text{-}last}$ (µg·h/mL)	441	704	1260

BW = body weight; [1] this C_{max} represents only one value/patient sampled at this timepoint.

As seen below in Table 9b, the PK estimates obtained from Study CCOA566B2303 was consistent with findings for the crushed tablet in Study CCOA566A2403.

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

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

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

The estimated C_{max} and AUC values of lumefantrine for the three body weight groups seemed to suggest an increase in exposure with rising doses (i.e. the number of tablets), despite the fact that the total dose of lumefantrine in mg/kg body weight did not vary substantially between body weight groups (66.7 to 82.9 mg/kg in Study CCOA566B2303). Lumefantrine exposure for the 25-<35 kg group was most likely overestimated due to the limited number of samples and some extreme values in this group. Therefore, the data for this group was only a rough estimate and was difficult to compare with other groups or other studies. However, as shown above, no difference in efficacy was observed. A food effect may have contributed to the trend to increasing lumefantrine exposure with rising body weight despite similar body weight normalized lumefantrine doses. Younger children, as opposed to older ones, were likely to eat less, and might not have taken enough food with all doses of

co-artemether. Since food was shown to increase bioavailability of lumefantrine by 16-fold on average in healthy adult subjects, small differences in dietary conditions (i.e. ability to eat, quantity and type of food) between weight groups may have been responsible for the above findings.

If lumefantrine concentrations of all children in Study CCOA566B2303 were pooled per treatment, C_{max} was 7.69 and 6.27 µg/mL and AUC_{last} was 636 and 574 µg·h/mL for the crushed and the dispersible tablet, respectively. Overall, lumefantrine exposure in pediatric patients was comparable to that reported recently in literature in adult malaria patients given the 6-dose regimen of co-artemether. In one study conducted in adult patients in Thailand, median C_{max} was 6.98 µg/mL and AUC_{last} was 410 µg·h/mL. Another study conducted in malaria pediatric and adult patients in Africa showed C_{max} of around 7.0 µg/mL in children up to 15 years (up to 25.0 kg body weight on average), and of 5.60 µg/mL in patients ≥15 years (i.e. up to 56.3 kg on average). A previous Novartis sponsored study in adult malaria patients Study CCOA566A025 showed median (model derived) C_{max} of 9.0 µg/mL and AUC of 561 µg·h/mL. Taken together, with the dose regimens and body weight groups used in the pediatric studies, the systemic exposure to lumefantrine in children is in the same order of magnitude as that in adults.

In the two pediatric studies Study CCOA566B2303 and CCOA566A2403, sparse sampling was conducted to measure the concentrations of artemether, DHA and lumefantrine. However, the applicant used a naïve pooled approach to analyze the data and did not use PK modeling to obtain estimates of the post hoc AUC and clearance. Thus, no relationship between CL/F and covariates such as body weight and age could be described.

Overall, when dosed according to their body weight in pediatric malaria patients the efficacy appeared to be high (>95%) and well-tolerated.

2.3.2.3.Gender

The influence of age, gender and bodyweight on the PK of lumefantrine has been first evaluated in malaria patients using a model-based population approach combining full (rich) profiles and sparse data. This prospective population evaluation was conducted using data from Study COA566A025 conducted in malaria patients in Thailand. The evaluation showed that age, body weight and gender had no effect on any of the main PK parameters of lumefantrine.

2.3.2.4.Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

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

2.3.2.5. Renal impairment

The contribution of the renal pathway to the elimination of Coartem is unknown. No specific pharmacokinetic studies have been performed in individuals with renal insufficiency. Thus the impact of degree of renal impairment on the PK of Coartem is unknown, but no dosage adjustments are being proposed in patients with renal impairment. Based on discussions with the clinical team, it was concluded that the clinical studies included patients with mild and moderate renal impairment but not patients with severe impairment. It will be stated in the product label that the product has not been studied in patients with severe renal impairment

2.3.2.6.Hepatic impairment

No specific pharmacokinetic studies have been performed in individuals with hepatic insufficiency. However, as is frequently seen in acute malaria, many patients included in the clinical studies showed a certain degree of hepatic impairment, as indicated by increased liver enzymes and/or hepatomegaly. A retrospective descriptive analysis of safety performed in those patients did not reveal any difference from the general study population. Given the above and knowing that artemether and lumefantrine are eliminated mainly through non-renal mechanisms (i.e., liver, biliary), Coartem should be administered with caution in patients with hepatic impairment.

2.3.2.7.What pregnancy and lactation use information is there in the application?

The product has not been tested in pregnant and lactating women and so the PK of Coartem in these sub-populations is unknown.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response? Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No information is available regarding the effect of herbal products, smoking and alcohol usage on the exposure and response. The effect of food will be described in section 2.5.3.

2.4.2. Drug-drug interactions

2.4.2.1.Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Lumefantrine was shown to inhibit CYP2D6-mediated metabolism *in vitro.* The concomitant administration of Coartem with drugs that are CYP2D6 substrates is to be avoided (see also response to 2.4.2.3).

Halofantrine and quinine were shown to inhibit the metabolism of lumefantrine *in vitro*, with Cmax/Ki ratios between 0.1 to 1.0, suggesting a possible drug-drug interaction *in vivo*. However, like lumefantrine, both halofantrine and quinine are known to prolong QT interval and so, concomitant administration of Coartem with these other anti-malarial drugs is to be avoided. Thus, follow-on *in vivo* drug-drug interaction studies are not indicated.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

See response to 2.2.5.6. The involvement of genetics in Coartem metabolism has not been studied.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

In human liver microsomes, artemether was not found to significantly inhibit the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A9/11 *in vitro*; the calculated [I]/Ki ratios were <0.1.

In human liver microsomes, lumefantrine inhibited CYP2D6 –mediated metabolism of dextromethorphan *in vitro*. The [I]/Ki ratio calculated for CYP2D6 at this test concentration range was ~ 11, suggesting a 'likely' drug interaction potential *in vivo*. On the other hand, lumefantrine did not inhibit the enzymatic activities of CYP1A2, 2A6, 2C9, 2C19, 2E1, 3A4/5, and 4A9/11 *in vitro*.

In vitro studies were not conducted to ascertain the metabolic induction potential of artemether and lumefantrine. The clinical pharmacology reviewer requested that the applicant provide information pertaining to the in vitro and/or in vivo studies that characterized the potential of Coartem as an inducer. However, the applicant was unable to provide any definitive studies to that effect. In vivo evidence in healthy volunteers and malaria patients revealed that repeat administration results in a lowered systemic exposure of artemether compared to single dose indicating that artemether may induce its own metabolism.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Not determined.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

Not determined.

2.5. General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Based on BCS principles, artemether and lumefantrine are not Class I compounds.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?.

No relative BA study was conducted to compare the clinical trial formulation and the to-be-marketed formulation (TBM). The TBM was used in 7 out of the 8 key clinical trials. In one trial (AB/M02), an older formulation (F.81) was used compared to the other 7 trials in which the TBM formulation (F.4) was used.

Given that there are 7 clinical trials which demonstrated effectiveness and safety of Coartem TBM formulation, a pivotal BE study to compare the F.4 and F.81 formulations was not conducted. The two formulations are markedly different as shown below:

1.3 Composition of clinical formulations

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

Component	20 + 120 mg Tablet F.81[1]	20 + 120 mg Tablet F.4	20 + 120 mg dispersible tablet Variant 009
Artemether	20.0	20.0	20.0
Lumefantrine	120.0	120.0	120.0
(b) (4)	(b) (4)		
Cellulose microcrystalline			
Croscarmellose sodium			
(b) (4)			
Hypromellose			
(b) (4)			
Polysorbate 80			
(b) (4)			
Magnesium stearate			
(b) (4)			
Tablet weight	319.1	240.0	285.2

According to the applicant. there were no direct PK comparisons of formulations F81, F4 and F5, and across-study comparisons are complex and difficult because

of the high inter-subject (and across-study) variability in drug exposure parameters and the different conditions of administration, in particular food intake. However, after single dose fed administration, C_{max} and AUC_{last} for artemether were from 59.8 to 104 ng/mL and 146 to 338 ng·h/mL, respectively, for F5 (Studies A020, B2102 and A024), and 83.8 to 104 ng/mL and 259 to 302 ng·h/mL, respectively, for F4 (Studies A2301 and B2104). For lumefantrine, values were 4.5 to 7.38 µg/mL and 69.9 to 158 µg·h/mL, respectively, for F5, and 7.91 to 9.8 µg/mL and 195 to 243 µg·h/mL, respectively, for F4. Moreover, across-study comparisons of clinical outcomes showed comparable clinical efficacy outcomes between formulations F4 (Study A023) and F81 (Study AB/MO1 and Study AB/MO2) as shown below:

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

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

Based on across study comparisons performed by the clinical pharmacology reviewer, the PK estimates of artemether, DHA and lumefantrine for the two formulations across various studies is given below. The Coartem doses used in the studies are the 6-dose regimen i.e., 4 tablets of 20/120 mg × 6 doses.

Study #	**Formulation used**	**Artemether**	
		C_{max} (ng/mL)	(ng-h/mL)
023	F.4	58.5±30.8	AUC_{0-360} - 767±671
AB/M02	F.81	83.9±62	AUC_{0-672} - 1711±770 $AUC_{0-8, FD}$ – 503 $AUC_{0-8, LD}$ – 260
028	F.4	66.2±54.3	$AUC_{0-8, FD}$ – 535±272 $AUC_{0-8, LD}$ – 211±109

Notes: FD – first dose, LD – last dose

Study #	**Formulation used**	**DHA**	
		C_{max} (ng/mL)	(ng-h/mL)

023	F.4	96.7± 49.9	AUC_{0-360} - 1160 ±553
AB/M02	F.81	217.7±65.5	AUC_{0-672} - 3032±1390
028	F.4	205±102	AUC_{0-8} - 604±259

Study #	**Formulation used**	**Lumefantrine**	
		C_{max} (µg/mL)	(µg-h/mL)
023	F.4	10.9±4.4	AUC_{0-360} - 620 ±356
AB/M02	F.81	13.3±5.7	AUC_{0-672} - 924.9±403
025	F.4	11.0±6.8	AUC_{0-inf} - 1132±771

Overall, given that 7/8 pivotal trials were conducted using the TBM, a pivotal BE study is not necessary.

2.5.2.1. What data support or do not support a waiver of in vivo BE data?

- BCS classification system: Not Applicable
- Formulation ingredient information: refer to ONDQA review
- Dissolution profiles: refer to ONDQA review
- Others: Not Applicable.

2.5.2.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not Applicable.

2.5.2.3. If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not Applicable.

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

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

adult/adolescent and pediatric patients were conducted with the recommendation to take co-artemether with food to the extent possible. In the clinical studies patients did take Coartem with food.

2.5.4. When would a fed BE study be appropriate and was one conducted?
Not Applicable

2.5.5. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?
The review of the dissolution conditions was performed by the ONDQA reviewer.

2.5.6. If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?
No pivotal BE study was performed by the applicant. The to-be-marketed formulation (F.4) was used in 7/8 clinical trials to demonstrate safety and efficacy. In one trial (Trial AB/M02) a earlier formulation, F.81 was used. However, given that 7 other trials were conducted to demonstrate the efficacy and safety in malaria patients, it was determined that a BE study to compare the F.81 and F.4 formulations is unnecessary. Please see response to 2.5.2 for a more detailed explanation.

2.5.7. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?
No other issues are unresolved related to *in vivo* BA or BE.

2.6. ***Analytical section***

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?
Artemether and its active metabolite DHA were initially measured in plasma using a high-performance liquid chromatography (HPLC) with electrochemical detection in the reductive mode (LOQ between 1.25 and 10 ng/mL). Later, high-performance liquid chromatography–mass spectrometry (HPLC-MS) or tandem mass spectrometry (HPLCMS/ MS) assays were used (LOQ = 5 ng/mL for both artemether and DHA).

Lumefantrine was initially measured in plasma using a HPLC with ultraviolet (UV) detection (LOQ between 5 and 100 ng/mL), and more later, by HPLC-MS/MS (LOQ = 50 ng/mL). Desbutyl-lumefantrine was measured by HPLC-MS/MS (LOQ = 5 ng/mL). The methods were validated according to FDA guidance "Bioanalytical Method Validation".

2.6.2. What bioanalytical methods are used to assess concentrations?

2.6.2.1. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Studies	Limit of quantification (in the study)*	Reference Validation Report	Method
CCOA566AAB/M01 CCOA566AAB/M02 CCOA566A027 CCOA566A1012	2.5 / 1.25 ng/mL 2.5 / 1.25 ng/mL 10 / 10 ng/mL 2.5 / 2.5 ng/mL	(Navaratnam, et al 1995)	HPLC-electrochemical detection
CCOA566A006 CCOA566A020 CCOA566A1014	5 / 5 ng/mL 5 / 5 ng/mL 10 / 10 ng/mL	(Melendez, et al 1991)	HPLC-electrochemical detection
CCOA566A022 CCOA566A023 CCOA566A024 CCOA566A028	10 / 10 ng/mL 10 / 10 ng/mL 10 / 10 ng/mL 10 / 10 ng/mL	[BPK(F) 1996/001] published in (Sandrenan, et al 1997)	HPLC-electrochemical detection
CCOA566A2301 CCOA566A2302	5 / 5 ng/mL 5 / 5 ng/mL	[BAPK(F) R00-1840] published in (Souppart, et al 2002)	HPLC-MS
CCOA566B2102 CCOA566B2104 CCOA566A2101 CCOA566B2303	5 / 5 ng/mL 5 / 5 ng/mL 5 / 5 ng/mL 5 / 5 ng/mL	[BAPK(EU) R0301212]	HPLC-MS/MS

* first value relates to artemether, second one to DHA

Studies	Limit of quantitation (in the study)	Reference Validation report	Method
CCOA566AAB/M01 CCOA566AAB/M02 CCOA566A1009 CCOA566A1012 CCOA566A020 CCOA566A023	5 ng/mL 5 ng/mL 5 ng/mL 20 ng/mL 50 ng/mL 20 ng/mL	(Zeng, et al 1996)	HPLC-UV
CCOA566A027 CCOA566A028	100 ng/mL 100 ng/mL	(Mansor, et al 1996)	HPLC-UV
CCOA566A004 CCOA566A006 CCOA566A1014 CCOA566A022	5 ng/mL 20 ng/mL 36.8 ng/mL 33 ng/mL	[BPK(CH) 1994/038]	HPLC-UV

Studies	Limit of quantitation (in the study)	Reference Validation report	Method
CCOA566A024 CCOA566A1025 CCOA566A1026	50 ng/mL 34.5 ng/mL 100 ng/mL		
CCOA566A2302	50 ng/mL	[DMPK(F) R00-2105]	HPLC-UV
CCOA566A2301 CCOA566A2403	50 ng/mL 50 ng/mL	[BAPK(F) R00-2105-02]	HPLC-UV
CCOA566A2101 CCOA566A2401 CCOA566B2102 CCOA566B2104 CCOA566B2303	50 ng/mL 50 ng/mL 50 ng/mL 50 ng/mL 50 ng/mL	[DMPK R0300924A]	HPLC-MS/MS

Studies	Limit of quantitation	Reference Validation report	Method
CCOA566A2401 CCOA566B2102	5 ng/mL 5 ng/mL	[DMPK R0300924B]	LC-MS/MS

26 pages of draft labeling has been withheld after this page as b4 (CCI/TS).

4. Appendices

4.1. Clinical pharmacology and biopharmaceutics individual study review
Available upon request.

4.2. Consult reviews
IRT-QT review is available upon request

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Phil Colangelo
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