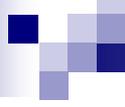


Coartem (artemether 20 mg/ lumefantrine 120 mg) Tablets

Division of Special Pathogen and Transplant Products

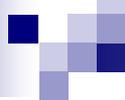
Office of Antimicrobial Products
Office of New Drugs, CDER

December 3, 2008



Coartem Tablets

- Novartis NDA 22-268
- 20 mg artemether/120 mg lumefantrine
- Uncomplicated malaria due to *Plasmodium falciparum* and mixed infections
- 6-dose (3-day) oral regimen, based on weight



Today's Agenda

- Presentation by Novartis
 - Background on malaria
 - Results from clinical studies
- Presentation by FDA
 - Safety and efficacy, selected issues
- Discussion and Questions to the Committee

Considerations

- Fixed-combination drug
 - Types of studies
- Patients studied
 - Adult patients
 - Pediatric patients
 - Studies conducted outside the US
- Endpoints and analyses
 - ITT vs. Evaluable analyses
 - Uncorrected vs. PCR-corrected cure rates
- Safety evaluations, e.g.
 - Neurologic
 - QT prolongation
- PK characteristics
- Activity against parasite
 - *P. falciparum*
 - *P. vivax*
 - Resistance?

Question 1

- Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be effective for the treatment of uncomplicated *Plasmodium falciparum* malaria, including demonstrating the contribution of artemether and lumefantrine to the treatment effect? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

Question 2

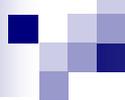
- Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be safe for the treatment of uncomplicated *P. falciparum* malaria? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

Question 3

- Do you consider the data presented for patients co-infected with *P. falciparum* and *P. vivax* sufficient to demonstrate efficacy and safety of Coartem in treating these patients? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional studies do you recommend?

Question 4

- If the answer to numbers 1 and 2 is yes, should any specific post-marketing studies be conducted?



Question 5

- Is there specific efficacy, safety or other information that you would recommend be reflected in the Coartem product labeling?

FDA Review Team

Joette Meyer, PharmD, Cross Discipline Team Leader

Gregory DiBernardo, Project Manager

ONDQA

- Norman Schmuff, PhD, Branch Chief
- Dorota Matecka, PhD
- Shrikant Pagay, PhD

Pharmacology/Toxicology

- William Taylor, PhD, Team Leader
- Owen McMaster, PhD
- Stephen Hundley, PhD
- Rama Dwivedi, PhD
- Terry Miller, PhD

Microbiology

- Shukal Bala, PhD, Team Leader
- Aaron Ruhland, PhD
- Simone Shurland, PhD

Clinical Pharmacology

- Philip Colangelo, PharmD, PhD, Team Leader
- Dakshina Chilakuri, PhD
- Gerlie Geiser, PhD

Clinical

- Elizabeth O'Shaughnessy, MD, Efficacy
- Sue Lim, MD, Safety
- Ozlem Belen, MD, Pediatric Safety

Statistics

- Karen Higgins, PhD, Team Leader
- Lan Zeng, MS
- Xianbin Li, PhD

Project Management

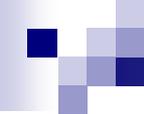
- Diana Willard, CPMS

Division of Scientific Investigations

- Leslie Ball, MD, Branch Chief
- Tejashri Purohit-Sheth, MD, Team Leader
- Susan Thompson, MD

Consultants

- DDMAC
- OSE: DMEPA, DRISK
- PMHS
- QT-IRT
- Division of Neurology
- SEALD



Anti-Infective Advisory Committee

December 3, 2008

Introductory Remarks

Renata Albrecht, M.D.

Clinical Efficacy

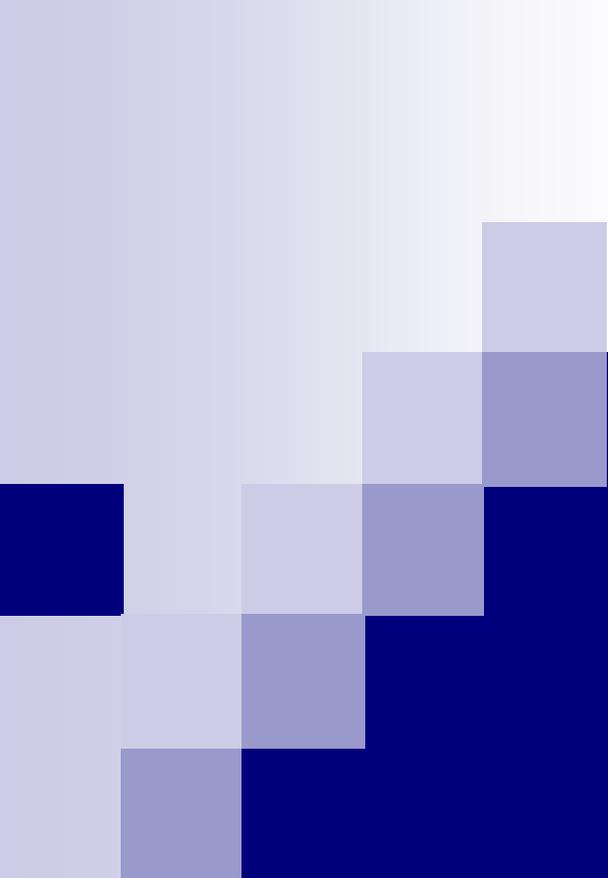
Elizabeth O'Shaughnessy, M.D.

Clinical Safety

Sue Lim, M.D.

Charge to the Committee

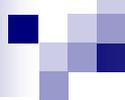
Edward Cox, M.D., M.P.H.



Coartem (artemether 20 mg/ lumefantrine 120 mg) Tablets

Clinical Efficacy

Elizabeth M. O'Shaughnessy, M.D.



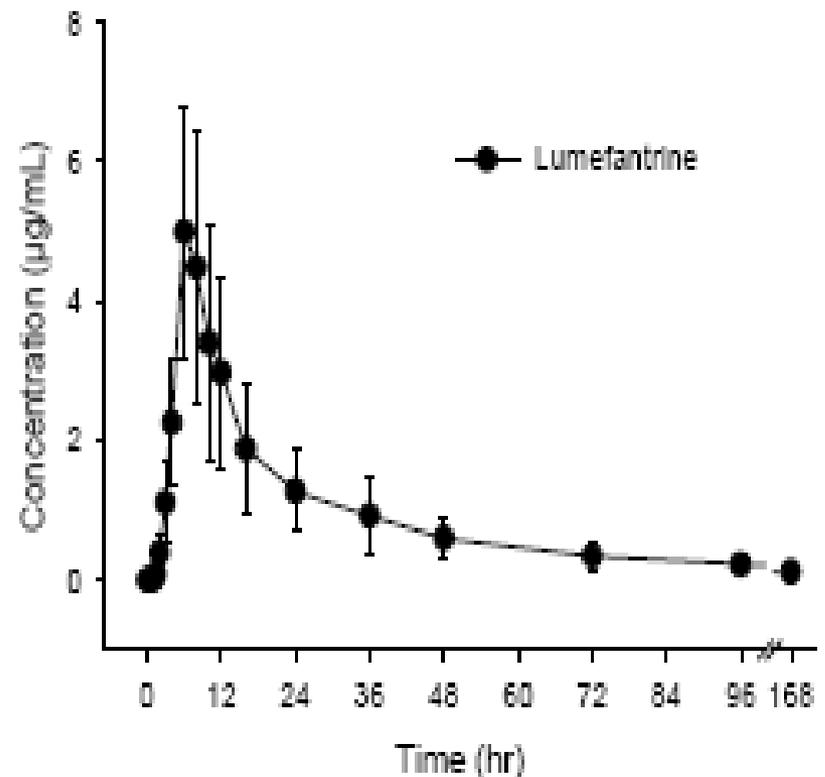
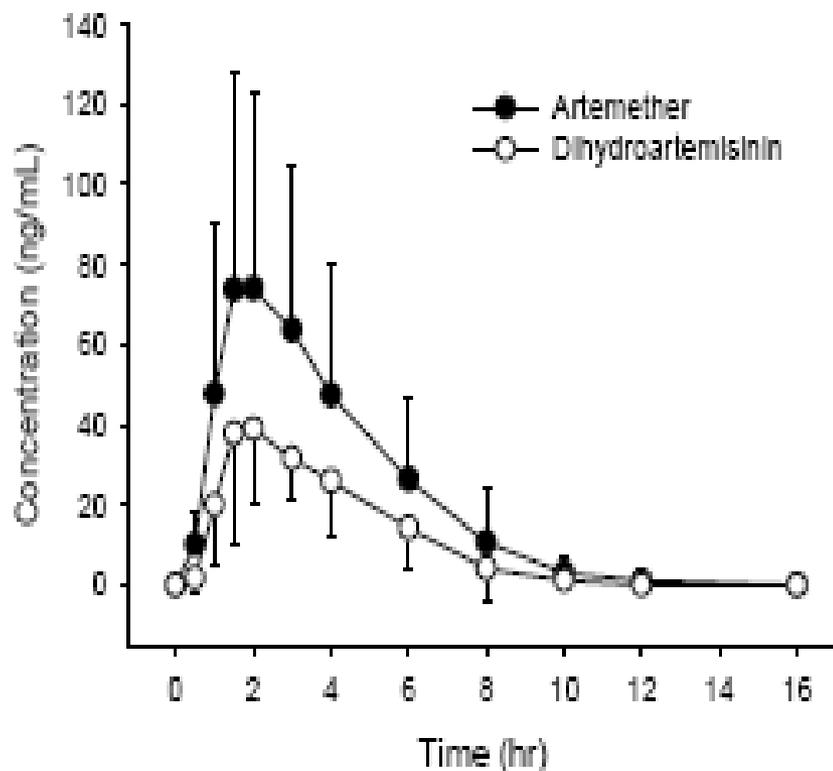
Overview

- Rationale for combination drug
- Brief overview of PK
- FDA approach to the review of the NDA
- Results of four-dose factorial design studies
- Results of six-dose studies
- Summary of efficacy of Coartem

Rationale for the Combination of Artemether and Lumefantrine

- Artemether and Lumefantrine act by different mechanisms of action
- Complimentary PK properties
 - Artemether: T_{\max} ~2 hours; Rapid Elimination ($T_{1/2}$ ~2 hours)
 - Lumefantrine: T_{\max} ~6-8 hours; Slower Elimination ($T_{1/2}$ ~3-6 days)
- Artemether has a rapid onset of action and clears malaria parasites and reduces fever during the first 24-48 hours
- Lumefantrine has a slower onset of action and is effective in preventing recurrence of malaria parasites

Plasma Concentration-Time Profiles: Healthy Subjects



Food Effect

- Food (containing high fat) significantly enhances drug exposure
 - Artemether exposure ↑ 2-fold (AUC)
 - DHA exposure ↑ 2-fold (AUC)
 - Lumefantrine exposure ↑ 16-fold (AUC)
- Subsequent studies in healthy volunteers and 6-dose clinical trials were conducted under fed conditions
- Coartem Tablets will be labeled to be taken with food
 - Children: food (formula, milk, broth)



Clinical Safety and Efficacy

- Eight primary studies
 - 4-dose studies:
 - Two, factorial design: AB/MO2, A023
 - 4-dose vs. 6-dose study
 - One, comparative: A025
 - 6-dose studies:
 - Two, descriptively comparative with MAS: A026, A028
 - One, non-comparative in non-immune travelers: 2401
 - Two, non-comparative in children: A2403, B2303
- Thirteen active controlled 4-dose and 6-dose studies

Design of Studies

■ Inclusion:

- *P. falciparum* and mixed *Plasmodium* infections with *P. vivax*
- Uncomplicated malaria
- Asexual parasite counts of 500/μl to 200,000/μl depending on the study
- Clinical signs and symptoms (other than fever in A2403 and B2303) were not systemically collected

■ Exclusion:

- Patients with signs and symptoms of severe malaria were excluded
- Prior antimalarial drugs for current episode (some studies)

Endpoints

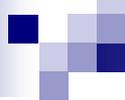
- Primary Endpoint: 28-day cure rate, which included clearance of asexual parasites within seven days without recurrence by day 28
- Secondary Endpoints, included:
 - Parasite Clearance Time (PCT) – in hours
 - Fever Clearance Time (FCT) – in hours
- Additional Endpoints (Early and Late Treatment Failures)

Populations Studied

- Partially immune and non-immune adults
- Children $\geq 5\text{kg}$ (~ 3 months old)
- Geographically diverse populations; China, Thailand, sub-Saharan Africa, South America

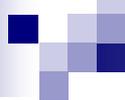
FDA Analysis

- ITT population was used as the primary analysis population, unless otherwise noted
 - Defined in most studies as all randomized subjects who took one dose of study drug
 - The vast majority of subjects had parasitemia at baseline (6/2012 did not have parasitemia)
 - 28-day cure rate was calculated as the percent cured out of all subjects treated
- PCR uncorrected rates are presented



Genotyping by PCR Assay

- Genotyping of paired isolates was performed in two laboratories using different methods for different studies
- Performance characteristics of the assay including quality control were not available for review
- FDA review of efficacy is based on PCR-uncorrected parasitological cure rates



4-Dose Studies

- Early 4-Dose Studies in China
- Factorial Design Studies
- 4-Dose Studies outside China
- 4-Dose vs. 6-Dose

Early 4-Dose Studies in China

- No formal dose finding studies were conducted
- Early studies determined (ITT, PCR-uncorrected) 28-day cure rate:
 - Optimal ratio of artemether to lumefantrine (1:5 vs. 1:6)
 - Three arm study determined the no. of doses and days of treatment
 - 3 doses x 3 days (N=22): **73%**
 - 4 doses x 2 days: (N=20): **80%**
 - 4 doses x 3 days: (N=24): **87%**
 - A second study of the 4-dose x 3 day regimen in 100 children aged 5-14 yrs: **93%**
- Based on these studies, the 4-dose regimen of 80 mg/480 mg (in adults) given at 0, 8, 24, and 48 hours was selected for further study in AB/MO2 and A023

Fixed-Combination Drugs

- 21 CFR 300.50:
 - “Two or more drugs may be combined in a single dosage form when **each component makes a contribution to the claimed effects** and the dosage of each component (amount, frequency, duration) is such that **the combination is safe and effective** for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

Study AB/MO2

ITT Population	Coartem 4-dose N = 53	Artemether N = 52	Lumefantrine Tablet N = 52
28-Day Cure n (%) [95% CI] P-value	50 (94%) [84, 99]% -	24 (46%) [32, 61]% < 0.001	47 (90%) [79, 97]% 0.4882
PCT , median hours [25 - 75 th percentile] P-value	30 [24 - 36] -	30 [24 - 33] 0.0275	54 [45 - 66] < 0.001
Evaluable, N FCT , median hours [25 - 75 th percentile] P-value	N = 38 24 [12 - 48] -	N = 30 21 [12 - 30] 0.3266	N = 38 60 [36 - 78] < 0.001

Study A023

ITT Population	Coartem 4-dose N = 52	Lumefantrine Tablet N = 51
28 day cure , n (%) [95% CI] P-value	50 (96%) [87, 100]% -	45 (88%) [76, 96]% 0.16
PCT median hours [25 th - 75 th percentile] P-value	30 [24 - 36] -	48 [42 - 60] < 0.001
Evaluable, N FCT median hours [25 th - 75 th percentile] P-value	N = 24 21 [6 - 33] -	N = 31 36 [12 - 60] 0.0297

4-Dose Studies Outside of China

- Ten 4-dose comparative studies conducted between 1993-97 achieved variable cure rates. Coartem demonstrated in relation to comparator:
 - Higher rates in 4 studies (CQ x 3; SP x 1)
 - Similar rates in 2 studies (Q + SP and SP alone)
 - Lower rates in 4 studies (Q, MQ, MAS (Thailand), and Hf (Europe))
- In three studies where Coartem was compared to chloroquine in resistant areas, results were:
 - A007 (India): Coartem 70% vs. CQ 17% at 28 d (ITT)
 - A011 (Tanzania): Coartem 84% vs. CQ 9% at 14 d (Eval.)
 - AIC04 (Senegal): Coartem 100% vs. CQ 65% at 14 d (ITT)

CQ = chloroquine; Hf = halofantrine; SP = Fansidar; MAS = mefloquine artesunate; MQ = mefloquine; Q = quinine

4 → 6-Dose Regimen in Thailand

- A012 was three-arm study in adults with a 28-day PCR-uncorrected cure rate in ITT population as follows:
 - 4 doses (2 tabs/dose) x 48h: **47%** (42/86)
 - 3 doses (4 tabs/dose) x 24h: **49%** (41/87)
 - 4 doses (4 tabs/dose) x 48h: **71%** (62/87)
- Trend for higher cures as total dose increased; 4-dose regimen still not adequate
- Therefore, Study A025 of 4-dose vs. 6-dose was conducted

Study A025: Thailand

ITT Population	Coartem 4 Dose N=120	Coartem 6-dose, 60 hrs N=118
28 day cure n (%) [95% CI] P-value	85 (71%) [62, 79]% -	96 (81%) [73, 88]% 0.069
PCT median hours [25 - 75th percentile] P-value	44 [34 - 51]	44 [22 - 47] 0.66
Evaluable, N FCT median hours [25 - 75th percentile] P-value	N = 61 23 [20 - 44] -	N = 59 35 [20 - 46] 0.26

6-Dose Studies

- A026 Thailand
- A028 Thailand
- A2401 Non-Immune Travelers
- A2403 African Pediatric Patients (5 to < 25 kg)
- B2303 African Pediatric Patients (5 to < 35 kg)

Comparative 6-Dose Studies (Thailand)

ITT Population	Study A026		Study A028	
	Coartem N = 150	MAS N = 50	Coartem N = 164	MAS N = 55
28 day cure n (%) [95% CI]	130 (87%) [80, 92]%	47 (94%) [83, 99]%	148 (90%) [85, 94]%	53 (96%) [87, 100]%
PCT median hours [25th – 75th percentile]	<i>134/150 (89%) cleared at 48h*</i>	<i>44/50 (88%) cleared at 48h*</i>	29 [26 - 32]	31 [26 - 32]
Evaluable, N FCT median hrs [25th – 75th percentile]	N = 87 22 [21 - 42]	N = 33 22 [21 - 41]	N = 76 29 [8 - 51]	N = 29 23 [15 - 30]

*Parasite clearance by day of study

Study A2401: Non-Immune Travelers

ITT Population	Coartem 6-Dose (Core study + PK) N=162
28 day cure n (%) [95% CI]	120 (74%) [67, 91]%
PCT median hours [25 th – 75 th percentile]	42 [32 - 62]
Evaluable, N FCT median hours [25 th – 75 th percentile]	N = 100 37 [18, 44]

Study A2401 : ITT vs. Evaluable

Reason for Failure	From ITT	From Evaluable
Parasite clearance not achieved by day 7	3	1
Reappearance of parasites	3	3
Anti-malaria rescue medication taken	4	0
Patient withdrawn due to lack of efficacy	1	1
Total Failure	11 (7%)	5
Reason for Missing		
Lost to follow-up/Patient withdrawn	26	0
Count not done or too early	5	0
Total Missing	31 (19%)	0



Pediatric 6-dose Studies

Drug Administration in Pediatric Patients

■ Preparation

- Crush tablet and mix in small amount of water (5 to 10 mL), administer with food

■ PK of crushed and intact tablet are similar

■ Replacement of dose

- If vomiting occurred - replace with one dose
- Overall, vomiting reported as AE in 18% of patients, both pediatric and adult

Pediatric Efficacy by Body Weight

Study No. Weight Category	Coartem 6-Dose Regimen	
	28-day Cure Rate ¹ n/N (%) patients	Median PCT ² [25 th - 75 th percentile]
Study A2403³		
5 - < 10 kg	133/154 (86)	24 [24 - 36]
10 - < 15 kg	94/110 (86)	35 [24 - 36]
15 - < 25 kg	41/46 (89)	24 [24 - 36]
Study B2303³		
5 - < 10 kg	61/83 (74)	36 [24 - 36]
10 - < 15 kg	160/190 (84)	35 [24 - 36]
15 - < 25 kg	123/145 (85)	35 [24 - 36]
25 - < 35 kg	30/34 (88)	26 [24 - 36]

1 all enrolled patients, PCR uncorrected cure rates

2 all enrolled patients

3 Coartem administered as crushed tablet with food

FCT and Use of Antipyretics

Pediatric Studies – Applicant Analysis

	Study A2403	Study B2303
Use of Antipyretics Day 1 - 4		
N	224	140
FCT Median hours [95% CI]	7.9 [7.9 - 8.2]	22 [8.4 - 23.5]
No Antipyretics Day 1 - 4		
N	85	183
FCT Median hours [95% CI]	7.8 [7.7 - 7.8]	7.7 [7.6 - 7.7]

Other Endpoints: Early and Late Failures

	Recrudescence, n/N (%), ITT population		
	Coartem	Artemether	Lumefantrine
Study AB/MO2	0/53 (0)	20/52 (39%)	4/52 (8%)
Study A023	1/52 (2%)	--	4/51 (8%)

■ Recrudescence 6-dose Studies

- Study A025 (6-dose, 60 hrs): 3%
- Study A026 and A028: 3% and 4%
- Study A2401: 2%
- Study A2403 and B2303: both 11%

■ Early Failures/Rescued

- Study A2401: 4%
- Studies A2403 and B2303 (crushed tablet): 0.6% and 3%*

*according to protocol, rescue medication was to be given if vomiting of replacement dose occurred within 2 hours of intake



FDA Additional Analyses

Summary 28-Day Cure and PCT Adults and Pediatrics, ITT Population

Study No.	28-Day Cure Rate, n/N (%)		PCT, median hours [25 th – 75 th percentile]	
	Adults	Pediatrics	Adults	Pediatrics
AB/MO2	38/41 (93%)	12/12 (100%)	30 [24 - 36]	36 [30 - 42]
A023	40/42 (95%)	10/10 (100%)	30 [24 - 36]	30 [24 - 36]
A025 6-dose, 60 hr	71/88 (81%)	25/30 (83%)	44 [40 - 53]	43 [22 - 45]
A026	94/109 (86%)	36/41 (88%)	ND	ND
A028	134/149 (90%)	14/15 (93%)	30 [18 - 40]	24 [22 - 40]
A2401	120/162 (74%)	NA	42 [32 - 62]	NA
A2403	NA	268/310 (87%)	NA	24 [24 - 36]
B2303 Crushed tablet	NA	374/452 (83%)	NA	35 [24 - 36]

NA = not applicable; ND = not done

28-Day Cure Rate by Body Weight Six-Dose Studies, Adults

	n/N (%) [95% CI], ITT Population				
	Study A025	Study A026	Study A028	Study A2401*	Total
≥ 70kg	2/3 (67%) -	0/1 (0%) -	4/4 (100%) -	66/98 (6%) [57, 77]%	72/106 (68%) [59, 77]%
< 70kg	94/115 (82%) [73, 88]%	130/149 (87%) [81, 92]%	144/160 (90%) [84, 94]%	53/61 (87%) [76, 94]%	421/485 (87%) [83, 90]%

* 3 subjects did not have weight listed in study 2401

Study A2401: ITT Population

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

28-Day Cure Rate in Patients with Baseline Parasite Count >100,000/ μ l

	n/N (%), ITT Population				
	Study A025	Study A026	Study A028	Study A2403	Study B2303
ITT	22/25 (88%)	10/11 (91%)	8/11 (73%)	3/3 (100%)	100/121 (83%)
Evaluable	21/21 (100%)	10/10 (100%)	8/9 (89%)	3/3 (100%)	52/64 (81%)

Mixed *Plasmodium* Infections with *P. falciparum* in 6-Dose Studies

- *Plasmodium vivax*, N = 43
 - All patients cleared parasitemia in 24 to 48 hrs
 - Relapse rate: 14/43 (33%)
- Limited number of other *Plasmodium* species
 - *P. malariae* (8), *P. ovale* (3)
- There was no patient infected with *P. vivax*, *P. malariae*, or *P. ovale* alone

Limitations of Studies

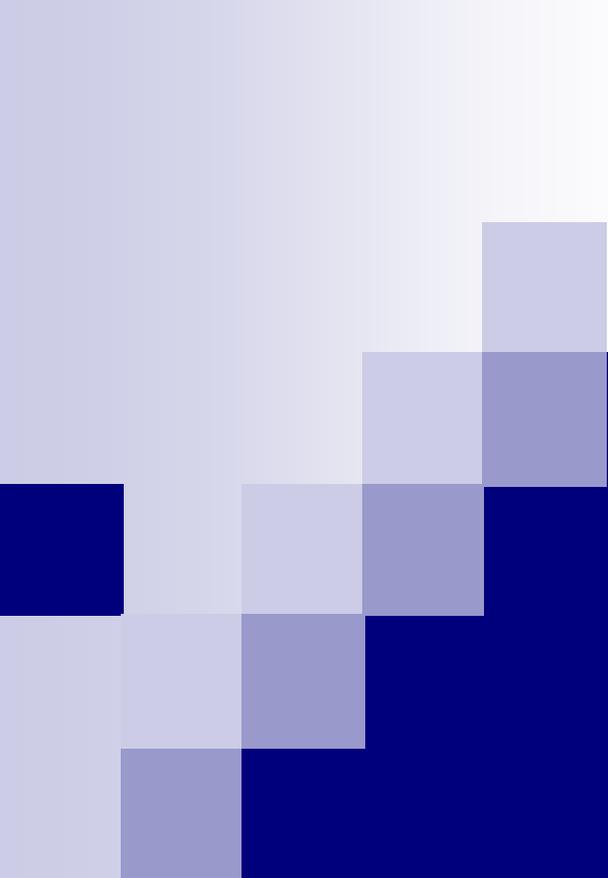
- Applicability to other populations
 - Factorial design studies AB/MO2 and A023 conducted at the same single site, only AB/MO2 contained artemether alone
 - 4-dose vs. 6-dose study A025 and comparative studies A026 and A028 were conducted at two sites
- Most studies unblinded and uncontrolled
- No patients with HIV infection
- Few adult patients enrolled
 - ≥ 65 years of age (N=7)

Efficacy Summary

- 4-dose Coartem has been shown to be superior to:
 - Artemether: 28-day cure rate
 - Lumefantrine: PCT and FCT
 - Chlorquine (India, Senegal, Tanzania)
- In Study A025 (Thailand) the 28-day cure rate (ITT population, PCR uncorrected):
 - 4-dose = 71% vs. 6-dose, 60 hr = 81%

Efficacy Summary (continued)

- Five open-label studies provide supportive evidence for the efficacy (28-day cure rate, ITT, PCR-uncorrected) of 6-dose regimen of Coartem
 - In the comparative studies A026 and A028, 6-dose regimen demonstrated similar cure rates to A025
 - In Study A2401, European travelers, cure rate somewhat lower than other 6-dose studies, but large number of patients lost-to-follow up
 - Similar cure rates also demonstrated in pediatric studies (A2403 and B2303)
- PCT and FCT across 6-dose studies also similar, although shorter in large pediatric studies
 - PCT median 24 to 44 hours
 - FCT median 22 to 37 hours
 - FCT median in A2403 and B2303: 8 hours



Backup Slides – Clinical Efficacy



Genotyping by PCR

Use of Genotyping for Corrected Cure Rates

■ Genotyping of paired isolates:

- Done in **two laboratories** using **different methods** for **different studies**

- Shoklo Malaria Research Unit (SMRU)

- analyzed samples from Studies A025, A026, and A028
- genotyping based on differences in amplified fragment lengths for **MSP-1, MSP-2 and GLURP**
- Differences were elucidated by linear regression and “binning” procedure.

(Binning procedure involves classifying amplified fragments into a particular group based on a size range e.g. Bin 1 may include fragments with estimated lengths of 400-439 bp, whereas Bin 2 may include 440-479 bp)

- Swiss Tropical Institute (STI)

- analyzed samples from Studies 2401, 2403, and 2303

- genotyping based on

- (1) differences in restriction fragment length polymorphisms (RFLP) using only *HinfI* digestion for **MSP-2**, and
- (2) differences in MSP-1 were discerned by differences in amplified fragment length

■ Performance Characteristics of the Assay including **quality control**: NOT AVAILABLE

Performance Characteristics of the Genotyping Assays

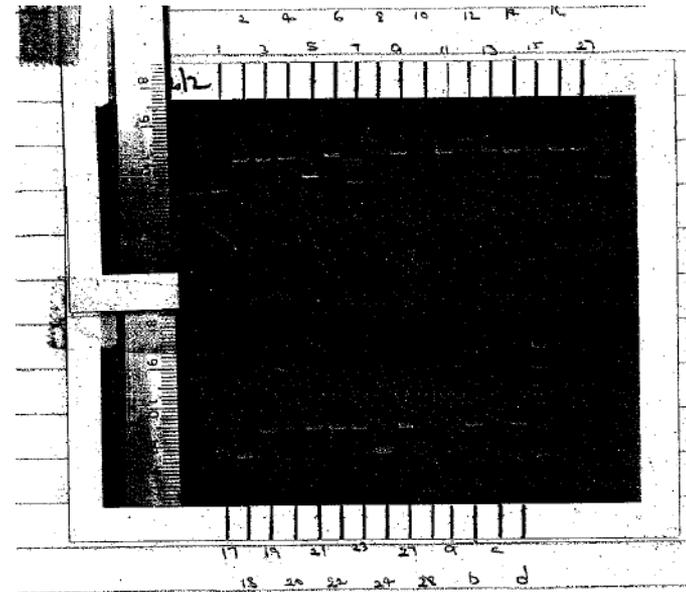
Performance Characteristics of the Assay: **NOT AVAILABLE** for review

- Specificity (i.e. no report of frequency of false positive or negative results)
- Sensitivity in infections with more than one strain
- Reproducibility
 - day to day, or
 - operator to operator
- Product confirmation
- Gel results – some gel results were unattainable, and some were of poor quality
- Quality control
 - WHO recommends that
 - at least 10% of the samples be repeated from the DNA extraction step all the way through to the interpretation of results.
 - gel results be interpreted by at least 2 qualified technicians.
 - The WHO stresses that this is of particular importance for regulatory purposes.
 - Applicant has provided no evidence that any quality control was performed and all results seem to only have been interpreted by a single reader

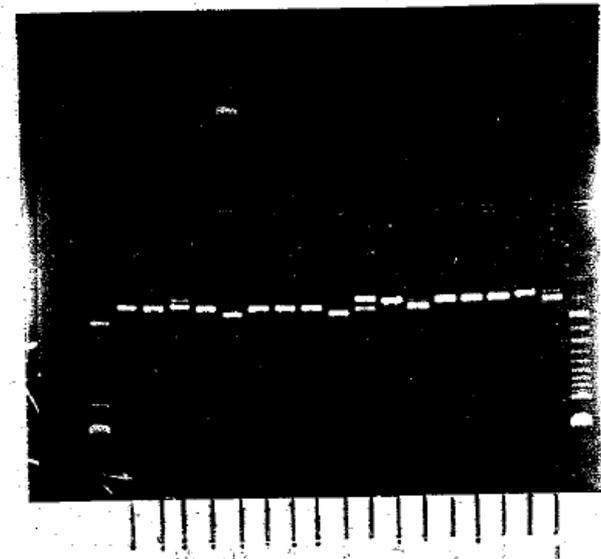
Example of low quality gel images/ unidentifiable patient IDs

MSP-1 NESTED Round
BLOCK 1

	Sample	res	mm	bp	mm	bp	
1	CT190	+	✓ x	110	108	459	484
2	OPD190	+	✓	110	108	459	
3	CT316	+	✓		109	484	
4	FM3004	+	✓		109	484	
5	CT211	+	✓	7.1	109	484	
6	OPD211	+	✓ x	107.5	109	524	484
7	CT268	+	✓	7	109	484	
8	FM2004	+	✓ x	107.5	109	538	484
9	CT284	+	✓	7	106	508	
10	FM2005	+	✓	107.5	107.5	524	
11	CT299	+	✓		107.5	524	
12	FM2003	+	✓		107.5	524	
13	CT296	+	✓	7.1	106	508	
14	FM2002	+	✓		108	511	
15	CT249	+	✓ x	109	108	484	511
16	FM3005	+	✓		108	511	
17	CT380	+	✓ x	50	52	491	446
18	FM3006	+	✓		52	446	
19	CT181	+	✓	52	51	446	468
20	OPD181	+	✓	52	51	446	468
21	CT203	+	✓		50	491	
22	FM3001	+	✓		50	491	
23	CT382	+	✓		50	479	
24	FM3007	+	✓		50	479	
25	LF3012	+	✓	52	50	446	471
26	LF6001	+	✓		50	491	
27	AA370 NB373	+			108	50	511 491
28	H2O	-					



MSP-1 1374



Limitations

■ Limitations of the Assays:

- Infections with multiple strains. Studies have shown day to day variability in genotypes detected; this may be due to sequestration of strains during the erythrocytic cycle or disproportionate MOIs.
- Inherent problems regarding interpretation of results
 - The combined use of linear regression and “binning” procedure may falsely classify two identical genotypes as different (i.e. estimation of fragment length for two products may fall on opposite sides of the cutoff for two adjacent “bins”).

Example: In Study A028, a 17bp difference was seen in the paired isolates for the estimated size of GLURP though each fell in the same bin = recrudescence (patient 145).

-In the same study, a 17bp difference was seen in the paired isolates for the estimated size of MSP-2, each was allocated to a different bin due to the cutoff = new infection (patient 296).
 - Twelve* (STI) or eight* (SMRU) PCRs must render identical products for the conclusion of recrudescence, whereas only a single difference would lead to the conclusion of a new infection. A single case of contamination, mislabeling or misinterpretation strongly favors the conclusion of a new infection.

Fragment Size “bin” Classification

used at Shoklo Malaria Research Unit

Allele code	MSP-1	MSP-2	GLURP
1	400 - 439	400 - 439	
2	440 - 479	440 - 479	
3	480 - 519	480 - 519	
4	520 – 559	520 – 559	580 - 639
5	560 – 599	560 – 599	640 - 699
6	600 – 639	600 – 639	700 - 759
7	640 – 679	640 – 679	760 - 819
8	680 - 719	680 - 719	820 - 879
9			880 - 939
10			940 - 999
11			1000 - 1059
12			1060 - 1119

Genotyping by PCR

- **Genotyping of paired isolates:**

- Done in **two laboratories** using **different methods** for **different studies**

- **Performance Characteristics** of the Assay including **quality control: NOT AVAILABLE** for review

- Efficacy should be based on parasitological cure rate

References

1. Felger I, Beck HP. Genotyping of *Plasmodium falciparum*. PCR-RFLP analysis. *Methods Mol Med*. 2002;72:117-129.
2. Ranford-Cartwright LC, Balfe P, Carter R, Walliker D. Frequency of cross-fertilization in the human malaria parasite *Plasmodium falciparum*. *Parasitology*. 1993;107 (Pt 1):11-18.
3. Paul RE, Packer MJ, Walmsley M et al. Mating patterns in malaria parasite populations of Papua New Guinea. *Science*. 1995;269:1709-1711.
4. Farnert A, Snounou G, Rooth I, Bjorkman A. Daily dynamics of *Plasmodium falciparum* subpopulations in asymptomatic children in a holoendemic area. *Am J Trop Med Hyg*. 1997;56:538-547.
5. World Health Organization. Methods and Techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization. Amsterdam, The Netherlands. 29-31 May 2007. Accessed at: <http://www.who.int/malaria/docs/drugresistance/MalariaGenotyping.pdf>. Available November 17, 2008. 2007.
6. FDA. Guidance for Industry on Malaria. Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis. Available at <http://www.fda.gov/CDER/guidance/7631dft.pdf> Accessed at November 17. 2008.

ITT/Evaluable Population for Primary Studies

Study	ITT, N	Evaluable, N (% of ITT)
AB/MO2	157 (2 missing)	145 (92)
A023	153 (all +)	149 (97)
A025	359 (all +)	306 (85)
A026	200 (1 -)	181 (91)
A028	219 (all +)	208 (95)
2401	162 (excluded 3 -)	124 (77)
2403	310 (all +)	300 (97)
2303*	452 (all +)	412 (91)

* Applicant excluded 8 subjects from the ITT for lack of post-baseline efficacy information (applicant's ITT population includes 444 subjects)

FDA vs. Applicant's 28-Day Cure

6-Dose Studies	ITT uncorrected	Evaluable PCR-corrected	Reasons for differences
A025	96/118 (81)	93/96 (97)	N=3 NE cures N=19 NE failures: 17 missing , 1 new infection, 1 unknown reason
A026	130/150 (87)	130/134 (97)	N=16 NE failures: 14 missing , 1 (-) at baseline, 1 UK reason
A028	148/164 (90)	148/154 (96)	N=10 NE failures: 9 missing , 1 had R1 recrudescence
A2401	120/162 (74)	119/124 (96)	N=1 NE cure N=37 NE failure: 26 missing , 2 early failure, 5 count done too early/late, 4 rescue therapy,
A2403	268/310 (87)	290/300 (97)	N= 23 E subjects with reappearance of parasites (PCR corrected cure, Non-PCR corr. failure) N=1 NE cure N=9 NE failures: 1 reappearance, 3 rescue therapy, 1 death, 4 Missing
B2303	374/452 (83)	403/412 (98)	N= 33 E subjects with reappearance of parasites (PCR corrected cure, Non-PCR corr. failure) N=4 NE cures N=39 NE failures: 10 missing PCR assessment , 6 received rescue therapy, 15 missing, 8 excluded from applicant's ITT (6 no complete dose due to vomiting, 2 missing post baseline info.)

E = evaluable; UK = unknown; NE=non-evaluable;

4 vs. 6-Dose, by Study Site

	28-Day Cure Rate, n/N (%), ITT population		
	Coartem 4-dose (48 hrs)	Coartem 6-dose (60 hrs)	Coartem 6-dose (96 hrs)
Bangkok	20/34 (59%)	27/32 (84%)	30/34 (88%)
MaeLa	65/86 (76%)	69/86 (80%)	74/87 (85%)

Gametocyte Clearance

6-Dose Studies	N	Baseline Count / μ l Mean (range)	Clearance Time (hrs) Median (range)
A025 6-dose, 60 hrs	9	464 (13-1366)	163 (44 - 497) ¹
A026	10	6942 (12-67870)	134 (43 - 719)
A028	12	1061 (25-8790)	122 (16 - 324) ²
A2401	19	Not Reported	289 (18 - 670)
A2403	11	124 (16 -254)	23 (8 - 67)
B2303 crushed tablets	21	51 (8-200)	NA ³

1 Two subjects were censored at 330 and 668 hours and excluded

2 Two subjects were censored at 656 and 659 hours and excluded

3 All 21 subjects were censored without clearance

Efficacy Results in AB/MO2 and A023 Adults and Children

ITT pop		Study AB/MO2 N=157			Study A023 N=153		
		Coartem	Art	Lume Tab	Coartem	Lume Tab	Lume Cap
28-day cure, n/N (%)	Children	12/12 (100%)	4/8 (50%)	11/12 (92%)	10/10 (100%)	8/9 (89%)	11/12 (92%)
	Adults	38/41 (93%)	20/44 (45%)	36/40 (90%)	40/42 (95%)	37/42 (88%)	36/38 (95%)
PCT median, hrs N	Children	36 (N=12)	30 (N=8)	54 (N=12)	30 (N=10)	48 (N=9)	48 (N=12)
	Adults	30 (N=41)	24 (N=44)	60 (N=40)	30 (N=42)	54 (N=42)	54 (N=38)
FCT median, hrs N, eval	Children	12 (N=9)	12 (N=6)	66 (N=9)	24 (N=9)	30 (N=8)	42 (N=12)
	Adults	24 (N=29)	24 (N=24)	54 (N=29)	18 (N=15)	42 (N=23)	30 (N=23)

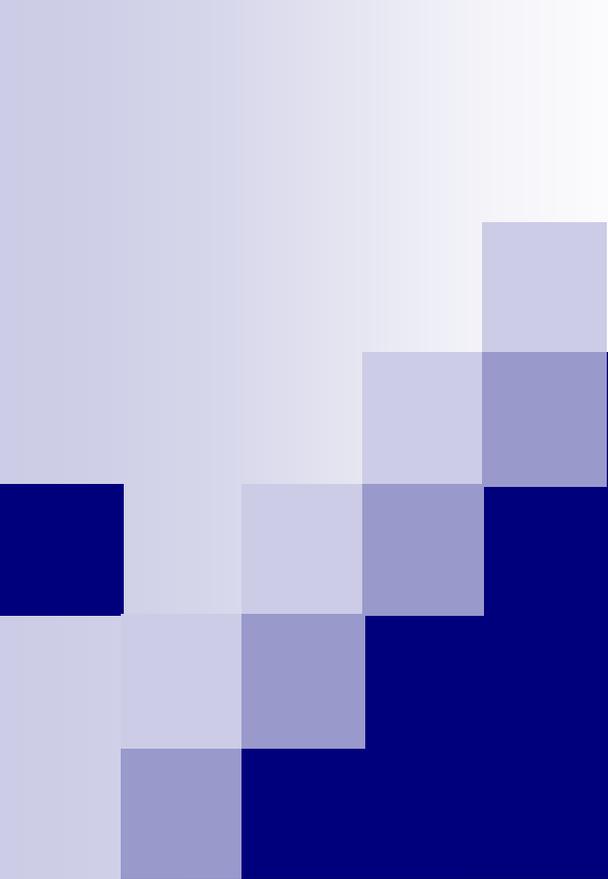
A025: Efficacy in Adults and Children

ITT population	4-dose (48 hrs)	6-dose (60 hrs)	6-dose (96 hrs)
Adults			
28-day cure , n/N (%)	67/99 (68%)	71/88 (81%)	78/92 (85%)
PCT median*, hrs [25 - 75 percentile]*	44 [40 - 52]	44 [40 - 53]	44 [37 - 50]
FCT median, hrs [25 - 75 percentile]*	34 [20 - 44]	36 [21 - 45]	21 [20 - 43]
Children			
28-day cure , n/N (%)	18/21 (86%)	25/30 (83%)	26/29 (90%)
PCT median*, hrs [25 - 75 percentile]*	44 [22 - 45]	43 [22 - 45]	44 [42 - 45]
FCT median*, hrs [25 - 75 percentile]*	22 [19 - 43]	27 [20 - 46]	22 [20 - 44]

Studies A026/A028: Efficacy in Adults and Children

ITT population		Study A026		Study A028	
		Coartem	MAS	Coartem	MAS
28-day cure , n/N (%)	Adults	94/109 (86%)	31/34 (91%)	134/149 (90%)	41/43 (95%)
	Children	36/41 (88%)	16/16 (100%)	14/15 (93%)	12/12 (100%)
PCT median hrs [25 – 75th percentile]	Adults	ND	ND	30 [18 - 40]	32 [25 - 40]
	Children	ND	ND	24 [22 - 40]	24 [16 - 32]
FCT median, hrs [25 – 75th percentile]	Adults	21 [19 – 44]	22 [20 – 42]	29 [8 – 48]	28 [15 – 35]
	Children	44 [21 – 45]	41 [21 – 66]	38 [25 – 54]	21 [15 – 23]

ND = not done



Coartem (artemether 20 mg/ lumefantrine 120 mg) Tablets

Clinical Safety Presentation

Sue Lim, M.D.

Study Data: Safety Populations

Population	Coartem 4-dose	Coartem 6-dose	Population total
Adult (>16 years)	787	647	1434
Pediatric (≤ 16 years)	659	1332	1991
Coartem (dose) total	1446	1979	3425

Only treatment-emergent adverse events considered

6-dose studies: [A025](#), [A026](#), [A028](#), [A2401](#), [A2403](#), [B2303](#); A2412

4-dose studies: [A023](#), [A025](#), [ABM02](#); A003, A004, A005, A007, A008, A009, A010, A011, A012, A014, ABM01

Limitations of Data (6-dose)

- Different study designs
 - Most non-controlled, open label
 - Variety of active comparator antimalarials but few used in > 1 study
- Different enrollment criteria
 - Presence of fever at entry
- Differences in capturing AEs
 - Systematic neurologic exams performed in few studies
 - ECGs performed in most but not all studies
 - Pre-printed AE case report forms for some of the 6-dose studies
 - Laboratory tests – different tests at different sites and variable from study to study

Adults: Deaths, Serious Adverse Events (SAEs) and Discontinuations

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

- **Deaths**
 - 4-dose group; accidents/trauma

- **SAEs: 6-dose: 1.4% (22 SAEs in 9 patients)**
 - Most single reports
 - 3 reports of increased transaminases; all abnormal at baseline
 - FDA attributed 2 of 3 cases as possibly related to study drug; LFTs normal by days 16 and 32
 - SAEs resolved except for 1 case of abdominal pain present before enrollment

- **Study Discontinuations**
 - 1 patient: 58 F with mild abdominal pain and diarrhea, both resolved without intervention
 - Lost to follow-up similar (11%) in 4- and 6-dose groups

Classification of Adverse Events (AEs) - MedDRA

- Medical Dictionary for Regulatory Activities
- Clinically validated international medical terminology developed by the ICH
- Hierarchical organization
 - System Organ Class (SOC)
 - High Level Group Term
 - High Level Term
 - Preferred Term (PT)
 - Lowest Level Term

Example of MedDRA Classification

Cardiac disorders (SOC)



Cardiac arrhythmias (HLGT)



Rate and rhythm disorders (HLT)



PT: Arrhythmia, Bradycardia, Tachyarrhythmia



LLT: Arrhythmia NOS, Arrhythmia,
Cardiac arrhythmia, Dysrhythmia

Healthy Volunteers: AE Profile

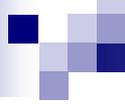
- Healthy volunteers, full 6-dose regimen
 - Thorough QT study
- Randomized, parallel group, single blind
- Coartem, Moxifloxacin, Placebo n=42 each arm
- Follow up for 18 days

AEs in Healthy Volunteers

System Organ Class and Preferred Term	Coartem 6-dose N=42 (%)	Placebo N=42 (%)	Moxifloxacin N=42 (%)
Nervous System Disorders – Total	3 (7)	3 (7)	1 (2)
Headache	1 (2)	3 (7)	0
Sciatica	2 (5)	0	0
Infections and Infestations – Total	2 (5)	4 (9)	1 (2)
Bronchitis	1 (2)	0	0
Herpes simplex	1 (2)	0	0
Rhinitis	1 (2)	2 (5)	0
Gastrointestinal – Total	1 (2)	1(2)	4 (9)
Dyspepsia	1 (2)	0	1 (2)
Musculoskeletal/Connective Tissue Disorders – Total	1 (2)	3 (7)	2 (5)
Back pain	1 (2)	0	1 (2)
Cardiac Disorders – Total	1 (2)	0	3 (7)
Extrasystoles	1 (2)	0	0
General Disorders – Total	1 (2)	0	0
Chills	1 (2)	0	0

Adults: AEs > 10% (6-dose)

System Organ Class	Preferred Term	Adults N=647 (%)
Nervous system disorders	Headache	360 (56)
	Dizziness	253 (39)
Metabolism and nutrition disorders	Anorexia	260 (40)
General disorders and administration site conditions	Asthenia	243 (38)
	Pyrexia	159 (25)
	Chills	147 (23)
	Fatigue	111 (17)
Musculoskeletal and connective tissue disorders	Arthralgia	219 (34)
	Myalgia	206 (32)
Gastrointestinal disorders	Nausea	169 (26)
	Vomiting	113 (18)
	Abdominal pain	112 (17)
	Diarrhea	46 (7)
Psychiatric disorders	Sleep disorder	144 (22)
Cardiac disorders	Palpitations	115 (18)



AE Conclusions

- AE profile in healthy volunteers different from malaria patients
 - Headache and chills are reported in both, rates differ
- Many of the AEs reported in clinical trials likely related to malaria
 - Even though only treatment-emergent AEs analyzed

Adults: Severe AEs

- 5.3% (34 patients) in 6-dose group
- Most single reports in a variety of SOCs
- Most frequently reported:
 - Pyrexia n=19, (1.9%)
 - Splenomegaly n=8, (1.2%)
 - Headache n=3, (0.5%)

Pediatrics (≤ 16 years): Deaths, SAEs and Discontinuations

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

Deaths

- All in the 6-dose arm; all infection except one; none attributed to study drug

Discontinuations

- 70/71 from Study B2303
 - 20/70 discontinued drug due to vomiting as specified in protocol
 - 50/70 *P. falciparum* infection (late re-appearance of parasites after clearance; no primary failures); completed treatment, discontinued from study
 - 1 case of urticaria
- MAS (N=150) had no deaths, SAEs or discontinuations

Pediatrics: SAEs

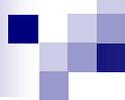
- 1.3% in 6-dose group (30 SAEs in 17 patients)
- Most were single reports
- Multiple cases:
 - Convulsion n=3 (0.2%)
 - Pyrexia n=3 (0.2%)
 - Anemia n=2, (0.2%)
- FDA attributed one SAE to study drug
 - 4 yo F with urticaria following 2 doses of Coartem; urticaria resolved on Day 6 with antihistamine
- SAEs resolved other than 1 case of viral hepatitis

Pediatrics: AEs > 6%

System Organ Class	Preferred Term	Children N=1332 (%)
General disorders and administration site conditions	Pyrexia	381 (29)
Respiratory, thoracic and mediastinal disorders	Cough	302 (23)
Gastrointestinal disorders	Vomiting	242 (18)
	Abdominal pain	112 (8)
	Diarrhea	100 (8)
Metabolism and nutrition disorders	Anorexia	175 (13)
Nervous system disorders	Headache	168 (13)
Blood and lymphatic system disorders	Splenomegaly	124 (9)
	Anemia	115 (9)
Hepatobiliary disorders	Hepatomegaly	75 (6)

Pediatrics: Severe AEs

- 7.3% (97 patients) in 6-dose group
- Most single reports in a variety of SOCs
 - Pyrexia n=53, (4%)
 - Splenomegaly n=12, (0.9%)
 - Anemia n=5, (0.4%)
 - Cough n=5, (0.4%)



Comparative data

Study A025

- Coartem 4 dose vs. 6 dose arms

Studies A026 and A028

- Coartem vs. Mefloquine plus artesunate (MAS) comparator arm

Study A025: Coartem 4 vs. 6 dose

- Only comparative study of 4 vs. 6 dose regimens
- Randomized, double blind study of 359 patients
 - **4-doses over 48 h**
 - **6-doses over 60 h**
 - 6-doses over 96 h

Population	4-dose	6-dose (60 hours)
Adult (n)	99	88
Pediatric (n)	21	30

- Treatment-emergent AEs comparable in both adult and pediatric patients
 - Types, rates

Study A025: AEs \geq 20% in Adult Patients

MedDRA system organ class	Preferred term	Coartem 4 dose N=99 (%)	Coartem 6 dose N=88 (%)
Nervous system disorders	Headache	93 (94)	81 (92)
	Dizziness	73 (74)	69 (78)
Metabolism and nutrition disorders	Anorexia	84 (85)	76 (86)
General disorders and administration site conditions	Asthenia	83 (84)	67 (76)
	Chills	40 (40)	39 (44)
	Fatigue	30 (30)	38 (43)
Musculoskeletal and connective tissue disorders	Arthralgia	71 (72)	66 (75)
	Myalgia	76 (77)	66 (75)
Gastrointestinal disorders	Nausea	49 (50)	41 (47)
	Vomiting	31 (31)	33 (38)
	Abdominal pain	37 (37)	25 (28)
Psychiatric disorders	Sleep disorder	44 (44)	39 (44)
Cardiac disorders	Palpitations	43 (43)	34 (39)

Study A025 : AEs \geq 20% in Pediatric Patients

MedDRA system organ class	Preferred Term	Coartem 4 dose N=21 (%)	Coartem 6 dose N=30 (%)
Nervous system disorders	Headache	20 (95)	27 (90)
	Dizziness	8 (38)	14 (47)
Metabolism and nutrition disorders	Anorexia	18 (86)	25 (83)
General disorders and administration site conditions	Asthenia	10 (48)	17 (57)
	Chills	7 (33)	11 (37)
Musculoskeletal and connective tissue disorders	Myalgia	11 (52)	15 (50)
	Arthralgia	6 (29)	10 (33)
Gastrointestinal disorders	Nausea	7 (33)	12 (40)
	Vomiting	9 (43)	9 (30)
	Abdominal pain	3 (14)	7 (23)
Blood and lymphatic system disorders	Splenomegaly	7 (33)	10 (33)
Hepatobiliary disorders	Hepatomegaly	3 (14)	9 (30)

Other Comparative Studies

- 2 studies (A026, A028) which descriptively compared Coartem with Mefloquine plus Artesunate (MAS)
- Randomized, open label parallel group studies

Population	Coartem	MAS
Adult (n)	258	77
Pediatric (n)	56	28

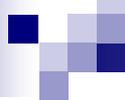
Adult A026/A028

Most Frequently Reported AEs

Preferred Term	Coartem N=258 (%)	Mefloquine Artesunate N=77 (%)
Fever	58	57
Headache	50	42
Palpitation	45	20
Dizziness	39	36
Fatigue	36	10
Asthenia	32	33
Arthralgia	32	31
Chills	32	21
Anorexia	30	34
Vomiting	26	13
Abdominal pain	26	14
Myalgia	25	18
Nausea	25	33

Pediatric A026/A028: Most Frequently Reported AEs

Preferred Term	Coartem N=56 (%)	Mefloquine Artesunate N=28 (%)
Headache	37 (66)	14 (50)
Pyrexia	34 (61)	19 (68)
Anorexia	30 (54)	11 (39)
Asthenia	25 (45)	8 (29)
Dizziness	23 (41)	9 (32)
Vomiting	23 (41)	12 (43)
Chills	19 (34)	4 (14)
Nausea	18 (32)	9 (32)
Splenomegaly	18 (32)	4 (14)
Abdominal pain	17 (30)	9 (32)
Hepatomegaly	17 (30)	4 (14)
Arthralgia	17 (30)	7 (25)



Specific Organ System AEs

- Nervous system disorders
- Ear and labyrinth findings
- Cardiac safety – QT prolongation



Nervous System Disorders

Nervous System Disorders

Nonclinical Data

- Brain lesions
 - Axonal, neuronal degeneration in auditory and balance pathways
- Artemether IM dosing: Dogs >10 mg/kg/day IM for ≥ 8 d (14x clinical exposure)
- Artemether levels are unpredictable and not dose proportional
- Dogs: oral Artemether 600 mg/kg/day x 8 d
 - 1st study AUC 55x clinical exposure
 - Animals exhibited clinical symptoms; dose \downarrow 300 mg/kg/day (~1.5x clinical exposure) x 7 d; sporadic vomiting
 - Minimal hearing loss 20dB, no histopathologic changes
 - 2nd study AUC 4x clinical exposure
 - No symptoms or lesions

Nervous System Disorders

Nonclinical Data - continued

Rats

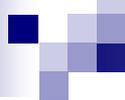
- Artemether 300 mg/kg/day po x 13 weeks
 - Similar to human clinical exposures; no brain lesions or clinical neurotoxicity

Dogs

- Artemether-lumefantrine 1000 mg/kg/day po x 7 days
 - 2x clinical exposure; no symptoms or lesions

Nonclinical Data: Conclusions

- Neurotoxicity appears to be associated with higher sustained artemether exposure
- IM dosing associated with higher exposures to artemether compared to oral dosing
- Repeat oral dosing leads to lower exposures of artemether (as measured by AUC) due to apparent self-induced metabolism
- Exposures to artemether do not decrease with repeat IM dosing
- IM may result in exposure to different artemether-related compounds since this route avoids the 1st pass metabolism that occurs after oral dosing



Clinical: Nervous System AEs

- No significant neurotoxicity attributed to Coartem reported in the Coartem clinical development program
- Systematic neurologic exams performed only in pediatric studies, and 1 of 2 sites in Studies A025, A026; remaining studies recorded neurological findings as AEs

Adults: Nervous System Disorders

Preferred Term	Coartem 6 dose N=647 (%)
Headache	360 (56)
Dizziness	253 (39)
Clonus	16 (3)
Tremor	16 (3)
Nystagmus	5 (0.8)
Hypoaesthesia	4 (0.6)
Ataxia	3 (0.5)
Somnolence	3 (0.5)
Fine motor delay	2 (0.3)
Coma	1 (0.2)
Mental impairment	1 (0.2)
Convulsion	0
Abnormal coordination	0
Dysgeusia	0
Hypersomnia	0
Lethargy	0
Paraesthesia	0
Syncope vasovagal	0

Adults: Severe Nervous System Disorder AEs (0.8%)

Preferred Term	Coartem 6 dose N=647 (%)	
Headache	360 (56)	→ 3
Dizziness	253 (39)	
Clonus	16 (3)	
Tremor	16 (3)	
Nystagmus	5 (0.8)	
Hypoaesthesia	4 (0.6)	
Ataxia	3 (0.5)	
Somnolence	3 (0.5)	→ 1
Fine motor delay	2 (0.3)	
Coma	1 (0.2)	
Mental impairment	1 (0.2)	→ 1
Convulsion	0	
Abnormal coordination	0	
Dysgeusia	0	
Hypersomnia	0	
Lethargy	0	
Paraesthesia	0	
Syncope vasovagal	0	

Adults: Nervous System Disorder SAEs (0.5%)

Preferred Term	Coartem 6 dose N=647 (%)
Headache	360 (56)
Dizziness	253 (39)
Clonus	16 (3)
Tremor	16 (3)
Nystagmus	5 (0.8)
Hypoaesthesia	4 (0.6)
Ataxia	3 (0.5)
Somnolence	3 (0.5)
Fine motor delay	2 (0.3)
Coma	1 (0.2)
Mental impairment	1 (0.2)
Convulsion	0
Abnormal coordination	0
Dysgeusia	0
Hypersomnia	0
Lethargy	0
Paraesthesia	0
Syncope vasovagal	0

→ 1 malaria
recurrence

→ 1 unrelated

→ 1 malaria
recurrence

Pediatrics:

Nervous System Disorders (6-dose)

Preferred term	Age group (years)			
	≤ 2 N=587 (%)	> 2 to ≤ 6 N=473 (%)	> 6 to ≤ 12 n=207 (%)	> 12 to ≤16 N=66 (%)
Ataxia	0	0	0	1 (1.5)
Clonus	9 (1.5)	1 (0.2)	0	1 (1.5)
Convulsion	2 (0.3)	2 (0.4)	0	0
Dizziness	1 (0.2)	2 (0.4)	17 (8.2)	36 (55.4)
Dyskinesia	0	1 (0.2)	0	0
Epilepsy	0	1 (0.2)	0	0
Headache	4 (0.7)	46 (9.7)	71 (34.3)	47 (72.3)
Hyperreflexia	5 (0.9)	1 (0.2)	0	0
Myoclonus	1 (0.2)	2 (0.4)	0	0
Nystagmus	0	0	0	1 (1.5)
Somnolence	0	3 (0.6)	1 (0.5)	0
Tremor	0	1 (0.2)	0	1 (1.5)

Falls – 1 patient

Abnormal behavior - none

Pediatrics:

Nervous System Disorders (6-dose)

- None attributed to study drug
- All cases resolved
- Severe AEs
 - 1 Convulsion 5 yo M related to meningitis
 - 1 Headache 6 yo F due to reinfection
- SAEs
 - Convulsion (3)
 - Cerebral malaria (2) and meningitis (1)

Clonus

Population	Coartem 4 dose (%)	Coartem 6 dose (%)
Adults	5 (0.6)	16 (2.5)
Pediatrics	7 (1.1)	11 (0.8)

- Mostly mild, reported between days 1-3, self-resolving

6-dose:

Adult

- All reported from 1 site
- Attributed to recoding “involuntary muscle contraction” as clonus

Pediatric

- 10/11 cases from 1 site which detected 9/10 during systematic neurological examinations

Nervous System Disorders: Summary

- Headache, dizziness most common
 - Non-specific
 - Likely malaria infection (days 1-3)
- Most AEs mild intensity
- All AEs and SAEs resolved
- No SAEs related to study drug
- AEs related to balance infrequently reported



Ear and Labyrinth Disorders

Ear and Labyrinth: Limitations of Data

- Systematic testing of hearing at baseline not performed - subclinical hearing loss would not be detected
- Study A2412
 - Open label, single center study using audiological measurements to evaluate Coartem, Malarone and MAS on auditory function
 - Preliminary findings rejected hypothesis that Coartem patients have $\geq 15\%$ auditory brainstem response audiometry wave III/V latency changes
- Similar study A2417 results pending

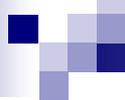
Adults: Ear and Labyrinth

Preferred Term	Coartem 6 dose N=647 (%)
Vertigo	21 (3.3)
Tinnitus	4 (0.6)
Motion sickness	2 (0.3)
Deafness	1 (0.2)
Middle ear inflammation	1 (0.2)
Otitis media	1 (0.2)

- Vertigo: 20/21 cases mild, most reported between days 1-3 and resolved; 1 case considered related to study drug
- Deafness: mild worsening of hearing loss that was present at baseline after 1 dose of Coartem; resolved by day 3
- Hypoacusis (n=11, 1.4%) in 4-dose group: mild, between days 1-3, 2 cases suspected to be related to study drug

Pediatrics: Ear and Labyrinth

Preferred Term	Age group (years)	
	0 - 2 N=587 (%)	> 2 to ≤ 6 N=473 (%)
Cerumen impaction	1 (0.2)	0
Ear pain	2 (0.3)	1 (0.2)
Ear pruritus	1 (0.2)	0
Otorrhea	1 (0.2)	0



Ear and Labyrinth: Summary

- AEs were of mild intensity and resolved
- Vertigo (3.3%) in 6-dose group
- Deafness: 1 patient with baseline hearing loss experienced worsening
- Hypoacusis (1.4%) in 4-dose group
- No auditory AEs in pediatrics



Cardiac Safety

QT Interval Prolongation

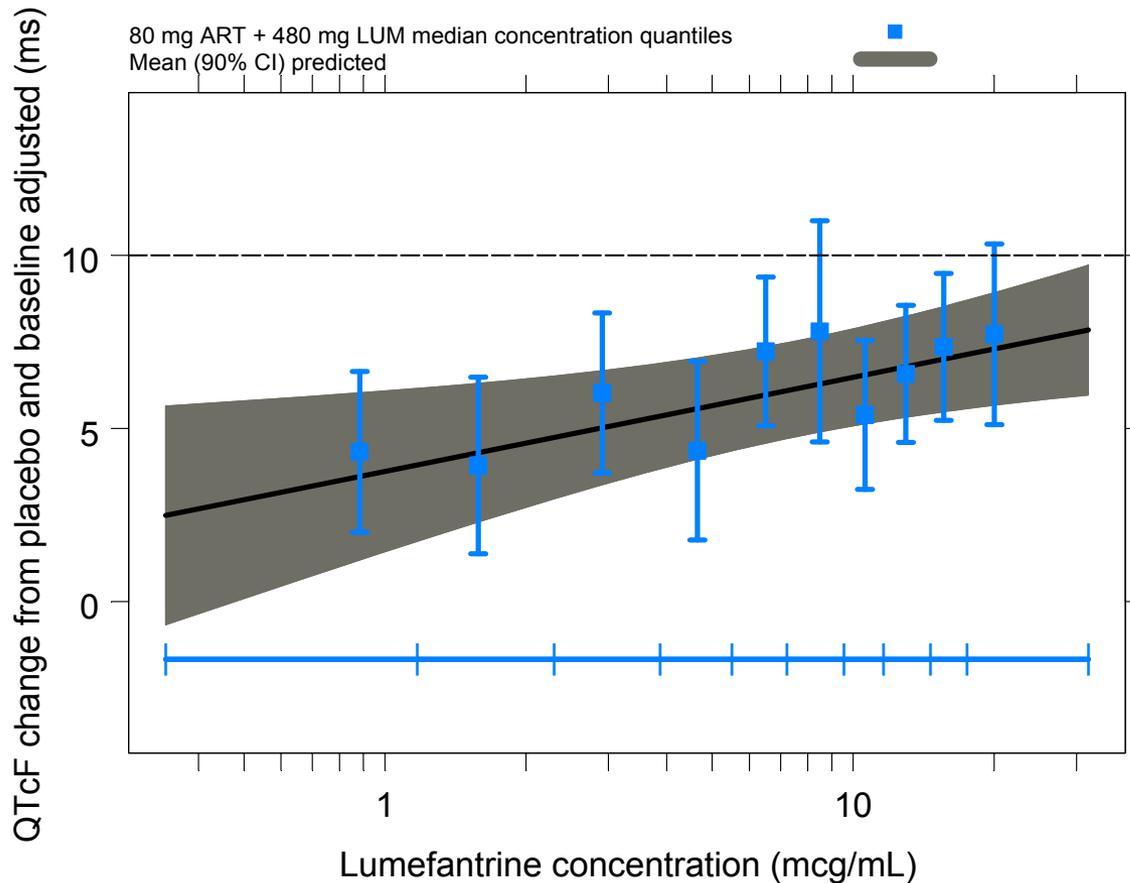
- Thorough QTc study reviewed by FDA Interdisciplinary Review Team for QT studies
- Followed ICH E14 guidelines (Moxifloxacin used for assay sensitivity). However,
 - Only therapeutic doses of Coartem studied, and not supra-therapeutic doses
 - Parallel design, not cross-over

Thorough QT study

Treatment	$\Delta\Delta\text{QTcF}$, msec	90% CI, msec
Coartem	7.29	(3.6, 11.0)
Moxifloxacin	14.1	(8.9, 19.4)

- Healthy volunteers, full 6-dose regimen
- ECGs performed in most clinical trials
 - Safety evaluation showed $\text{QTcF} > 500$ ms in 0.3% of adult patients and no pediatric patients
- No clinical cardiac AEs related to QT prolongation

Mean (90% CI) predicted $\Delta\Delta$ QTc vs. Lumefantrine Concentration (black line and shaded grey area) and observed median-quantile concentrations and associated mean $\Delta\Delta$ QTcF (90% CI)



Laboratory Findings

- Hemoglobin: Anemia
 - 6-dose: Adults 4%, Pediatrics 9%
- LFTs: Hepatic AEs
 - Adults: 3 patients had AST 5-10x ULN, 3 had ALT 5-10x ULN, 2 normalized
 - Pediatrics: 4 patients with elevated LFTs 5-10x ULN which normalized at day 42; 2 patients >10x ULN, 1 normalized

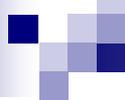
Subgroup Analysis: Age, Sex, Race

- No differences in AEs in any subgroup

Race	Pediatrics ≤ 16 years N=1991 (%)	Adult > 16 years* N=1434 (%)
Black	1209 (61)	80 (6)
Caucasian	0	101 (7)
Oriental	9 (1)	44 (3)
Other (Hispanic)	0	47 (3)
Not collected **	774 (39)	1162 (81)

* Includes 7 patients greater than 65 years of age: 1 Caucasian, 2 Other, 4 Not collected

** Studies performed in Thailand



Hepatic and Renal Impairment

- No specific PK or mass balance studies
- AE profile in patients with mild and moderate hepatic or renal impairment at baseline not different compared to AE profile in patients with normal hepatic and renal function
- Limited data in patients with severe hepatic and renal impairment

Pregnancy: Nonclinical Data

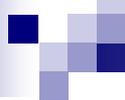
■ Fetal loss

- Pregnant rats dosed at or higher than a dose of ~50% the highest clinical dose of 1120 mg artemether-lumefantrine per day had increased fetal loss, early resorptions and post-implantation losses
- No adverse birth effects in animals dosed at ~1/3 the highest clinical dose

■ No teratogenicity identified

Pregnancy: Clinical Data

- Data from an observational study of 1000 pregnant women exposed to either Coartem or SP during pregnancy
- 33% first trimester; remainder 2nd and 3rd trimesters
- No difference between treatment groups for following birth outcomes
 - Primary outcome: Incidence of perinatal mortality (stillbirth >28 weeks gestation) and early neonatal death within 7 days of birth
 - Other outcomes: gestational age, birth weight, SA, preterm delivery, neonatal mortality, maternal mortality, birth defects
- No increase in teratogenic effects over background rate



Pregnancy: Conclusions

- No teratogenicity or increased fetal loss above background rate in observational clinical study
 - Fetal loss seen in animal studies
- Proposed labeling:
 - Coartem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Overall Summary

- Safety data adequate: 3400 exposures; ~1980 with 6-dose
- 6-dose regimen administered over 3 days
 - Few discontinuations due to AEs (adults 0.2%, pediatrics 5%)
 - Many AEs mild intensity, likely related to malaria and resolved
 - Few deaths and SAEs

Overall Summary (continued)

- Nervous system disorder AEs
 - Most mild; headache and dizziness most common
 - All AEs and SAEs resolved, most in few days
 - No SAEs attributed to study drug
 - Balance AEs infrequently reported
- Ear/labyrinth AEs
 - Few reported, mild intensity and resolved
- No clinical cardiac AEs or deaths
- No reported difference in birth outcomes in women exposed to Coartem during pregnancy

Question 1

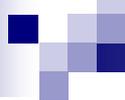
- Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be effective for the treatment of uncomplicated *Plasmodium falciparum* malaria, including demonstrating the contribution of artemether and lumefantrine to the treatment effect? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

Question 2

- Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be safe for the treatment of uncomplicated *P. falciparum* malaria? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

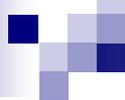
Question 3

- Do you consider the data presented for patients co-infected with *P. falciparum* and *P. vivax* sufficient to demonstrate efficacy and safety of Coartem in treating these patients? (vote yes or no)
 - Please discuss your rationale for your vote.
 - If the answer is no, what additional studies do you recommend?



Question 4

- If the answer to numbers 1 and 2 is yes, should any specific post-marketing studies be conducted?



Question 5

- Is there specific efficacy, safety or other information that you would recommend be reflected in the Coartem product labeling?