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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: NDA 22-268

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1 EXECUTIVE SUMMARY

1.1 *Conclusions and Recommendations*

The information in this review showed that a 6-dose regimen of Coartem appears more effective than a 4-dose regimen. Additionally, two studies using the 6-dose regimen conducted in Thailand, shows that 28-day cure rates for the intent-to-treat population were greater than 80% and for the evaluable population greater than 90%. Parasite reduction on day 1 was high with a median reduction of 99% - 100%, with interquartile range from 96.5% to 100%. This information along with information reviewed by Lan Zeng in her statistical review on the efficacy of the components of Coartem in 4-dose studies supports the efficacy of Coartem in the treatment of acute uncomplicated *P. falciparum* malaria. However, given the limited numbers of participating study centers and countries, generalization to other populations should be done with caution.

1.2 *Brief Overview of Clinical Studies*

The sponsor submitted 8 key clinical studies with complete data to support the efficacy of Coartem to treat malaria. The sponsor additionally submitted study reports from supportive 4-dose and 6-dose studies. This review focuses on the 6-dose key comparative studies, namely Study 025, Study 026, and Study 028.

Study 025 was a randomized, double-blind, parallel group, two-center study including subjects aged 2 or more years in Thailand, to compare the efficacy and safety of 4-dose and two 6-dose Coartem regimens, a 6-dose-over-60-hour regimen (the requested regimen) and a 6-dose-over-96-hour regimen.

Study 026 was a randomized, open-label, two-center trial including subjects in Thailand with age ≥ 2 years to confirm the efficacy and safety of the 6-dose-over-60-hour regimen, with a non-FDA approved comparator for comparison with historical data.

Study 028 was a randomized, open-label, single-center trial including subjects in Thailand with age ≥ 12 years and weight ≥ 35 kg to confirm the efficacy and safety of the 6-dose-over-60-hour regimen, with a non-FDA approved comparator for comparison with historical data.

The primary endpoint in the three studies was non-PCR corrected 28-day cure rate. The two active controlled studies were not designed for comparative analysis between the Coartem arms and the controls.

Important secondary endpoints included time to parasite clearance, time to fever clearance, and negative parasite slides at 24 and 48 hours.

1.3 Statistical Issues and Findings

In Study 025, the primary endpoint 28-day cure rates of the 6-dose-over-60-hour (96.9%, 93/96) and 6-dose-over-96-hour regimens (98.1%, 104/106) were significantly higher than the 4-dose regimen (80.8%, 84/104) in the evaluable population, with a difference in the day 28 cure rates between the 6-dose-over-60-hour and 4-dose regimen being 16.1% [97.5% CI 6.0%, 26.7%], $p < 0.001$ and with the difference between the 6-dose-over-96-hour and 4-dose regimen being 17.3% [7.6%, 27.7%], $p < 0.001$. In the ITT population, the 28-day cure rates of the 6-dose-over-60-hour (81.4%, 96/118) and 6-dose-over-96-hour regimens (98.1%, 104/106) were borderline significantly and statistically significantly higher than the 4-dose regimen, with a difference in cure rates of 10.5% [97.5% CI: -1.9%, 22.8%], $p = 0.069$ and 15.1% [97.5% CI: 2.8%, 27.3%], $p = 0.0048$, respectively. There was no statistically significant difference in time to parasite clearance and time to fever clearance between the study arms, as expected given that the treatment arms did not differ from one another until after 36 hours.

In Study 026, the 28-day cure rate was 97.0% (130/134) [95% CI: 92.5%, 99.2%] in the evaluable population and 86.7% (130/150) [95% CI: 80.2%, 91.7%] in the ITT population. In Study 028 the 28-day cure rate was 95.5% (148/155) [95% CI: 90.9%, 98.2%] in the evaluable population and 90.2% (148/164) [95% CI: 84.6%, 94.3%] in the ITT population.

The limitation of these studies was that there were only at most two centers in one country (Bangkok and Maela in Thailand) in each trial and that one investigator in one center participated in the three studies, so generalizing these results to a wider population should be done with caution.

2 INTRODUCTION

2.1 Overview

Coartem is an oral fixed-dose tablet containing artemether (20 mg) and lumefantrine (120 mg). The applicant conducted 21 clinical studies, eight of which were considered as key studies by the FDA and the applicant, and 13 studies which were considered as supportive studies. The eight key studies included two 4-dose studies, one 4-dose and 6-dose study, and five 6-dose studies (with or without comparators). The two 4-dose studies which compared Coartem with the individual components are reviewed by Ms Lan Zeng. This review will cover the 4-dose and 6-dose study (Study 025), and two 6-dose comparative studies (Study 026 and 028), with Study 025 being a randomized, double-blind study comparing 4-dose versus 6-dose-over-60-hour, and 6-dose-over-96-hour and Study 026 and 028 being open-label studies, with a non-FDA approved medication for comparison with historical data.

2.2 Data Sources

The data sets for these studies were submitted electronically and can be found at the following location: \\fdswa150\nonec.td. The reviewer found the data sets to be

well organized and of good quality. The following data sets were used in the review process: a_eff, a_pc, and vpdisc.

3 STATISTICAL EVALUATION

Study 025, 026, and 028 will be reviewed in this section.

3.1 Evaluation of Efficacy

3.1.1 Study 025

3.1.1.1 Objectives

The objectives of this study was to compare the efficacy, safety, and pharmacokinetics of two 6-dose regimens (6 doses over 60 hours and over 96 hours) with the 4-dose regimen (4 doses over 48 hours) of Coartem in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults and children > 2 years in Thailand.

3.1.1.2 Study Design

This was a Phase II randomized, double-blind, parallel group, 2-center, 4-week trial, conducted in Thailand from March, 1997 to July, 1997. Eligible male or female patients who had microscopic confirmation of *P. falciparum* or mixed (including *P. falciparum*) infection and had parasitaemia > 500 per μL at baseline in two study hospitals were randomized to one of the following three trial treatments (each tablet: 20 mg artemether and 120 mg benflumetol)

- 4-dose 48-hour regimen: 4 doses of 1, 2, 3, or 4 tablets based on body weight over 48 hours (plus placebo at 4 time points)
- 6-dose 60-hour regimen: 6 doses of 1, 2, 3, or 4 tablets based on body weight over 60 hours (plus placebo at 2 time points)
- 6-dose 96-hour regimen: 6 doses of 1, 2, 3, or 4 tablets based on body weight over 96 hours

Table 1. Dosage of trial medications and time of administration in Study 025

Dose	1	2	3	4	5	6	7	8
Time (hr.)	0	8	24	36	48	60	72	96
4 doses over 48 hours	x	x	x	p	x	p	p	p
6 doses over 60 hours	x	x	x	x	x	x	p	p
6 doses over 96 hours	x	x	x	p	x	p	x	x

p: placebo. x: Coartem (dosage adjusted for body weight)

Adapted from sponsor's study report, Exhibit 3.4.-1.

Patients in Bangkok (Center 1) were aged 12 years or more and treated as inpatients during the 28-day trial period. Patients in MaeLa (Center 3) were aged 2 years or more and treated as outpatients, seen daily for the first week and weekly thereafter until Day 28 with a long-term follow-up visit on Day 63. The dosage in Center 3 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

Comment: In this review, Day 0 was the day of initiation of treatment, to be consistent with the test-of-cure visit.

3.1.1.3 Statistical Considerations

3.1.1.3.1 Primary Endpoint and Secondary Endpoints

The primary efficacy endpoint was 28-day cure rate, which was defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without subsequent recrudescence.

Secondary efficacy endpoints included time to parasite clearance (PCT), parasite reduction at 24 hours, time to fever clearance (FCT), and anti-gametocyte activity.

Comment: As Table 1 shows, the three arms were identical for the first three doses (up to 36 hours). Therefore, there should be no differences in parasite reduction at 24 hours. PCT and FCT should be similar for the first 36 hours.

3.1.1.3.2 Primary Analysis

Analysis population

The intention-to-treat (ITT) population included all randomized patients who received at least one dose of trial medication.

The evaluable patient population included patients who took no other anti-malarial drugs and had the parasite counts recorded up to Day 28 or discontinued due to “unsatisfactory therapeutic effect” because of reappearance of *P. falciparum*.

Analysis Methods

A six-dose regimen of Coartem would be considered superior if there was a clinically and statistically significant difference in the 28-day cure rate between the six dose group and the standard 4-dose group in the evaluable population with a significance level of 0.025.

The 95% confidence interval (CI) for each of the treatment arms’ 28-day cure was calculated using Pearson-Clopper limit by the sponsor. Cochran-Mantel-Haenszel and row mean scores methods were use for the comparison of 28-day cure rates between each of the two 6-dose groups and the standard 4-dose group for the evaluable patients.

Comment: In the protocol the analysis populations were not specified. In the study report, the sponsor only considered evaluable population. Note that especially given that this was a superiority study, we would be most interested in results from an intent-to-treat analysis.

3.1.1.3.3 Sample Size Calculation

To compare the 28-day cure rates, Casagrande’s method was used for the calculation of sample size:

$$n = \frac{(\sqrt{A} + \sqrt{A + 4\delta})^2}{4\delta^2},$$

where $\sqrt{A} = z_{1-\alpha/2}\sqrt{(P_1 + P_2)\left(1 - \frac{P_1 + P_2}{2}\right)} + z_{1-\beta}\sqrt{P_1(1 - P_1) + P_2(1 - P_2)}$ (two-sided).

Bonferroni method was used to adjust for comparisons of the two 6-dose groups with the standard 4-dose group. Assuming $\alpha=2.5\%$, power=80%, $P_1=0.95$, $P_2=0.80$, 104 patients per group were needed. To allow for a 15% drop-out rate before Day 28, the number of patients in each group was 122. Therefore, 366 subjects were planned to be enrolled.

Because of lower 28-day cure rates observed in other trials (69.3% in trial 004 in Bangkok, 82.1% in trial 008 in MaeLa), more patients were planned to be enrolled in Maela (246 compared to 120 subjects in Bangkok).

Comment: in the protocol, Center 1 (Bangkok) and Center 2 were planned to enroll 80 and 40 patients, respectively. However, Center 2 was not initiated, and the reason for this change was not provided. Therefore, enrollment at Center 1 (Bangkok) was increased to 120 subjects.

3.1.1.4 Sponsor’s Analysis Results

3.1.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

Table 2. Distribution of patients by treatment group in Study 025

	4 doses	6 doses 60 hours	6 doses 96 hours
Enrolled/Randomized	120	118	121
Study Center 1 (Bangkok) / Study Center 3 (Maela)	34/86	32/86	34/87
Premature discontinuation	35(29.2%)	23(19.5%)	18(14.9%)
Unsatisfactory therapeutic response	20(16.7%)	4(3.4%)	2(1.7%)
Lost to follow-up	11(9.2%)	19(16.1%)	15(12.4%)
Death	2	0	0
Administrative problems: quinine treatment	0	0	1
Failure to meet protocol criteria*	1	0	0
Non-compliance	1	0	0
Concomitant use of co-trimoxazole	1	3	0
Sample size in efficacy analyses			
ITT population	120	118	121
Evaluable patient population	104 (86.7%)	96 (81.4%)	106 (87.6%)

Adopted from sponsor’s Exhibit 6.1-1, study report (page 29).

*Major protocol violator, due to renal impairment with abnormal lab values.

As Table 2 shows, among 359 subjects randomized to the three groups, 76 (21%) subjects discontinued within 28 days, 26 of whom were due to unsatisfactory therapeutic response and 45 of whom were lost to follow-up. A higher proportion of subjects in the 4-dose group had unsatisfactory therapeutic response (16.7% versus 3.4% and 1.7%). Two deaths were due to accidents (killed by a military group or by stepping on a landmine).

Table 3: Demographic and baseline data (all patients) in Study 025

	4 doses N=120	6 doses 60 hours N=118	6 doses 96 hours N=121
Sex (males (%))	83(69%)	86(73%)	81(67%)
Age (median[range] in years)	24 [3-75]	23 [3-62]	21[5-60]
Weight (median[range] in kg)	49.5 [12.5-92]	49.3 [10-90]	48[12-76]
Height (median[range] in cm)	158 [92-180]	158[84-177]	158[90-182]
Haematocrit (median [range] in %)	37.7[19.8-56.0]	37.4[18.8-51.0]	37.5[18.0-50.8]
Haematocrit<25%†	7(6%)	4(3%)	5(4%)
Previous malaria infection within 3 months	11(9%)	5(4%)	8(7%)
Hepatomegaly	21(18%)	22(19%)	23(19%)
Splenomegaly	28 (23%)	24(20%)	24(20%)
Temperature (°C)			
Median(mean)	37.6 (37.8)	37.6 (38.0)	38.0 (38.1)
Range	36-40.8	36-40.8	36-41.5
≤ 37.5	59(49.2%)	59(50.0%)	41(33.9%)
37.5-39	38 (31.7%)	34 (28.8%)	52 (43.0%)
≥ 39	23 (19.2%)	25 (21.2%)	28 (23.1%)
Parasite density (/uL)			
Median (geometric mean)	11,891 (10,273)	6,276 (9,260)	7,480(7,480*)
Range	381 - 199,980	415 - 195,735	290 - 464,880
Number (%) by density			
<5,000	44 (36.7%)	55 (46.6%)	52 (43.0%)
5,000-<15,000	19 (15.8%)	12 (10.2%)	13 (10.7%)
15,000-<50,000	34 (28.3%)	22 (18.6%)	27 (22.3%)
≥50,000	23 (19.2%)	29 (24.6%)	29 (24.0%)

Adopted from sponsor's Exhibit 7.1.-1 and 7.1.-3, study report (page 32 and 33).

*The geometric mean should be 10,153.

†14(11.7%), 7(5.9%), and 6(5.0%) were in each arm, respectively, based on the reviewer's analysis.

Baseline characteristics were comparable between the three groups, except for fever and parasite density. The 6-dose-over-96-hour group had a higher proportion of patients with temperature 37.5-39°, compared with the other two arms. The 6-dose groups appeared to have lower parasite medians and have higher proportions of subjects with less than 5,000 or more than 50,000.

Comment: Larger proportions of subjects in the 6-dose groups were in the lowest and highest parasite categories. A sensitive analysis will be considered by adjusting for the difference in baseline parasite counts between the groups in Section 3.1.1.5.

3.1.1.4.2 Efficacy Analysis Results

As shown in Table 1, the three arms were identical for the first three doses (up to 36 hours), there should be no differences in efficacy between the three arms for the first 36 hours.

28-day Cure Rate

The 28-day non-PCR corrected cure rates by treatment and analysis population are shown in the following table.

Table 4. 28-day cure rate and CI in ITT and evaluable populations in Study 025

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

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

Comments:

There was one patient who was cured based on PCR corrected result but not cured based on non-corrected result in the 4-dose and 6-dose-over-96-hour arms.

The two-sided 95% CIs for evaluable population were from the study report. In addition, the differences in cure rates and their CIs in the ITT population were not reported in the study report. Note the sponsor used Bonferroni method to adjust for multiple testing in the sample size calculation. Therefore, 97.5% CIs for the differences in cure rates should be reported and 97.5% CIs in both populations were calculated by the reviewer.

Based on current malaria draft guidance, parasitological and clinical endpoints generally should be combined into a composite study endpoint. The sponsor only used 28-day cure rate, defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without subsequent recrudescence.

Parasite Reduction and Number of Patients with Negative Slide on Days 1, 2, and 3

More than 22%, 77%, and 92% of subjects had a negative slide after one, two, and three days of treatment, respectively. It appeared that there were no obvious differences between the groups.

Table 5. Patients with negative slide on Days 1, 2, or 3 in ITT population in Study 025

Slide		4 doses (48 hours) N=120	6 doses (60 hours) N=118	6 doses (96 hours) N=121
Day 1	Negative	27 (22.5%)	31 (26.3%)	27 (22.3%)
	Positive	90 (75.0%)	87 (73.7%)	92 (76.0%)
	Missing	3 (2.5%)		2 (1.7%)
Day 2	Negative	94 (78.3%)	93 (78.8%)	93 (76.9%)
	Missing (negative before)	0	1 (0.8%)	4 (3.3%)
	Positive	22 (18.3%)	23 (19.5%)	23 (19.0%)
	Missing	4 (3.3%)	1 (0.8%)	1 (0.8%)
Day 3	Negative	116 (96.7%)	109 (92.4%)	114 (94.2%)
	Missing (negative before)	3 (2.5%)	6 (5.1%)	4 (3.3%)
	Positive	0	2 (1.7%)	3 (2.5%)
	Missing	1 (0.8%)	1 (0.8%)	0

From Exhibit 8.1.-7 in sponsor's Exhibit 8.1.-7 in the study report (page 40).

On Day 1 the median reduction was 99.1%, 99.1%, and 98.3% in the 4-dose, 6-dose-over-60-hour, 6-dose-over-96-hour groups, respectively, although there were patients with an increased parasite count compared with the baseline value.

Table 6. Parasite reduction on Day 1 in evaluable population in Study 025

	4 doses (48 hours) N=120	6 doses (60 hours) N=118	6 doses (96 hours) N=121
N (available slides)	117	118	119
Median	99.1%	99.1%	98.3%
25-75 percentiles	96.8% –99.9%	94.0%–100%	93.4% –99.9%
Range	Increase – 100%	Increase – 100%	Increase – 100%

From Exhibit 8.1.-7 in sponsor's Exhibit 8.1.-8 in the study report (page 40).

Time to Parasite Clearance

All but two subjects had time to parasite clearance within 81 hours after start of treatment (one patients was assigned 166 hours due to no slide available between day 1 and 7, one was assigned 90 hours based on first available negative slide).

Table 7. Time to parasite clearance (in hours) in ITT population in Study 025

	4 doses (48 hours) N=120	6 doses (60 hours) N=118	6 doses (96 hours) N=121
Median*[95%CI†]	44[43, 44]	44[43, 45]	44[43, 44]
25-75 percentiles*	34 - 51	22 - 47	40 - 47
Range**	18 - 72	17 - 166	17 - 90

From Exhibit 8.1.-7 in sponsor's study report (page 39). *Kaplan-Meier method. **Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

Time to Fever Clearance

Fever clearance time is reported in the following table for the patients with fever at baseline. Though there is some variability in results across the three treatment arms, no significant differences were found.

Table 8. Time to fever clearance (in hours) in evaluable population in Study 025

	4 doses (48 hours) N=61	6 doses (60 hours) N=59	6 doses (96 hours) N=80
Median*[95%CI†]	23 [21, 36]	35 [22, 43]	22 [21,34]
25-75 th percentile*	20 - 44	20 - 46	20 - 44
Range**	12 - 95	9 - 160	9 - 164

From Exhibit 8.1.-9 in sponsor's study report (page 41). * Kaplan-Meier method.

** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

P. Vivax

At baseline, 21 patients had mixed infection including *P. vivax*. These parasites were cleared within 48 hours after the start of treatment, but reappeared in 9 subjects. Another 45 subjects acquired *P. vivax* during the follow-up period.

Table 9. Number (%) of patients with detected *P. Vivax* by time during the trial in Study 025

Time	4 doses (48 hours) N=120	6 doses (60 hours) N=118	6 doses (96 hours) N=121
Days 0-2	7 (5.8%)	8(6.8%)	6 (5.0%)
Days 3-6	0	0	0
Days 7-13	1 (0.8%)	0	0
Days 14-28	15 (12.5%)	12 (10.2%)	5 (4.1%)
Day > 28	7 (5.8%)	11 (9.3%)	10 (8.3%)

3.1.1.5 Reviewer's Analysis Methods and Results

The following are results of analysis performed by this reviewer including results of some additional endpoints included in the FDA malaria draft guidance.

Late parasitological failure--recrudescence of *P. falciparum* during the study

The late parasitological failure-recrudescence was defined as reappearance of *P. falciparum* during the study period (up to Day 28). The parasite reappearance days ranged from Day 13 to 28. In the ITT population, in the 4-dose arm, 20/120 patients recrudesced in the 4-dose arm between days 14 to 28; in the 6-dose-over-60-hour arm 4/118 patients recrudesced (days 13, 14, 20, and 26), and in the 6-dose-over-96-hour arm 2/121 patients recrudesced (days 14 and 28). The recrudescence rates in the 4-dose

group, 6-dose-over-60-hour, and 6-dose-over-96-hour were 16.7%, 3.4% and 1.7%, respectively, in the ITT population; 19.2%, 3.1%, and 1.9% in the evaluable population. Compared with the 4-dose group, the 6-dose groups had significantly lower late parasitological failure rates both in the ITT and evaluable populations.

Table 10. Recrudescence of *P. falciparum* and exact CI in ITT and evaluable populations in Study 025

	4-dose	6-dose (60 hours)	6-dose (96 hours)
ITT			
n/N (%)	20/120 (16.7%)	4/118(3.4%)	2/121 (1.7%)
95% CI	[10.5%, 24.6%]	[0.9%, 8.4%]	[0.2%, 5.8%]
Diff [97.5% CI]		-13.3%[-22.8%,-4.6%]	-15.0%[-24.3%,-6.5%]
Evaluable			
n/N (%)	20/104 (19.2%)	3/96 (3.1%)	2/106 (1.9%)
95% CI	[12.2%, 28.3%]	[0.6%, 8.9%]	[0.3%, 6.3%]
Diff [97.5% CI]		-16.1%[-26.7%, -6.0%]	-17.3%[-27.7%, -7.6%]

Parasite count change from baseline and proportion of patients with 75% reduction On Day 1 and Day 2 in the ITT and evaluable populations

Table 11. Parasite change from baseline on Day 1 in the ITT and evaluable populations in Study 025

	4-dose	6-dose (60 hours)	6-dose (96 hours)
ITT population	N=118*	N=118	N=119*
Mean Change %	-93.9	-85.6	-62.6
Median %	-99.5	-99.4	-98.9
([min, max]%)	[-100.0, 175]	[-100.0, 875.0]	[-100, 3463.5‡]
75% reduction	95.8% (113/118)	92.4% (109/118)	94.1 (112/119)
Evaluable population	N=102†	N=96	N=104†
Mean Change %	-94.1	-93.0	-58.5
Median %	-99.5	-99.3	-98.9
([min, max]%)	[-100.0, 175]	[-100, 20.0]	[-100.0, 3463.5‡]
75% reduction	96.1% (98/102)	91.7% (88/96)	95.2% (99/104)

*Parasite count data of 4 subjects (2 in each group) in ITT population were missing

†Parasite count data of 4 (2 in each group) subjects in evaluable population were missing

‡One one-year-old male subject with parasite count 1548, 56445, and 238, and 0, at days 0, 1, 2, and 3, respectively.

The reviewer summarized the parasite count change from baseline and proportion of patients with 75% reduction on Day 1 and Day 2, using the last observation if there were multiple observations for a subject per day. On Day 1 (Table 11), mean parasite count percentage reduction in the 6-dose groups appeared to be less than that in the 4-dose group, due to increased parasite counts of a few subjects; however, the difference in means and the differences in 75% reduction rate between either of 6-dose groups and the 4-dose group were not statistically significant. The median changes were close to -99%. On Day 2, the same trends held and all subjects in both populations achieved 75%

reduction. On Day 2, the mean changes and 75% reduction rates were all comparable (Table 12).

Table 12. Parasite change from baseline on Day 2 in the ITT and evaluable populations in Study 025

	4-dose	6-dose (60 hours)	6-dose (96 hours)
ITT population	N=117*	N=116*	N=119*
Mean Change %	-100.0	-100.0	-99.8
([min, max]%)	[-100.0,-99.7]	[-100.0, 97.3]	[-100, 85.0]
75% reduction	100% (117/117)	100% (116/116)	100% (119/119)
Evaluable population†	N=101	N=94	N=104
Mean Change %	-100.0	-100.0	-99.8
([min, max]%)	[-100, -99.8]	[-100, 98.7]	[-100, -85.0]
75% reduction	100% (101/101)	100% (94/94)	100% (104/104)

*3, 2, and 3 subjects in three groups, respectively, in the ITT population had missing data.

†3, 2, and 2 subjects in three groups, respectively, in the evaluable population had missing data.

3.1.2 Study 026

3.1.2.1 Objectives

The primary objective of this study was to confirm the efficacy and safety of the 6-dose regimen of Coartem given over 3 days in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults and children ≥ 2 years in Thailand.

The secondary objective was to explore any relationship between changes in QTc measurements and benflumetol plasma levels.

3.1.2.2 Study Design

This was a randomized, open-label, comparative, parallel group, 2-center, 4-week trial. Eligible male or female patients with symptoms of acute uncomplicated *P. falciparum* malaria and microscopic confirmation of *P. falciparum* or mixed (including *P. falciparum*) infection, and *P. falciparum* parasitaemia above 500 per μL at baseline were randomized 3:1 to Coartem or mefloquine and artesunate (MAS). MAS was included for comparison with historical data rather than for a formal statistical comparison. Since MAS could not be blinded, the study was designed as an open-label study.

The number of Coartem tablets per dose was adjusted according to body weight (one tablet per dose for 10-20 kg, 2 tablets per dose for 21-30 kg, 3 tablets per dose for 31-40 kg, and 4 tablets for 40+ kg), according to an amendment to the protocol before patient enrollment.

Patients in the MAS group received artesunate 4 mg/kg/day once daily for 3 days, plus mefloquine 25 mg/kg given as a split dose of 15 mg/kg plus 10 mg/kg on Days 2 and 3.

Patients in Center 1 (Bangkok) were planned to be admitted for inpatient observation for the 28-day trial period, whereas in Center 2 (MaeLa), patients were treated as outpatients.

All patients were planned to be followed daily (from Day 0) for the first week, on Day 7, 14, 21, and 28.

3.1.2.3 Statistical Considerations

3.1.2.3.1 Primary Endpoint and Secondary Endpoints

The primary endpoint of this study was the 28-day cure rate, defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without subsequent recrudescence.

The secondary endpoints included parasite reduction and proportion of patients with a negative slide on Days 1, 2, and 3, and anti-gametocyte activity. The parasite reduction was calculated as percentage reduction of baseline parasitaemia approximately 24, 48 and 72 hours after initiation of trial treatment. Anti-gametocyte activity was measured by the clearance of existing gametocytes without the need for further antimalarials.

3.1.2.3.2 Primary Analysis

Analysis population

Two analysis populations were defined. The intent-to-treat (ITT) population included all randomized patients. The evaluable patient population included patients with parasite counts recorded up to day 28 or patients discontinued due to “unsatisfactory therapeutic effect” because of reappearance of *P. falciparum*.

Analysis Methods

Assuming a cure rate of at least 95% in the control group, which was based on the cure rate of 97.3% from Trial 5669701 008, the protocol specified that the 6-dose regimen of Coartem would be considered effective if the lower limit of the 90% confidence interval (CI) for the 28-day cure rate exceeded 90%.

The 90% CI for the 28-day cure rate for each treatment in both populations (and the 95% CI's for each centre) were calculated using Pearson-Clopper limits.

Comments: The sponsor used a cure rate of 90% as the efficacy criterion. We defer to the medical reviewers to decide if this rate could be used as the efficacy criterion. In addition, we would typically limit the type I error to 0.05 (2-sided). Therefore, the lower limit of a one-sided 97.5% CI (or two-sided 95% CI) should be used. More importantly, the sponsor did not specify the analysis population(s) for the primary endpoint analysis. In fact, as discussed below, only the analysis results from the evaluable population met the sponsor's efficacy criterion.

Based on the study report (page 21), “no statistical testing was performed for variables other than the 28 day cure rate, as the MAS group was only used for the "bridging" to previous results rather than for a formal statistical comparison”. However, comparative

analysis versus MAS was conducted by the sponsor. In the study report, the 90% CI for the difference in cure rates was calculated using the normal approximation to the binomial distribution. The 28-day cure rates were tested for the evaluable patient population between the two treatment groups using Van Elteren test ($\alpha=5\%$, two-sided test) and row mean scores, i.e. testing the association between treatment and the 28-day cure rate adjusting for center.

3.1.2.3.3 Sample Size Calculation

In order to demonstrate a 28-day cure rate $> 90\%$, 120 patients were required ($H_0: p \leq 0.90$ versus $H_1: p > 0.90$, $\alpha=0.05$ (one-sided) and power=95% at $p=0.97$). Allowing for a 20% drop-out rate, the number of patients allocated to Coartem was 150. Another 50 patients were planned for the MAS group.

Comment: MAS is not a FDA approved regimen for malaria. Therefore, a typical noninferiority analysis comparing the two treatment regimens would have been difficult to justify. Based on the FDA malaria draft guidance, unapproved comparators may be appropriate if they represent the local standard of care. Although the study was not designed a comparative study, we will perform a comparative analysis later.

3.1.2.4 Sponsor's Analysis Results

3.1.2.4.1 Patient Disposition, Demographic and Baseline Characteristics

Table 13. Distribution of patients by treatment group in Study 026

	Coartem	MAS
Enrolled/Randomized	150	50
Study Center 1 / Study Center 2	21/ 129	7/43
Premature discontinuation	23(15.3%)	5(10.0%)
Unsatisfactory therapeutic response	4(2.7%)	0
Lost to follow-up*	17(11.3%)	5(10.0%)
Non-compliance	1	0
Failure to meet protocol criteria	1	0
Sample size for efficacy analyses		
ITT population	150	50
Evaluable patient population	134(89.3%)	47(94.0%)

* 6 patients (4 in the Coartem group and 2 in the MAS group) were included in the evaluable population because of negative parasite counts after Day 28.

Adopted from sponsor's Exhibit 6.1-1, study report (page 26).

A total of 200 subjects were enrolled in the trial (Table 13). Among 28 subjects (23 and 5 subjects in the Coartem group and MAS group, respectively) who were discontinued prematurely, those with unsatisfactory therapeutic response and six (4+2) patients who were lost to follow-up during the 28 days were included in the evaluable population. The 6 subjects who were lost to follow-up were included because of negative counts after Day 28. Therefore, 18 (15+3) patients due to lost to follow-up, noncompliance and failure to meet protocol criteria were not evaluable. In addition, one in the Coartem group was not

evaluable due to i.v. quinine use on Day 14 when having febrile coma of unknown origin. Thus, the evaluable population included 181 (134+47) patients.

Table 14 reports demographic and baseline data for study 26.

Table 14. Demographic and baseline data (all patients) in Study 026

	Coartem N=150	MAS N=50
Sex (males (%))	110 (73%)	37 (74%)
Age (median[range] in years)	22 [2-63]	25 [3-61]
Weight (median[range] in kg)	50 [8-81]	50 [11-66]
Height (median[range] in cm)	155 [77-175]	158[84-172]
Haematocrit (median [range] in %)	37.0[18.7-50.9]	38.8[25.1-60.8]
Haematocrit<25%	3(2%)	0
Previous malaria infection within 3 months	6(4%)	0
Hepatomegaly	51(34%)	9(18%)
Splenomegaly	40 (27%)	13 (26%)
Temperature (°C)		
Median(mean)	37.7 (37.9)	38.0 (38.0)
Range	[35.6-40.2]	[36.0-39.9]
≤ 37.5	63(42.0%)	17(34.0%)
37.5-39	63(42.0%)	20(40.0%)
≥ 39	24(16.0%)	13(26.0%)
Parasite density (/uL)		
Median (geometric mean)	9374(9162)	5285(8452)
Range	[264-254,490]	[625-177,840]
Number (%) by density		
Not detected	1 (0.7%)	0
<5,000	66(44.0%)	22(44.0%)
5,000-<15,000	15(10.0%)	7(14.0%)
15,000-<50,000	40(26.9%)	14(28.0%)
≥50,000	28(18.8%)	7(14.0%)

Adopted from sponsor's Exhibits 7.1-1 and 7.1-3, study report (page 29 and 30).

3.1.2.4.2 Efficacy Analysis Results

28-Day Cure Rate

The cure rates in the ITT population and evaluable population are shown in the following table. The cure rates in the ITT and evaluable populations were 86.7% and 97%, respectively. The sponsor's reported 90% confidence intervals and the reviewer's calculated 95% confidence interval are also reported. Note that using the sponsor's efficacy criterion of the confidence interval excluding 90%, this was only met for the evaluable population.

Table 15. 28-day cure rate in ITT and evaluable populations in Study 026

	Coartem	MAS	Difference (Coartem-MAS) [95%CI]
ITT	130/150 (86.7%)	47/50 (94.0%)	-7.3%
	90% CI [81.2%,91.0%]	90% CI [85.2%, 98.3%]	[-15.6%, 3.6%]
	95% CI [80.2%, 91.7%]	95% CI [83.5%, 98.7%]	
Evaluable	130/134 (97.0%)	47/47 (100%)	-3.0%
	90% CI [93.3%, 99.0%]	90% CI [93.8%, 100%]	[-7.9%, 4.4%]
	95% CI [92.5%, 99.2%]	95% CI [92.5%, 100%]	

Adopted from sponsor’s Exhibits 8.1-1 and 8.1-2, study report (page 34).
95% confidence intervals were calculated by reviewer using the exact method.

Comments: Based on current malaria draft guidance, parasitological and clinical endpoints generally should be combined into a composite study endpoint. The sponsor only used 28-day cure rate, defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without subsequent recrudescence.

The study was designed as a two-arm trial. However, as aforementioned, MAS was included for comparison with historical data, i.e. for the “bridging” to previous results rather than for a formal statistical comparison. We were interested in the difference in the primary endpoint between the two treatment groups. The differences in 28-day cure rates and 95% confidence intervals as calculated by this reviewer are reported in the above table. Note that without a valid non-inferiority margin, little conclusion regarding Coartem’s efficacy can be made from this comparison other than in comparison to MAS. Coartem’s 28-day cure rate could be as much as 15.6 or 7.9 percent worse for the ITT or evaluable population, and as much as 3.6 or 4.4 percent better.

Parasite Reduction and Number of Patients with Negative Slide on Days 1, 2, and 3

During the first 3 days, all patients could be evaluated for parasite reduction, except one patient who discontinued after first dose as no *P. falciparum* was detected at baseline. The parasite slide on Day 1, 2, and 3 was taken between 17 and 28, 40 and 53, and 57 and 72 hours, respectively, after initiation of treatment. Table 16 shows the parasite slide results on Day 1, 2, or 3 in the ITT population. On Day 1, less than 26% patients had negative parasite slide. On Day 2, almost 90% of patients were free of parasites. On day 3, only 3 patients in the Coartem arm had positive slide.

On Day 1 the median reduction was 99.1% and 99.7% in the evaluable population in the Coartem and MAS groups, although there were 4 patients with an increased parasite count compared with the baseline value (Table 17).

Table 16. Patients with negative slide on Days 1, 2, or 3 in ITT population in Study 026

Slide		Coartem N=150	MAS N=50
Day 1	Negative	32(21.3%)	13(26.0%)
	Positive	117(78.0%)	37(74.0%)
	Missing	1(0.7%)	0
Day 2	Negative	134(89.3%)	44(88.0%)
	Positive	13(8.7%)	5(10.0%)
	Missing	3(2.0%)	1(2.0%)
Day 3	Negative	127(84.7%)	38(76.0%)
	Missing (negative before)	19(12.7%)	12(24.0%)
	Positive	3(2.0%)	0
	Missing	1(0.7%)	0

From Exhibit 8.1.-7 in sponsor's study report (page 36).

Table 17. Parasite reduction on Day 1 in evaluable population in Study 026

	Coartem N=149	MAS N=50
Median	99.1%	99.7%
25-75 percentiles	96.5% –100%	98.6%–100%
Range	Increase – 100%	73.0% –100%

Adapted from sponsor's study report (page 37).

P. vivax forms were observed in 6 patients at baseline, 12 patients in the Coartem acquired *P. vivax* within the 28-day follow-up.

3.1.2.5 Reviewer's Analysis Methods and Results

Additional endpoints based on FDA malaria Draft Guidance

The following are results of analysis performed by this reviewer including results of some additional endpoints included in the FDA malaria draft guidance.

Late parasitological failure--recrudescence of *P. falciparum* during the study

The late parasitological failure-recrudescence was defined as reappearance of *P. falciparum* during the study period (up to Day 28). The recrudescence rates in the Coartem and MAS groups were 2.7% and 0%, respectively, in the ITT population; 3.0% and 0 in the evaluable population.

Table 18. Recrudescence of *P. falciparum* [exact 95% CI] in ITT and evaluable populations in Study 026

	Coartem	MAS
ITT	4/150(2.7%) [0.7%, 6.7%]	0/50 (0) [0, 7.1%]
Evaluable	4/134 (3.0%) [0.8%, 7.5%]	0/47 (0) [0, 7.5%]

Parasite count change from baseline and proportion of patients with 75% reduction on Day 1 and Day 2 in the ITT and evaluable populations

The reviewer summarized the parasite count change from baseline and proportion of patients with 75% reduction on Day 1 and Day 2. On Day 1 (Table 19), parasite count percentage reduction in the Coartem group appeared to be less than that in the MAS group, due to a few subjects' increased parasite count; however, the difference was not statistically significant. On Day 2 (Table 20), the reduction proportions were comparable.

Table 19. Parasite change from baseline on Day 1 in the ITT and evaluable populations in Study 026

	Coartem	MAS	Difference in percentage [95% CI] p-value
ITT population	N=149*	N=50	
Mean Change %	-63.2	-97.6	34.3
([min, max]%)	[-100.0, 1952†]	[-100.0, -73.0]	[-30.7, 99.3] 0.07
Proportion of reaching a 75% reduction	93.9% (140/149)	98.0% (49/50)	-4.04 [-9.8, 4.5] 0.31
Evaluable population	N=134	N=47	
Mean Change %	-60.1	-97.3	37.2
([min, max]%)	[-100.0, 1952†]	[-100.0, -73.0]	[-33.5, 108.0] 0.08
Proportion reaching a 75% reduction	94.8% (127/134)	97.9% (46/47)	-3.1 [-9.0, 5.9] 0.45

* One patient did not have parasite count on Day 1. †One 11-year-old male subject with parasite count of 1300, 26677, 39, and 0, at days 0, 1, 2, and 3, respectively, had a change of 1952%.

Table 20. Parasite change from baseline on Day 2 in the ITT and evaluable populations in Study 026

	Coartem	MAS	Difference in percentage [95% CI], p-value
ITT population*	N=147	N=49	
Mean Change %	-99.93	-99.99	0.06[-0.00, 0.17], 0.09
([min, max] %)	[-100.0, -97.0]	[-100.0, -99.6]	
75% reduction	100% (147/147)	100% (49/49)	0[-2.9, 7.3], 1
Evaluable population†	N=133	N=46	
Mean Change %	-99.93	-99.99	0.06[-0.00, 0.18], 0.11
([min, max])	[-100.0, -97.0]	[-100.0, -99.6]	
75% reduction	100% (133/133)	100% (46/46)	0.0 [-3.2, 7.7], 1

* 3 and 1 patient did not have parasite count data on Day 2.

† 1 and 1 patient did not have parasite count data on Day 2.

Time to parasite clearance (PCT)

Time to parasite clearance was not reported in the sponsor's study report. Parasite counts were taken only once a day in this study. The results calculated using parasite count data over time (variable HRS_1n) by this review are reported in the following table.

Table 21. Time to parasite clearance (in hours) in ITT population in Study 026

	Coartem N=149	MAS N=50
Median*[95%CI†]	44[43, 44]	44[43, 45]
25-75 percentiles*	42 - 45	22 - 47
Range	18 - 96	17 - 72

* Kaplan-Meier method. †Based on the sign test (Brookmeyer and Crowley, 1982).

3.1.3 Study 028

3.1.3.1 Objectives

The primary aim was to confirm the safety and efficacy of the 6-dose regimen of Coartem given over 3 days in comparison with MAS. Further, plasma samples were collected to measure artemether, dihydroartemisinin and lumefantrine pharmacokinetics following intake of Coartem.

3.1.3.2 Study Design

This was a randomized, open-label, comparative, parallel group, single-center, 4 week trial. For comparison with previous trials, a control arm of mefloquine and artesunate (MAS) with 55 patients was included. The trial was conducted from 9/30/1998 to 1/8/1999 at a single center in Bangkok, Thailand.

Eligible male and female patients >12 years and \geq 35 kg, with confirmed acute, uncomplicated *P. falciparum* malaria were enrolled and randomized 3:1 to Coartem or MAS.

The dosing of Coartem was 4 tablets (each tablet containing 20 mg artemether + 120 mg lumefantrine) twice daily for three days. MAS dosing was artesunate 4 mg/kg 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.

A total of 200 patients were planned to be recruited. Patients were followed on Days 0-7 (daily), 14, 21, and 28.

3.1.3.3 Statistical Considerations

3.1.3.3.1 Primary and Secondary Endpoints

The primary endpoint was defined as follows:

- 28-day cure rate which was defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without subsequent recrudescence within 28 days after start of trial treatment.

- Parasite reduction at 24 hours after initiation of trial treatment (percentage reduction of parasites/uL at 24 hours compared to parasite density before the first dose of treatment).
- Time to parasite clearance (PCT): time from first dose until first total and continued disappearance of asexual parasite forms which remains for at least a further 48 hours.

Comment: In this study three primary endpoints were listed by the sponsor.

A secondary endpoint was fever clearance time (FCT) defined as time from first dose until the first time body temperature fell below 37.5°C and remains below 37.5°C for at least a further 48 hours (only for patients with temperature > 37.5° C at baseline).

3.1.3.3.2 Primary Analysis

Analysis Populations

Two analysis populations were defined. The ITT population included all randomized patients. The evaluable patient population included patients whose parasite counts were recorded up to Day 28 or the patient discontinued due to “unsatisfactory therapeutic effect” because of reappearance of *P. falciparum*.

Analysis Methods:

The 6-dose Coartem regimen would be considered effective if the lower limit of the 90% two-sided confidence interval for the 28-day cure rate for evaluable patients exceeds 85%. The 90% two-sided confidence interval for the 28-day cure rate for each treatment was calculated using Pearson-Clopper limits.

Comment: We would typically limit a type I error to 0.05 (2-sided); therefore we will calculate a two-sided 95% CI instead of a 90% CI. Note that the efficacy criterion was 85%, compared with 90% in Study 026.

The parasite reduction at 24 hours was calculated using all available measurements. The time to parasite clearance was analyzed for the ITT population. This time was censored at the last measurement of parasites, if no clearance was reached by that time.

3.1.3.3.3 Sample Size Calculation

To test whether the 28-day cure rate with the 6-dose regimen of Coartem was significantly higher than 85% ($H_0 \leq 0.85$) using a one-sided test with a 5% type I error, a total of 127 patients in Coartem were needed to achieve a 90% power at a cure rate of

93.1% using the normal approximation method. To allow for a 15% drop-out rate, the number of patients in the Coartem group was 150.

3.1.3.4 Sponsor’s Analysis Results

3.1.3.4.1 Patient Disposition, Demographic, and Baseline Characteristics

A total of 219 patients were enrolled in the trial. Eighteen patients discontinued prematurely (Table 22).

Table 22. Distribution of patients by treatment group in Study 028

	Coartem	MAS
Enrolled/Randomized	164	55
Premature discontinuation	16(9.8%)	2(3.6%)
Unsatisfactory therapeutic response	7(4.3%)	0
Lost to follow-up	9(5.5%)	2(3.6%)
Sample size for the efficacy analyses		
ITT population	164	55
Evaluable patient population*	155	53

Adopted from Exhibit 6.1.-1 & 2 in sponsor’s study report (page 26).

* 11 patients were not evaluable for the primary endpoint as they were lost to follow-up.

Table 23 reports the demographic and baseline data.

3.1.3.4.2 Efficacy Analysis Results

28-Day Cure Rate

The cure rates in the ITT population and evaluable population are shown in Table 24. As the lower limit of the 90% CI for the cure rate in the Coartem group in the evaluable population exceeded 85%, the sponsor claimed that the effectiveness of 6-dose Coartem was confirmed in this trial.

According to the sponsor’s analysis, using the Pearson-Clopper limits method, the 90% CI for the difference in 28-day cure rates between the Coartem and MAS groups in evaluable population was [-9.2%, 0.2%] (p=0.195, two-sided Fisher’s test). This analysis should be regarded as exploratory because comparison between the treatment arms was not pre-planned.

Comments: The level of the CIs for the cure rates and difference in cure rates should be 95%. The lower limit of the 95% CI for the cure rate in the Coartem group was 84.6%, not meeting the efficacy criteria in the ITT population. The difference in cure rates between the two groups was -6.1% [95% CI: -12.8%, 3.0%] in the ITT population and -4.5% [95% CI: -9.3%, 2.1%] in the evaluable population.

Table 23: Demographic and baseline data (all patients) in Study 028

	Coartem N=164	MAS N=55
Sex (males (%))	115 (70%)	41 (75%)
Age (median[range] in years)	25 [12-71]	24 [12-60]
Weight (median[range] in kg)	50 [35-81]	52 [35-77]
Height (median[range] in cm)	160 [132-179]	160[125-180]
Haematocrit (median [range] in %)	35.5[15.0-50.0]	36.0[17.0-54.0]
Haematocrit<25%	9(5%)	2(4%)
Previous malaria infection within 3 months	23(14%)	11(20%)
Hepatomegaly	54(33%)	20(36%)
Splenomegaly	53 (32%)	21 (38%)
Temperature (°C)		
Median(mean)	37.5 (37.6)	37.6 (37.8)
Range	[36.0-40.3]	[36.5-40.5]
≤ 37.5	88(53.7%)	26(47.3%)
37.5-39	57(34.8%)	22(40.0%)
≥ 39	19(11.6%)	7(12.7%)
Parasite density (/uL)		
Median (geometric mean)	1608(2063)	5130(3329)
Range	[13-436050]	[21-207840]
Number (%) of observations by density		
<5,000	93(56.7%)	27(49.1%)
5,000-<15,000	24(14.6%)	10(18.2%)
15,000-<50,000	23(14.0%)	9(16.4%)
≥50,000	24(14.6%)	9(16.4%)

Adopted from Exhibit 7.1.-1 & 2 in sponsor's study report (page 28 and 29)

Table 24. 28-day cure rate and CI in ITT and evaluable populations in Study 028

	Coartem	MAS
ITT	148/164 (90.2%)	53/55 (96.4%)
90%CI	85.6%, 97.9%	89.0%, 99.4%
95%CI	84.6%, 94.3%	87.5%, 99.6%
Diff(Coartem-MAS) [95%CI]	-6.1%[-12.8%, 3.0%]	
Evaluable	148/155 (95.5%)	53/53 (100%)
90%CI	91.7%, 97.9%	94.5%, 100%
95%CI	90.9%, 98.2%	93.3%, 100%
Diff(Coartem-MAS) [95%CI]	-4.5%[-9.3%, 2.1%]	

Adopted from Exhibit 8.1.-1 & 2 in sponsor's study report (page 31). 95% CIs were calculated by the reviewer.

Parasite Reduction and Number of Patients with Negative Slide on Days 1, 2, and 3

On Day 1, about 24 hours after start of treatment, parasitaemia was cleared in more than 43% of the patients. On Day 2 more than 93% of patients in both groups had cleared

their parasitaemia, and on Day 3 all patients were free of parasitaemia (including these missing values but with negative slides before).

Table 25. Patients with negative slide on Days 1, 2, or 3 in ITT population in Study 028

Slide		Coartem N=164	MAS N=55
Day 1	Negative	76(46.3%)	24(43.6%)
	Missing (negative before)	1(0.6%)	0
	Positive	87(53.0%)	31(56.4%)
Day 2	Negative	154(93.9%)	52(94.5%)
	Positive	10(6.1%)	3(5.5%)
Day 3	Negative	104(63.4%)	32(58.2%)
	Missing (negative before)	60(36.6%)	23(41.8%)
	Positive	0	0

From Exhibit 8.1.-4 in sponsor's study report (page 34).

On Day 1 the median reduction was 100% in the evaluable population in the Coartem and MAS groups. There were 4 patients with an increased parasite count compared with the baseline value.

Table 26. Parasite reduction on Day 1 in evaluable population in Study 028

	Coartem N=163 [†]	MAS N=55
Median	100%	100%
25-75 percentiles	99.0% –100%	99.8%–100%
Range	Increase*– 100%	Increase* –100%

* 4 patients had a higher count at 24 hours than at baseline. [†] One missing value.

Adapted from Exhibit 8.1-5 sponsor's study report (page 35).

Time to parasite clearance

The median PCT time was 29 and 31 hours for the Coartem and MAS group, respectively. There was no significant difference in survival curves (log-rank test, p-value 0.59).

Table 27. Time to parasite clearance (in hours) in ITT population in Study 028

	Coartem N=164	MAS N=55
Median*[95% CI [†]]	29[26, 32]	31[26, 32]
25-75 percentiles*	18 - 40	24 - 35
Range **	7 - 64	7 - 57

*Using Kaplan-Meier method. ** Not including censored times, PCT was rounded [†]Using the sign test (Brookmeyer and Crowley, 1982)

From Exhibit 8.1.-3 in sponsor's study report (page 33).

Time to fever clearance

A total of 105 out of 219 patients had fever at baseline. The median FCT was shorter in MAS group than in the Coartem group (Table 28).

Table 28. Time to fever clearance (in hours) in ITT population in Study 028

	Coartem N=76	MAS N=29
Median*[95% CI†]	29[23, 37]	23[15, 30]
25-75 percentiles*	8 –51	15 –31
Range **	3 –163	6 – 155

*Using Kaplan-Meier method. ** Not including censored times. †Using the sign test (Brookmeyer and Crowley, 1982)
From Exhibit 8.1.-6 in sponsor's study report (page 35).

Comment:

This table was for FCT in the ITT population, not for FCT in the evaluation population, as indicated in the study report.

3.1.3.5 Reviewer's Analysis Results

Late parasitological failure--recrudescence of *P. falciparum* during the study

The late parasitological failure-recrudescence was defined as reappearance of *P. falciparum* during the study period (up to Day 28). The recrudescence rates in the Coartem and MAS groups were 4.3% and 0%, respectively, in the ITT population; 4.5% and 0% in the evaluable population.

Table 29. Recrudescence of *P. falciparum* [exact 95% CI] in ITT and evaluable populations in Study 028

	Coartem	MAS
ITT	7/164 (4.3%) [1.7%, 8.6%]	0/55 (0%) [0, 6.5%]
Evaluable	7/155 (4.5%) [1.8%, 9.1%]	0/53 (0%) [0, 6.7%]

Parasite count change from baseline and proportion of patients with 75% reduction on Day 1 in the ITT and evaluable populations

The reviewer summarized the parasite count change from baseline and proportion of patients with 75% reduction on Day 1 and Day 2. On Day 1, parasite count percentage reduction in the Coartem group appeared to be less than that in the MAS group, due to a few subjects who had an increased parasite count; however, the difference was not statistically significant. On Day 2, all subjects reached 75% reduction in parasite count.

Table 30. Parasite change from baseline on Day 1 in the ITT and evaluable populations in Study 028

	Coartem	MAS	Difference in percentage [95% CI] p-value
ITT population*	N=141	N=51	
Mean Change % ([min, max]%)	-83.2 [-100.0, 1868.6]	-99.0 [-100.0, -73.3]	15.8 [-30.2, 61.7] 0.26
Proportion of reaching a 75% reduction	97.9% (138/141)	98.0% (50/51)	-0.17 [-4.7, 4.3] 0.94
Evaluable population†	N=134	N=49	
Mean Change % ([min, max]%)	-83.2 [-100.0, 1868.6]	-99.0 [-100.0, -73.3]	15.8 [-32.2, 63.9] 0.28
Proportion reaching a 75% reduction	98.5% (132/134)	98.0% (48/49)	0.5 [-3.9, 5.0] 0.79

* 23 and 4 subjects in the two treatment groups in the ITT population and †21 and 4 subjects in the two treatment groups in the evaluable population had missing parasite count on Day 1.

Table 31. Parasite change from baseline on Day 2 in the ITT and evaluable populations in Study 028

	Coartem	MAS
ITT population*	N=141	N=51
Mean Change % ([min, max] %)	-100.0 [-100.0, -99.7]	-100.0 [-100.0, -99.9]
75% reduction	100%(141/141)	100% (51/51)
Evaluable population†	N=134	N=49
Mean Change % ([min, max]%)	-100.0 [-100.0, -99.7]	-100.0 [-100.0, -99.95]
75% reduction	100.0% (134/134)	100.0% (49/49)

* 23 and 4 subjects in the two treatment groups in the ITT population and †21 and 4 subjects in the two treatment groups in the evaluable population had missing parasite count on Day 2.

3.2 Evaluation of Safety

The following safety information is as reported by the sponsor. This reviewer did not conduct any additional safety analyses.

3.2.1 Study 025

Adverse Events

Using the maximum severity grade for each AE experience, all AEs were summarized by the sponsor. All symptoms at baseline, including those related to malaria were reported as AEs. Headache (>90%), anorexia (>75%), asthenia (>66%), arthralgia (>60%), myalgia (>59%), and dizziness (>58%) were among the most common symptoms.

The sponsor summarized most frequent AEs during the trial, listed by time period of onset, and are shown in the following figures.

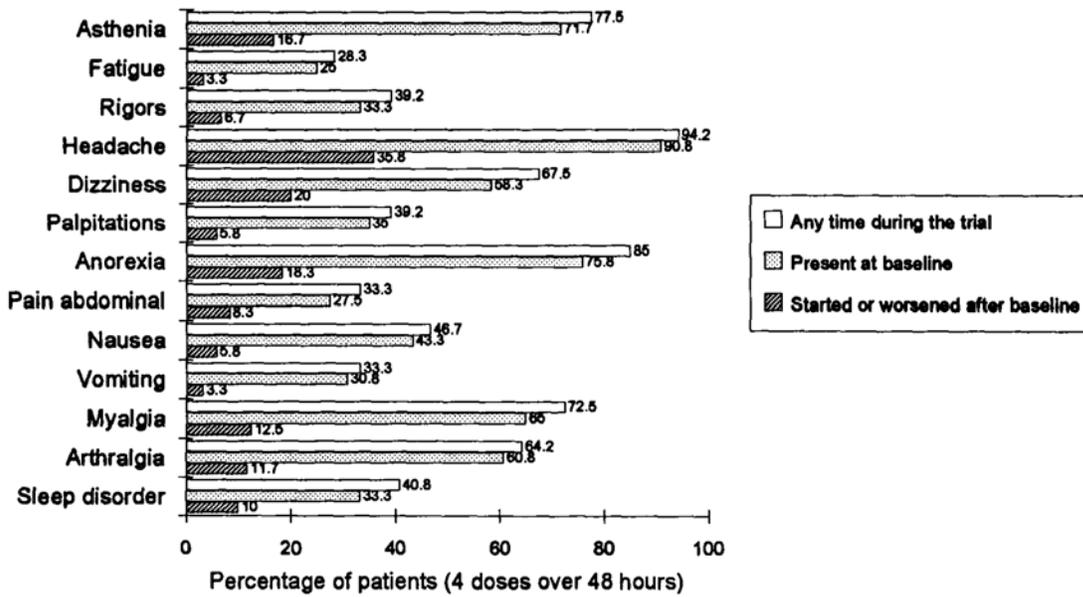


Figure 1. Most frequent adverse experiences in the 4-dose arm in Study 025

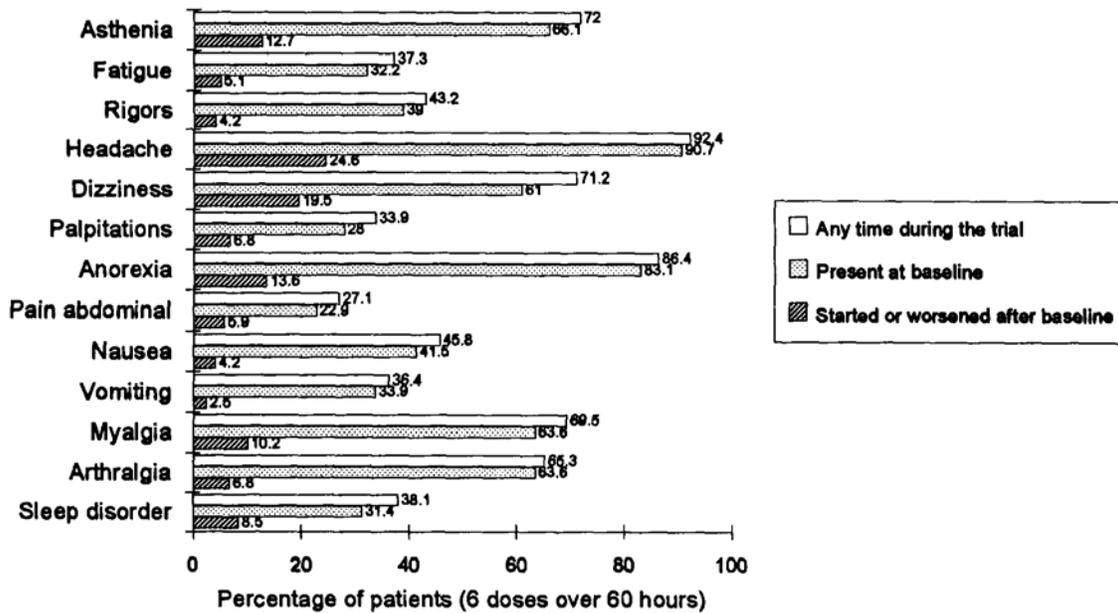


Figure 2. Most frequent adverse experiences in the 6-dose-60-hour arm in Study 025.

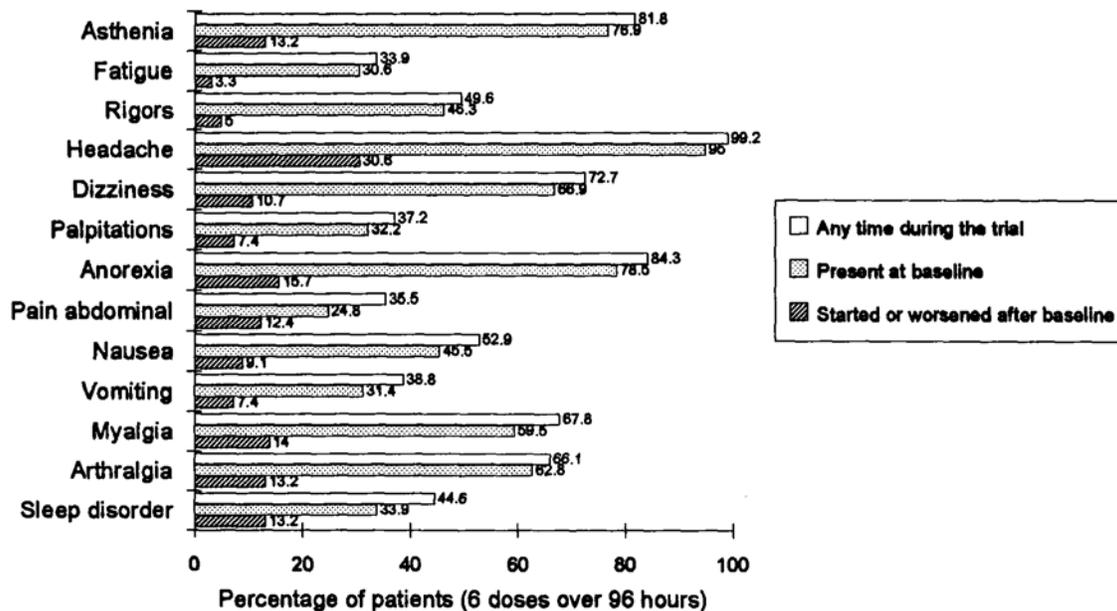


Figure 3. Most frequent adverse experiences in the 6-dose-96-hour arm in Study 025.

3.2.2 Study 026

Adverse Events

All AEs were summarized using the maximum severity grade for each experience. At baseline all symptoms experienced by the patients, including those related to malaria, were recorded as AEs. Headaches (>86%), asthenia (>66%), arthralgia (62%), fever (>60%), dizziness (>58%) and anorexia (>54%) were the most common symptoms.

AEs, which started after baseline but before reappearance of *P. falciparum/vivax*, were regarded by the sponsor as a more reliable indication of the number of patients who experienced AEs related to trial treatment. During this time period 102 (68%) patients in the Coartem group and 44 (88%) patients in the MAS group experienced AEs, the majority of which were symptoms typical of malaria. Digestive system symptoms occurred in 42.7% of the patients in the Coartem group and 54% in the MAS group. There were no pronounced differences in AEs for other systems between the two treatment groups. Most AEs were rated as mild or moderate in severity. In the Coartem group, 20 AEs (in 19 patients, 12.7%) were severe, including fever and hepato/splenomegaly; 2 AEs (fever and splenomegaly) occurred after baseline. One serious AE (febrile coma) occurred two weeks after initiation of treatment. In the MAS group, there were 5 severe AEs (in 4 patients, 8.0%), all being present at baseline. There were no severe AEs occurring after baseline. One serious AE (generalized pruritic urticaria) was observed one day after starting treatment.

In both treatment groups, the percentages of symptoms tended to drop rapidly with treatment. After baseline but before reappearance of *P. falciparum/vivax*, the percentages of patients with sleep disorder, dizziness, vomiting, nausea, abdominal pain, and anorexia

were lower in the Coartem group (>10% in difference between the treatment groups). Lower proportion of patients in the Coartem group experienced palpitation. Percentages of other symptoms were comparable in both treatment groups (with a difference less than 5%). Please note, AEs “related to trial drug” were determined by the sponsor.

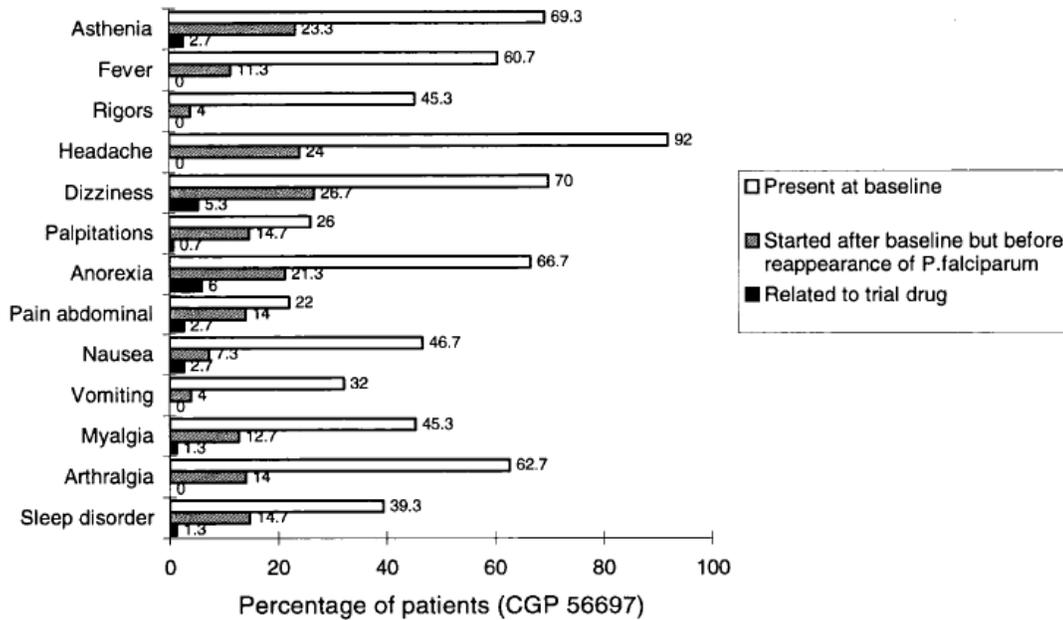


Figure 4. Most frequent adverse experiences in Coartem group in Study 026

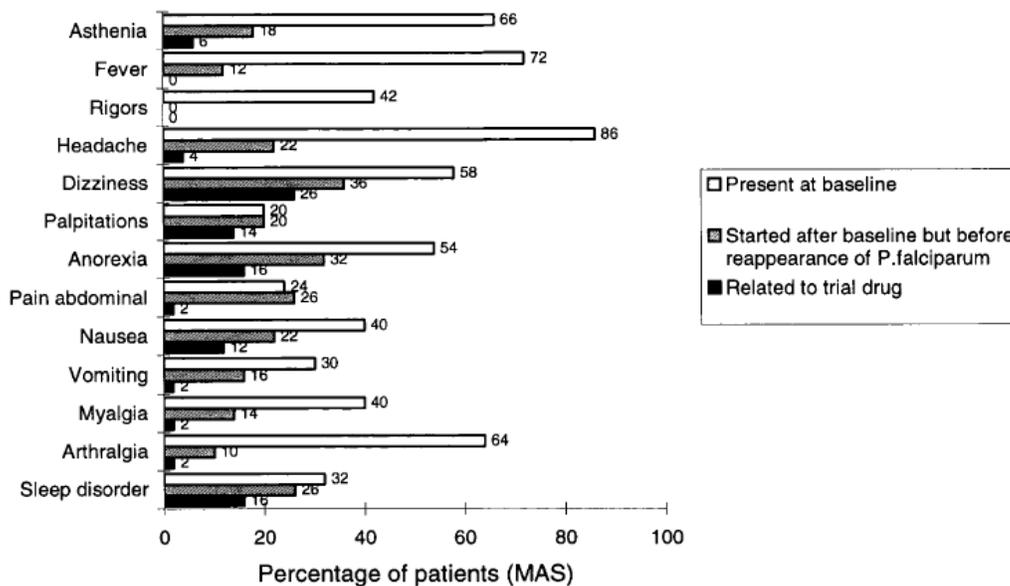


Figure 5. Most frequent adverse experiences in MAS group in Study 026

Serious adverse experiences and premature discontinuations

Two SAEs were reported (coma and fever in one patient on Coartem, and generalized pruritic urticaria in one patient on MAS). The latter patient was discontinued from the trial and the two patients recovered completely.

No death occurred during the trial.

3.2.3 Study 028

Adverse Events

The sponsor summarized all AEs recorded during the trial using the maximum severity grade for each experience. All symptoms at baseline, including those related to malaria, were recorded as AEs. The most common symptoms in subjects were headache (> 92%), asthenia (> 75%), fatigue (> 67%), fever (> 67%), dizziness (> 65%), nausea (>60%), myalgia (> 59%) and anorexia (> 52%). Other malaria symptoms /signs such as rigors, arthralgia, vomiting, sleep disorders, hepato- and splenomegaly, and abdominal pain were experienced less frequently.

AEs which started after baseline but before reappearance of *P. falciparum/vivax* were considered as treatment emergent symptoms and signs, a more reliable indication of the AEs possibly related to treatment assumed by the sponsor. During this period, 104 (63.4%) and 34 (61.8%) patients in the Coartem group and the MAS group experienced AEs. The following two figures show most frequent AEs by treatment group.

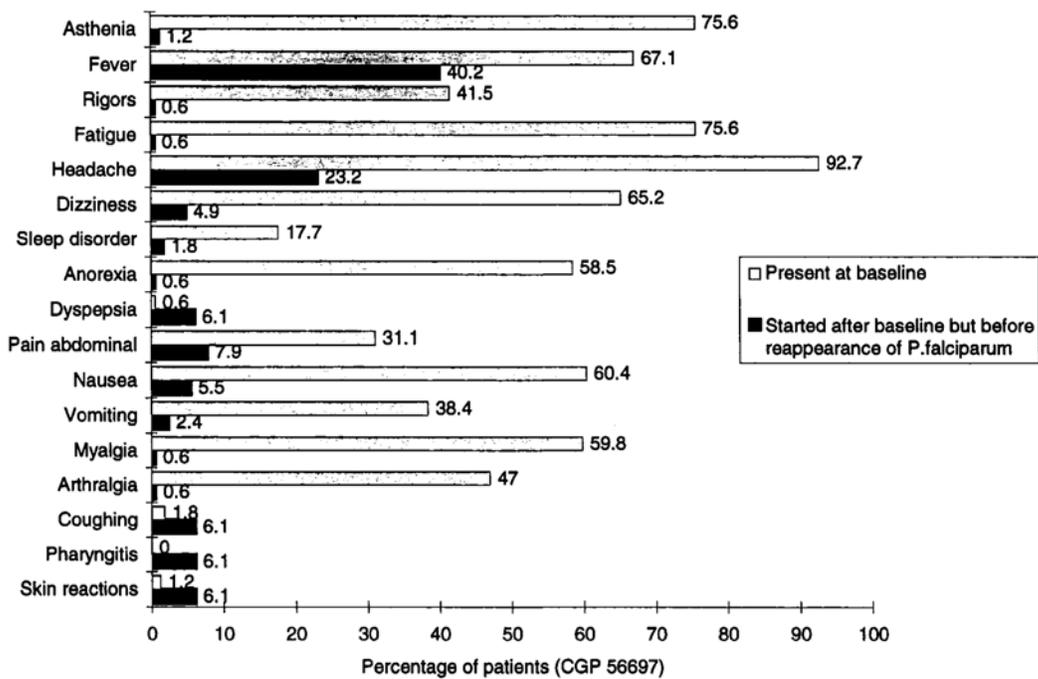


Figure 6. Most frequent adverse experience-Coartem in Study 028

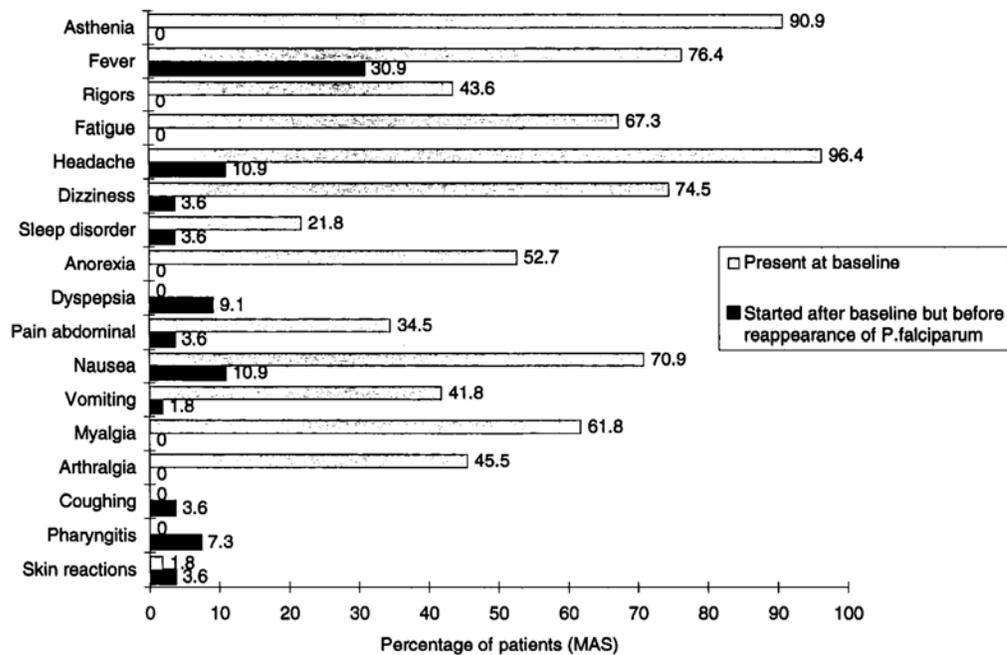


Figure 7. Most frequent adverse experience-MAS in Study 028

Most AEs during the trial were rated as of mild or moderate severity. In one patient, severe AEs were reported (dyspnea and pulmonary edema due to fluid overload) and this patient was discontinued due to loss to follow-up.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

4.1.1 Study 025

The study was conducted in Thailand, and race was not collected. The primary endpoint by gender and age in the ITT population and evaluable population was analyzed.

Table 32. 28-day cure rate by gender and age in the ITT population in Study 025

	4-dose	6-dose 60 hours	6-dose 96 hours
Gender			
Male	58/83(69.9%)	69/86(80.2%)	71/81(87.7%)
Female	27/37 (73.0%)	27/32(84.4%)	33/40(82.5%)
Age			
2-16	18/21 (85.7%)	25/30 (83.3%)	26/29 (89.7%)
>16	67/99 (67.7%)	71/88 (80.7%)	78/92 (84.8%)

Table 33. 28-day cure rate by gender and age in the evaluable population in Study 025

	4-dose	6-dose 60 hours	6-dose 96 hours
Gender			
Male	57/70(81.4%)	67/69(97.1%)	71/73(97.3%)
Female	27/34 (79.4%)	26/27(96.3%)	33/33(100%)
Age			
2-16	18/20(90.0%)	24/24(100%)	26/26(100%)
>16	66/84(78.6%)	69/72(95.8%)	78/80(97.5%)
Age			
2-11	10/11(90.9%)	12/16 (75.0%)	8/9 (88.9%)
12-16	8/10 (80%)	13/14 (92.9%)	18/20 (90.0%)

The trend in treatment effect across gender and age is fairly consistent with the overall population results. The only difference is seen in the youngest age group where there is little difference between the 4-dose group and the 6-dose groups in the ITT population. A few subjects in the youngest age group in the ITT population were excluded from the evaluable population and were considered failures in the ITT: 1 subject (age 13) in the 4-dose arm due to noncompliance at Day 17; 5 (ages 7, 7, 10, 10, and 15) out of 6 subjects excluded in the 6-dose over-60-hour due to lost to follow-up at Days 2, 9, 12, 21, and 28; 3 subjects (ages 11, 14, and 16) in the 6-dose over-96-hour excluded due to lost to follow-up at Day 0, 4, and 20.

4.1.2 Study 026

Table 34. 28-day cure rate by gender and age in the ITT population in Study 026

	Coartem	MAS
Gender		
Male	94/110(85.5%)	35/37(94.6%)
Female	36/40 (90.0%)	12/13(92.3%)
Age		
2-16	36/41(87.8%)	16/16(100%)
>16	94/109 (86.2%)	31/34 (91.2%)

Table 35. 28-day cure rate by gender and age in the evaluable population in Study 026

	Coartem	MAS
Gender		
Male	94/96(97.9%)	35/35(100.0%)
Female	36/38 (94.7%)	12/12(100.0%)
Age		
2-16	36/39(92.3%)	16/16(100.0%)
>16	94/95(99.0%)	31/31(100.0%)

This study was conducted in Thailand and Race was not reported in the data set. Therefore, we only analyzed the primary endpoint by gender and age in the ITT population and evaluable population. As Table 34 and Table 35 show, the trend in treatment effect across gender and age is fairly consistent with the overall population results.

4.1.3 Study 028

This study was conducted in Thailand. Race was not reported in the data set. Therefore, we only analyzed the primary endpoint by gender and age in the ITT population and evaluable population. As the following two tables show, the trend in treatment effect across gender and age is fairly consistent with the overall population results.

Table 36. 28-day cure rate by gender and age in the ITT population in Study 028

	Coartem	MAS
Gender		
Male	100/115(87.0%)	39/41(95.1%)
Female	48/49 (98.0%)	14/14(100.0%)
Age		
2-16	14/15 (93.3%)	12/12(100%)
>16	134/149 (89.9%)	41/43 (95.4%)

Table 37. 28-day cure rate by gender and age in the evaluable population in Study 028

	Coartem	MAS
Gender		
Male	100/107(93.5%)	39/39(100.0%)
Female	48/48(100.0%)	14/14(100.0%)
Age		
2-16	14/15 (93.3%)	12/12(100%)
>16	134/140 (95.7%)	41/41 (100.0%)

4.2 Other Special/Subgroup Populations

4.2.1 Study 025

In this study patients were enrolled in two centers. We will analyze the baseline parasite counts, 28-day cure rates, parasite clearance time, and fever clearance time by center. The interaction between treatment and center would be the focus of these analyses.

Baseline parasite count by center

The baseline parasite count by center was reported by the sponsor (Table 38). The Wilcoxon rank sum test indicates that there was a significant difference in the underlying distributions of baseline parasite counts between the two centers (p-value=0.0075). The median parasite counts in Bangkok were significantly higher than in Maela.

Table 38. Baseline parasite count by study center in Study 025

	4 doses 48 hours	6 doses 60 hours	6 doses 96 hours	Total
Center1(Bangkok)	N=34	N=32	N=34	N=100
Median	19,905	14,585	17,305	16,500
Geometric mean	16,110	12,113	17,536	15,135
Range	552 - 158,360	512 -189,740	612 - 464,880	512 - 464,880
Number (%)				
<5,000	5 (14.7%)	11 (34.4%)	10 (29.4%)	26 (26.0%)
5,000 - 15,000	11 (32.3%)	5 (15.6%)	5 (14.7%)	21 (21.0%)
15,000 -50,000	12 (35.3%)	9 (28.1 %)	9 (26.5%)	30 (30.0%)
>50,0000	6 (17.7%)	7 (21.9%)	10 (29.4%)	23 (23.0%)
Center 3(Maela)	N=86	N=86	N=87	N=259
Median	6,884	4,433	5,252	5,450
Geometric mean	8,599	8,380	8,201	8,391
Range	381 - 199,980	415 -195,735	290 -151,112	290 - 199,980
Number (%)				
<5,000	39 (45.4%)	44 (51.2%)	42 (48.3%)	125 (48.3%)
5,000 - 15,000	8 (9.3%)	7 (8.1%)	8 (9.2%)	23 (8.9%)
15,000 -50,000	22 (25.6%)	13 (15.1%)	18 (20.7%)	53 (20.5%)
>50,0000	17 (19.8%)	22 (25.6%)	19 (21.8%)	58 (22.4%)

28-day cure rates by center

The 28-day cure rates by center in ITT and evaluable populations are shown in the following two tables.

Table 39. 28-day cure rate by study center in the ITT population in Study 025

	4 doses	6 doses 60 hours	6 doses 96-hours
Center 1 (Bangkok)	20/34 (58.8%)	27/32 (84.4%)	30/34(88.2%)
Center 3 (Maela)	65/86 (75.6%)	69/86 (80.2%)	74/87(85.1%)

It appeared that in the ITT population, patients in the 4-dose group at Center 1 had a lower 28-day cure rate than in the 6-dose groups. However, the interaction between center and treatment group in a separate logistic regression models with logarithm of baseline parasite count was not significant. Therefore, there was no evidence that there were differential treatment effects between the two centers. In a simpler model without the treatment-center interaction terms, center effect was not significant. Thus, there was no center effect. In addition, as expected, the main treatment effect (a 6-dose-over-96 versus the 4-dose) was statistically significant

Table 40. 28-day cure rate by study center in the evaluable population in Study 025

	4 doses	6 doses 60 hours	6 doses 96-hours
Center 1 (Bangkok)	20/30 (66.7%)	27/29 (93.1%)	30/31(96.8%)
Center 3 (Maela)	64/74 (86.5%)	66/67 (98.5%)	74/75(98.7%)

In the evaluable population, at both centers, the 28-day cure rate in the 4-dose group was lower than those in the 6-dose groups. Center 3 appeared to have higher cure rates. In a regression model with logarithm of baseline parasite count, center, and treatment, the two 6-dose groups had significantly higher rates than the 4-dose group and center 3 had significantly higher cure rates; logarithm of baseline parasite count was significantly associated with the outcome. In addition, there were no significant interaction terms between treatment and center. That is, there was no evidence that the treatment effect varied across centers. Therefore, only in the evaluable population, center effect was statistically significant after controlling for baseline parasite count.

Parasite clearance time by center

Table 41. Time to parasite clearance in ITT population in Study 025

	4 doses	6 doses 60 hours	6 doses 96-hours
Center 1 (Bangkok)	N=34	N=32	N=34
Median*[95%CI†]	52[46, 56]	53[45, 60]	50[43, 59]
25-75 percentile*	41-59	44-65	42-63
Range**	32-69	17-76	33-90
Center 3 (Maela)	N=86	N=84	N=85
Median*[95%CI†]	44[43,44]	43[42,44]	43[42.8, 43.8]
25-75 percentile*	21,45	21-45	22-45
Range**	18-72	17-166	18-71

Subjects in Maela had a lower parasite count at baseline compared with subjects in Bangkok. Therefore, as might be expected PCT were longer in Bangkok compared to Maela. Since children <12 years old were only included in Maela, we used a Cox proportional hazards model to control for age and baseline parasite count.

Table 42. The Cox proportional hazards model of time to parasite clearance in ITT population in Study 025

	Estimate	SE	RR[95% CI]	p-value
6-dose Coartem (60 hrs)	-0.12190	0.13221	0.89 [0.68, 1.15]	0.36
6-dose Coartem (96 hrs)	-0.00047	0.13023	1.00 [0.77, 1.29]	0.99
Log BPC	-0.25489	0.03160	0.78 [0.73, 0.82]	<0.0001
Maela	0.46076	0.12412	1.59 [1.24, 2.02]	0.0002
Age > 16	-0.12253	0.12953	0.88 [0.69, 1.14]	0.34

After controlling for categorical age, logarithm of baseline parasite count, and treatment, subjects in Maela were still more likely to have statistically significant shorter parasite

clearance time. In addition, there was no significant difference between males and females in the model which included covariate sex. The interaction terms between treatment and center were not statistically significant. Meaning that, even though the centers were different and had different parasite clearance time, the difference between the 4 dose regimen and the 6-dose regimens were consistent between centers.

Fever clearance time by center

Table 43. Time to fever clearance in ITT population in Study 025

	4 doses	6 doses 60 hours	6 doses 96-hours
Center 1 (Bangkok)	N=17	N=18	N=20
Median*[95% CI†]	36[35, 58]	38[32, 46]	36[23, 60]
25-75 percentile*	35-58	24-47	23-60
Range**	12-95	9-160	9-142
Center 3 (Maela)	N=44	N=41	N=60
Median*[95% CI†]	21[20, 22]	22[21, 43]	21[20, 22]
25-75 percentile*	21,43	20-45	20-42
Range**	18-70	18-70	18-164

*Using Kaplan-Meier method. ** Not including censored times, FCT was rounded †Using the sign test (Brookmeyer and Crowley, 1982)

Subjects in Maela tended to have shorter median FCT. The following table shows the results after controlling for some variables at baseline, including logarithm of baseline parasite count. Similar to the results from the study report (page 42), still there was a statistically significant center effect on FCT. However, there were no statistically significant interaction terms between center and treatment.

Table 44. The Cox proportional hazards model of fever clearance time in ITT population in Study 025

	Estimate	SE	RR[95% CI]	p-value
6-dose Coartem (60 hrs)	-0.18084	0.18499	0.83 [0.58, 1.20]	0.32
6-dose Coartem (96 hrs)	-0.09680	0.17421	0.91 [0.65, 1.28]	0.58
Log BPC	-0.14747	0.04193	0.86 [0.79, 0.94]	0.0004
Maela	0.70820	0.17649	2.03 [1.44, 2.87]	<0.0001
Age > 16	0.20022	0.17618	1.22 [0.86, 1.73]	0.26

4.2.2 Study 026

In this study patients were enrolled in two centers. The mean baseline parasite counts are shown in the following table.

Table 45. Baseline parasite count by study center for all patients in Study 026

	Coartem	MAS	Total
Center1(Bangkok)	N=21	N=7	N=28
Median	20,900	10,580	38,667
Geometric mean	12,121	13,244	12,392
Range	510 – 254,490	1425 -177,840	510 – 254,490
Number (%)			
<5,000	7 (33.3%)	3 (42.9%)	10 (35.7%)
000 - 15,000	1 (4.8%)	2 (28.6%)	3 (10.7%)
15,000 - 50,000	9 (42.9%)	0	9 (32.1%)
>50,0000	4 (19.0%)	2 (28.6%)	6 (21.4%)
Center 2(Maela)	N=129	N=43	N=172
Median	6,302	5,216	5,450
Geometric mean	8,751	7,856	8,517
Range	0 - 165,189	625 -127,032	0 - 165,189
Number (%)			
<5,000	60 (46.5%)	19(44.2%)	79(45.9%)
5,000 - 15,000	14 (10.9%)	5(11.6%)	19(11.0%)
15,000 -50,000	31(24.0%)	14(32.6%)	45(26.2%)
>50,0000	24(18.6%)	5(11.6%)	29(16.9%)

It appeared that in the ITT population (Table 46), patients in the Coartem group at Center 1 had a higher 28-day cure rate than in the MAS group while patients in the MAS group at Center 2 had a higher cure rate than in the Coartem group. However, the interaction between center and treatment group in a generalized linear regression with the binomial distribution and log link function was not statistically significant, even if controlling for logarithm of baseline parasite count. Both center and treatment were not significant in a model with treatment and center only.

Table 46. 28-day cure rate by study center in the ITT population in Study 026

	Coartem	MAS	Difference [95% CI]p-value
Center 1(Bangkok)	19/21 (90.5%)	6/7 (85.7%)	4.8%[-21.4%, 46.4%] 0.95
Center 2(Maela)	111/128 (86.7%)	41/43 (95.4%)	-8.6% [-17.1%, 2.9%] 0.12

In the evaluable population (Table 47), at both centers, the 28-day cure rate in the Coartem group was slightly lower than that in the MAS group; however, the differences were not statistically significant. The results were similar to the sponsor's reported results.

Table 47. 28-day cure rate by study center in the evaluable population in Study 026

	Coartem	MAS	Difference [95% CI] p-value
Center 1 (Bangkok)	19/20 (95.0%)	6/6 (100.0%)	-5.0% [-25.9% 40.8%] 0.98
Center 2 (Maela)	111/113 (98.2%)	41/41(100.0%)	-1.8% [-6.6%, 6.7%] 0.12

5 Conclusions and Recommendation

5.1 Statistical Issues and Collective Evidence

Three studies were reviewed in this statistical review, Study 025, 026, and 028. These three studies were conducted in Thailand and were designed to demonstrate the efficacy of a 6-dose regimen of Coartem. Study 025 compared a 4-dose regimen with two 6-dose regimens with the primary endpoint being 28-day cure rate. The 6-dose regimens appeared to have higher cure rates than the 4-dose regimen and the 6-dose regimen given over 60 hours was chosen by the sponsor for further study due to a simpler dosing administration. Note that this 6-dose regimen showed significantly higher cure rates in the evaluable population only compared to the 4-dose regimen. In study 026 and 028, the 28-day cure rates were greater than 80% in the ITT population and greater than 90% in the evaluable population. This information along with the information on studies ABMO2 and A023 which assessed Coartem versus its components (artemether and lumefantrine) supports the efficacy of 6-dose Coartem.

The limitation of these studies was that there were only at most two centers in one country (Bangkok and Maela in Thailand) in each trial and that one investigator in one center participated in the three studies, so generalizing these results to a wider population should be done with caution.

5.2 Conclusions and Recommendations

The information in this review showed that a 6-dose regimen of Coartem appears more effective than a 4-dose regimen. Additionally, two studies using the 6-dose regimen conducted in Thailand showed that 28-day cure rates for the intent to treat population were greater than 80% and for the evaluable population greater than 90%. Parasite reduction on day 1 was high with a median reduction of 99% - 100%, with interquartile range from 96.5% to 100%. This information along with information reviewed by Lan Zeng in her statistical review on the efficacy of the components of Coartem in 4-dose studies supports the efficacy of Coartem in the treatment of acute uncomplicated *P. falciparum* malaria. However, given the limited numbers of participating study centers and countries, generalization to other populations should be done with caution.

References

Brookmeyer, R. and Crowley, J. (1982), A Confidence Interval for the Median Survival Time, *Biometrics*, 38, 29 - 41.

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/s/

Xianbin Li
11/24/2008 10:56:34 AM
BIOMETRICS

Karen Higgins
11/24/2008 11:01:47 AM
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OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIostatISTICS

Statistical Review and Evaluation

SECONDARY REVIEW — NEW DRUG APPLICATION

NDA: 22-268
Name of drug: Coartem (artemether 20mg/lumefantrine 120mg) tablets
Applicant: Novartis
Indication: Acute, uncomplicated malaria
Document reviewed: Primary review by Lan Zeng, M.S. and Xianbin Li, Ph.D.
Project manager: Gregory DiBernardo
Clinical reviewer: Elizabeth O'Shaughnessy, M.D., Medical Officer
Joette Meyer, Pharm.D., (acting) Medical Team Leader
Dates: Submitted: June 27, 2008
PDUFA: December 27, 2008
Statistical Reviewer: Karen Higgins, Sc.D., Statistical Team Leader

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1 INTRODUCTION

This is a secondary review to the primary statistical reviews by Lan Zeng and Xianbin Li. This review will outline the statistical review strategy and briefly discuss the collective evidence of the 6-dose studies and the noted limitation of the submission.

The applicant, Novartis, seeks approval of Coartem, a fixed combination drug of artemether and lumefantrine, for the treatment of acute uncomplicated *P. falciparum* malaria. Coartem has been approved and marketed in Europe (initially) since 1998. Numerous studies have been conducted over many years to assess the efficacy and safety of Coartem for the treatment of malaria. Many of the studies date back a number of years and complete data was not available for all studies conducted. During pre-NDA discussions, the applicant and the Division discussed the adequacy of the available data to support an NDA.

The Division and applicant agreed that complete information, including electronic datasets, from eight clinical studies would constitute substantial evidence of effectiveness. The clinical section of the NDA submission (safety and efficacy) includes complete information on these eight primary studies, including electronic data sets. The eight primary studies are composed of two 4-dose studies assessing the efficacy of the components of the regimen (1994-1996) using a factorial study design, a study comparing a 4-dose versus a 6-dose regimen (1996), and 5 additional 6-dose regimen studies (1997-2007). Limited information, in some cases only the study reports, was submitted for an additional 16 studies that tested primarily the 4-dose regimen. These studies include two non-comparative 4-dose studies (1993-1996), a dose response (3 vs. 4-dose) study (1995), and 13 active controlled studies of which 10 included the 4-dose regimen (1993 – 2000) and three studied the 6-dose regimen (2000 – 2003). More details of the eight primary studies are given below (Table 1).

Table 1: Eight Primary Studies

Study #	Design
<i>Two factorial designed 4 dose studies</i>	
ABMO2	A double-blind, comparative trial of Coartem versus Artemether and Lumefantrine tablets conducted in China
A023	A partially blinded, comparative trial of Coartem versus Lumefantrine tablets and capsules conducted in China
<i>One comparative study of the 4-dose vs. 6-dose regimen</i>	
A025	A double-blind, comparative trial of Coartem 4-dose versus Coartem 6-dose over 60-hours and Coartem 6-dose over 96-hours conducted in Thailand
<i>Two descriptively comparative 6-dose studies, using a non FDA-approved comparator of mefloquine and artesunate (MAS)</i>	
A026	An open-label, comparative trial of Coartem versus MAS (2:1) conducted in Thailand
A028	An open-label, comparative trial of Coartem versus MAS (2:1) conducted in Thailand
<i>One non-comparative 6-dose study in non-immune travelers</i>	
A2401	An open-label, non-comparative trial of Coartem conducted in non-immune patients living in Europe who contracted malaria while traveling in endemic regions
<i>Two non-comparative 6-dose studies in children</i>	
A2403	An open-label, non-comparative trial of Coartem in African infants and children weighing 5 to 25 kg conducted in Kenya, Nigeria and Tanzania
B2303	A partially blinded trial of Coartem crushed tablets versus dispersible tablets in children weighing 5 to <35 kg conducted sub-Saharan Africa

2 STATISTICAL REVIEWS

The plan for the statistical review was to first assess the contribution of each component of the combination of Coartem, artemether and lumefantrine. Since Coartem is a combination product of two drugs, under 21 CFR 300.50, data are required to demonstrate that each component of a fixed-combination drug makes a measurable contribution to the claimed effects of the product. Studies ABM02 and A023 compared the efficacy of 4-doses of Coartem compared to lumefantrine and artemether alone (ABM02) and to lumefantrine alone (A023).

The statistical review by Lan Zeng reviews these two studies in full. Using both early and late time points, the applicant was able to demonstrate the superiority of 4-doses of Coartem compared to artemether alone on 28-day cure rate and compared to lumefantrine on time to parasite clearance (PCT), time to fever clearance, and parasite reduction at 24 hours (Table 2). Note that this review will focus on polymerase chain reaction (PCR) uncorrected 28-day cure rates. See microbiology review for a discussion of PCR corrected versus uncorrected cure rates.

Table 2: Clinical efficacy of Coartem Tablets versus components

Study No. Region/patient population	28-day cure rate ¹ n/N (%) patients	Median PCT ² [25 th ,75 th percentile]
Study ABM02: China, ages 13 - 57 years		
Coartem Tablets	50/53 (94.3)	30 hours [24, 36]
Artemether ³	24/52 (46.2)	30 hours [24, 33]
Lumefantrine tablets ⁴	47/52 (90.4)	54 hours [45, 66]
Study A023: China, ages 12 - 65 years		
Coartem Tablets	50/52 (96.2)	30 hours [24, 36]
Lumefantrine tablets ⁴	45/51 (88.2)	48 hours [42, 60]

¹ All randomized patients, PCR uncorrected cure rates.

² All randomized patients

³ 95% C.I. (Coartem Tablets – artemether) on 28-day cure rate: (33.3%, 63.1%)

⁴ P-value comparing Coartem Tablets to lumefantrine on PCT: < 0.001

The next step in the statistical review of this NDA was to assess the 6-dose regimen of Coartem, which is the proposed regimen in this application. While Studies ABM02 and A023 demonstrated the efficacy of 4-doses of Coartem in China, a low transmission area, the 4-dose regimen achieved lower parasite clearance rates (<90%) in Thailand in studies conducted between 1995 and 1996, therefore the applicant decided to pursue a 6-dose regimen. The rationale for the proposed 6-dose regimen in adults and children has been addressed with the comparison for efficacy and safety between the 4-dose and 6-dose regimens in Study A025.

Two additional comparative 6-dose studies were submitted by the applicant as primary studies which included complete electronic data, A026 and A028.

The statistical review by Xianbin Li reviewed these three studies, Study A025, A026, and A028. These three studies were conducted in Thailand and were designed to demonstrate the efficacy of a 6-dose regimen of Coartem. Study A025 compared a 4-dose regimen with two 6-dose regimens (a 6-dose over 60 hours regimen and a 6-dose over 96 hours regimen) with the primary endpoint being 28-day cure rate (Table 3). The 6-dose regimens appeared to have higher cure rates than the 4-dose regimen and the 6-dose regimen given over 60 hours was chosen by the applicant for further study due to a simpler dosing administration. The 6-dose over 60 hours regimen showed significantly higher cure rates compared to the 4-dose regimen in the evaluable population only. However, the lack of significantly higher results in the ITT population, the population considered primary by this reviewer, is not felt to be of concern. There are two reasons for this. The first is that typically efficacy of a lower dose would be considered supportive of a higher dose, i.e., the efficacy seen in ABMO2 and A023 for the 4-dose regimen of Coartem is supportive of the 6-dose regimen of Coartem as well. The second is that it does appear from study A025 that the cure rates of the 6-dose regimens were higher than the 4-dose regimens. Given the severity of the disease and the lack of concern of the safety of the 6-dose regimen compared to the 4-dose regimen (see medical safety review by Sue Lim, M.D.), a 6-dose regimen of Coartem appears appropriate. The conclusions from studies A026 and A028 were that the 28-day cure rates were greater than 80% in the ITT population and greater than 90% in the evaluable population. Though these two studies did include an active control, that control, mefloquine/artesunate, is not currently approved in the US and the study was not designed for formal comparisons between the treatment arms.

Table 3: Clinical efficacy of 6-dose regimens of Coartem versus 4-dose, Study A025

Study No. Region/patient population	28-day cure rate ¹ n/N (%) patients	Median PCT ² [25 th ,75 th percentile]
Study A025: Thailand, ages 3 - 62 years		
Coartem 4-dose	85/120 (70.8)	44 hours [34, 51]
Coartem 6-dose over 60 hours ³	96/118 (81.4)	44 hours [22, 47]
Coartem 6-dose over 96 hours ⁴	104/121 (86.0)	44 hours [40, 47]

¹ All randomized patients, PCR uncorrected cure rates.

² All randomized patients

³ 97.5% C.I. (Coartem 6-dose over 60 hours – 4-dose) on 28-day cure rate: (-1.9, 22.8)

⁴ 97.5% C.I. (Coartem 6-dose over 96 hours – 4-dose) on 28-day cure rate: (2.8, 27.3)

The information from studies ABMO2 and A023 which assessed Coartem versus its components (artemether and lumefantrine) and study A025 which assess the efficacy of Coartem 6-dose, along with supportive information from Study A026 and A028, support the efficacy of Coartem 6-dose.

3 COLLECTIVE EVIDENCE OF 6-DOSE COARTEM STUDIES

There were six primary studies submitted in this NDA which contained the 6-dose regimen, a study comparing a 4-dose versus 6-dose regimens and five 6-dose regimen studies (two

comparative and three non-comparative). Study reports were submitted for an additional three 6-dose regimen active controlled studies.

Note that complete statistical reviews were not conducted for the three primary non-comparative studies (2401, 2403 and 2303). Since the results from these studies will be included in the labeling, if approved, brief reviews of these studies can be found in the appendices of this review. See medical review by Elizabeth O'Shaughnessy for a more comprehensive review of these three studies. Complete statistical reviews could not be conducted on the additional 3 studies submitted as study reports only. However, this section briefly summarizes the results from these three active controlled 6-dose studies.

The efficacy results of the Coartem 6-dose regimen for the six primary 6-dose regimen studies are reported here. Note that patients lost to follow-up are considered as failures in this analysis. The results vary across the 6-studies, due to differing patient populations, as well as, differing study designs and conduct. Though the 28-day cure rates are lower for some studies, there was no confirmed unexpected lack of efficacy seen in these studies.

Table 4: Clinical efficacy of Coartem 6-dose studies

Coartem Tablets 6-dose		
Study No. Region/ages	28-day cure rate¹ n/N (%) patients 95% CI	Median PCT² [25th, 75th percentile]
Study A025: Thailand, ages 3 - 62 years	96/118 (81.4) [73.1, 87.9]	44 hours [22, 47]
Study A026: Thailand, ages 2 - 63 years	130/150 (86.7) [80.2, 91.7]	44 hours [42, 45]
Study A028: Thailand, ages 12 - 71 years	148/164 (90.2) [84.6, 94.3]	29 hours [18, 40]
Study 2401:³ Europe/Colombia, ages 16 - 66 yrs	120/162 (74.1) [66.6, 80.6]	42 hours [34, 63]
Study 2403: Africa, ages 0 - 9 years	268/310 (86.5) [82.1, 90.1]	24 hours [24, 36]
Study 2303: Africa, ages 0 - 12 years	374/452 (82.7) [78.9, 86.1]	35 hours [24, 36]

¹All enrolled/randomized patients, PCR uncorrected cure rates.

²All enrolled/randomized patients

³Three subjects excluded due to no non-immune uncomplicated *P. falciparum* malaria.

Three additional 6-dose regimen Coartem active controlled studies were conducted but complete information on these studies was not submitted. These studies were A030, ABD01 and ABR01. The following is a brief summary of these studies. Note that two of these studies are smaller than the primary 6-dose studies (A030 and ABR01), one of which contains only limited follow-up data (ABR01). The third study (ABD01) while fairly large shows very acceptable results for Coartem. Therefore, from the brief reviews of the

additional comparative studies, there does not appear to be any selection bias in the studies that were submitted as complete studies to the NDA.

A030 was a randomized, open-label, controlled trial comparing Coartem with artesunate-mefloquine (MAS) for uncomplicated falciparum malaria in Vietnam. It was conducted at (b) (4). Forty-five subjects were randomized to Coartem and 38 to MAS. There were 9 Coartem subjects and 4 MAS subjects who were lost to follow-up. Mean time to parasite clearance was reported to be 1.8 (SD=0.7) days for Coartem and 1.7 (SD=0.7) days for MAS. The number of subjects cured at 28 days was 36 (77.7% in an ITT analysis, 97.2% in an evaluable analysis) on the Coartem arm and 34 (89.5% in an ITT analysis, 100% in an evaluable analysis) on the MAS arm. MAS is not a U.S. approved regimen for the treatment of malaria.

ABD01 was a randomized, partially blinded (site personnel were blind to treatment assignment), controlled trial comparing Coartem with Quinine-Fansidar (3 days of oral quinine 10 mg/kg, 8 hourly, followed by a single dose of fansidar) in the treatment of uncomplicated malaria in a multidrug resistant falciparum area in Bangladesh. It was conducted at (b) (4). Parasitological and clinical cure rate was the primary efficacy endpoint. The number of randomized subjects was 103 per arm. The number of subjects cured at 28 days was 93 (90.3% in an ITT analysis, 95.9% in an evaluable analysis) on the Coartem arm and 90 (87.4% in an ITT analysis, 88.2% in an evaluable analysis) on the control arm. Results of parasite clearance time were not clearly reported in the study report.

ABR01 was a randomized, open-label study of the efficacy of Coartem versus quinine/doxycycline for the treatment of uncomplicated malaria *falciparum* in Western Amazon. This study was conducted at two sites in Brazil from 2000-2002. Twenty-eight subjects were randomized to Coartem and 31 to Quinine/doxycycline. It does not appear that 28 day cure rate was measured in this study. Time to parasite clearance appears significantly shorter in the Coartem group compared to quinine/doxycycline. Median parasite clearance time for Coartem was 2 days and for quinine/doxycycline was 3 days.

4 LIMITATION

A limitation with the three studies which are most useful in their support of the efficacy of Coartem, ABMO2, A023 and A025, is that they were conducted in a very limited number of centers. Both ABMO2 and A023 were conducted in one center in China, while A025 was conducted in two centers in Thailand. Additionally, the two additional primary 6-dose controlled trials were conducted in these same two centers in Thailand. This causes a concern regarding the ability to generalize these results to a larger population or different geographic areas.

Table 5: Sites in controlled primary studies

Study	Country	Center(s)
ABMO2	China	- Navy Military Hospital, Sanya, Hainan Province
A023	China	- Navy Military Hospital, Sanya, Hainan Province
A025	Thailand	- Hospital for Tropical Diseases, Mahidol University, Bangkok - MaeLa Camp, SMRU, Mae Sot
A026	Thailand	- Hospital for Tropical Diseases, Mahidol University, Bangkok - MaeLa Camp, SMRU, Mae Sot
A028	Thailand	- Hospital for Tropical Diseases, Mahidol University, Bangkok

However, a few points in favor of studies ABMO2 and A023 are that the results obtained by these studies were as expected, i.e., it was expected that Coartem would have a higher 28 day cure rate than artemether and a faster and greater reduction in parasite counts than lumefantrine, and the results were robust. The results were highly significant and were maintained across gender, age, and baseline parasite counts.

The remaining uncontrolled 6-dose studies were studied in more centers and countries. Study 2401 contained 16 centers in Europe and Columbia, Study 2403 contained 3 centers in Africa (1 in Nigeria, 1 in Kenya, and 1 in Tanzania) and Study 2303 contained 7 centers in Africa (2 in Kenya, 2 in Tanzania, 1 in Mozambique, 1 in Mali, and 1 in the Republic of Benin). Additionally, though not fully reviewed, the results of the additional active controlled 6-dose studies (A030, ABD01 and ABR01) were conducted in 1 site in Vietnam, 1 site in Bangladesh and 2 sites in Brazil.

So though the number of sites which enrolled subjects in the studies which are most heavily relied on to support the efficacy of Coartem is very limited, the entire efficacy section of the NDA does contain a reasonable number of sites. Additionally, there was no unexpected lack of efficacy seen in these studies.

5 OVERALL CONCLUSIONS

The information from studies ABMO2 and A023 which assessed Coartem versus its components (artemether and lumefantrine) and study A025 which assessed the efficacy of Coartem 6-dose versus 4-dose support the efficacy of the Coartem 6-dose regimen.

The additional 6-dose studies of Coartem, though essentially uncontrolled, support the efficacy of the 6-dose regimen in a broader population and an increased number of sites and countries.

Though the NDA submitted by the applicant does not contain complete information on all studies conducted to assess the efficacy of Coartem, from the brief reviews of the additional comparative studies, there does not appear to be any selection bias in the studies that were submitted as complete studies to the NDA.

APPENDIX A: STUDY 2401

Study 2401 is an open label, multi-center, non-comparative efficacy, safety, and tolerability study of Coartem in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in non-immune patients. This study was conducted from 2001 to 2005. It enrolled non-immune travelers with confirmed *P. falciparum* malaria at 16 sites in Europe and Columbia. The study contains two parts, the core study which contains 150 subjects and a rich PK sub-study which enrolled an additional 15 subjects after the core study was completed. We will consider only the combined group of 165 patients in our summary of this study.

Reviewer's comment: Given that this is a non-comparative study, the focus of the review will be on the inclusion and exclusion of subjects from the analysis populations.

The primary endpoint of the study was 28 day cure rate. Coartem was administered as 6 doses of 4 tablets (20 mg artemether and 120 mg lumefantrine per tablet) over 3 days. The dosing was adjusted by weight.

The sponsor's analysis populations were defined in the study report as

- Intent to treat: All patients with confirmed malaria who received at least one dose of study drug
- Per protocol: All patients in the intent-to-treat population who completed the study and did not have major protocol violations. *Note that this population was defined in the protocol as all subjects who met all selection criteria, has documented Plasmodium infection with a positive thick or thin film, and attends all scheduled visits.*

The number of subjects listed in the sponsor's analysis populations are as follows:

Table 6: Study 2401 Analysis Populations

Population	Number (%) patients
Treated population	165 (100.0)
Intent-to-treat population	162 (98.2)
Per protocol population	126 (76.4)

Source: Table 2-2 sponsor's study report

Though the sponsor's table 2-2 states that there were 126 subjects included in the per protocol population, the sponsor's per protocol analysis of 28-day cure rate contains only 124 subjects since two subjects were excluded due to protocol violations from the point of the violation onwards.

Reviewer's comment: In the post text table 7.3-1, it states that patients with concomitant anti-malarial treatment were excluded from the per protocol population from the date of violation onwards. If other anti-malarial treatment was started on Day 0 the patient was completely excluded.

The following table reports the patient discontinuations as reported by the sponsor.

Table 7: Study 2401 Discontinuations

Primary Reason for Discontinuation	Number (%) patients
Loss to follow-up	17 (10.3)
Protocol Violation	6 (3.6)
Unsatisfactory therapeutic effect	2 (1.2)
Subject withdrew consent	2 (1.2)
Adverse event	1 (0.6)
Abnormal test procedure result	1 (0.6)
Subject's condition no longer requires study drug	1 (0.6)

Source: Table 2-1 sponsor's study report

The three subjects excluded from the sponsor's ITT population were included in the table above under "Subject's condition no longer requires study drug," one under "Protocol violation" and one under "Abnormal test procedure result." The remaining subjects were failures in the ITT population analysis. All of the patients in the above table were excluded from the sponsor's per protocol population except the two subjects who had an unsatisfactory response. An additional 13 subjects (one cure, 12 failures) were excluded from the per protocol population.

The following table details the reason for exclusion from the sponsor's per protocol population.

Table 8: Study 2401 Exclusions from Per Protocol Population

Reason for exclusion from per protocol population	Number of patients
Incomplete documentation of parasite counts after clearance	34
Less than 6 doses of study medication taken	7
Other concomitant treatment for malaria	6
No non-immune, uncomplicated <i>P. falciparum</i> malaria	3
Intake of halofantrine/other drug with influence on cardiac function prior to screening	1

Source: Post-text table 7.2-1 from sponsor's study report and A_VIOPTO.xpt
 Patients may be in more than one category

Reviewer's comment: The 6 subjects who were excluded due to taking other concomitant treatment for malaria is concerning if these subjects were failing therapy. One subject, considered a cure, was given primaquine for p. vivax. The remaining 5 subjects received medication to treat their malaria, are considered failures in the ITT and are excluded from the per protocol population. More details on these subjects are given here.

- 2_00011 Received quinine on day 1 for complicated malaria
- 4_00007 Received quinine on day 2 due to progression of disease
- 42_00002 Received Quinmax on days 1-8 as rescue med. due to vomiting
- 42_00007 Received Quinmax on days 1-6
- 43_00004 Received Malarone on days 3-5 as rescue medication

Baseline demographic and disease characteristics are reported in the following table.

Table 9: Study 2401 Baseline Demographics and Disease Characteristics

Variable	Statistic	Treated patients (n = 165)
Age (years)	Mean (+/- SD)	37.7 (+/- 12.44)
	Median (range)	37.0 (17 – 66)
Sex – n (%)	Male	113 (68.5)
	Female	52 (31.5)
Race – n (%)	Caucasian	80 (48.5)
	Black	40 (24.2)
	Other	45 (27.3)
Body Weight (kg)	Mean (+/- SD)	72.9 (+/- 13.76)
	Median (range)	73.0 (41 – 119)
Parasite Density per 1000 red cells (i.e. per mille)	Mean (+/- SD)	6.2 (+/- 9.45)
	Median (Range)	2.4 (0 – 70)
	None	3 (1.8%)

Source: Table 2-3 and 2-4 sponsor's study report

The results of the primary endpoint, 28 day parasitological cure rate, are presented in the following table.

Table 10: Study 2401 28-day Cure Rate

Population	Results
<i>ITT population</i>	
28-day cure rate, n/N (%)	120/162 (74.1)
95% CI	[66.6, 80.6]
<i>Per protocol population</i>	
28-day cure rate, n/N (%)	119/124 (96.0)
95% CI	[90.8, 98.7]

Source: Table 4-1 sponsor's study report
 95% CI calculated using Person Clopper limits

Reviewer's comment: If the 5 excluded subjects who received rescue medication are included in the per protocol population, the 28 day cure rate would be 119/129 (92.2) with 95% C.I. of [86.2, 96.2].

The sponsor's secondary efficacy results regarding parasite and fever clearance are presented in the following table.

Table 11: Study 2401 Time to Parasite and Fever Clearance

	ITT population N = 162
Time to parasite clearance (hrs)	
Median [95% C.I.]	41.8 [40.3, 43.8]
[25 th , 75 th percentile]	[32, 61.7]
Time to fever clearance	
Median [95% C.I.]	36.5 [27.8, 39.5]
[25 th , 75 th percentile]	[18, 43.8]

Source: Table 4-2 from sponsor's study report and c_eff.xpt
 One hundred subjects had fever at baseline.

Only limited conclusions can be drawn from this uncontrolled study. The primary endpoint of interest is 28-day cure rate. The result from the ITT analysis differs substantially from that of the per protocol population. The ITT analysis, considering missing data as failures, most likely under estimates the 28-day cure rate, while the per protocol which excludes many subjects quite likely over estimates the 28-day cure rate. Thirty-eight subjects (23%) from the ITT population were excluded from the per protocol population, most due to incomplete documentation of parasite counts after clearance. The ITT 28-day cure rate was 74.1 with a confidence interval ranging from 66.6% to 80.6%. The sponsor's per protocol results were 96.0 with a confidence interval ranging from 90.8 to 98.7. An alternative per protocol analysis, including 5 subjects treated with additional anti-malarials, gives 92.2 with 95% C.I. of ranging from 86.2 to 96.2.

APPENDIX B: STUDY 2403

Study 2403 is an open label, multi-center, non-comparative efficacy and safety study of Coartem in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in African infants and children. This study was conducted from 2002 to 2003. It enrolled infants and children weighing between $\geq 5\text{kg}$ and $\leq 25\text{ kg}$ with confirmed *P. falciparum* malaria at three sites, one in Nigeria, one in Tanzania, and one in Kenya. Coartem was administered as 6 doses of 1-2 tablets (20 mg artemether and 120 mg lumefantrine per tablet) over 3 days. The dosing was adjusted by weight. Clinical assessments included time to fever clearance and development of signs of severe malaria. Laboratory assessments included 28-day cure rate and time to parasite clearance.

Reviewer's comment: Given that this is a non-comparative study, the focus of the review will be on the inclusion and exclusion of subjects from the analysis populations.

The sponsor's analysis populations were defined in the protocol as

- Intent to treat: All patients who received at least one dose of study drug
- Per protocol: All patients in the intent-to-treat population who did not have major protocol violations. Major protocol violations include non-compliance with study medication, no *P. falciparum* at baseline, baseline parasite not within window, and severe malaria at baseline.

An additional analysis population, an evaluable population, was defined in the study report only. This population excludes subjects with unsatisfactory therapeutic effect unless it is due to reoccurrence of *P. falciparum* and subjects who have taken medication with efficacy against *P. falciparum* for reason other than rescue medication.

The number of subjects listed in the sponsor's analysis populations are as follows:

Table 12: Study 2403 Analysis Populations

Population	Number (%) patients
Intent-to-treat population	310 (100.0)
Per protocol population	293 (94.5)

Source: Table 7-3 sponsor's study report

The following table reports the patient discontinuations as reported by the sponsor.

Table 13: Study 2403 Discontinuations

Primary Reason for Discontinuation	Number (%) patients
Loss to follow-up	2 (0.6)
Death	1 (0.3)
Protocol Violation	1 (0.3)
Subject withdrew consent	2 (0.6)
Adverse event	1 (0.3)

Source: Table 7-1 sponsor's study report

All of the patients in the above table were excluded from the sponsor's per protocol population and all but the subject with the protocol violation was considered a failure. An additional 10 subjects (9 cures, 1 failure) were excluded from the per protocol population.

The following table details the reason for exclusion from the sponsor's per protocol population.

Table 14: Study 2403 Exclusions from Per Protocol Population

Reason for exclusion from per protocol population	Number of patients
Parasite count is missing	7
Discontinued for reason other than unsatisfactory response	7
Less than 6 doses of medication	4
Other concomitant treatment for malaria (including re-infection)	4
Severe malnutrition	4
Parasite count < 1,000 or > 100,000/mm ³ on day 0	3
Informed consent given after patient treated	1
No dose replacement if patient vomited within 2 hours	1

Source: Post-text table 7.2-1 from sponsor's study report

Patients may be in more than one category

Reviewer's comment: The 4 subjects who were excluded due to taking other concomitant treatment for malaria is concerning if these subjects were failing therapy. Two patients were considered cures and received the malaria treatment prior to therapy. The remaining 2 subjects received medication as rescue therapy to treat their malaria, are considered failures in the ITT and are excluded from the per protocol population. More details on these subjects are given here.

1_104 Received Fansidar as rescue treatment

1_222 Received amodiaquine syrup as rescue treatment

Baseline demographic and disease characteristics are reported in the following table.

Table 15: Study 2403 Baseline Demographics and Disease Characteristics

Variable	Statistic	Treated patients (n = 310)
Age (years)	Mean (+/- SD)	2.5 (+/- 1.96)
	Median (range)	2.0 (0.2 – 9.9)
Sex – n (%)	Male	161 (51.9)
	Female	149 (48.1)
Race – n (%)	Black	310 (100)
Body Weight (kg)	Mean (+/- SD)	11.1 (+/- 3.88)
	Median (range)	10.0 (5.0 – 25.0)
Parasite Density (/µL)	Mean (+/- SD)	33,050 (+/- 32,976)
	Median (Range)	18,488 (1000 – 137,760)

Source: Table 7-4 and 7-5 sponsor's study report

The results of the primary endpoints, 28 day parasitological cure rate are presented in the following table.

Table 16: Study 2403 28-day Cure Rate

Population	Results
<i>ITT population</i>	
28-day cure rate, n/N (%)	268/310 (86.5)
95% CI	[82.1, 90.1]
<i>Per protocol population</i>	
28-day cure rate, n/N (%)	258/293 (88.1)*
95% CI	[83.8, 91.5]

Source: Table 9-2 sponsor's study report

95% CI calculated using Person Clopper limits by sponsor

*Calculated by reviewer using c_eff.xpt. Sponsor reported only 291 subjects in the per protocol population in Table 9-2.

Reviewer's comment: If the 2 excluded subjects who were received rescue medication are included in the per protocol population, the 28 day cure rate would be 258/295 (87.5) with 95% C.I. of [83.1, 91.0].

The sponsor's secondary efficacy results regarding parasite and fever clearance are presented in the following table.

Table 17: Study 2403 Time to Parasite and Fever Clearance

	ITT population N = 310
Time to parasite clearance (hrs)	
Median [95% C.I.]	24.0 [24.0, 35.4]
[25 th , 75 th percentile]	[23.8, 36.0]
Time to fever clearance	
Median [95% C.I.]	7.8 [7.8, 7.9]
[25 th , 75 th percentile]	[7.8, 23.8]

Source: Table 9-3 from sponsor's study report and c_eff.xpt

Only limited conclusions can be drawn from this uncontrolled study. The primary endpoint of interest is 28-day cure rate. The result from the ITT analysis differs only slightly from

that of the per protocol population. The ITT 28-day cure rate was 86.5 with a confidence interval ranging from 82.1% to 90.1%. The per protocol results were 88.1 with a confidence interval ranging from 83.8% to 91.5%. An alternative per protocol analysis, including 2 subjects treated with additional anti-malarials, gives 87.5 with 95% C.I. of 83.1 to 91.0.

APPENDIX C: STUDY 2303

Study 2303 is an investigator blinded, multi-center, efficacy and safety study to compare Coartem dispersible tablet formulation to Coartem crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children. This study was conducted from 2006 to 2007. It enrolled infants and children weighing between ≥ 5 kg and ≤ 35 kg with confirmed *P. falciparum* malaria at 7 sites in Africa. *The focus of this review will be of the crushed tablet arm only.* Coartem was administered as 6 doses of 1-3 tablets (20 mg artemether and 120 mg lumefantrine per tablet) over 3 days. The dosing was adjusted by weight. The primary endpoint is PCR-corrected 28-day cure rate.

Reviewer's comment: Given that this review will summarize only the results from one treatment arm, the focus of the review will be on the inclusion and exclusion of subjects from the analysis populations. The division's endpoints of interest are PCR uncorrected 28-day cure rate, parasite clearance time and fever clearance time.

The sponsor's analysis populations were defined in the protocol as

- Intent to treat: All patients with acute, uncomplicated *P. falciparum* malaria at baseline, who had a least one relevant post-baseline efficacy assessment, and who took at least one dose of study drug
- Primary analysis: All ITT patients that completed 28 days with a valid PCR evaluation or all ITT patients that would be classified as treatment failures prior to Day 28
- Per protocol: All Primary analysis patients that meet all of the following: took at least 80% of scheduled study drug, had parasite counts between 2000 and 200,000/ μ L at baseline, had a body weight of ≥ 5 kg and < 35 kg.

Reviewer's comment: The sponsor's defined intent to treat population is quite different from the other studies submitted in support of Coartem. It is also quite different from how we would expect it to be defined. In the sponsor's definition, many subjects can be excluded based on post-baseline information. It will quite possibly bias the results towards higher cure rates. For this review, the intent to treat population will include all subjects randomized to the Coartem crushed tablet arm.

It appears from the definition of the per protocol population that subjects who do not have a valid PCR evaluation at day 28 will be excluded. The Division is only considering PCR uncorrected rates (see microbiology review for details). Therefore, exclusion from the per protocol analysis for not having a valid PCR evaluation is not appropriate.

The number of subjects listed in the FDA's ITT and the sponsor's per protocol populations are as follows:

Table 18: Study 2303 Analysis Populations- Crushed Tablet arm only

Population	Number (%) patients
FDA defined ITT	452 (100)
Per protocol population	406 (89.8)

Source: Table 7-3 sponsor's study report

The following table reports the patient discontinuations as reported by the sponsor.

Table 19: Study 2303 Discontinuations - Crushed Tablet arm only

Primary Reason for Discontinuation	Number (%) patients
Loss to follow-up	12 (2.7)
Death	1 (0.2)
Protocol Violation	11 (2.4)
Adverse event	40 (8.8)

Source: Table 7-1 sponsor's study report

Not all the patients in the above table were excluded from the sponsor's per protocol population or considered failures. Twenty-eight subjects with an AE were included in the per protocol population of which 7 were considered as having a 28-day cure. Four subjects who were lost to follow-up were also included in the per protocol population of which 2 were considered as having a 28-day cure. An additional 14 subjects not listed in the table above were also excluded from the per protocol population.

The following table details the reason for exclusion from the sponsor's per protocol population.

Table 20: Study 2303 Exclusions from Per Protocol Population - Crushed Tablet arm only

Reason for exclusion from per protocol population	Number of patients
No day 28 parasite count without being a failure prior to day 28	34
Less than 80% of study medication taken	17
Vomiting of replacement dose	11
No relevant post baseline efficacy data	8
No full dose of study drug taken	6
Reappearance of parasite but no valid PCR analysis until day 28	3
Baseline parasite count < 2000 / μ L or \geq 200,000/ μ L	3
Switch to rescue medication for other reasons (elevated liver enzymes at baseline)	1
Use of concomitant anti-malarial other than rescue medication	1

Source: Table 7.2 from sponsor's study report and viopo.xpt

Patients may be in more than one category

Reviewer's comment: There were 10 subjects who were excluded from the per protocol analysis who appeared to be failing therapy. These subjects were all considered failures for the PCR uncorrected day 28 cure. Of these 10 subjects, 7 patients had reappearance of parasites prior to day 28 which was considered a new infection. These 7 were counted under the category "No 28 day parasite count without being a failure prior to day 28" in the table above. Three had reappearance of parasites prior to Day 28 but no PCR data

available on day 28. The subject numbers of these subjects are 102_16, 103_30, 201_69, 301_158, 301_203, 601_7, 601_17, 601_22, 601_43, and 601_109.

The reviewing microbiologists do not agree with the use of the PCR corrected rates to differentiate between a new infection and a relapse. For that reason, the division is focusing on PCR uncorrected cure rates. An analysis of PCR uncorrected cure rates should consider these 10 subjects as failures in a per protocol analysis. See additional per protocol analysis below.

Baseline demographic and disease characteristics are reported in the following table.

Table 21: Study 2303 Baseline Demographics and Disease Characteristics - Crushed Tablet only

Variable	Statistic	Treated patients (n = 452)
Age (years)	Mean (+/- SD)	3.7 (+/- 2.84)
	Median (range)	3.0 (0.0 – 12.0)
Sex – n (%)	Male	247 (54.6)
	Female	205 (45.4)
Race – n (%)	Black	452 (100)
Body Weight (kg)	Mean (+/- SD)	14.5 (+/- 5.53)
	Median (range)	13.1 (6.0 – 34.0)
Parasite Density (/µL)	Median (Range)	32,288 (1581 – 628571)

Source: Table 7-4 and 7-5 sponsor's study report

The results of the FDA's analysis of PCR uncorrected 28 day parasitological cure rates are presented in the following table. The ITT analysis includes all subjects randomized to the crushed tablet arm. The per protocol population contains the sponsor's per protocol population plus the 10 subjects with parasitemia prior to Day 28.

Table 22: Study 2303 28-day Cure Rate- Crushed Tablet arm only

Population*	Results**
<i>ITT population</i>	
28-day cure rate, n/N (%)	374/452 (82.7)
95% CI	[78.9, 86.1]
<i>Per protocol population</i>	
28-day cure rate, n/N (%)	367/416 (88.2)
95% CI	[84.7, 91.2]

*ITT analysis includes all subjects randomized to the crushed tablet arm. The per protocol population contains the sponsor's defined per protocol population plus the 10 subjects with parasitemia prior to Day 28.

**Calculated by reviewer using c_eff.xpt.

95% CI calculated using Person Clopper limits by sponsor

The secondary efficacy results regarding parasite and fever clearance are presented in the following table.

Table 23: Study 2303 Time to Parasite and Fever Clearance - Crushed Tablet arm only

	ITT population N = 452
Time to parasite clearance (hrs) Median [95% C.I.] [25 th , 75 th percentile]	34.9 [25.2, 35.6] [23.9, 36.0]
Time to fever clearance Median [95% C.I.] [25 th , 75 th percentile]	7.8 [7.8, 7.9] [7.5, 23.5]

Source: c_eff.xpt

Analysis using Kaplan-Meier method. 19 observations censored for time to parasite clearance. Of the 333 with fever at baseline, 20 were censored for fever clearance time.

Only limited conclusions can be drawn from this essentially uncontrolled study regarding the efficacy of Coartem crushed tablets. The primary endpoint of interest is 28-day PCR uncorrected cure rate. The sponsor removed subjects from the ITT population based on criteria different than the remainder of the studies in this submission. For ease of comparison across studies, this reviewer re-defined the ITT population as all randomized subjects. Additionally, the sponsor based inclusion into a per protocol population on availability and results of PCR. Since only PCR uncorrected cure rates are being considered in the assessment of 28-day cure rates, this reviewer re-defined the per protocol population as well. The 28 day cure rate was 82.7 (374/452) with a confidence interval ranging from 78.9% to 86.1% for the re-defined ITT population and 88.2 (367/416) with a confidence interval ranging from 84.7% to 91.2% for the re-defined per protocol population.

SIGNATURES

Reviewer: Karen Higgins, Sc.D., Statistics Team Leader

Concurring Reviewer: Daphne Lin, Ph.D., Deputy Division Director
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: NDA 22-268

Drug Name: Coartem (artemether 20 mg/lumefantrine 120 mg) tablets

Indication(s): Acute, uncomplicated malaria

Applicant: Novartis Pharmaceuticals Corporation

Date(s): Submission date: June 27, 2008.
PDUFA due date: December 27, 2008

Review Priority: Priority Review

Biometrics Division: Division of Biometrics IV

Statistical Reviewer: Lan Zeng, M.S.

Concurring Reviewers: Karen Higgins, Sc.D.

Medical Division: Division of Special Pathogen and Transplant Products

Clinical Team: Elizabeth O'Shaughnessy, MD; Joette Meyer, Pharm.D. (acting TL)

Project Manager: Gregory DiBernardo

Keywords: Clinical studies, NDA review, superiority

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of 4-dose Coartem tablets for the treatment of acute, uncomplicated malaria were supported by two studies conducted during 1994 to 1996 in China. These studies assessed the efficacy of Coartem and its individual components using a factorial design. Results demonstrated the superiority of Coartem compared to artemether alone on 28-day parasitological cure rate and compared to lumefantrine on time to parasite clearance, time to fever clearance, and parasite reduction at 24 hours. An additional 13 studies conducted in other geographic areas supported the safety of 4-doses of Coartem but failed to demonstrate consistently acceptable 28-day cure rates. Consequently, the applicant decided to pursue a 6-dose regimen.

For a discussion of the 6-dose regimen studies, please see statistical review by Xianbin Li.

1.2 Brief Overview of Clinical Studies

Two studies, Study ABMO2 and A023, have been submitted to provide support for the superiority of the fixed-combination drug Coartem to its components, artemether and lumefantrine. Study ABMO2 compared Coartem to artemether and lumefantrine. Study A023 compared Coartem with a powder (tablet) and a liquid (capsule) formulation of lumefantrine. Both were randomized, comparative, 4-dose trials conducted over 4 weeks in the same single center in China. In both studies, Coartem, artemether, or lumefantrine tablets were administered at hours 0, 8, 24, and 48. In Study A023, lumefantrine capsule was given at hours 0, 24, 48, and 72. Study ABMO2 was double blinded while in Study A023 the Coartem arm and the lumefantrine tablet arm were blinded.

In Study ABMO2, the primary efficacy variables were 28-day parasitological cure rate, time to parasite clearance, and time to fever clearance. In Study A023, the primary efficacy variables were 28-day parasitological cure rate, time to parasite clearance, and parasite reduction at 24 hours.

1.3 Statistical Issues and Findings

A total of 157 and 153 patients were randomized in Study ABMO2 and A023, respectively. All received at least one dose of study drug and were included in the intent-to-treat (ITT) population. Patients with missing data for 28-day cure rate were included as failures in the ITT population. In Study ABMO2, the 28-day cure rate in the ITT population was significantly higher for Coartem (94.3%) compared to artemether (46.2%), while the median time to parasite clearance was significantly shorter for Coartem (30 hours) compared to lumefantrine tablets (54 hours). In Study A023, there was no statistically significant difference between the 28-day cure rates for the three treatment arms. The median time to parasite clearance was significantly longer for both

lumefantrine formulations than for Coartem, i.e. 54 and 48 hours compared to 30 hours. Twenty-four patients in Study ABMO2 (20 on artemether, 4 on lumefantrine) and seven patients in Study A023 (1 on Coartem, 4 on lumefantrine tablet, 2 on lumefantrine capsule) had a recrudescence of parasitemia. All were considered R-I treatment failures.

In Study A023, the Coartem arm had less fever and a lower parasite density at baseline than the lumefantrine arms. Results of analysis accounting for baseline parasite density showed similar pattern among treatment arms as the overall results. Compared to either lumefantrine formulation, Coartem treatment was associated with greater parasite reduction, as well as quicker parasite and fever clearance. Overall 28-day cure rate remained similar across the three arms. For both studies, analyses of patients with more severe disease or pediatric patients (age ≤ 16 years) led to similar overall efficacy results for 28-day cure rate, time to parasite clearance, and parasite reduction at 24 hours.

2 INTRODUCTION

2.1 Overview

Coartem® (co-artemether, CGP 56697) is a combination of 20 mg artemether and 120 mg lumefantrine (formerly known as benflumetol) originally developed by the Academy of Military Medical Sciences in China. Ciba (subsequently Novartis) began further development in collaboration with Chinese partners in 1992 and conducted studies in a broader range of clinical circumstances and geographical regions. In Coartem, artemether has a rapid onset of action, whereas lumefantrine is eliminated more slowly and provides a high long-term cure rate after a short treatment course. The combination thus provides rapid clearance of parasitemia and most malaria-related symptoms, coupled with prevention of recrudescence. The current NDA is for registration of the 6-dose regimen of Coartem in the treatment of acute uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Registration is sought for the Coartem tablet, as marketed in other countries and distributed in endemic countries through a variety of procurement agencies.

2.2 Data Sources

Datasets and all modules containing clinical study reports were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:

\\Fdswa150\nonectd\N22268

The data sets were adequately documented and generally represented the data described in the study reports.

3 STATISICAL EVALUATION

The efficacy of Coartem was evaluated in 24 studies which were conducted in various geographic regions outside the United States. Eight of these 24 studies were considered primary and complete information were received by the FDA, including raw data and electronic data sets. The eight primary studies are composed of two 4-dose studies assessing the efficacy of the components of the regimen (Studies ABMO2 and A023, 1994-1996) using a factorial study design, a study comparing a 4-dose versus a 6-dose regimen (Study A025, 1996), and 5 additional 6-dose regimen studies (Studies A026, A028, A2401, A2403, B2303, 1997-2007). Limited information, in some cases only the study reports, was submitted for the other 16 studies that tested mainly the 4-dose regimen. These studies include two non-comparative 4-dose studies (1993-1996), a dose response study (1995), and 13 active controlled studies of which 10 included the 4-dose regimen (1993 – 2000) and 3 studied the 6-dose regimen (2000 – 2003).

The eight primary studies were reviewed in detail to evaluate efficacy. This document contains a statistical review of two of the 4-dose studies (ABMO2 and A023) and a summary of ten supportive active controlled trials with the 4-dose Coartem regimen. The other six studies with the 6-dose Coartem regimen are reviewed by either the statistical review by Xianbin Li (Studies A025, A026, and A028) or the clinical review by Elizabeth O'Shaughnessy (Studies A2401, A2403, and B2303).

3.1 Evaluation of Efficacy

Study ABMO2 and A023 are studies of a 4-dose regimen of Coartem that assess the added benefit of the components (lumefantrine and artemether) to the combination. Although one included both a lumefantrine and an artemether arm and one included two lumefantrine arms, they had very similar design and conduct. This review will first describe these studies as a whole and then present and discuss each study in detail. Additional review on supportive 4-dose studies is presented in Section 3.1.2.

3.1.1 Primary 4-dose Studies

Protocol ABMO2: A double-blind, comparative trial of an oral anti-malarial drug combination Coartem and its respective individual components, artemether and benflumetol, given in 48 hours to patients with naturally occurring Plasmodium falciparum infection: a combined pharmacokinetic and efficacy trial in China

Protocol 5669701 023: A randomised, parallel group, comparative trial of an oral anti-malarial drug combination, Coartem, and one of its components, benflumetol (2 formulations), given to patients with Plasmodium falciparum infection: a combined pharmacokinetic and efficacy trial in China

3.1.1.1 Objectives and Study Design

The study design for the 4-dose regimen trials is summarized in Table 1.

Table 1 Summary of Design of Studies ABMO2 and A023

	Study ABMO2	Study A023
Dosing Coartem Regimen (80 mg Artemether + 480 mg Lumefantrine)	hours 0, 8, 24, 48	hours 0, 8, 24, 48
Dosing Comparators Regimen		
Artemether 80 mg	hours 0, 8, 24, 48	-
Lumefantrine tablet 480 mg	hours 0, 8, 24, 48	hours 0, 8, 24, 48
Lumefantrine capsule*	-	800 mg at hour 0 400 mg at hours 24, 48, 72
Dosage Adjusted by Weight for patients <35 kg	Yes	No
Study Timeline	6/2/1994 to 10/6/1994	6/21/1996 to 11/5/1996
Number of Patients Recruited	157	153
Number of Study Centers	1 (Navy Military Hospital, Sanya, Hainan Province)	1 (Navy Military Hospital, Sanya, Hainan Province)
Countries Where Studies Were Conducted	China	China
Blinding	Double-blind	Double-blind – Coartem and Lumefantrine Tablets only
*In Study A023, lumefantrine capsules were dosed according to the dosing regimen in use at the time in China.		

Study ABMO2 was a randomized, double-blinded, comparative, single center 4 week trial to compare Coartem with artemether (20 mg per tablet) and lumefantrine (120 mg per tablet). Study A023 was a randomized, partially-blinded comparative, single center 4 week trial to compare oral tablet of Coartem with a powder (120 mg per tablet) and a liquid (100 mg per capsule) formulation of lumefantrine. Each oral tablet of Coartem contains 20 mg artemether and 120 mg lumefantrine. In both studies, 4 doses of 4 tablets per dose of Coartem were administered over 48 hours (hours 0, 8, 24, 48). The same dosage regimen was applied to comparator arms in study ABMO2 as well as the lumefantrine tablet comparator in Study A023. Another comparator in Study A023, lumefantrine capsule, was given as follows: 8 capsules at start, then 4 capsules each at hours 24, 48, and 72. In study ABMO2, the number of tablets was adjusted for patient's body weight (≥ 45 kg 4 tablets at each dose, 35-44 kg 3 tablets and 25-34 kg 2 tablets) while no dose adjustment was made for weight in Study A023. In Study A023, only the Coartem and lumefantrine tablet arms were blinded; the lumefantrine capsule arm was not blinded for logistic reasons. Study ABMO2 was conducted from June 2 to October 6 in 1994 and enrolled 157 patients in China. Study A023 was conducted from June 21 to November 5 in 1996 and recruited 153 patients in China.

Reviewer's comments: Both studies were conducted in the same single center (Navy Military Hospital, Sanya, Hainan Province) with single racial group. Thus, extrapolation of study conclusions beyond this one center, and especially, to other geographical regions and/or different ethnic groups maybe limited.

The clinical trial report for Study ABMO2 states that “Patients showing poor compliance during the trial and those who did not cooperate were withdrawn and replaced.” In response to the FDA’s query, the sponsor provided the following explanation: “The statement in section 3.7 of the study report is adopted from section 5.5 of the protocol. It appears that the ‘replacement’ of patients was foreseen to compensate for any prematurely discontinued patients by enrolling as many more than the targeted 144 patients. No patients were replaced in a sense that their data was discarded, i.e., all randomized patients were included in efficacy and safety analyses based on the ITT population.”

The following efficacy parameters were evaluated:

- 28-day parasitological cure rate: proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent recrudescence
- Parasite reduction (PR) at 24 hours: percentage of parasites per μL at 24 hours compared to parasite density before the first dose of treatment
- Time to parasite clearance (PCT): time from first dose until first total and continued disappearance of asexual parasite forms which remained for at least a further 48 hours
- Time to fever clearance (FCT): time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature $>37.5^{\circ}\text{C}$ at baseline)
- Anti-gametocyte activity: clearance of existing gametocytes without the need for further anti-malarials

In Study ABMO2, the primary efficacy variables were 28-day parasitological cure rate, PCT, FCT and the secondary variables were PR at 24 hours and anti-gametocyte activity. In Study A023, the primary efficacy variables were 28-day parasitological cure rate, PCT, and PR at 24 hours and the secondary variable was FCT.

Reviewer’s comments: The FDA draft guidance states that “Cure -The complete resolution of clinical signs and symptoms, malaria-related laboratory abnormalities, and elimination of asexual parasites by day 7, with no reoccurrence up to day 28 (+/- 2 days). This definition also includes that a study assessment 48 hours after initiation of therapy demonstrate a decrease in the level of parasitemia to less than 25% of baseline with no clinical deterioration.... Both crude cure rates and rates adjusted by genotypic and phenotypic information should be reported.” Evaluation of FDA-defined cure is not possible due to lack of information on clinical signs and symptoms as well as malaria-related laboratory abnormalities from the sponsor. For both studies, only non-PCR corrected 28-day parasitological cure rate was reported by the sponsor and will be reviewed here. Please refer to microbiological review for more discussion about non-PCR corrected and PCR corrected 28-day parasitological cure rate.

Furthermore, the Society of Critical Care Medicine defines fever as a body temperature of 38.3°C (101°F) or higher. This is evaluated further in Section 3.1.1.4.

Treatment failures were classified into three groups in both studies:

- R-I: clearance of asexual parasitaemia within 7 days, followed by recrudescence
- R-II: marked reduction of asexual parasitaemia but no clearance (asexual parasite counts <25% of baseline within 48 hours after initiation of treatment but no, or only temporary clearance within 7 days).
- R-III: no marked reduction of asexual parasitaemia (asexual parasite counts remain >25% of baseline at 48 hours, or actually rise above baseline levels at 48 hours, without clearance of asexual parasitaemia within 7 days).

Patients with parasitaemia >25% of baseline at 48 hours but clearance within 7 days were counted as responders and not as treatment failures.

Reviewer's comments: The 48 hours parasite clearance is an important indicator of parasitological efficacy. Parasitemia at 48 hours greater than or equal to 25% of count at baseline is further examined in Section 3.1.1.4.

For both studies, Day 1 was defined as the first day of treatment. Day 8 was the last measurement of the first week and Day 29 the last measurement of the 28 day observation period.

Four analysis groups of interest were defined as follows:

- Intent-to-Treat (ITT) population: All randomized patients who received at least one dose of trial medicine. Patients who discontinued before Day 29 and/or received rescue medication were counted as treatment failures
- Evaluable patient for parasite reduction at 24 hours: All patients who at least had asexual parasites recorded at baseline and at 24 hours
- Evaluable patients for 28-day cure rate: Patients whose parasite counts were recorded up to Day 29 or who discontinued due to "Unsatisfactory therapeutic effect" because of recrudescence of *P. falciparum*
- Evaluable patients for fever clearance: Patients who had a body temperature >37.5°C at baseline

The trial population in study ABMO2 consisted of male or female patients aged between 13 and 60 years, with symptomatic, previously untreated *P. falciparum* infection. Subjects with weight < 25 kg or > 75 kg were excluded. The exclusion criteria included *P. falciparum* asexual parasitaemia < 1,000 or > 100,000 per μL . In Study A023, the trial population consisted of patients aged 13 years or more and weighed over 35 kg with acute, uncomplicated malaria. The inclusion criteria included microscopic confirmation of *P. falciparum* or mixed (including *P. falciparum*) infection with parasitaemia >1,000 and <150,000 per μL . Female patients who were breast-feeding or pregnant were excluded from both studies. A block randomization scheme was used to allocate eligible patients in both studies and randomization was stratified by patients' inclusion in the pharmacokinetic part in study ABMO2.

Reviewer's comments: There were some violations to the inclusion and exclusion criteria in both studies, including 17 subjects in Study ABMO2 and 2 subjects in Study A023. This is further discussed in Section 3.1.1.4 of this review.

Study ABMO2 was conducted to show a significantly higher 28-day cure rate for Coartem than for artemether ($P < 0.05$) as well as a significantly lower PCT and FCT for Coartem than for lumefantrine alone. Assuming the 28-day cure rate was at least 90% for Coartem and at most 60% for artemether, the calculated sample size was 48 patients per group to achieve 90% power at a two-sided $\alpha = 0.05$.

In Study A023, Coartem was considered more effective if there was a clinically and statistically significant difference between Coartem and lumefantrine in the PCT or PR at 24 hours ($P < 0.05$). Assuming PCT was 30 hours for Coartem and 54 hours for lumefantrine tablets, the calculated sample size using the Kaplan-Meier method was 50 patients per group to achieve 80% power at a two-sided $\alpha = 0.05$. The 28-day parasitological cure rates were assumed to be 90% or higher, and were also to be considered for the interpretation of clinical efficacy.

The 28-day cure rates, together with the 95% confidence intervals using Pearson-Clopper limits, were calculated for each treatment group in both studies. P-values to test treatment effect on the 28-day cure rates were calculated using Fisher's Exact test. The treatment effect on parasite reduction at 24 hours was tested using a non-parametric Wilcoxon rank-sum test. Time to parasite clearance (PCT) and time to fever clearance (FCT) were analyzed by the Kaplan-Meier method and the treatment effect was tested using the Wilcoxon test. The Cox's proportional hazard regression was also applied to evaluate prognostic influence of selected baseline characteristics on PCT and FCT in Study A023.

Reviewer's comments: A change of analysis method was noted in clinical study report of Study ABMO2. While the sample size computation was primarily based on 28-day cure rate, the sponsor claimed in the protocol that the suggested patient number was sufficient to show significant difference in PCT and FCT between Coartem and lumefantrine alone according to a two-sample T-test. The protocol originally planned to use the two-sample T-test for testing PCT and FCT. The clinical study report stated that the Kaplan-Meier method was more appropriate for "Time to event" data and was actually utilized in final analyses. However, it is unclear whether or not this was decided prior to unblinding of the study. No relevant information is available in the protocol amendment which was largely administrative.

Please note that analysis using the original planned two-sample T-test does not change the qualitative conclusions of the study. Coartem continues to obtain significantly shorter time to parasite and fever clearance compared to lumefantrine.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Study ABMO2

A total of 157 subjects were enrolled and randomized, all received at least one dose of study treatment. There were 36 patients who discontinued the trial before Day 29, 1 (#223) due to withdraw consent, 5 (#71, #138, #159, #169, and #230) due to non-compliance, and 30 due to "Unsatisfactory therapeutic effect". These patients were counted as treatment failures in the Intention-to-treat analysis of the 28-day parasitological cure rate. Parasite reduction at 24 hours was evaluated for 155 patients, excluding 2 patients (#71 and #230) who had no parasite measurements recorded during the trial. The evaluable patient population for 28-day cure rate contained 145 patients, excluding 1 who withdrew consent, 5 who were non-compliant, and 6 (#64, #74, #133, #147, #203, and #211) who received rescue medication because of recrudescence of *P. vivax*. Time to fever clearance was analyzed only for those 106 patients who had a temperature of $>37.5^{\circ}\text{C}$ at baseline. A total of 17 patients did not meet inclusion and exclusion criteria at screening but were still included in all analyses. Table 2 below shows number of subjects discontinued prematurely and numbers included in different analyses.

Reviewer's comments: The sponsor reported that only one patient (Patient #71) did not receive the full 48 hours treatment. According to dataset provided, Patient #71 and #230 in the Coartem group completed 2 and 3 doses, respectively. Both discontinued the study due to non-compliance. The 17 patients with protocol violations are further analyzed in Section 3.1.1.4.

Study A023

A total of 153 subjects were enrolled and randomized, all of whom received at least one dose of study drug. There were 11 patients who discontinued from the study prematurely, including 3 (#1, #2, and #106) who did not receive the full treatment course due to non-compliance or withdraw consent and 1 (#28) who was considered as having a protocol violation for receiving artesunate for *P. vivax* on Day 22. These 4 patients were excluded from the evaluable population for the 28-day cure rate. The other 7 patients (#16, #23, #30, #40, #45, #48, and #53) terminated before Day 29 due to unsatisfactory therapeutic effect but were included in all analyses. Patient #1 did not have parasite count measured at 24 hours and was also excluded from the evaluable population for parasite reduction at 24 hours. Furthermore, 63 patients (28 Coartem, 20 lumefantrine tablets, 15 lumefantrine capsules) were excluded from the evaluable population for fever clearance because they had a temperature of $\leq 37.5^{\circ}\text{C}$ at baseline. There were 2 patients (#24 aged <13 years old, #81 weighted <35 kg) who were considered as having minor protocol violations and were included in all analyses. Table 2 below details the number of subjects discontinued prematurely and numbers included in different analyses.

Table 2 Distribution of Patients in Studies ABMO2 and A023

	Study ABMO2 N=157			Study A023 N=153		
	Coartem	Artemether	Lumefantrine	Coartem	Lumefantrine Tablet	Lumefantrine Capsule
Enrolled/ Randomized	53	52	52	52	51	50
Complete treatment	51*	52	52	51	50	49
Complete until Day 29	50	24	47	50	45	47
Discontinued prematurely Total	3	28	5	2	6	3
For unsatisfactory effect	-	26	4	1	4	2
For non-compliance	3	1	1	1	-	-
For withdraw consent	-	1	-	-	1	1
For protocol violation	-	-	-	-	1	-
Number of Patients in Efficacy Analyses						
ITT (28-day cure rate, PCT)	53	52	52	52	51	50
Evaluable for PR at 24 hours	51	52	52	52	51	49
Evaluable for 28-day cure rate	50	44	51	51	49	49
Evaluable for FCT	38	30	38	24	31	35

*The sponsor reported that only one patient (Patient #71) did not receive the full 48 hours treatment. According to dataset provided, Patient #71 and #230 in the Coartem group completed 2 and 3 doses, respectively.

Selected demographic characteristics and baseline covariates were compared among treatment groups for both studies in Table 3. With the exception of fever and parasite counts in Study A023, differences among the comparative groups were minimal. In Study A023, the Coartem group had less fever and fewer parasites at baseline than the lumefantrine groups. This difference was statistically significant for temperature ($P < 0.05$) but not for parasite density ($P = 0.0697$ for Coartem vs. lumefantrine tablets, $P = 0.1763$ for Coartem vs. lumefantrine capsules). The majority of patients in both studies were young adult males. Body weight, pulse rate, diastolic blood pressure, and systolic blood pressure were comparable among the comparative arms in each study.

Table 3 Demographics and Baseline Characteristics in Studies ABMO2 and A023

	Study ABMO2 N=157			Study A023 N=153		
	Coartem N=53	Artemether N=52	Lumefantrine N=52	Coartem N=52	Lumefantrine Tablet N=51	Lumefantrine Capsule N=50
Gender (N, %)						
Male	43(81%)	45(87%)	44(85%)	45(87%)	41(80%)	39(78%)
Female	10(19%)	7(13%)	8(15%)	7(13%)	10(20%)	11(22%)
Age (year)						
Median	23	21.5	22	24	22	19
Range	13 - 57	13 - 54	13-53	13 - 56	13 - 65	12- 47
Children (12-16)	12(23%)	8(15%)	12(23%)	10(19%)	9(18%)	12(24%)
Adults (>16)	41(77%)	44(85%)	40(77%)	42(81%)	42(82%)	38(76%)
Weight (kg)						
Median	50	50	50	50	50	50
Range	25 – 62	27 – 62	26 - 79	34 - 65	35 - 70	35 - 61
Pulse rate(bpm)						
Median	90	90	92	89.5	96	91
Range	72 – 120	64 – 120	58 - 120	51 – 155	66 – 150	66 - 140
Diastolic blood pressure (/mmHg)						
Median	65	60	60	65	65	60
Range	45 – 110	40 – 100	45 - 90	50 – 90	45 – 97	50 - 90
Systolic blood pressure (/mmHg)						
Median	105	105	105	110	110	105
Range	80 – 140	75 – 140	80 - 135	90 – 135	90 – 140	80 - 180
Temperature (°C)						
Median	38.2	38	38.3	37.45	37.9	38
≤ 37.5	15(28%)	22(42%)	14(27%)	28(54%)	20(39%)	15(30%)
37.5 - 39	25(47%)	19(37%)	22(42%)	18(35%)	17(33%)	22(44%)
≥ 39	13(25%)	11(21%)	16(31%)	6(12%)	14(27%)	13(26%)
Parasite Density (/µL)						
Median	23,479	19,602	26,697	11,778	25,508	23,781
missing	2(4%)	-	-	-	-	-
<5,000	6(11%)	8(15%)	8(15%)	13(25%)	10(20%)	9(18%)
≥ 5,000 but < 15,000	13(25%)	12(23%)	10(19%)	15(29%)	6(12%)	9(18%)
≥15,000 but < 50,000	21(39%)	19(37%)	18(35%)	19(37%)	24(47%)	26(52%)
≥ 50,000	11(21%)	13(25%)	16(31%)	5(10%)	11(22%)	6(12%)

Reviewer's comments: The potential bias due to unequal distribution of fever and parasites at baseline in Study A023 was investigated by the sponsor using a Cox's proportional hazard model. Treatment effect was tested with adjustment for baseline characteristics such as age, gender, weight, body temperature, and parasite level (0 for <5,000 per μL , 1 for $\geq 5,000$ but < 15,000 per μL , 2 for $\geq 15,000$ but < 50,000 per μL , and 3 for $\geq 50,000$ per μL). Additional analysis of efficacy outcomes with respect to baseline parasite density was conducted by the FDA reviewer and is presented in Section 3.1.1.4.

Most patients in Study ABMO2 previously had infections, whereas 7 patients in Study A023 documented malaria infection in the previous 3 months. No concomitant medications or rescue medications were recorded during the ABMO2 trial. During the Study A023 trial, 9 (5.9%) patients received additional anti-malarials and 120 (78.4%) patients received concomitant medications.

3.1.1.3 Efficacy Results

Key Efficacy Results

The sponsor's efficacy assessment for both Study ABMO2 and A023 was based on the analyses of 28-day non-PCR corrected cure rate, parasite reduction at 24 hours, as well as time to parasite and fever clearance.

Study ABMO2

Table 4 summarizes the key efficacy results for Study ABMO2. The 28-day parasitological cure rate was statistically higher in the Coartem group than the artemether monotherapy group ($P < 0.001$). For patients who completed the 28 day trial period, all of the 50 patients treated with Coartem were cured, whereas 20 patients treated with artemether monotherapy and 4 patients treated with lumefantrine alone had recrudescence of *P. falciparum* (R-I treatment failure). Compare to lumefantrine monotherapy, the Coartem group had a significantly greater parasite reduction at 24 hours and significantly shorter time to parasite and fever clearance.

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Table 4 Key Efficacy Results in Study ABMO2

	Coartem N=53	Artemether N=52	Lumefantrine N=52
28-day parasitological cure rate			
ITT population, N	53	52	52
Cure	50(94.3%)	24(46.2%)	47(90.4%)
Difference [95% CI]*	-	48.2% [32.2%, 63.0%]	4.0% [-7.3%, 16.1%]
P-value	-	<0.001	0.4882*
Evaluable patients, N	50	44	51
Failure	0(-)	20(45.5%)	4(7.8%)
Cure	50(100%)	24(54.5%)	47(92.2%)
Difference [95% CI]*	-	45.5% [30.4%, 61.2%]	7.8% [0.2%, 18.9%]
P-value	-	<0.001	0.1176*
Parasite reduction (PR) at 24 hours			
Evaluable patients, N	51	52	52
Range	29.3 – 100%	84.4 – 100%	Increase- 100%
Median	99.3%	99.9%	78.2%
25 th – 75 th percentile	93.5 – 100%	98.8 – 100%	46.5 – 91.8%
P-value	-	0.0291*	<0.001
Time to parasite clearance (PCT)			
ITT population, N	53	52	52
PCT ≤ 24 hours	16 (30%)	24 (46%)	2 (4%)
PCT > 24 but ≤ 48 hours	30 (57%)	26 (50%)	17 (33%)
PCT > 48 hours	5 (9%)	1 (2%)	33 (63%)
PCT not achieved	2 (4%)	1(2%)	-
Range	24 – 54 hours	18 – 66 hours	24 – 90 hours
Median	30 hours	30 hours	54 hours
25 th – 75 th percentile*	24 – 36 hours	24 – 33 hours	45 – 66 hours
95% CI	[30, 36] hours	[24, 30] hours	[54, 60] hours
P-value	-	0.0275*	<0.001
Time to fever clearance(FCT)			
Evaluable patients, N	38	30	38
FCT ≤ 24 hours	20(53%)	19(63%)	6(16%)
FCT > 24 but ≤ 48 hours	8(21%)	7(23%)	10(26%)
FCT > 48 hours	8(21%)	4(13%)	22(58%)
FCT not achieved	2(5%)	-	-
Range	6 – 126 hours	6 – 144 hours	6 – 234 hours
Median	24 hours	21 hours	60 hours
95% CI	[12, 36] hours	[12, 30] hours	[48, 66] hours
P-value	-	0.3266*	<0.001

P-values to test treatment effect on the 28-day cure rates were calculated using Fisher’s Exact test. The treatment effect on parasite reduction at 24 hours was tested using a non-parametric Wilcoxon rank-sum test. The treatment effect on time to parasite clearance (PCT) and time to fever clearance (FCT) were tested using the Wilcoxon test.

*Reviewer’s calculation based on datasets as follows:

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 \\Fdswa150\nonectd\N22268\R_019\2008-06-05\crt\datasets\ABM02\Customized data\derived\ a_eff.xpt

Reviewer's comments: Patient #71 and #230 who had no parasite measurement recorded during the entire trial were excluded from the analysis of parasite reduction at 24 hours. They were censored at 0 hour in the sponsor's analysis of time to parasite clearance. Analysis excluding these 2 subjects gives the same result. Patient #71 and #230 also had their last temperature measured at 24 and 48 hours, respectively, leading to censored observations in the analysis of time to fever clearance.

There is a mistake in the sponsor's dataset named 'A_pc.xpt', where no parasite records for Patient #120 were listed at 0, 6, 12, 18 hours and his baseline and 24 hour parasite counts were both listed as 52,657 per μL . In response to the FDA's query, the sponsor provided the following clarification:

For subject no. 120 in Study ABMO2 there is a data entry error in the Study database. While the date and time of first dose is entered as 25-Jul-94, 14:00 on the paper CRF, the date and time of first dose intake in the clinical database is 24-Jul-94, 14:00. The 'hours since first dose'(variable hrs_1n) in the dataset a_pc was calculated using this incorrect day of first dose of study drug. As a consequence the pre-treatment parasite count, correctly dated 25-Jul-94, 14:00 appears to be assessed 24 hours after the first intake of study drug (incorrectly entered as 24-Jul-1994, 14:00 in the database). All values for variable hrs_1n are spuriously incremented by 24 hours for that patient, i.e. 0, 6, 12, 18 hours parasite counts are labeled as 24, 30, 36, and 42 hours counts.

This mistake did not have had an impact on any data analysis performed for the Study Report as the allocation of assessment data to study time points was based on the visit schedule preprinted on the CRFs rather than on time points calculated from the date and time of first dose. For this reason, 'P. falc. asexual form baseline value' (variable asexb1n in dataset a_pc) is correctly populated with the pre-treatment parasite count of 52'657 / μL .

Please note that this patient belongs to the artemether treatment arm which is not included in any of the data tables or listings of the pooled analysis submitted with the Clinical Overview.

Study A023

The 28-day parasitological cure rate was slightly higher in the Coartem group than either formulation of lumefantrine; however, these differences were not statistically significant (Table 5). Seven of the 149 evaluable patients were not cured by Day 28, all of whom had reappearance of parasites before Day 29 and were judged as R-I type treatment failures.

Patients treated with Coartem had significantly greater and quicker reduction in parasite counts than those treated with lumefantrine tablets or capsules. Time to fever clearance was significantly lower for patients on Coartem than for those on lumefantrine tablets, but the difference between Coartem and lumefantrine capsules was borderline.

Table 5 Key Efficacy Results in Study A023

	Coartem N=52	Lumefantrine Tablet N=51	Lumefantrine Capsule N=50
28-day parasitological cure rate			
ITT population N	52	51	50
Cure	50(96.2%)	45(88.2%)	47(94.0%)
Difference [95% CI]*	-	7.9% [-3.0%, 20.7%]	2.2% [-7.9%, 13.2%]
P-value	-	0.160	0.675
Evaluable patients N	51	49	49
Failure	1(2.0%)	4(8.2%)	2(4.1%)
Cure	50(98%)	45(91.8%)	47(95.9%)
Difference [95% CI]*	-	6.2% [-3.4%, 17.7%]	2.1% [-6.8%, 12.2%]
P-value	-	0.2	0.614
Parasite reduction (PR) at 24 hours			
Evaluable patients N	52	51	49
Range	63.1 – 100%	Increase- 100%	Increase – 100%
Median	99.9%	78.7%	86.7%
25 th – 75 th percentile	99 – 100%	53.9 – 95.9%	60.6 – 95.3%
P-value	-	<0.001	<0.001
Time to parasite clearance (PCT)			
ITT population N	52	51	50
PCT ≤ 24 hours	21(40.4%)	1 (2.0%)	2 (4.0%)
PCT > 24 but ≤ 48 hours	28 (53.8%)	25 (49.0%)	20 (40.0%)
PCT > 48 hours	2 (3.8%)	24 (47.1%)	27 (54.0%)
PCT not achieved	1 (1.9%)	1 (2.0%)	1 (2.0%)
Range	12 – 66 hours	24 – 84 hours	24 – 108 hours
Median	30 hours	48 hours	54 hours
25 th – 75 th percentile*	24 – 36 hours	42 – 60 hours	42 – 66 hours
95% CI	[24, 30] hours	[42, 60] hours	[48, 60] hours
P-value	-	<0.001	<0.001
Time to fever clearance(FCT)			
Evaluable patients N	24	31	35
FCT ≤ 24 hours*	15(62%)	9(29%)	13(37%)
FCT > 24 but ≤ 48 hours*	4(17%)	8(26%)	8(23%)
FCT > 48 hours*	5(21%)	12(39%)	13(37%)
FCT not achieved*	-	2(6%)	1(3%)
Range	0 – 90 hours	0 – 120 hours	0 – 168 hours
Median	21 hours	36 hours	36 hours
95% CI	[12, 24] hours	[30, 54] hours	[18, 54] hours
P-value	-	0.0297	0.0992

P-values to test treatment effect on the 28-day cure rates were calculated using Fisher’s Exact test. The treatment effect on parasite reduction at 24 hours was tested using a non-parametric Wilcoxon rank-sum test. The treatment effect on time to parasite clearance (PCT) and time to fever clearance (FCT) were tested using the Wilcoxon test.

* Reviewer’s calculation based on dataset:

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Reviewer's comments: The results listed above are consistent with the results from the sponsor's study report. This reviewer calculated the number and percentage of patients in each FCT category according to the data provided.

Because of the unequal distribution of parasite density at baseline, the sponsor performed a Cox's proportional hazard regression to evaluate the possible effect of baseline parasite density on PCT or FCT. After adjusting for baseline characteristics such as age, gender, weight, body temperature, and parasite level (0 for <5,000 per μ L, 1 for $\geq 5,000$ but < 15,000 per μ L, 2 for $\geq 15,000$ but < 50,000 per μ L, and 3 for $\geq 50,000$ per μ L), the treatment effect on PCT between Coartem and lumefantrine formulations remained highly significant ($p < 0.001$). Likewise, after adjusting for baseline characteristics, Coartem was significantly better in FCT than lumefantrine tablets or capsules ($p < 0.05$). The FDA analysis was slightly different where baseline parasite level was included as a categorical instead of ordinal variable. The conclusions drawn, however, are the same for both PCT and FCT. The FDA's analysis of key efficacy results by baseline parasite level is presented in Section 3.1.1.4.

Other Efficacy Results

Study ABMO2 had a total of 14 patients with gametocytes detected in the blood sample, including 5 (3 on artemether and 2 on lumefantrine) at baseline and 9 (2 on Coartem, 2 on artemether and 5 on lumefantrine) with first occurrence after the initial dose.

Anti-gametocyte activity was not a planned efficacy outcome in Study A023; however, it was reported that a total of 21 patients had gametocytes forms detected in the blood sample, 8 (4 on Coartem, 3 on lumefantrine tablets, and 1 on lumefantrine capsules) at baseline and the other 13 (2 on Coartem, 5 on lumefantrine tablets, and 6 on lumefantrine capsules) had first occurrence within 72 hours of initial dose.

3.1.1.4 Additional Analyses

The following analyses were performed by the FDA statistical reviewer.

Assessment of Post Treatment Parasitemia

Post treatment parasitemia for evaluable patients (155 in Study ABMO2, 152 or 151 in Study A023) was assessed by change from baseline in parasite counts at 24 and 48 hours after the start of treatment (Table 6). No early treatment failures indicated by parasitemia at 48 hours greater than or equal to 25% of count at baseline was observed in the Coartem group.

In Study ABMO2, six patients treated with lumefantrine had an increase in parasite count compared to baseline; 5 (#61, #113, #139, #154, and #168) at 24 hours since first intake of study drug and 2 (#70 and #154) at 48 hours but reached clearance within 7 days. Patient #154 had reappearance of *P. falciparum* forms by Day 29. Three patients (#113, #128, and #135) on lumefantrine had a reduction of <75% of baseline at 48 hours.

In Study A023, parasite count was assumed to be 0 for patients whose 48 hours records were missing but showed evidence of clearance without recrudescence. This included 15 patients (#5, #19, #33, #36, #37, #41, #43, #44, #57, #76, #95, #99, and #127) on Coartem, 2 patients (#29, #38) on lumefantrine tablets, and 2 patients (#21, #130) on lumefantrine capsules. Their parasites were all cleared within 30 hours and no recrudescence was observed until Day 29. At 24 hours after initial dose, 3 patients (#88, #128, #153) treated with lumefantrine tablets and 6 patients (#6, #18, #48, #49, #93, #108) treated with lumefantrine capsules had a higher parasite count compared to baseline. Patient #6 also had parasitemia at 48 hours greater than its baseline count, but all nine were cleared of parasites within 4 days. Patient #143 on lumefantrine tablets and Patient #40 on lumefantrine capsules had a reduction <75% compared to baseline. Patient #2 who had parasite measured only at 0, 6, 12, 18, and 24 hours was excluded from the 48 hours analysis.

Table 6 Assessment of Post-dosing Parasitemia in Studies ABMO2 and A023

Time since first dose	Parasite Count compared to baseline	Study ABMO2 N=157			Study A023 N=153		
		Coartem	Artemether	Lumefantrine	Coartem	Lumefantrine Tablet	Lumefantrine Capsule
24 hours	N [@]	51	52	52	52	51	49
	Increase	0	0	5	0	3	6
	Reduction	51	52	47	52	48	43
	<75%	2(3.9%)	0(-)	20(42.6%)	1(1.9%)	19(39.6%)	9(20.9%)
	>=75%	49(96.1%)	52(100%)	27(57.4%)	51(98.1%)	29(60.4%)	34(79.1%)
48 hours	N ^{@@}	51	52	52	52	50	49
	Increase	0	0	2	0	0	1
	Reduction	51	52	50	52*	50*	48*
	<75%	0(-)	0(-)	3(6.0%)	0(-)	1(2%)	1(2.1%)
	>=75%	51(100%)	52(100%)	47(94.0%)	52(100%)	49(98%)	47(97.9%)

[@] Excluding 2 patients on Coartem (#71 and #230) who had no parasite records in Study ABMO2 and 1 patient on lumefantrine capsule (#1) who had no parasite record at 24 hours in Study A023

^{@@} Excluding 2 patients on Coartem (#71 and #230) who had no parasite records in Study ABMO2, 1 patient on lumefantrine capsule (#1) and 1 patient on lumefantrine tablet (#2) who had no parasite record at 48 hours in Study A023

* Including 15 patients on Coartem (#5, #9, #14, #19, #33, #36, #37, #41, #43, #44, #57, #76, #95, #99, #127), 2 patients on lumefantrine tablets (#29, #38), and 2 patients on lumefantrine capsules (#21, #130) whose records were missing but assumed to be 0 at 48 hours.

Assessment of Patients with Severe Disease

Table 7 contains key efficacy results for severe case patients who either had a body temperature $\geq 38.3^{\circ}\text{C}$ or a parasite count $\geq 100,000$ *per* μL at baseline. Seventy-nine (50%) patients in Study ABMO2 and 56 (37%) patients in Study A023 were included in this evaluation. Patients on Coartem had a higher 28-day cure rate than those on artemether (100% vs 47.8% for evaluable patients in Study ABMO2) and greater parasite reduction at 24 hours than those on lumefantrine (99.1% vs 79.2% for Study ABMO2; 99.9% vs 76% or 84.1% for Study A023). Compared to patients treated with lumefantrine, those on Coartem had shorter time to parasite clearance (36 hours vs 60 hours for Study ABMO2; 30 hour vs 57 hours for Study A023) and shorter time to fever clearance (24 hours vs 57 hours for Study ABMO2; 24 hours vs 42 or 36 hours for Study A023). Overall, results from patients with either a body temperature $\geq 38.3^{\circ}\text{C}$ or parasite count $\geq 100,000$ *per* μL at baseline showed similar efficacy as those from the complete patient population.

Table 7 Results for Patients with Severe Disease in Studies ABMO2 and A023

	Study ABMO2 N=79			Study A023 N=56			
	Coartem	Artemether	Lumefantrine	Coartem	Lumefantrine Tablet	Lumefantrine Capsule	
28-day parasitological cure rate							
ITT population	N	26	26	27	13	21	22
Cure		25(96.2%)	11(42.3%)	25(92.6%)	12(92.3%)	19(90.5%)	20(90.9%)
Evaluable	N	25	23	26	13	20	22
Failure		0(-)	12(52.2%)	1(3.8%)	0(-)	1(5%)	2(9.1%)
Cure		25(100%)	11(47.8%)	25(96.2%)	12(92.3%)	19(95.0%)	20(90.9%)
Parasite reduction (PR) at 24 hours							
Evaluable	N	26	26	27	13	21	22
Median		99.1%	99.6%	79.2%	99.9%	76%	84.1%
Time to parasite clearance (PCT)							
ITT population	N	26	26	27	13	21	22
Median		36 hours	30 hours	60 hours	30 hours	57 hours	57 hours
Time to fever clearance (FCT)							
Evaluable	N	25	23	26	13	20	21
Median		24 hours	18 hours	57 hours	24 hours	42 hours	36 hours

Assessment of Protocol Violation in Study ABMO2

A total of 17 patients in Study ABMO2 did not meet the inclusion and exclusion criteria at screening but were still included in the sponsor's analyses, including 3 who had a temperature > 40.5°C, 1 who had a glucose < 2.2 mmol/L, 1 who had a weight >75 kg, and 12 who had parasite density >100,000/uL. All were males except one in the artemether group. An analysis of patients with or without a protocol violation was conducted and overall efficacy results from the 17 patients with protocol violation were analogous to those 140 patients without protocol violations

Assessment of Baseline Parasite Imbalance in Study A023

In study A023, there was an imbalance in the baseline parasite densities for the Coartem and lumefantrine (tablets and capsules) arms. The lower baseline count for Coartem compared to the other two treatment arms (median values of 11,778/ μ L versus 25,508 and 23,781/ μ L) may have introduced a bias which led to improved results in the Coartem arm. In order to assess the impact of this imbalance, the following analyses were conducted:

- 1) Summary of key efficacy outcomes by treatment group and by baseline parasite level (<5,000 *per* μ L, \geq 5,000 but < 15,000 *per* μ L, \geq 15,000 but < 50,000 *per* μ L, and \geq 50,000 *per* μ L);
- 2) Cox's regression analysis of time to parasite and time to fever clearance. Parameters included in the model are treatment, age, gender, weight, body temperature, and parasite density level as a categorical variable;
- 3) Cox's regression analysis of time to parasite clearance including treatment, baseline parasite density (continuous, ordinal, or categorical variable), and their interactions in the model.

The effects of treatment and baseline parasite density were statistically significant in all of the above models. There was no statistically significant interaction between treatment group and baseline parasite density. Table 8 contains the 28-day parasitological cure rates by treatment group and by baseline parasite level (<5,000 *per* μ L, \geq 5,000 but < 15,000 *per* μ L, \geq 15,000 but < 50,000 *per* μ L, and \geq 50,000 *per* μ L). In general, results were similar among the treatment groups. Table 9 summarizes parasite reduction at 24 hours and time to parasite or fever clearance by baseline parasite density. The median parasite reduction at 24 hours was 100% regardless of baseline parasite density for patients treated with Coartem and was generally higher than patients on lumefantrine treatment. As the baseline parasite density increased, the median time to parasite clearance increased in all 3 treatment arms. For patients with the same baseline parasite level, the Coartem therapy led to shorter time to parasite clearance compared to either lumefantrine formulation. Time to fever clearance showed a similar pattern in that Coartem had a shorter time to fever clearance than the lumefantrine arms for all levels of baseline parasite density. Overall, the analysis of the primary efficacy variables with respect to different baseline parasite density showed similar pattern as the primary analysis of the whole population.

Table 8 28-day Cure Rate by Baseline Parasite Density in Study A023
Number of Cured/Total Subjects, n/N (%)

	Baseline Parasite Density (/μL)	Coartem	Lumefantrine Tablet	Lumefantrine Capsule
ITT population	<5,000	N=52 13/13(100%)	N=51 7/10(70%)	N=50 7/9(77.8%)
	≥ 5,000 but < 15,000	15/15(100%)	5/6(83.3%)	8/9(88.9%)
	≥15,000 but < 50,000	18/19(94.7%)	23/24(95.8%)	26/26(100%)
	≥ 50,000	4/5(80%)	10/11(90.9%)	6/6(100%)
Evaluable patients	<5,000	N=51 13/13(100%)	N=49 7/8(87.5%)	N=49 7/8(87.5%)
	≥ 5,000 but < 15,000	15/15(100%)	5/6(83.3%)	8/9(88.9%)
	≥15,000 but < 50,000	18/19(94.7%)	23/24(95.8%)	26/26(100%)
	≥ 50,000	4/4(100%)	10/11(90.9%)	6/6(100%)

Table 9 Parasite Reduction at 24 Hours, Time to Parasite Clearance, and Time to Fever Clearance by Baseline Parasite Density in Study A023

	Baseline Parasite Density (/μL)	Coartem		Lumefantrine Tablet		Lumefantrine Capsule	
		N	Median	N	Median	N	Median
Parasite reduction (PR) at 24 hours (%) Evaluable patients	<5,000	13	100	10	90.0	8	80.0
	≥ 5,000 but < 15,000	15	100	6	80.0	9	100
	≥15,000 but < 50,000	19	100	24	70.0	26	80.0
	≥ 50,000	5	100	11	80.0	6	100
Time to parasite clearance (PCT) (hours) ITT population	<5,000	13	24	10	36	9	39
	≥ 5,000 but < 15,000	15	30	6	45	9	48
	≥15,000 but < 50,000	19	30	24	54	26	60
	≥ 50,000	5	30	11	60	6	59.8
Time to fever clearance (FCT) (hours) Evaluable patients	<5,000	3	17.9	6	54.0	6	24.0
	≥ 5,000 but < 15,000	11	24.0	5	29.8	6	30.0
	≥15,000 but < 50,000	9	23.9	15	30.0	20	36.0
	≥ 50,000	1	24.0	5	66.0	3	36.0

3.1.2 Supportive 4-dose Studies

A number of studies of the 4-dose regimen of Coartem were performed between 1993 and 2000, including 2 (Study ABMO1 and A009) which were open, non-comparative studies to confirm efficacy and tolerability, 1 (Study A012) which was a double-blind, parallel-group, dose optimization study to compare the 4-dose regimen with two lower doses, and 10 comparative studies which compared the 4-dose regimen of Coartem with other antimalarials. All tablets were administered over 48 hours (hours 0, 8, 24, 48). These studies were submitted as study reports only without efficacy data sets. Table 10 presents the design of the 10 comparative studies, the number of patients treated and the countries where they were conducted. Table 11 shows efficacy results from these supportive studies. The results vary greatly across these studies and Table 9 is broken down into three sections. The first section of Table 11 reports the 4 studies where Coartem lead to higher 28 day cure rates compared to the comparator. Parasite reduction at 24 hours was also higher. The next section shows the studies where Coartem had similar results as the comparator. In the last section Coartem had lower 28 day cure rates compared to the comparator. Note that parasite reduction at 24 hours was high in these studies. While the safety of 4-doses of Coartem was further supported by these studies, its superiority to various comparators in 28-day cure rate could not be established. These studies were conducted in areas of high transmission, as compared to Studies ABMO2 and A023, which were conducted in China.

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Table 10 Summary of Supportive Studies with 4-Dose Coartem Regimen

Study No.	Study Design / Objective	No. of patients		Population	Year/ Study Location
		Coartem	Comparator		
A003	Open, randomized, parallel group efficacy/safety Coartem vs quinine	111	Quinine: 108	Children (2-12 yr)	1995-96 Thailand
A004	Double-blind, randomized, parallel group efficacy/safety Coartem vs mefloquine	126	Mefloquine: 126	Adults Children (≥13 yr)	1995-96 Thailand
A005	Open, randomized, parallel group efficacy/safety Coartem vs quinine/fansidar	12	Quinine/ Fansidar: 11	Adults	1996-97 UK
A007	Double-blind, randomized, parallel group efficacy/safety Coartem vs chloroquine	89	Chloroquine: 90	Adults	1996-97 India
A008	Open, randomized, parallel group efficacy/safety Coartem vs MAS	309	MAS: 308	Adults Children (≥5 yr)	1995-96 Thailand
A010	Double-blind, randomized, parallel group efficacy/safety Coartem vs fansidar	144	Fansidar: 143	Children (≤5 yr)	1996-97 Gambia
A011	Open, randomized, parallel group efficacy/safety Coartem vs chloroquine	130	Chloroquine: 130	Children (≤5 yr)	1996 Tanzania
A014	Double-blind, randomized, parallel group efficacy/safety Coartem vs halofantrine	51	Halofantrine: 52	Adults (≥17 yr)	1996-97 Europe
AIC04	Open, randomized, parallel group efficacy/safety Coartem vs chloroquine	36	Chloroquine: 36	Adults	2000 Senegal
AIC04	Open, randomized, parallel group efficacy/safety Coartem vs fansidar	30	Fansidar: 30	Adults	2000 Cameron

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Table 11 Efficacy Results from Supportive Studies with 4-Dose Coartem Regimen

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
A007	Coartem	89	-	-	69.7%	36 hr	98.8%	18 hr
	Chloroquine	90	-	-	16.7%	60 hr	70.7%	27 hr
A011	Coartem	130	83.8%	84.1%*	-	-	97.8%	-
	Chloroquine	130	26.2%	8.6%*	-	-	59%	-
AIC04 Senegal	Coartem	36	-	100%	-	1 day**	94.3%	-
	Chloroquine	36	-	63.9%	-	2 days**	54.7%	-
AIC04 Cameroon	Coartem	30	-	93.3%	-	2 days**	76.8%	-
	Fansidar	30	-	53.3%	-	7 days**	49.2%	-
A003	Coartem	111	-	-	43.2%	40 hr	98.6%	52 hr
	Quinine	108	-	-	47.2%	77 hr	67.3%	88 hr
A014	Coartem	51	-	-	76.5%	32 hr	99.7%	24 hr
	Halofantrine	52	-	-	78.8%	48 hr	89.6%	32 hr
A004	Coartem	126	-	-	62.7%	43 hr	98.6%	32 hr
	Mefloquine	126	-	-	77.8%	66 hr	76.1%	54 hr
A005	Coartem	12	-	-	58.3%	36 hr	99.2%	-
	Quinine/ Fansidar	11	-	-	72.7%	69 hr	87.6%	-
A008	Coartem	309	-	-	73.1%	-	100%	-
	MAS	308	-	-	84.1%	-	100%	-
A010	Coartem	144	-	77.1%	-	-	99.2%	-
	Fansidar	143	-	87.4%	-	-	92.5%	-

*Based on evaluable population

** Unclear from the study reports for AIC04 Senegal and AIC04 Cameroon whether mean or median PCT was represented.

Studies showing higher cure associated with Coartem than comparator

Study A007 was a two center, double-blind, randomized, parallel-group study comparing oral Coartem versus oral chloroquine in adult patients in India. All efficacy endpoints were statistically significantly better for Coartem than for chloroquine (P<0.001 for 28-day cure rates, time to parasite clearance, parasite reduction at 24 hours; P=0.0456 for time to fever clearance). No R-II or R-III failures were seen for Coartem, whereas on chloroquine 8 patients developed R-II and 4 patients had R-III failures. Note only 15 (16.7%) patients in the chloroquine group completed the trial mainly due to unsatisfactory therapeutic effect of chloroquine treatment and requirement of other anti-malarials. The trial was terminated as the response to chloroquine was suspected to have decreased to levels too low to permit its use as comparator.

Study A011 evaluated a pediatric strength of Coartem which was half of the adult dosage and consisted of 10mg artemether plus 60mg lumefantrine per tablet. Coartem was compared to chloroquine in small children aged 1 to 5 years and weighed 5 to 25 kg in Tanzania. Coartem as 4 doses of 1, 2, 3, or 4 pediatric tablets were given according to body weight (i.e. 5-10 kg, 10-15 kg, 15-20 kg, 20-25 kg) over 48 hours. Both the 7 and 14 day cure rates showed that Coartem was statistically significantly superior to

chloroquine ($P < 0.001$). By 24 hours the median parasite reduction with Coartem was 97.8% and 59% for chloroquine; 20.8% of children on Coartem had a negative slide but only 2.3% on chloroquine. By Day 3 the respective proportions were 70% versus 8.5%. Note 23 (17.7%) of children on Coartem and 94 (72.3%) children on chloroquine discontinued the trial. Other anti-malarials were given to 25 children on Coartem and 93 children on chloroquine during the trial either for unsatisfactory therapeutic effect or recurrent parasitaemia.

Study AIC04 in Senegal (29/09/2000 to 15/10/2000) found that the 14-day cure rate was 100% in Coartem versus 63.9% in chloroquine with difference statistically significant in favor of Coartem. Parasite clearance was more rapid and extensive following Coartem therapy compared to chloroquine.

Study AIC04 in Cameroon (17/02/2000 to 30/05/2000) found the 14-day cure rate was 93.3% in Coartem versus 53.3% in fansidar with difference statistically significant in favor of Coartem. Parasite clearance was more rapid and extensive following Coartem therapy compared to fansidar.

In all of the above studies, Coartem proved both highly effective and well-tolerated in the treatment of *P. falciparum* malaria.

Studies showing similar cure between Coartem and comparator

Study A003 was a 3-center study comparing Coartem versus quinine in children aged 2 to 12 years in Thailand. Coartem as doses of 1, 2, 3, or 4 tables was given according to body weight (i.e. < 20 kg, 21-30 kg, 31-40 kg, >40 kg) over 48 hours. While parasite reduction and clearance were significantly better in Coartem, the 28-day cure rates were similarly low for both treatments. A large difference among centers for the 28-day cure rates was also noted.

Study A014 compared Coartem with halofantrine in adults in Europe. While efficacy parameters such as parasite reduction at 24 hours and time to parasite clearance were significantly better for Coartem ($P < 0.001$), the 28-day cure rate was similar to halofantrine. Seven out of the 8 patients on Coartem who had reappearance of parasites were considered non-immune. Note one interim analysis of 59 patients was conducted during the trial, with drug codes available to Novartis personnel in Basel. After the interim analysis a further 44 patients were recruited.

As reported by the sponsor, these two studies showed that Coartem was similar to its comparators in the treatment of *P. falciparum* malaria. No side effects and safety issues related to administration of Coartem were identified.

Studies showing lower cure associated with Coartem than comparator

Study A004 compared Coartem versus mefloquine in adolescents and adults in Thailand. This trial found that the 28-day cure rate was statistically significantly better for

mefloquine than for Coartem ($P=0.02$), whereas all other efficacy endpoints were better for Coartem ($P<0.001$).

Study A005 was a comparative trial of oral Coartem versus quinine followed by fansidar in adults in Europe. Only 23 of the planned 100 patients were recruited into this trial, out of which 9 were judged by the investigator to be “non-immune”. The 28-day cure rate was lower for Coartem than for quinine/fansidar. Coartem was found to reduce parasite much faster and complete clearance was reached within less than 2 days after the start of treatment. This study was closed ahead of schedule because of low enrollment and results should be interpreted with caution due to limited amount of information.

Study A008 was a long-term study with 9 weeks follow up to compare Coartem versus MAS (artesunate and mefloquine) in children and adults in Thailand. The objective was to determine if Coartem was equivalent to MAS based on 63-day cure rate. Coartem as doses of 1, 2, 3, or 4 tablets was given according to body weight (i.e. < 20 kg, 21-30 kg, 31-40 kg, >40 kg) over 48 hours. Both treatments cleared parasite rapidly. The 63-day cure rates for the ITT population were not statistically significantly different between the two arms ($P=0.187$). In the evaluable patients, the 63-day cure rates of 75% for Coartem and 87.8% for MAS could not be assumed equivalent. MAS also produced numerically higher 28-day cure rates than Coartem.

Study A010 compared Coartem versus fansidar in small children aged 1 to 5 years and weighed >6 kg in The Gambia, West Africa. Children with body weight < 15 kg received 1 tablet whereas those with body weight ≥ 15 kg received 2 tablets of Coartem at each dose. Coartem was significantly superior to fansidar with respect to the proportion of evaluable children with a negative slide on Day 4 (100% for Coartem and 93.4% for fansidar, $P=0.003$). Although Coartem cleared parasites more rapidly than fansidar, the 14-day cure rate showed more patients on Coartem failed the treatment. The difference, however, was not statistically significant.

While safety of Coartem was further supported in the above studies, its superiority to comparative arm in 28-day cure could not be established, especially for those non-immune patients and multi-drug resistant areas.

3.2 Evaluation of Safety

Study ABMO2

At the screening visit, all 157 patients had fever, 153 had chills, 32 had headache, 22 had dizziness, 18 had rigors, 14 had general aching, 3 had backache, and 1 had abdominal pain and 1 had stomach ache. Most symptoms were recorded as "still present" at the trial start 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.

In total 3 patients had "signs and symptoms of complicated/severe malaria" at the start or during the trial. Patient #91 from the artemether group had enlarged spleen from baseline until Day 8. Patient #59 from the Coartem group had enlarged liver from baseline until Day 8 and Patient #79 from the lumefantrine group had enlarged liver during whole trial period. None of the patients treated with Coartem had any "other signs/physical findings not related to malaria" during the trial. This was recorded for 5 patients treated with artemether and 6 patients treated with lumefantrine. Thirty patients were recorded having a cold, 11 in the Coartem group, 9 in the artemether group, and 10 in the lumefantrine group.

During the trial two adverse experiences were recorded: patient #214 treated with lumefantrine had diarrhoea on Days 3, 4 and 5 and purulent and bloody stool on Days 4 and 5. None of the patients had a serious adverse experience or discontinued due to an adverse experiences and/or laboratory abnormalities. There was no death reported during the trial.

Reviewer's comments: The above is just a summary of the safety results presented by the sponsor in the study reports. For details, please see the medical officer's review.

Study A023

All adverse events (AEs) occurred during the trial were mild or moderate. At baseline, a total of 146 patients presented AEs or malaria symptoms with the most frequent ones being headache (>84%), fatigue (>76%), anorexia (>62%), rigors (>50%), dizziness (>34%), nausea (>32%), and sleep disorder (>30%). These malaria symptoms disappeared within 2-4 days. Twenty-five patients (7 on Coartem, 9 on lumefantrine tablets, and 9 on lumefantrine capsules) reported at least one AE starting or worsening after baseline. Anorexia, abdominal pain and headache were each seen in two patients (3.8%) treated with Coartem. All other AEs starting or worsening after baseline were reported for one patient on Coartem. In the lumefantrine tablet group, 5 patients (9.8%) had headache and 3 patients had nausea (5.9%) starting or worsening after baseline. In the lumefantrine capsule group, 3 patients (6%) reported headache starting or worsening after baseline. All other AEs occurred only in one or two patients.

None of the patients had a serious adverse experience or discontinued due to an adverse experiences and/or laboratory abnormalities. There was no death reported during the trial.

Reviewer's comments: The above is just a summary of the safety results presented by the sponsor in the study reports. For details, please see the medical officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Study ABMO2 and A023 were both conducted in a single center in China. Comparisons by race could not be completed as all patients involved were expected to have been of the same race. Table 12 summarizes 28-day parasitological cure rate according to gender and age categories in each treatment group for Study ABMO2 and A023. In general, the conclusions for 28-day cure rate by gender and age were the same as the study population as a whole; the rates for Coartem were higher than for artemether and similar to lumefantrine.

Table 12 28-day Cure Rate by Gender and Age in Studies ABMO2 and A023
Number of Cured/Total Subjects, n/N (%)

		Study ABMO2 N=157			Study A023 N=153		
		Coartem	Artemether	Lumefantrine	Coartem	Lumefantrine Tablet	Lumefantrine Capsule
ITT Population	N	53	52	52	52	51	50
Gender	Male	42/43(97.7)	19/45(42.2)	40/44(90.9)	43/45(95.6)	36/41(87.8)	38/39(97.4)
	Female	8/10(80)	5/7(71.4)	7/8(87.5)	7/7(100)	9/10(90.0)	9/11(81.8)
Age(Years)	12-16	12/12(100)	4/8(50.0)	11/12(91.7)	10/10(100)	8/9(88.9)	11/12(91.7)
	>16	38/41(92.7)	20/44(45.5)	36/40(90.0)	40/42(95.2)	37/42(88.1)	36/38(94.7)
Evaluable Patients	N	50	44	51	51	49	49
Gender	Male	42/42(100)	19/37(51.4)	40/43(93.0)	43/44(97.7)	36/40(90.0)	38/38(100)
	Female	8/8(100)	5/7(71.4)	7/8(87.5)	7/7(100)	9/9(100)	9/11(81.8)
Age(Years)	12-16	12/12(100)	4/7(57.1)	11/12(91.7)	10/10(100)	8/9(88.9)	11/12(91.7)
	>16	38/38(100)	20/37(54.1)	36/39(92.3)	40/41(97.6)	37/40(92.5)	36/37(97.3)

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Median values for parasite reduction at 24 hours, time to parasite and fever clearance for both studies were summarized in Table 13 according to gender and age categories in each treatment group. For both studies, similar results were seen as with the overall population. Coartem showed greater parasite reduction at 24 hours and shorter time to parasite and fever clearance compared to lumefantrine.

Table 13 Parasite reduction, Time to Parasite Clearance, and Time to Fever Clearance by Gender and Age in Studies ABMO2 and A023

	Study ABMO2 N=157						Study A023 N=153					
	Coartem		Artemether		Lumefantrine		Coartem		Lumefantrine Tablet		Lumefantrine Capsule	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Parasite reduction at 24 hours (%)												
Gender												
Male	42	99.2	45	99.9	44	80	45	99.9	41	76.0	38	89.3
Female	9	100	7	100	8	17.5	7	99.7	10	92.4	11	84.7
Age(Years)												
12-16	12	94.2	8	98.8	12	80.0	10	99.9	9	75.0	12	90.7
>16	39	99.4	44	100	40	71.1	42	99.8	42	80.8	37	84.7
Time to Parasite Clearance (hours)												
Gender												
Male	43	36.0	45	30.0	44	60.0	45	30.0	41	48.0	39	48.0
Female	10	24.0	7	24.0	8	48.0	7	30.0	10	48.0	11	59.5
Age(Years)												
12-16	12	36.0	8	30.0	12	54.0	10	29.9	9	48.0	12	48.0
>16	41	30.0	44	24.0	40	60.0	42	30.0	42	53.9	38	54.0
Time to Fever Clearance (hours)												
Gender												
Male	29	24.0	26	21.0	32	60.0	20	15.0	22	33.0	26	36.0
Female	9	12.0	4	18.0	6	48.0	4	39.1	9	60.0	9	36.0
Age(Years)												
12-16	9	12.0	6	12.0	9	66.0	9	24.0	8	30.1	12	42.0
>16	29	24.0	24	24.0	29	54.0	15	17.9	23	42.0	23	30.0

4.2 Other Special/Subgroup Population

Subgroup analysis by baseline parasite density in Study A023 is presented in Section 3.1.1.4.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The results from Studies ABMO2 and A023 submitted to support the use of Coartem for the treatment of acute, uncomplicated malaria suggest that Coartem is superior to artemether or lumefantrine as assessed by the 28-day parasitological cure rate, parasite reduction at 24 hours, time to parasite clearance and time to fever clearance. In Study A023, patients on Coartem had less fever and fewer parasites at baseline. Comprehensive analyses after accounting for baseline parasite imbalance continued to demonstrate a shorter time to parasite and fever clearance for Coartem compared to lumefantrine. For both studies, analysis of patients who had either a body temperature $\geq 38.3^{\circ}\text{C}$ or a parasite count $\geq 100,000$ *per* μL at baseline showed similar overall efficacy in 28-day cure rate, parasite reduction at 24 hours, and time to parasite and fever clearance. Subgroup analysis by gender and age resulted in similar conclusion.

Although Coartem was proved more efficacious than artemether or lumefantrine in both studies, extrapolation of study conclusions is limited by the fact that both were conducted in the same single center in China. The additional 13 studies conducted in other geographic areas supported the safety and quicker time to parasite clearance of 4-doses of Coartem but failed to demonstrate consistently acceptable 28-day cure rates.

5.2 Conclusions and Recommendations

The sponsor's primary and secondary efficacy results support that the combination of artemether and lumefantrine was more effective than either of the constituent compounds used as monotherapy or either formulation of lumefantrine. The combination, Coartem, had a greater 28-day cure rate than artemether and it had greater reduction in parasites at 24 hours and faster fever and parasite clearance times than lumefantrine. The interpretation of results is limited by the fact that they were single center studies, both performed at the same site in China, and only Study ABMO2 included an arm of artemether alone.

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/s/

Lan Zeng
11/24/2008 03:35:43 PM
BIOMETRICS

Karen Higgins
11/24/2008 03:38:32 PM
BIOMETRICS

NDA Number: 22-268

Applicant: Novartis

Stamp Date: 6/27/2008

Drug Name: Coartem

NDA/BLA Type:

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.		x		Individual study index available but no central one to link different studies
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			Only for pooled data from several studies
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

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/s/

Xianbin Li
8/18/2008 03:18:41 PM
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Lan Zeng
8/18/2008 03:23:14 PM
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Karen Higgins
8/21/2008 10:21:58 PM
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