

# **Coartem (artemether-lumefantrine) Tablets**

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**United States Food and Drug Administration  
Anti-Infective Drugs Advisory Committee Meeting**

**December 3, 2008**

# **Coartem (artemether-lumefantrine) Tablets**

## **Introduction**

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**Mathias Hukkelhoven, PhD**

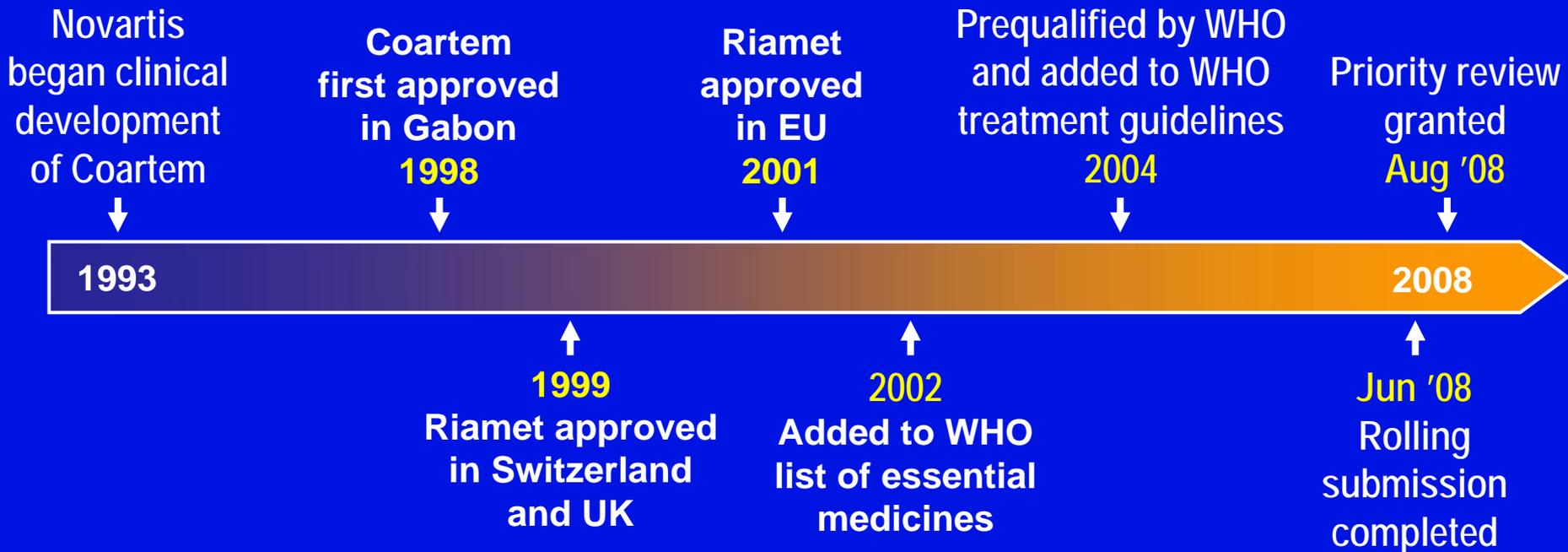
**Senior Vice President, Global Head**

**Drug Regulatory Affairs**

**Novartis Pharmaceuticals Corporation**



# Coartem/Riamet Regulatory History



- ✦ For 15 years, Novartis has worked to make Coartem available worldwide, particularly in endemic regions
- ✦ Since 1998, Novartis has provided more than 190 million courses of Coartem on a not-for-profit basis

# Coartem Is Widely Used for Treatment of *P falciparum* Malaria Worldwide

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- ✦ Registered in > 85 countries in Africa, Asia, Australia, Europe, and South America
- ✦ Included in treatment guidelines in the UK, France, Switzerland, and Australia
- ✦ Used as a reference treatment in clinical development of new antimalarial drugs

# Need for Coartem in the United States (1)

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- ✦ Risk for malaria in the United States is real
  - ~1500 US cases reported to CDC annually
  - Millions of Americans travel to malaria-endemic regions annually<sup>a</sup>
  - Millions of people travel from malaria-endemic regions to the US annually<sup>a</sup>
- ✦ WHO recommends artemisinin-based combination therapy (ACTs) as first-line treatment for uncomplicated *P falciparum* malaria
- ✦ No artemisinin derivatives or ACTs are currently approved in the US

<sup>a</sup> US Department of Commerce, International Trade Administration, Manufacturing and Services, Office of Travel and Tourism Services, 2007

## Need for Coartem in the United States (2)

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- ✦ Many US organizations need effective antimalarial drugs overseas but may be required to use only FDA-approved drugs
- ✦ US-based charities are supplying Coartem
- ✦ The CDC and US Army have taken steps to make IV artesunate available through a treatment IND
- ✦ Mefloquine and Malarone<sup>®</sup> used extensively for prophylaxis; therefore, other drugs needed for treatment
- ✦ Since 2005, The CDC recommends immigrants from Africa be treated with Coartem prior to arrival in the US

## Proposed Indication

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**Coartem Tablets is a combination product of artemether and lumefantrine, both blood schizontocides, indicated for treatment of acute, uncomplicated malaria due to infections with *Plasmodium falciparum* or mixed infections including *P falciparum*.**

# Extensive Clinical Development Program for Coartem

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- ✦ In agreement with FDA, submission includes 20 Novartis-sponsored studies conducted over a 14-year period
  - Studies not conducted under US INDs
  - Efficacy results meet WHO criteria for 28-day PCR-corrected cure rate in evaluable population
  - Favorable safety profile demonstrated in ~ 3600 Coartem-treated patients
- ✦ Favorable benefit-to-risk profile

# Today's Agenda

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**Disease Background/  
Epidemiology**

**Philip Rosenthal, MD**  
Professor of Medicine  
University of California,  
San Francisco, School of Medicine

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**Clinical Development  
Program and Efficacy  
and Safety**

**Anne Claire Marrast, MD**  
Global Program Medical Director  
Tropical Medicine  
Novartis Pharma AG

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**Benefit/Risk  
Assessment**

**Professor Nicholas White, FRS**  
Director, Wellcome Trust  
Faculty of Tropical Medicine  
Mahidol University  
Bangkok, Thailand

# Consultants

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- ✦ **Hans Peter Beck, PhD**  
Swiss Tropical Institute
- ✦ **Joel Morganroth, MD**  
eResearch Technology  
Philadelphia, Pennsylvania

# **Coartem (artemether-lumefantrine) Tablets**

## **Disease Background/Epidemiology**

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**Philip Rosenthal, MD**

**Professor, Department of Medicine  
University of California, San Francisco  
School of Medicine**

# ***P falciparum* Malaria Is a Global Life-Threatening Disease**

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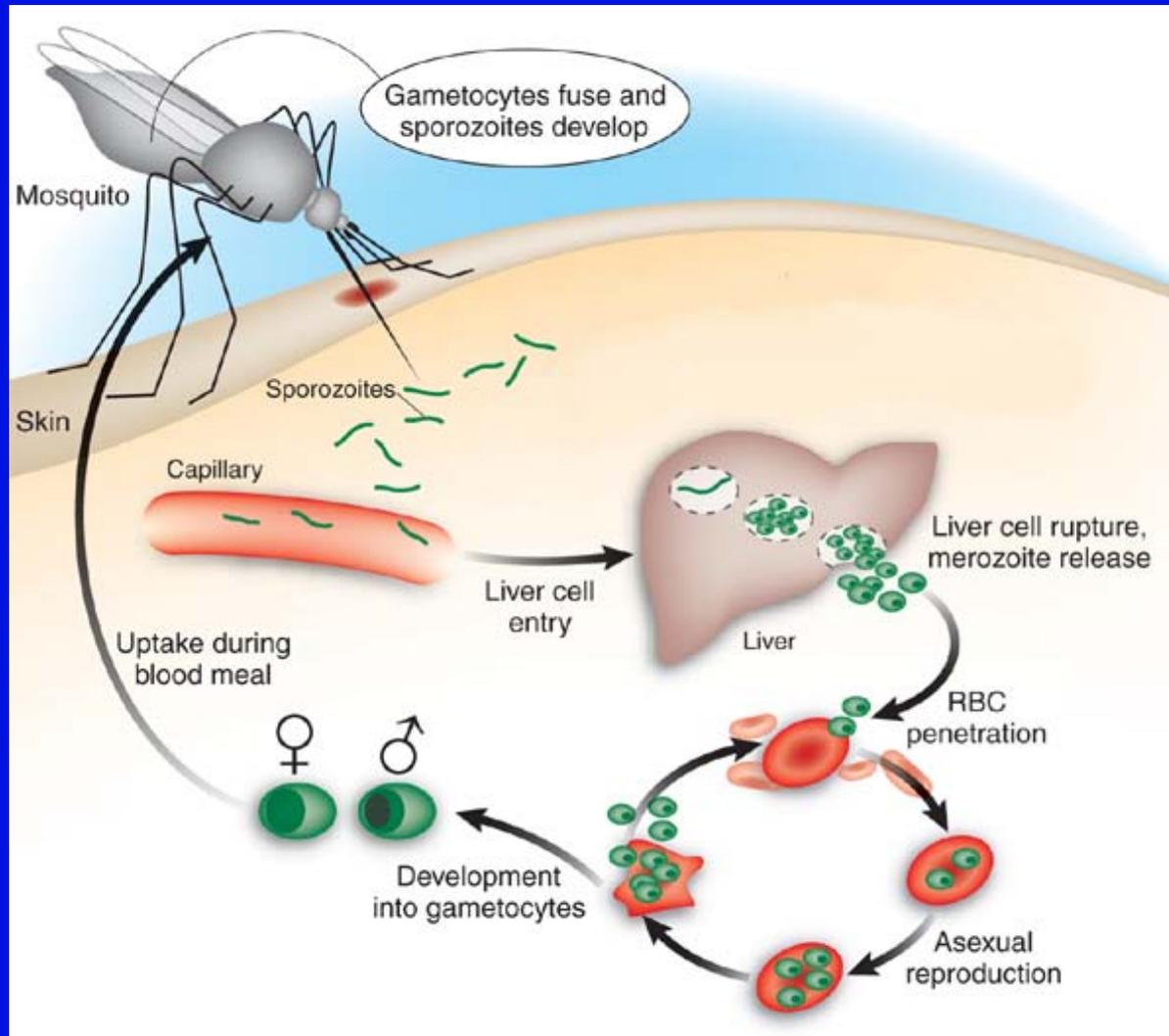
- ✦ **Most common and deadly form**
  - ~ 2.4 billion people at risk<sup>a</sup>
  - Affects > 500 million people annually<sup>b</sup>
  - Usually an uncomplicated febrile illness, but can be a potentially fatal disease
  - Causes more than 1 million deaths annually<sup>b</sup>
    - Most morbidity and mortality in children
    - Pregnant women also at increased risk
- ✦ **There is a risk for malaria everywhere because of people traveling to and from endemic regions**

<sup>a</sup> Global Plasmodium falciparum limits. Malaria Atlas Project.

<sup>b</sup> WHO Guidelines for the Treatment of Malaria 2006.

# How Is Malaria Contracted?

## Life Cycle of *P. falciparum*



# Clinical Features of *P falciparum* Malaria

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- ✦ Uncomplicated malaria commonly presents with nonspecific symptoms
  - Fever, chills, sweats, headache, myalgias
- ✦ Large majority of episodes are uncomplicated
  - Treated orally
  - Prompt treatment prevents progression to severe disease
- ✦ Small minority of episodes do become severe
  - Requires parenteral therapy
- ✦ Nonspecific symptoms make it difficult to distinguish drug-related adverse events from signs and symptoms of acute malaria

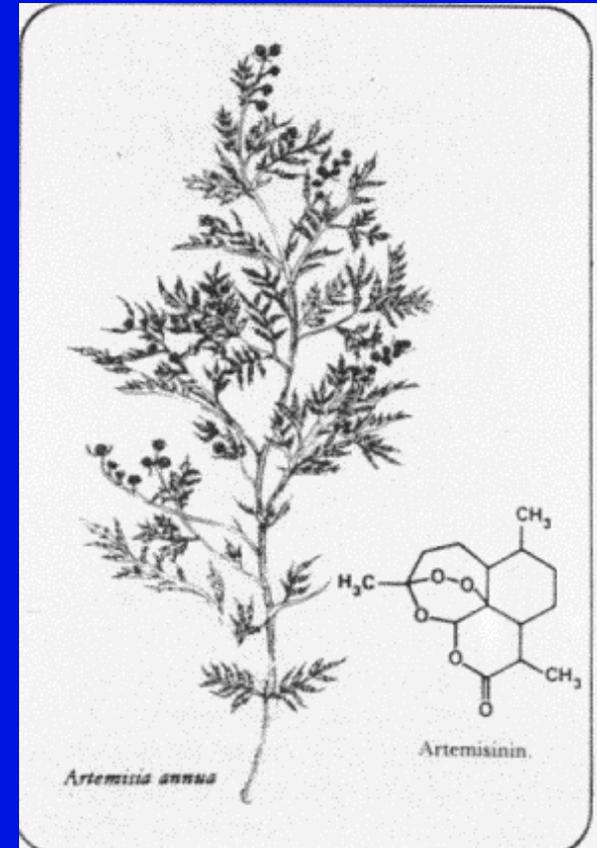
# Drug Resistance Is a Major Impediment to Treatment of *P falciparum* Malaria

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- ✦ Chloroquine was the standard therapy for > 50 years
  - Drug resistance identified in late 1950s
  - Prevalence of resistance now very high in nearly all endemic regions
- ✦ Sulfadoxine-pyrimethamine (SP)
  - Common replacement for chloroquine until recently
  - Efficacy now limited due to increasing resistance
- ✦ Resistance to other drugs has been seen
  - Mefloquine
  - Malarone<sup>®</sup> (atovaquone-proguanil)
  - Amodiaquine, piperazine
  - Quinine

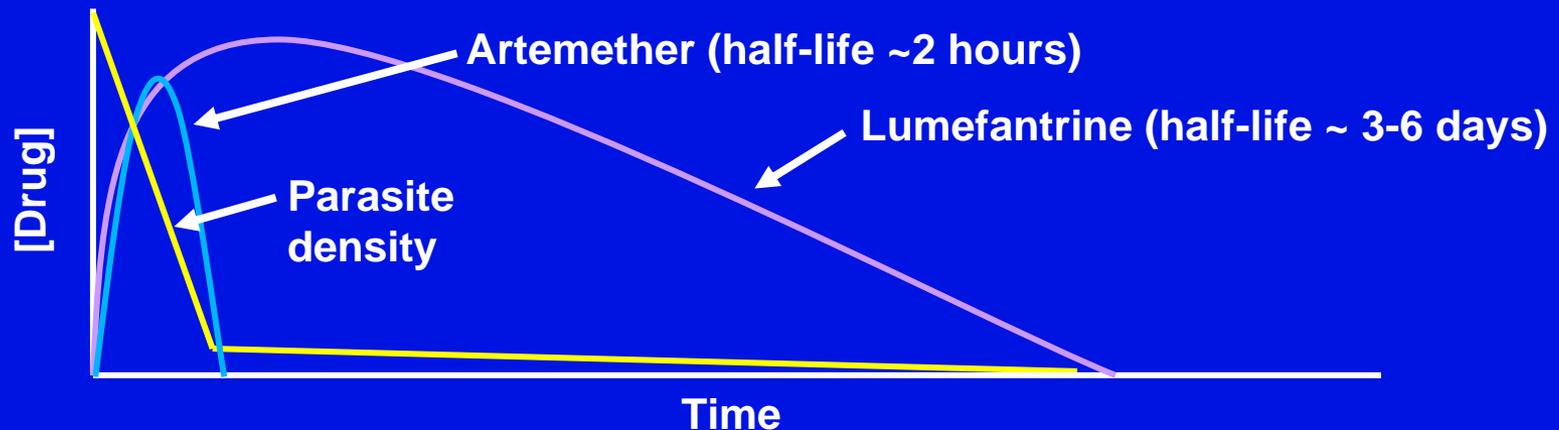
# Artemisinin

- ✦ Extracted from *Artemisia annua*
- ✦ Used as herbal remedy for fevers in China for thousands of years
- ✦ Artemisinin and derivatives extensively tested in China since late 1970s
- ✦ Used widely to treat malaria in Asia since 1980s
- ✦ Artemisinin-based combination therapy (ACT) is now the international standard-of-care for the treatment of uncomplicated malaria



# WHO Treatment Guidelines for Uncomplicated *P falciparum* Malaria

- ✦ WHO recommends ACTs as first-line treatment because
  - Limited (if any) resistance to artemisinin derivatives
  - Artemisinin derivatives act rapidly, with short half-lives
    - Rapid clearance of parasitemia and symptoms
    - Limits selection of resistant parasites
  - Combining with long half-life partner drug provides high long-term cure rate with short treatment course



# Malaria in the United States: Factors Contributing to Risk

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- ✦ **Extensive travel between the United States and endemic regions**
  - US citizens visiting or living in endemic regions
  - People from endemic regions traveling to the United States
- ✦ **Common lack of compliance with available prophylactic measures**

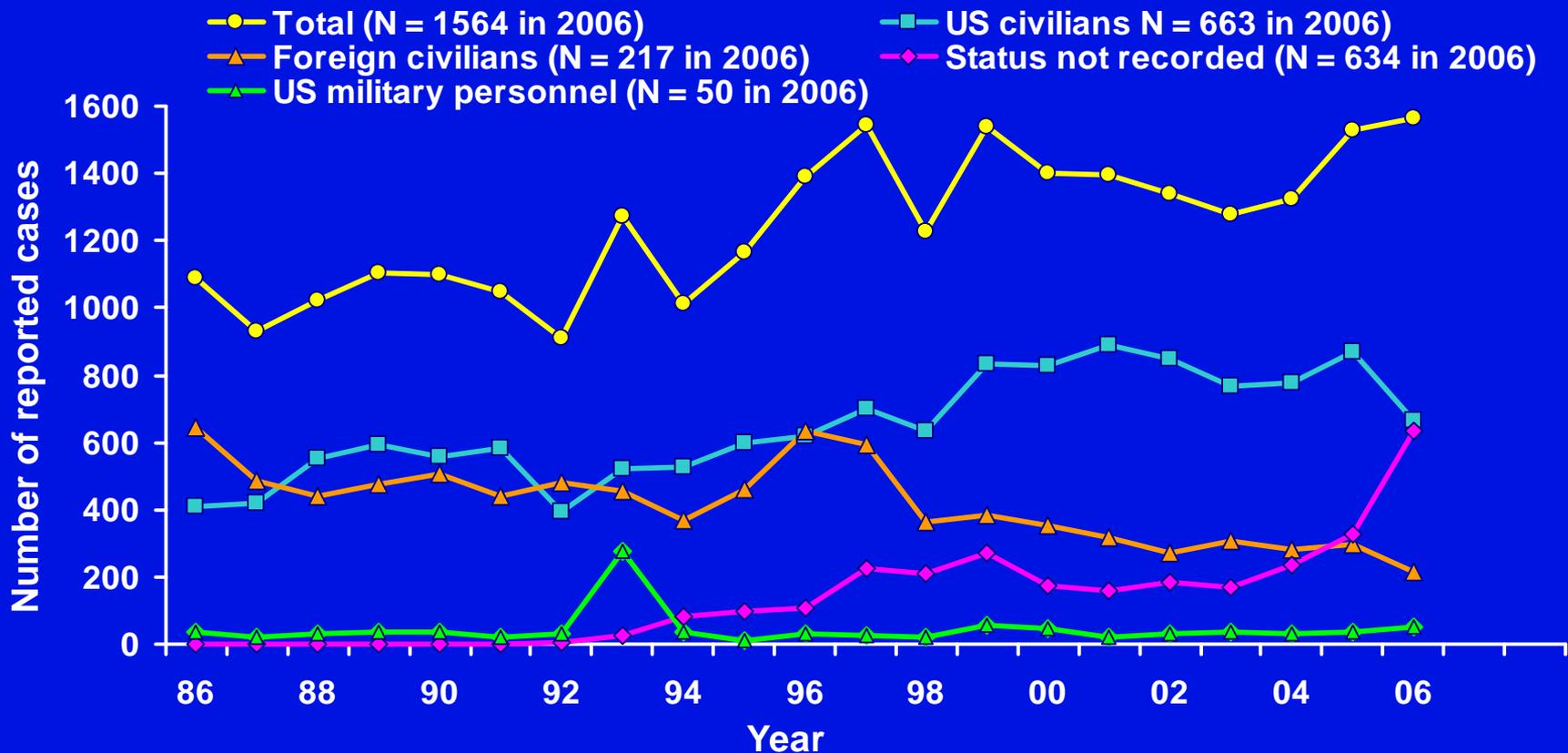
# Malaria in Endemic Regions Versus the United States

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- ✦ In highly endemic regions, most individuals have some level of antimalarial immunity
  - Most episodes occur in young children
  - Re-infection is common
- ✦ In the US, most individuals have never been exposed to malaria and thus have no immunity
  - High risk of progression to severe disease
  - No risk of re-infection after treatment

# Incidence of Malaria in the United States as Reported to the CDC, 1986-2006

✦ ~ 1,500 cases in 2006 and ~ 5 - 10 deaths annually



# Region of Malaria Acquisition for Cases Diagnosed in the United States, 2006<sup>a</sup>

Area or region	Imported malaria cases, n (%)		
	US resident n = 713	Foreign resident n = 217	Total N = 930
Africa	511 (71.7)	131 (60.3)	642 (69.0)
Asia	116 (16.3)	52 (24.0)	168 (18.1)
Central America and the Caribbean	42 (5.9)	25 (11.5)	67 (7.2)
South America	18 (2.5)	3 (1.4)	21 (2.3)
North America	4 (0.5)	2 (0.9)	6 (0.6)
Oceania	17 (2.4)	1 (0.5)	18 (1.9)
Unknown <sup>b</sup>	5 (0.7)	3 (1.4)	8 (0.9)

<sup>a</sup> Persons for whom US or foreign status is not known are excluded.

<sup>b</sup> Region of acquisition is unknown.

# *P falciparum* Is the Most Common Cause of Malaria in the United States

<i>Plasmodium</i> species	Malaria cases, n (%)		
	2004	2005	2006
<i>P falciparum</i>	656 (49.5)	742 (48.6)	613 (39.2)
<i>P vivax</i>	315 (23.8)	337 (22.1)	275 (17.6)
<i>P malariae</i>	47 (3.5)	54 (3.5)	46 (2.9)
<i>P ovale</i>	27 (2.0)	38 (2.5)	47 (3.0)
Mixed	17 (1.3)	12 (0.8)	10 (0.6)
Unreported/undetermined	262 (19.8)	345 (22.6)	573 (36.6)
<b>Total</b>	<b>1324</b>	<b>1528</b>	<b>1564</b>

# CDC Treatment Guidelines for *P falciparum* Malaria in the United States

Clinical diagnosis	Region	Recommended drug
Uncomplicated	Chloroquine-sensitive	Chloroquine phosphate (Aralen®) Hydroxychloroquine (Plaquenil®)
	Chloroquine-resistant	Quinine sulfate plus one of the following: doxycycline, tetracycline, or clindamycin Atovaquone-proguanil (Malarone®) Mefloquine (Lariam®)
Severe	All regions	Quinidine gluconate plus one of the following: doxycycline, tetracycline, or clindamycin IV artesunate: available under an IND treatment protocol followed by doxycycline, atovaquone-proguanil, clindamycin, or mefloquine

# Summary

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- ✦ Malaria remains a significant risk in the US
- ✦ *P falciparum* most common cause of malaria in the US
  - Highest potential to cause severe illness or death
- ✦ Current treatments in the US may be inadequate
  - Concerns regarding efficacy, tolerability, toxicity, and potential for resistance
- ✦ No artemisinin derivatives or ACTs currently approved in the US
- ✦ In line with WHO recommendations, Coartem should be made available for treatment of *P falciparum* malaria in the US

# **Coartem (artemether-lumefantrine) Tablets Efficacy and Safety**

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**Anne Claire Marrast, MD**

**Global Program Medical Director Tropical Medicine**

**Novartis Pharma AG**

# Presentation Agenda

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- ✦ Description of the compound
- ✦ Clinical development program
  - Overview
  - Dose selection rationale
    - Efficacy of combination vs active components
    - Selection of the 6-dose regimen
  - Efficacy of the 6-dose regimen
  - Safety profile
    - Overview
    - Safety topics of special interest
- ✦ Summary

# Coartem

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- ✦ **Coartem is an oral fixed-dose combination**
  - **20 mg artemether (artemisinin derivative)**
  - **120 mg lumefantrine**
- ✦ **Both are blood schizonticides**
  - **Artemether is rapidly metabolized into the active metabolite dihydroartemisinin**
    - **Antimalarial activity may result from production of free radicals attributed to the endoperoxide moiety**
    - **Reduce parasites by factor of 10,000 per cycle**
  - **Exact mechanism of action of lumefantrine is not well defined**

# Pharmacokinetics<sup>a</sup> (1)

	Artemether	DHA	Lumefantrine
Mean C <sub>max</sub> ± SD	83.8 ± 59.7 ng/mL	90.4 ± 48.9 ng/mL	9.8 ± 4.2 µg/mL
T <sub>max</sub>	2 h	2 h	6 – 8 h
AUC <sub>last</sub> ± SD	259 ± 150 ng.h/mL	285 ± 98 ng.h/mL	243 ± 117 µg.h/mL
Half-life	2 – 3 h	2 – 3 h	3 – 6 days

DHA = dihydroartemisinin.

<sup>a</sup> Study B2104 in healthy volunteers: Coartem intact standard tablet (80 mg artemether/480 mg lumefantrine) administered as single dose under fed conditions (FDA standard breakfast).

# Pharmacokinetics (2)

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## ✦ Metabolism

- Both drugs metabolized in liver mainly by CYP3A4
  - CYP3A4 inhibitors (eg, ketoconazole) increase exposure to artemether and lumefantrine by ~ 2-fold
- At clinically relevant concentrations, lumefantrine inhibits CYP2D6 in vitro

## ✦ Excretion

- Animal data suggest no significant renal excretion

## ✦ Food effect (standard FDA breakfast)

- Exposure to artemether and DHA increased 2 to 3-fold
- Exposure to lumefantrine increased 16-fold

# Coartem Dosing Regimens

- ✦ Two dosing regimens tested
  - 4-dose (0, 8, 24, and 48 hours)
  - 6-dose (0, 8, 24, 36, 48, and 60 hours)
- ✦ Dose adjusted by body weight (6-dose regimen)

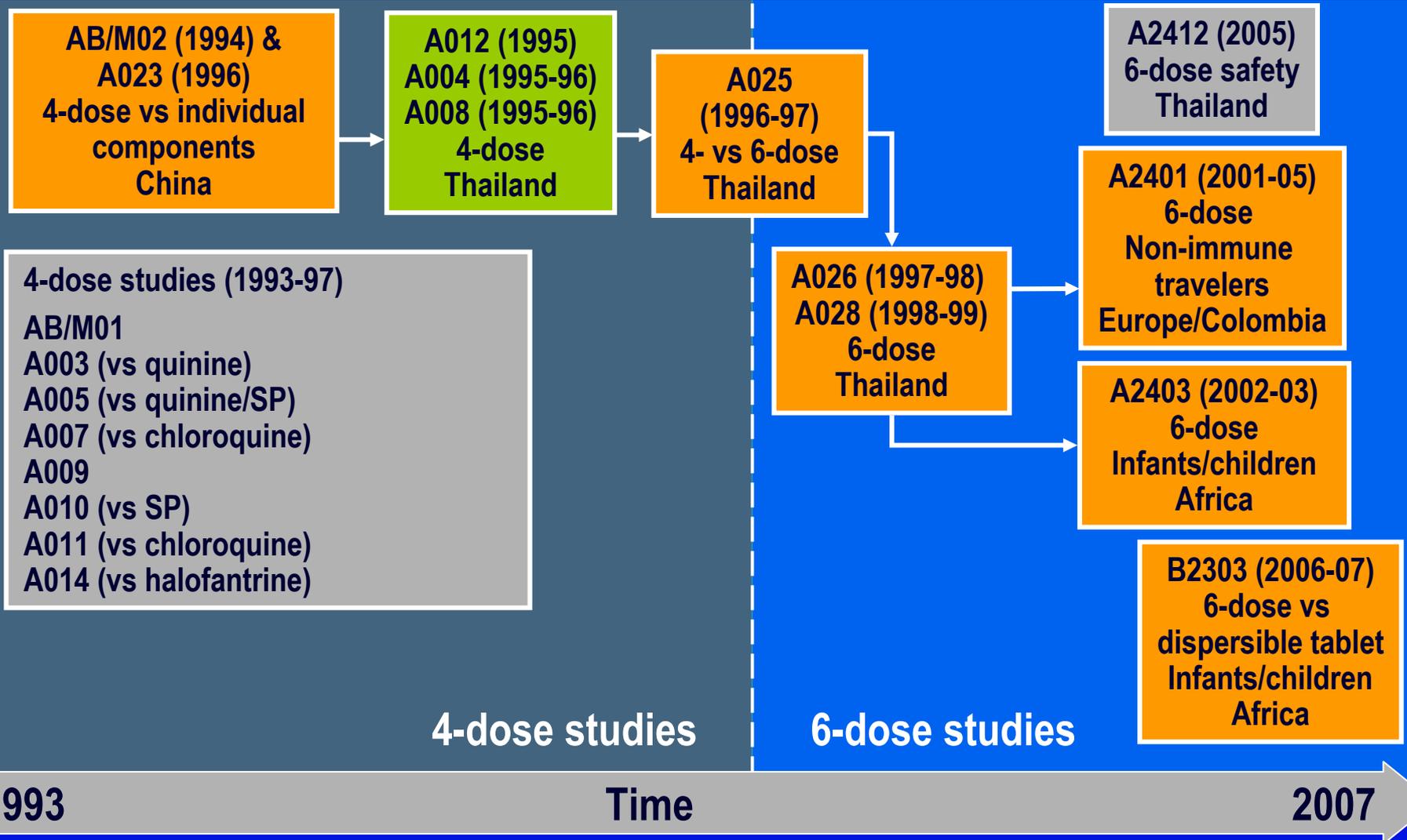
Body weight	Tablets per dose	Total mg per dose	
		Artemether	Lumefantrine
5 to < 15 kg	1	20	120
15 to < 25 kg	2	40	240
25 to < 35 kg	3	60	360
≥ 35 kg	4	80	480

# Clinical Development Program (1)

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- ✦ This NDA includes data from 20 Novartis-sponsored studies performed between 1993 and 2007
  - 4911 patients with malaria
  - 3599 treated with Coartem
    - 1572 adults ( $> 16$  years of age)
    - 2027 pediatric patients ( $\leq 16$  years of age)
- ✦ Of these 20 studies, 8 studies have been identified as key

# Clinical Development Program (2)



# Rationale for Selecting 8 Studies as Key

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- ✦ Efficacy of Coartem versus individual components (AB/MO2, A023)
- ✦ Efficacy of Coartem 4-dose versus 6-dose regimens (A025)
- ✦ Efficacy of Coartem 6-dose regimen (A026, A028, A2403, B2303, and A2401)
- ✦ The remaining studies were not selected as key as they were evaluating the efficacy of the Coartem 4-dose regimen

# Primary Efficacy Endpoint

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## ✦ 28-day parasitological cure rate

- Proportion of patients with clearance of asexual parasitemia within 7 days without recrudescence (recurrence) at day 28
- PCR correction distinguishes between new infections and recrudescence of the original infection
  - Important in endemic regions where re-infection occurs very frequently

# Analysis Populations

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- ✦ **Evaluable**: all patients with confirmed *P falciparum* malaria who received at least 1 dose of study drug and had parasite counts performed at the pre-specified time points, including day 28, or who discontinued due to unsatisfactory therapeutic effect
  - Primary efficacy analysis
- ✦ **mITT**: all patients with confirmed *P falciparum* malaria who received at least 1 dose of study drug
  - Patients who did not have a parasite count performed at day 7 or day 28 were classified as a treatment failure

## Secondary Efficacy Endpoints

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- ✦ **7-day, 14-day, and/or 42-day cure rate**
- ✦ **Fever clearance time (FCT)**
  - Time from first dose until normal body temp (37.5° C) is achieved (maintained for 48 hours)
- ✦ **Parasite clearance time (PCT)**
  - Time from first dose to disappearance of asexual parasites (maintained for 48 hours)
- ✦ **Gametocyte clearance time (GCT)**
  - Time from first dose to disappearance of gametocytes (maintained for 48 hours)

# Design of the Dose Selection Studies

	Combination vs components		4-dose vs 6-dose
	AB/MO2	A023	A025
<b>Design</b>	Randomized double-blind	Randomized double-blind	Randomized double-blind
<b>Comparison</b>	4-dose vs artemether or lumefantrine tablets	4-dose vs lumefantrine tablets or capsules <sup>a</sup>	4- vs 6-dose
<b>N</b>	157	153	359
<b>Patients</b>	Adults & adolescents (> 12 years)	Adults & adolescents (> 12 years)	Adults & adolescents (> 12 years) & children (> 2 years)
<b>Geography</b>	China	China	Thailand

<sup>a</sup> Open label for lumefantrine capsules. Lumefantrine tablets contained 120 mg of lumefantrine, whereas lumefantrine capsules contained 100 mg lumefantrine.

# Baseline Demographic and Disease Characteristics

## Study AB/MO2—China

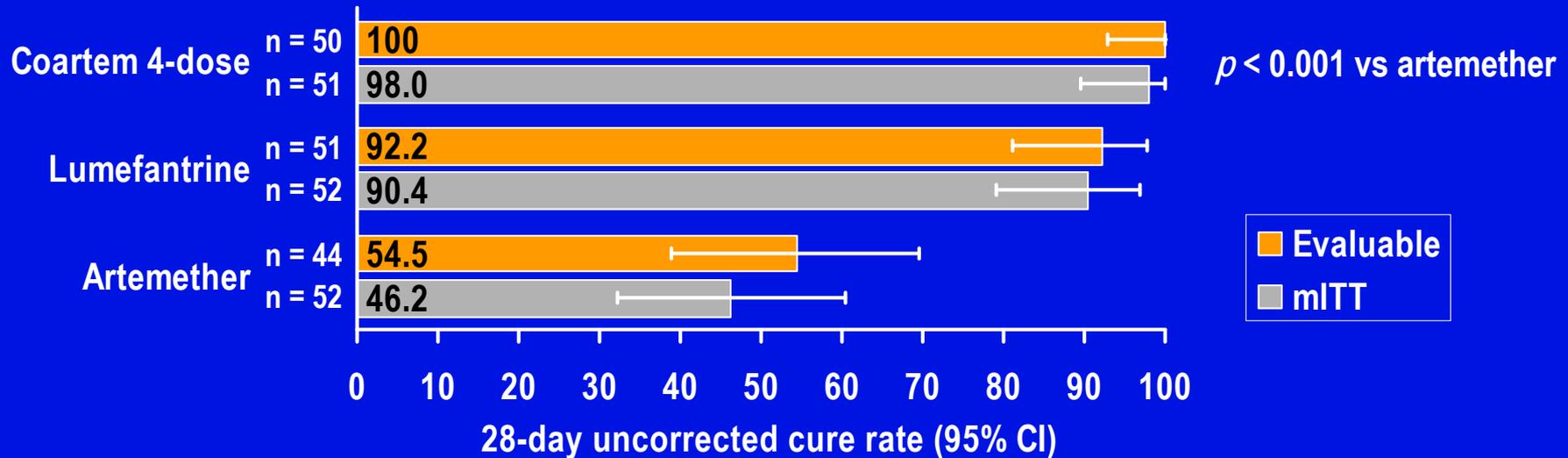
<b>Characteristic</b>	<b>Coartem n = 53</b>	<b>Artemether n = 52</b>	<b>Lumefantrine n = 52</b>
Male, n (%)	43 (81)	45 (86)	44 (85)
Female, n (%)	10 (19)	7 (14)	8 (15)
Median age, years (range)	23 (13 - 57)	22 (13 - 54)	22 (13 - 53)
Median weight, kg (range)	50 (25 - 62)	50 (27 - 62)	50 (26 - 79)
<b>Parasite density, asexual forms/<math>\mu</math>L<sup>a</sup></b>			
Median	23,479	19,602	26,697
Geometric mean	19,431	20,386	22,415
Median temperature, °C	38.2	38.0	38.2

Study designed to show that Coartem would achieve at least a 90% cure rate and reduce parasite clearance time by a clinically relevant 10 hours compared with lumefantrine.

<sup>a</sup> Sensitivity analysis showed that baseline parasite density did not affect treatment comparisons.

# Efficacy

## Study AB/MO2—China



Efficacy parameter	Coartem (4 × 80/480 mg)	Artemether (4 × 80 mg)	Lumefantrine (4 × 480 mg)
Median FCT, hrs (pts with fever at baseline)	24 (n = 36)	21 (n = 30)	60 (n = 38) ( $p < 0.001$ )
Median PCT, hrs (mITT)	30 (n = 51)	30 (n = 52)	54 (n = 52) ( $p < 0.001$ )

# Baseline Demographic and Disease Characteristics

## Study A023—China

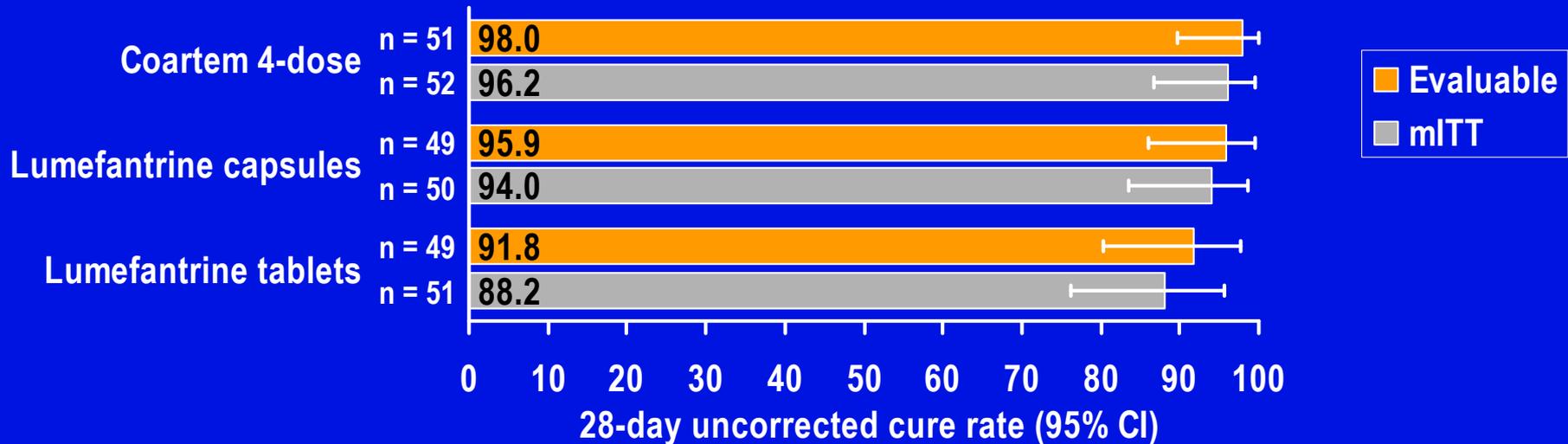
Characteristic	Coartem 4-dose n = 52	Lumefantrine	
		Tablets n = 51	Capsules n = 50
Male, n (%)	45 (87)	42 (80)	39 (78)
Female, n (%)	7 (13)	9 (20)	11 (22)
Median age, years (range)	24 (13 - 56)	22 (13 - 65)	19 (12 - 47)
Median weight, kg (range)	50 (34 - 65)	50 (35 - 70)	50 (35 - 61)
Parasite density,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

Study designed to have 80% power to show a 14-hour difference in parasite clearance time between Coartem and lumefantrine tablets.

<sup>a</sup> Sensitivity analysis showed that baseline parasite density did not affect treatment comparisons.

# Efficacy

## Study A023—China



Efficacy parameter	Coartem	Lumefantrine	
	4-dose	Tablets	Capsules
Median FCT, hrs (pts with fever at baseline)	21 (n = 24)	36 (n = 31) ( <i>p</i> = 0.017)	36 (n = 35) ( <i>p</i> = 0.046)
Median PCT, hrs (mITT)	30 (n = 52)	48 (n = 51) ( <i>p</i> < 0.001)	54 (n = 50) ( <i>p</i> < 0.001)

# Rationale for Assessing 6-Dose Regimen

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- ✦ Subsequent 4-dose studies were conducted in Thailand (A004, A008, A012)
  - Efficacy of 4-dose regimen from previous studies was not reproduced
    - 28-day cure rate<sup>a</sup> < 85%  
(69.3%, 82.1%, 76.5%, respectively)
- ✦ Therefore, 6-dose regimen was investigated
  - Goal: to achieve adequate cure rate<sup>a</sup>  
(ie, > 90%)

<sup>a</sup> Uncorrected cure rate in the evaluable population.

# Study Comparing Coartem 4-Dose vs 6-Dose Regimen Study A025

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# Baseline Demographic and Disease Characteristics

## Study A025—Thailand

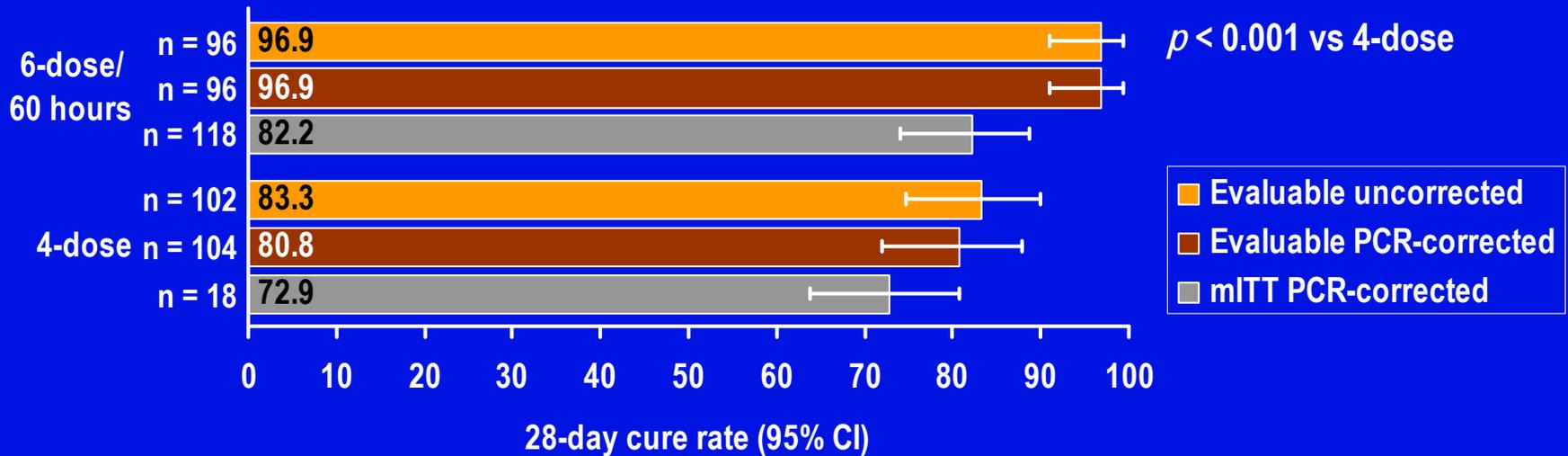
Characteristic	Coartem treatment regimen	
	4-dose n = 120	6-dose/60 hours n = 118
Male, n (%)	83 (69)	86 (73)
Female, n (%)	37 (31)	45 (27)
Median age, years (range)	24 (3 - 75)	23 (3 - 62)
Median weight, kg (range)	49.5 (12.5 - 92)	49.3 (10 - 90)
Parasite density, asexual forms/ $\mu\text{L}^{\text{a}}$		
Median	11,891	6,276
Geometric mean	10,273	9,260
Range	381 - 199,980	415 - 195,735
Median temperature, $^{\circ}\text{C}$ (range)	37.6 (36.0 - 40.8)	37.6 (36.0 - 40.8)

Study designed to have 80% power to show a 15% difference in 28-day cure rate between the 6-dose and 4-dose regimen.

<sup>a</sup> Sensitivity analysis showed that baseline parasite density did not affect treatment comparisons.

# Efficacy

## Study A025—Thailand



Efficacy parameter	Coartem treatment regimen		<i>p</i> value
	4-dose	6-dose/60 hours	
Median FCT, hrs (pts with fever at baseline)	23 (n = 61)	35 (n = 59)	<i>p</i> = 0.38
Median PCT, hrs (mITT)	43.8 (n = 120)	43.6 (n = 118)	<i>p</i> = 0.96

# Design of 6-Dose Regimen Studies

	A025	A026	A028	A2403	B2303	A2401
<b>Design</b>	Randomized double-blind	Randomized open-label	Randomized open-label	Open-label	Randomized Investigator-blind	Open-label
<b>Comparator</b>	4-dose regimen	MAS <sup>a</sup>	MAS <sup>a</sup>	–	Coartem dispersible tablet	–
<b>Patients</b>	Adults & children (> 2 years)	Adults & children (≥ 2 years)	Adults & adolescents (> 12 years)	Infants & children (5 to 25 kg)	Infants & children (5 to < 35 kg)	Adult non-immune travelers
<b>n Coartem/ N total</b>	118/359	150/200	164/219	310	452/899	165
<b>Geography</b>	Thailand	Thailand	Thailand	Africa	Africa	EU & Colombia

MAS = Mefloquine + artesunate.

<sup>a</sup> Study was not designed to compare Coartem with mefloquine + artesunate.

# Design of 6-Dose Regimen Studies

	A025	A026	A028	A2403	B2303	A2401
<b>Design</b>	Randomized double-blind	Randomized open-label	Randomized open-label	Open-label	Randomized Investigator-blind	Open-label
<b>Comparator</b>	4-dose regimen	MAS <sup>a</sup>	MAS <sup>a</sup>	–	Coartem dispersible tablet	–
<b>Patients</b>	Adults & children (> 2 years)	Adults & children (≥ 2 years)	Adults & adolescents (> 12 years)	Infants & children (5 to 25 kg)	Infants & children (5 to < 35 kg)	Adult non-immune travelers
<b>n Coartem/ N total</b>	118/359	150/200	164/219	310	452/899	165
<b>Geography</b>	Thailand	Thailand	Thailand	Africa	Africa	EU & Colombia

MAS = Mefloquine (25 mg/kg as split dose: 15 mg/kg on second day; 10 mg/kg on third day) + artesunate (4 mg/kg/day × 3 days).

<sup>a</sup> Study was not designed to compare Coartem with mefloquine + artesunate.

# Baseline Demographic and Disease Characteristics

## Study A026—Thailand

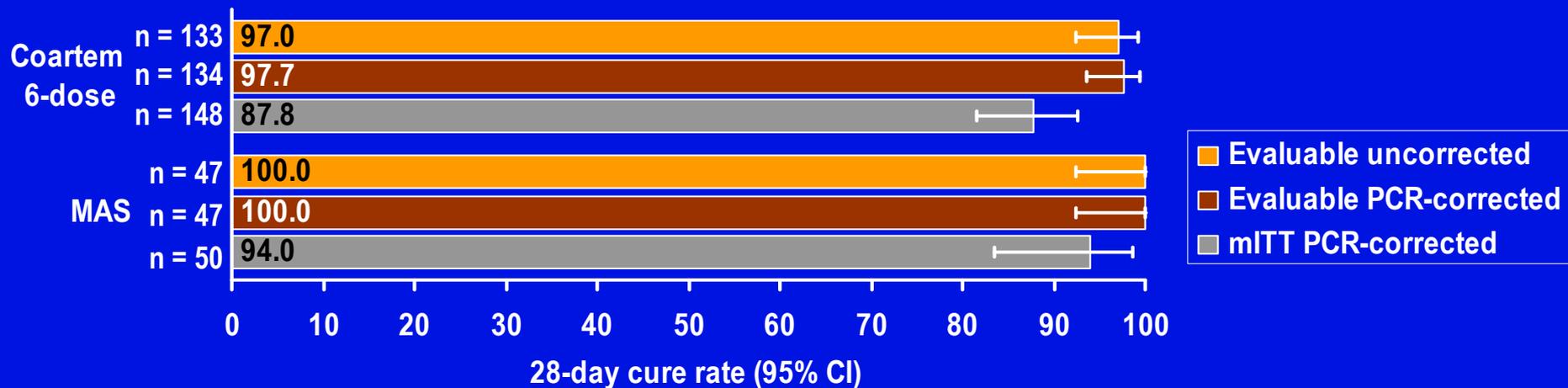
<b>Characteristic</b>	<b>Coartem n = 150</b>	<b>MAS n = 50</b>
Male, n (%)	110 (73)	37 (74)
Female, n (%)	40 (27)	13 (26)
Median age, years (range)	22 (2 - 63)	25 (3 - 61)
Median weight, kg (range)	50 (8 - 81)	50 (11 - 66)
Parasite density, asexual forms/ $\mu$ L		
Median	9,374	5,285
Geometric mean	9,162	8,452
Range	264 - 254,490	625 - 177,840
Median temperature, $^{\circ}$ C (range)	37.7 (35.6 - 40.2)	38.0 (36.0 - 39.9)

Study designed to show that the lower limit of the one-sided 95% confidence interval around the 28-day cure rate achieved with Coartem was above 90%.

MAS = Mefloquine + artesunate.

# Efficacy

## Study A026—Thailand



### Efficacy parameter

### Coartem

### MAS

Median FCT, hrs (pts with fever at baseline)

22 (n = 87)

22.2 (n = 33)

Median PCT, hrs (mITT)

48 (n = 149)

48 (n = 50)

# Baseline Demographic and Disease Characteristics

## Study A028—Thailand

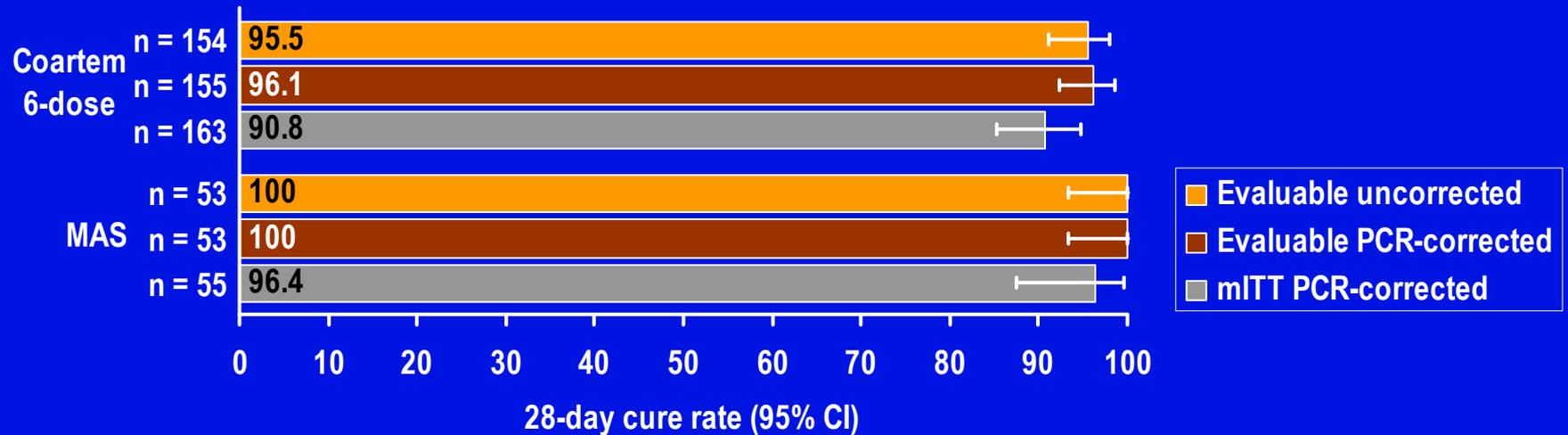
<b>Characteristic</b>	<b>Coartem n = 164</b>	<b>MAS n = 55</b>
Male, n (%)	115 (70)	41 (75)
Female, n (%)	49 (30)	14 (25)
Median age, years (range)	25 (12 - 71)	24 (12 - 60)
Median weight, kg (range)	50 (35 - 81)	52 (35 - 77)
Parasite density, asexual forms/ $\mu$ L		
Median	1,608	5,130
Geometric mean	2,063	3,329
Range	13 - 436,050	21 - 207,840
Median temperature, $^{\circ}$ C (range)	37.5 (36.0 - 40.3)	37.6 (36.5 - 40.5)

Study designed to show that the lower limit of the one-sided 95% confidence interval around the 28-day cure rate achieved with Coartem was above 85%.

MAS = Mefloquine + artesunate.

# Efficacy

## Study A028—Thailand



### Efficacy parameter

Median FCT, hrs (pts with fever at baseline)

**Coartem**

29 (n = 76)

**MAS**

23 (n = 29)

Median PCT, hrs (mITT)

29.3 (n = 164)

31 (n = 55)

# Design of 6-Dose Regimen Studies

	A025	A026	A028	A2403	B2303	A2401
<b>Design</b>	Randomized double-blind	Randomized open-label	Randomized open-label	Open-label	Randomized Investigator-blind	Open-label
<b>Comparator</b>	4-dose regimen	MAS <sup>a</sup>	MAS <sup>a</sup>	–	Coartem dispersible tablet	–
<b>Patients</b>	Adults & children (> 2 years)	Adults & children (≥ 2 years)	Adults & adolescents (> 12 years)	Infants & children (5 to 25 kg)	Infants & children (5 to < 35 kg)	Adult non-immune travelers
<b>n Coartem/ N total</b>	118/359	150/200	164/219	310	452/899	165
<b>Geography</b>	Thailand	Thailand	Thailand	Africa	Africa	EU & Colombia

MAS = Mefloquine + artesunate.

<sup>a</sup> Study was not designed to compare Coartem with mefloquine + artesunate.

# Baseline Demographic and Disease Characteristics

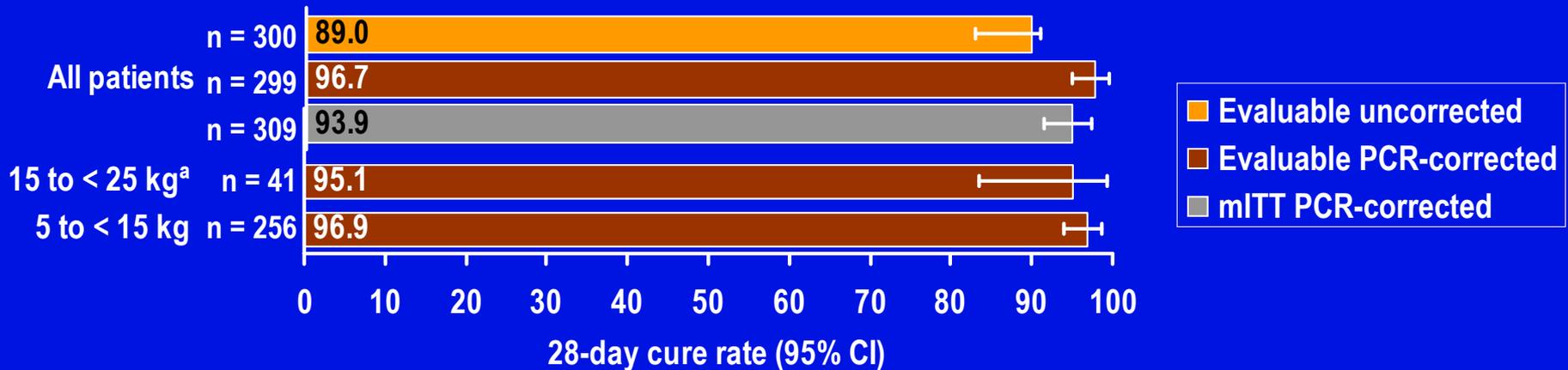
## Study A2403—Africa

<b>Characteristic</b>	<b>All patients N = 310</b>
Male, n (%)	161 (52)
Female, n (%)	149 (48)
Median age, months (range)	24.0 (2.4 – 118.8)
Median weight, kg (range)	10.0 (5.0 – 25.0)
Parasite density, asexual forms/ $\mu$ L	
Median	18,488
Mean $\pm$ SD	33,050 $\pm$ 32,976
Range	1,000 – 137,760
Median temperature, $^{\circ}$ C (range)	38.5 (37.5 – 40.9)

Primary objective was to assess the safety of the 6-dose regimen in young children, particularly infants with a body weight of 5 to less than 10 kg. Efficacy was a secondary objective.

# Efficacy

## Study A2403—Africa



Efficacy parameter	Body weight group		
	5 to < 15 kg	15 to < 25 kg <sup>a</sup>	All patients
Median FCT, hours (pt with fever at baseline)	7.9 (n = 263)	7.8 (n = 44)	7.8 (n = 309)
Median PCT, hours (mITT)	24.1 (n = 264)	24 (n = 44)	24.0 (n = 310)

<sup>a</sup> 2 patients were exactly 25 kg and are not included in the analysis; both were cured of malaria on day 28.

# Baseline Demographic and Disease Characteristics

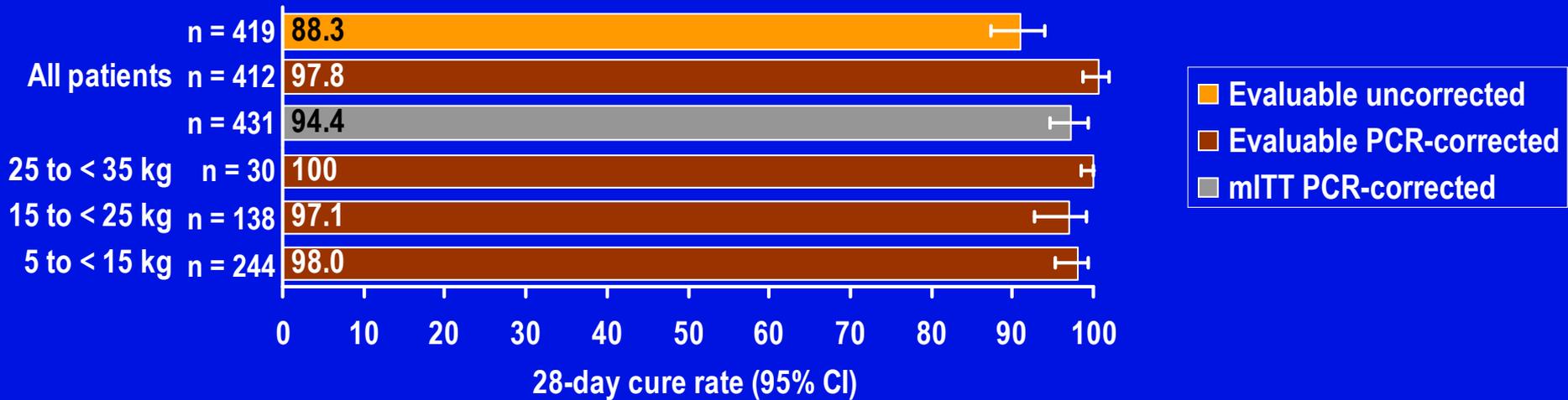
## Study B2303—Africa

<b>Characteristic</b>	<b>Coartem crushed n = 452</b>
Male, n (%)	247 (55)
Female, n (%)	205 (45)
Median age, months (range)	36 (2 - 144)
Median weight, kg (range)	13.1 (6 - 34)
Parasite density , asexual forms/ $\mu$ L	
Median	32,288
Range	1,581 - 628,571
Median temperature, °C (range)	37.9 (35.6 - 41.1)

Primary objective was to demonstrate non-inferiority of the dispersible tablet compared with the crushed tablet based on the 28-day PCR-corrected cure rate.

# Efficacy

## Study B2303—Africa



Efficacy parameter	Body weight group			
	5 to < 15 kg	15 to < 25 kg	25 to < 35 kg	All patients
Median FCT, hrs (pts with fever at baseline)	7.9 (n = 188)	7.8 (n = 102)	7.7 (n = 21)	7.8 (n = 311)
Median PCT, hrs (mITT)	35.3 (n = 273)	34.6 (n = 145)	25.8 (n = 34)	34.9 (n = 452)

# 6-Dose Regimen Studies

	A025	A026	A028	A2403	B2303	A2401
<b>Design</b>	Randomized double-blind	Randomized open-label	Randomized open-label	Open-label	Randomized Investigator-blind	Open-label
<b>Comparator</b>	4-dose regimen	MAS <sup>a</sup>	MAS <sup>a</sup>	–	Coartem dispersible tablet	–
<b>Patients</b>	Adults & children (> 2 years)	Adults & children (≥ 2 years)	Adults & adolescents (> 12 years)	Infants & children (5 to 25 kg)	Infants & children (5 to < 35 kg)	Adult non-immune travelers
<b>n Coartem/ N total</b>	118/359	150/200	164/219	310	452/899	165
<b>Geography</b>	Thailand	Thailand	Thailand	Africa	Africa	EU & Colombia

MAS = Mefloquine + artesunate.

<sup>a</sup> Study was not designed to compare Coartem with mefloquine + artesunate.

# Baseline Demographic and Disease Characteristics

## Study A2401—Non-Immune<sup>a</sup> Travelers

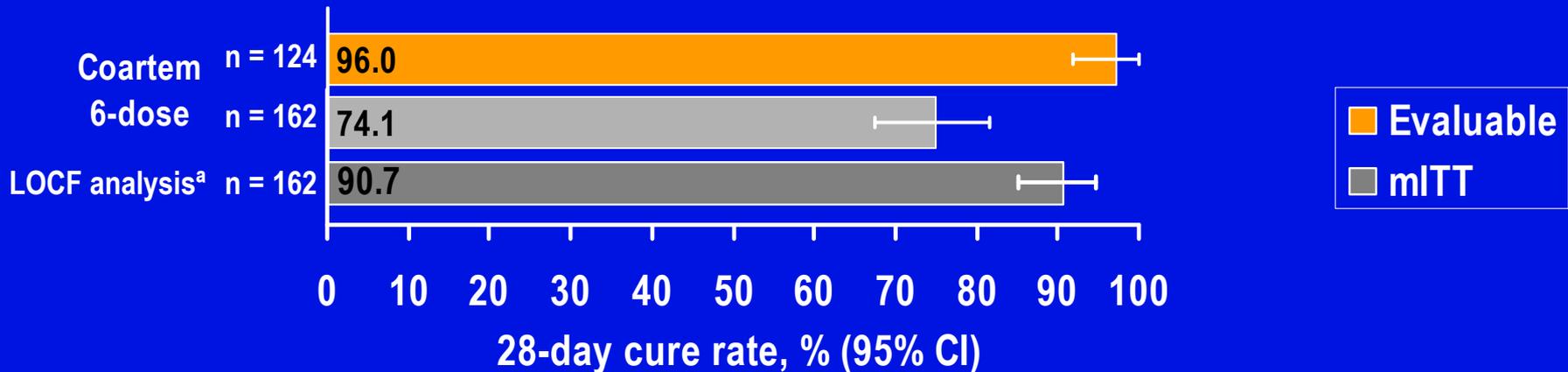
Characteristic	N = 165
Male, n (%)	113 (68)
Female, n (%)	52 (32)
Race, n (%)	
Caucasian	80 (48.5)
Black	40 (24.2)
Other	45 (27.3)
Median age, yrs (range)	37 (17 – 66)
Median weight, kg (range)	73 (41 - 119)
Parasite density per 1,000 RBCs	
Median	2.4
Mean $\pm$ SD	6.2 $\pm$ 9.45
Range	0 - 70
Median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

The sample size of 140 was based on an assumed cure rate of 90% in the evaluable population. The study was powered to assess cure rate with a precision of  $\pm$  5% (ie, confidence interval of 10%).

<sup>a</sup> Non-immune patients were defined as those who neither spent the first 5 years of their life nor the last 5 years prior to study entry in a malaria endemic area and who did not have acute *P falciparum* malaria diagnosed in the last 5 years.

# Efficacy

## Study A2401—Non-Immune Travelers



### Efficacy parameter

**N = 162**

Median FCT, hrs (pts with fever at baseline)

36.5 (n = 100)

Median PCT, hrs (mITT)

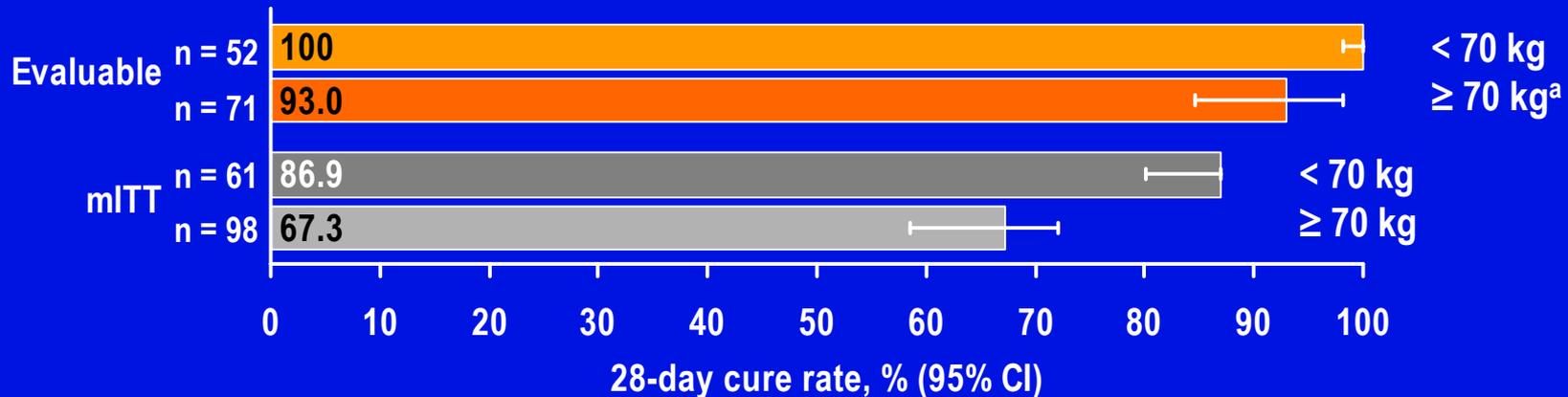
41.8 (n = 162)

<sup>a</sup> Posthoc analysis; patient considered a responder if parasite clearance reached by hour 216 (or day 7 blood microscopy missing) and the latest available blood microscopy is negative and no reappearance or rescue medication intake documented in study.

LOCF = Last observation carried forward.

# Efficacy by Body Weight

## Study A2401—Non-Immune Travelers



### Efficacy parameter

< 70 kg

≥ 70 kg

Median FCT, hrs (mITT)

24.5 (n = 61)

38.7 (n = 98)

Median PCT, hrs (mITT)

41.5 (n = 61)

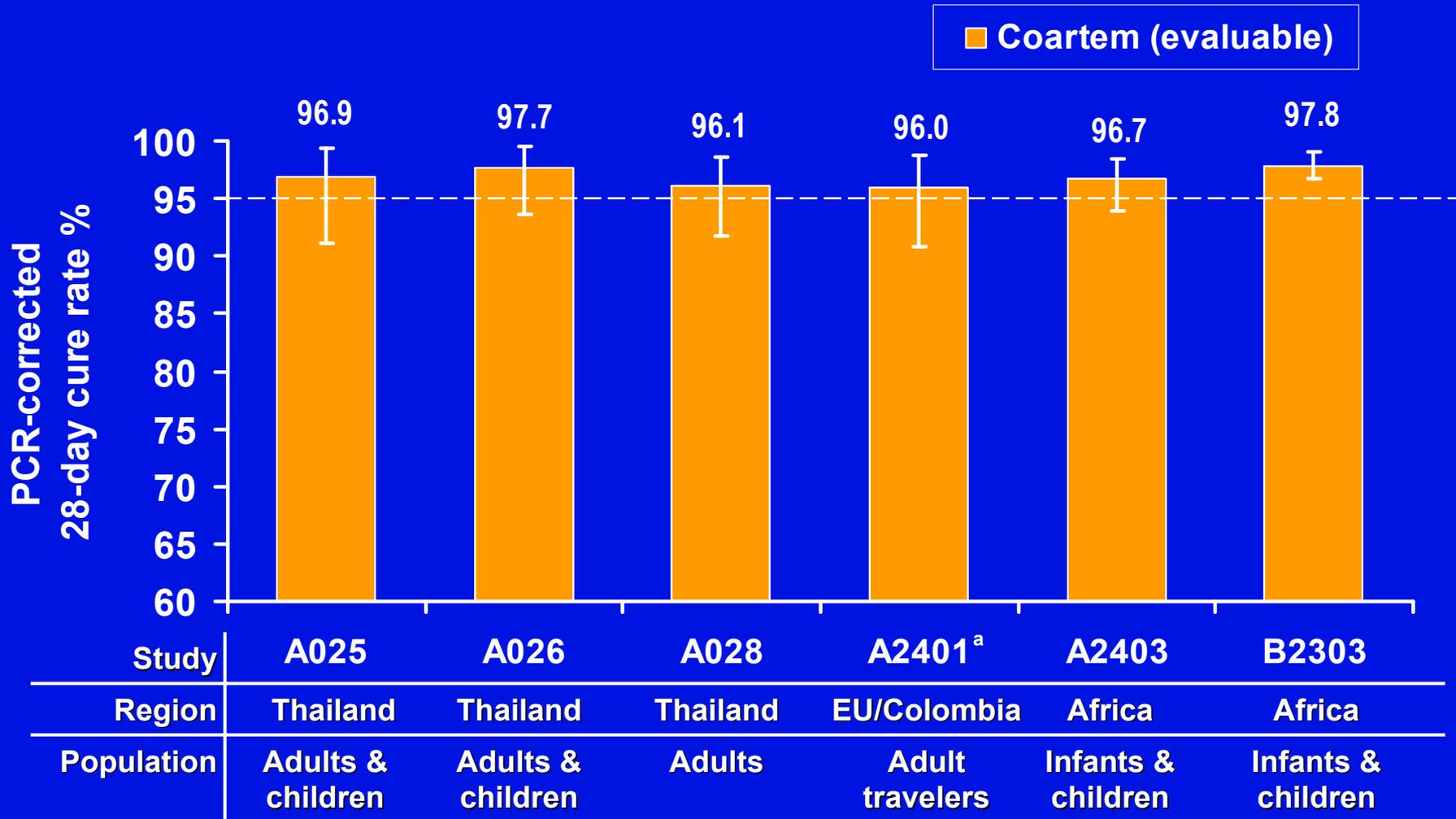
41.8 (n = 98)

- Five patients > 100 kg (maximum 115 kg) were all cured at day 28 except for one lost to follow-up who was cured at day 7

<sup>a</sup> 3 patients had recrudescence (D22 and D28) 1 progressed to severe malaria after the second dose, and 1 patient without a day 7 or day 28 assessment was clear of parasites at day 10.

# Summary—PCR-Corrected 28-Day Cure Rates

## Key 6-Dose Studies—Evaluable



<sup>a</sup> Uncorrected cure rate.

# Coartem in Mixed Infections Including *P falciparum*

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# Efficacy in Patients With Mixed Infections Including *P falciparum*

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

## Overall Efficacy Conclusions (1)

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- ✦ **Combination of artemether-lumefantrine was more effective than either drug as monotherapy**
- ✦ **6-dose regimen was significantly more effective than the 4-dose regimen**
- ✦ **28-day PCR-corrected cure rate achieved with 6-dose regimen in evaluable patients consistently met WHO criteria for efficacy ( $\geq 95\%$ )<sup>a</sup>**
- ✦ **Rapid clearance of parasitemia and fever**

## Overall Efficacy Conclusions (2)

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- ✦ **Comparable efficacy was achieved in**
  - **Diverse patient populations from a range of geographic regions with varying endemicity**
  - **Travelers from non-endemic regions**
  - **Children and infants  $\geq 5$  kg (2 months old)**
- ✦ **Although Coartem does not provide radical cure for *P vivax* or *P ovale*, treatment provides rapid clearance of parasites**

# Coartem (artemether-lumefantrine) Tablets Safety

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# Pooled Clinical Safety Database

## Entered Study Population

- ✦ 20 Novartis-sponsored studies
  - Adult patients (> 16 years of age)
  - Pediatric patients ( $\leq$  16 years of age)

Population	Patients, n		
	Coartem 4-dose	Coartem 6-dose	Coartem total
Adult	925	647	1572
Pediatric	694	1333 <sup>a,b</sup>	2027
<b>Total</b>	<b>1619</b>	<b>1980</b>	<b>3599</b>

<sup>a</sup> One patient did not receive treatment.

<sup>b</sup> Includes patients treated with the dispersible tablet.

# Safety Evaluations

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- ✦ **Adverse events**
  - Reporting of AEs varies according to age
- ✦ **Serious adverse events**
- ✦ **Laboratory assessments performed locally**
- ✦ **Systematic neurological evaluations performed in studies A025, A026, A2403, and B2303**
- ✦ **EKG evaluations performed in most studies**

# Patient Disposition

## Adult > 16 Years

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

<sup>a</sup> Discontinuation at any time during studies, not only discontinuation of treatment. <sup>b</sup> Two patients discontinued treatment due to unsatisfactory effect; 1 patient on the 4-dose regimen on day 2 (received rescue medication) and 1 patient on the 6-dose regimen on day 1 because of signs of severe malaria.

# Patient Disposition

## Pediatric $\leq 16$ Years

	Patients, n (%)		
	Coartem 4-dose n = 694	Coartem 6-dose <sup>a</sup> n = 1332	Coartem total N = 2026
Safety population (received $\geq 1$ dose)	694 (100.0)	1332 (100.0)	2026 (100)
Completed study	513 (73.9)	1190 (89.3)	1703 (84.0)
Discontinued study prematurely <sup>b</sup>	181 (26.1)	143 (10.7)	324 (16.0)
Adverse event(s)	4 (0.6)	71 (5.3)	75 (3.7)
Unsatisfactory therapeutic effect <sup>c</sup>	99 (14.3)	6 (0.5)	105 (5.2)
Protocol violation	12 (1.7)	2 (0.2)	14 (0.7)
Subject withdrew consent	4 (0.6)	19 (1.4)	23 (1.1)
Lost to follow-up	55 (7.9)	40 (3.0)	95 (4.7)
Administrative problems	5 (0.7)	0	5 (0.2)
Death	0	4 (0.3)	4 (0.2)
Non-compliance	2 (0.3)	0	2 (0.1)

<sup>a</sup> Includes patients treated with the dispersible tablet.

<sup>b</sup> Discontinuation at any point during studies, not only discontinuation of treatment.

<sup>c</sup> One patient on the 4-dose regimen discontinued treatment due to unsatisfactory effect.

# Overall Safety Profile

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# Deaths, SAEs, and Premature Study Drug Discontinuations Due to AEs

Adult > 16 Years

Serious or significant AE	Adults, n (%)		
	Coartem 4-dose n = 925	Coartem 6-dose n = 647	Coartem total N = 1572
Death	3 (0.2)	0	3 (0.2)
Non-fatal SAE	6 (0.6)	9 (1.4)	15 (0.7)
AE leading to study drug discontinuation	0	1 (0.1)	1 (0.05)

Study	Age/ Sex	Day of last dose	Day of death	Cause of death
A008	20 yr/M	3	9	Gun shot wound
A025	37 yr/M	3	15	Gun shot wound
A025	36 yr/M	3	20	Land mine

# Serious Adverse Events (1)

## Adult > 16 Years

### Coartem 6-Dose Regimen

Study No	Age/ Sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
A2401	55 yr/F	Malaria progression (severe)	2	7	Yes
		Increased bilirubin (moderate)	2	7	Yes
		Increased transaminases (moderate)	2	7	Yes
		Mental impairment (moderate)	2	4	Yes
		Vomiting (moderate)	2	3	Yes
A2401	54 yr/M	Malaria recrudescence (severe)	21	29	Yes
		EKG abnormal T wave (severe)	22	—	Unknown
A2401	62 yr/F	Malaria recrudescence (severe)	23	27	No
		Chills (moderate)	23	27	No
		Fever (moderate)	23	27	No
		Headache (moderate)	23	—	No

# Serious Adverse Events (2)

## Adult > 16 Years

### Coartem 6-Dose Regimen

Study No	Age/ Sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
A2401	30 yr/M	Hematuria (mild)	1	5	No
		Malaise (mild)	1	8	No
		Abdominal pain (moderate)	2	39	Unknown
		Elevated liver tests (moderate)	4	26	Yes
		Thrombocytopenia (moderate)	4	8	No
A2401	37 yr/F	Liver cell injury (moderate)	8	16	No
A2401	55 yr/M	Endocarditis (moderate)	3	43	No
A025	20 yr/M	Typhoid fever (moderate)	8	19	No
A026	17 yr/M	Febrile coma <sup>a</sup> (life-threatening)	14	24	No
A028	28 yr/M	Dyspnoea (severe)	2	4	No
		Pulmonary edema due to fluid overload (severe)	2	5	No

<sup>a</sup> Unknown etiology not related to malaria; patient treated with empirical antibiotic treatment for pneumonia and meningitis.

# Deaths, SAEs, Premature Study Drug Discontinuations Due to AEs

## Pediatric $\leq 16$ Years

Serious or significant AE	Pediatric patients, n (%)		
	Coartem 4-dose n = 694	Coartem 6-dose <sup>a</sup> n = 1332	Coartem total N = 2026
Death	0	4 (0.3)	4 (0.2)
Non-fatal SAE	7 (1.0)	13 (1.0)	20 (1.0)
AE leading to study drug discontinuation <sup>b</sup>	0	21 (1.6)	21 (1.0)

<sup>a</sup> Includes patients treated with the dispersible tablet.

<sup>b</sup> 17 patients in Study B2303 discontinued (per protocol) because they developed severe vomiting or vomited more than 2 doses of study drug within 1 hour of administration or vomited a replacement dose within 2 hours of intake; 3 patients in Study B2303 discontinued due to severe malaria (n = 2) or severe respiratory tract infection (n = 1); 1 patient in Study A2403 discontinued due to severe urticaria.

# Deaths

## Pediatric $\leq 16$ Years

- ✦ All deaths occurred in the 6-dose group
- ✦ None considered related to study drug

Study No	Age/ Sex	Day of last dose	Day of death	Cause of death
B2303	4 mo/M	2	3	<b>Unspecified infection</b> with pyrexia and dehydration, treated with quinine, paracetamol, metoclopramide, and amoxicillin
B2303	2 yr/M	4	7	<b>Hemorrhage</b> on day 5 following scarification by traditional therapist
A2403	4 yr/F	4	9	<b>Severe gastroenteritis</b> at day 9 with moderate diarrhea, treated with oral rehydration therapy
B2303	5 mo/M	4	31	<b>Severe malaria</b> on day 29, reinfection or recrudescence undetermined, cleared parasites within 24h and still cleared on day 14

# Serious Adverse Events (1)

Pediatric  $\leq$  16 Years

Coartem 6-Dose Regimen

Study No	Age/ Sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
B2303	7 mo/M	Malaria (severe)	1	8	No
		Anemia (severe)	1	29	No
B2303	9 mo/M	Malaria (severe)	2	3	No
		Anemia (severe)	2	29	No
B2303	5 mo/M	Malaria (severe)	26	32	No
		Pneumonia (severe)	26	43	No
B2303	1 yr/M	Malaria (severe)	27	34	No
A2403	8 mo/F	Malaria (severe)	28	—	No
		Convulsion (moderate)	28	28	No
B2303	2 yr/M	Malaria (severe)	42	—	No
		Convulsions (mild)	42	—	No

# Serious Adverse Events (2)

## Pediatric ≤ 16 Years

### Coartem 6-Dose Regimen

Study No	Age/ Sex	Serious adverse event (severity)	Day of onset	Day of resolution	Relationship to study drug
A2403	1 yr/M	Viral hepatitis (severe)	2	—	No
A2403	4 yr/F	Urticarial rash (severe)	2	6	Yes
		Atypical pneumonia (moderate)	22	29	No
B2303	2 yr/F	Lower respiratory tract infection (severe)	2	4	No
B2303	4 yr/F	Anemia (severe)	4	15	No
		Fever (severe)	4	15	No
		Facial edema (severe)	6	15	No
B2303	6 mo/M	Acute laryngeal tracheal bronchitis (severe)	22	29	No
B2303	5 yr/M	Convulsions (severe)	29	30	No
		Pyrexia (mild)	29	30	No
		Epilepsy	44	64	No
B2303	1 yr/F	Dehydration (moderate)	43	—	No
		Diarrhea (moderate)	43	—	No
		Vomiting (mild)	43	—	No

# AEs ≥ 5%: Coartem 4-Dose Versus 6-Dose Regimen (1)

## Study A025

Preferred term	Patients, n (%)	
	4-dose n = 120	6-dose <sup>a</sup> n = 239
Headache	113 (94.2)	228 (95.4)
Anorexia	102 (85.0)	203 (84.9)
Asthenia	93 (77.5)	183 (76.6)
Dizziness	81 (67.5)	171 (71.5)
Myalgia	87 (72.5)	163 (68.2)
Arthralgia	77 (64.2)	156 (65.3)
Nausea	56 (46.7)	117 (49.0)
Chills	47 (39.2)	110 (46.0)
Sleep disorder	49 (40.8)	99 (41.4)
Vomiting	40 (33.3)	89 (37.2)
Palpitations	47 (39.2)	84 (35.1)
Fatigue	34 (28.3)	84 (35.1)
Abdominal pain	40 (33.3)	75 (31.4)

<sup>a</sup> 6-dose includes both 60-hour and 96-hour regimens.

# AEs ≥ 5%: Coartem 4-Dose Versus 6-Dose Regimen (2)

## Study A025

Preferred term	Patients, n (%)	
	4-dose n = 120	6-dose <sup>a</sup> n = 239
Splenomegaly	29 (24.2)	49 (20.5)
Hepatomegaly	22 (18.3)	46 (19.2)
Anemia	10 (8.3)	18 (7.5)
Clonus	5 (4.2)	17 (7.1)
Tremor	9 (7.5)	16 (6.7)
Pruritus	13 (10.8)	14 (5.9)
Rash	13 (10.8)	14 (5.9)
Diarrhea	7 (5.8)	13 (5.4)
Helminthic infection	4 (3.3)	13 (5.4)
Parasitic gastroenteritis	3 (2.5)	12 (5.0)

<sup>a</sup> 6-dose includes both 60-hour and 96-hour regimens.

# AEs $\geq$ 5%: Coartem 6-Dose Regimen in Adults Versus Pediatric Patients (1)

## Study A025

Preferred term	Patients, n (%)	
	Adult n = 88	Pediatric n = 30
Headache	81 (92.0)	27 (90.0)
Anorexia	76 (86.4)	25 (83.3)
Dizziness	69 (78.4)	14 (46.7)
Asthenia	67 (76.1)	17 (56.7)
Arthralgia	66 (75.0)	10 (33.3)
Myalgia	66 (75.0)	15 (50.0)
Nausea	41 (46.6)	12 (40.0)
Chills	39 (44.3)	11 (36.7)
Sleep disorder	39 (44.3)	6 (20.0)
Fatigue	38 (43.2)	5 (16.7)
Palpitations	34 (38.6)	5 (16.7)
Vomiting	33 (37.5)	9 (30.0)
Abdominal pain	25 (28.4)	7 (23.3)

# AEs $\geq$ 5%: Coartem 6-Dose Regimen in Adults Versus Pediatric Patients (2)

## Study A025

Preferred term	Patients, n (%)	
	Adult n = 88	Pediatric n = 30
Splenomegaly	14 (5.9)	10 (33.3)
Hepatomegaly	13 (14.8)	9 (30.0)
Clonus	8 (9.1)	0
Tremor	8 (9.1)	0
Anemia	6 (6.8)	3 (10.0)
Pruritus	7 (8.0)	0
Rash	7 (8.0)	0
Helminthic infection	6 (6.8)	2 (6.7)
Nasopharyngitis	5 (5.7)	0
Parasitic gastroenteritis	0	6 (20.0)
Pneumonia	0	3 (10.0)
Ascariasis	0	2 (6.7)

# AEs $\geq$ 5%: Coartem Versus Mefloquine-Artesunate

## Studies A026 & A028

Preferred term	Patients, n (%)	
	Coartem 6-dose n = 314	MAS n = 105
Pyrexia	183 (58.3)	63 (60.0)
Headache	166 (52.9)	46 (43.8)
Dizziness	123 (39.2)	37 (35.2)
Anorexia	108 (34.4)	37 (35.2)
Asthenia	108 (34.4)	33 (31.4)
Arthralgia	99 (31.5)	31 (29.5)
Nausea	82 (26.1)	34 (32.4)
Myalgia	74 (23.6)	19 (18.1)
Sleep disorder	70 (22.3)	30 (28.6)
Chills	67 (21.3)	20 (19.0)
Abdominal pain	61 (19.4)	20 (19.0)
Palpitations	55 (17.5)	17 (16.2)
Vomiting	50 (15.9)	22 (21.0)
Hepatomegaly	48 (15.3)	8 (7.6)
Splenomegaly	40 (12.7)	12 (11.4)
Fatigue	34 (10.8)	8 (7.6)

# Postmarketing Experience

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- ✦ 137 spontaneous cases reported between October 1998 and August 2008
  - 60% of reports from Africa
  - Only 13% concerned children  $\leq$  16 years
- ✦ “General Disorders” (22 cases) and “Infections” (11 cases) were the most reported System Organ Classes
  - Mostly persistence or recurrence of malaria
- ✦ Other cases included
  - Hypersensitivity and/or skin reactions (27 cases)
  - Hemolysis and hemoglobinuria (13 cases)

# Safety Topics of Special Interest

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# Nervous System and Ear/Labyrinth Safety

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# Preclinical Neurotoxicology Data in Dogs

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- ✦ Coartem 1000 mg/kg/day (contains 143 mg/kg/day artemether) resulted in no neurologic symptoms or brain lesions after 13 weeks of oral dosing
- ✦ Artemether 300 mg/kg/day orally for 13 weeks resulted in exposure similar to humans and no neurologic symptoms or brain lesions
- ✦ IM doses of artemether  $\geq 20$  mg/kg/day for 7 days were associated with brain stem and cerebellum root nuclei lesions
  - Exposure was 8.7 times greater than that in humans following oral dosing

# Nervous System Disorders: 6-Dose Group

## Adult > 16 Years

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Preferred term	Coartem 6-dose, n (%) n = 647
Headache	360 (55.6)
Dizziness	253 (39.1)
Tremor	16 (2.5)
Clonus	16 (2.5)
Nystagmus	5 (0.8)
Hypoesthesia	4 (0.6)
Ataxia	3 (0.5)
Somnolence	3 (0.5)
Fine motor delay	2 (0.3)
Mental impairment	1 (0.2)
Coma	1 (0.2)

# Nervous System Disorders: 6-Dose Group

## Pediatric ≤ 16 Years

Preferred term	Coartem 6-dose <sup>a</sup> , n (%) n = 1332
Headache	168 (12.6)
Dizziness	56 (4.2)
Clonus	11 (0.8)
Hyperreflexia	6 (0.5)
Convulsion	4 (0.3)
Somnolence	4 (0.3)
Myoclonus	3 (0.2)
Tremor	2 (0.2)
Dyskinesia	1 (0.1)
Epilepsy	1 (0.1)
Nystagmus	1 (0.1)
Ataxia	1 (0.1)

<sup>a</sup> Includes patients treated with the dispersible tablet.

# Nervous System Disorders by Age Group: 6-Dose Group<sup>a</sup>

## Pediatric ≤ 16 Years

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

<sup>a</sup> Includes patients treated with the dispersible tablet.

# Ear and Labyrinth Disorders: 6-Dose Group Adult > 16 Years

Preferred term	Coartem 6-dose, n (%) n = 647
Vertigo <sup>a</sup>	21 (3.2)
Tinnitus	4 (0.6)
Motion sickness	2 (0.3)
Middle ear inflammation	1 (0.2)
Deafness <sup>b</sup>	1 (0.2)

<sup>a</sup> All cases reported in Study A2401 where vertigo was preprinted on case report form.

<sup>b</sup> Transient worsening of hearing impairment present at baseline.

# Ear and Labyrinth Disorders: 6-Dose Group Pediatric $\leq$ 16 Years

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Preferred term	Coartem 6-dose <sup>a</sup> , n (%) n = 1332
Ear pain	3 (0.2)
Cerumen impaction	1 (0.1)
Ear pruritus	1 (0.1)
Otorrhea	1 (0.1)

<sup>a</sup> Includes patients treated with the dispersible tablet.

# Postmarketing Experience Since 1998

## Nervous System and Ear/Labyrinth Disorders<sup>a</sup>

	Patients, n		
	Adult n = 34	Children n = 18	Unknown n = 4
<b>Nervous system reports</b>			
Spontaneous (AEs and SAEs)	18	4	4
SAEs from clinical trials <sup>b</sup>	16	14	0

- ✦ Most frequent AEs in adults: headache and dizziness
- ✦ Most frequent AEs in pediatric patients: febrile convulsions
- ✦ Review of serious cases does not suggest any new safety signals

<sup>a</sup> There were no cases of ear and labyrinth disorders.

<sup>b</sup> Includes ongoing trials, post-marketing surveillance studies, and investigator-initiated trials

# Auditory Function and Auditory Brain Response (ABR)

## Study A2417—Ongoing Study

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- ✦ Open-label, randomized, single-center, parallel group study of Coartem, Malarone, and Mefloquine + artesunate
- ✦ **Assessments**
  - Tympanometry, pure tone threshold, and ABR Wave III latency
    - At baseline and on day 3, 7, 28, and 42
  - Pharmacokinetics
- ✦ DSMB review of data from first 85 patients did not raise any safety concerns – study allowed to proceed
- ✦ Patient accrual is complete (N = 265)

# Cardiac Safety

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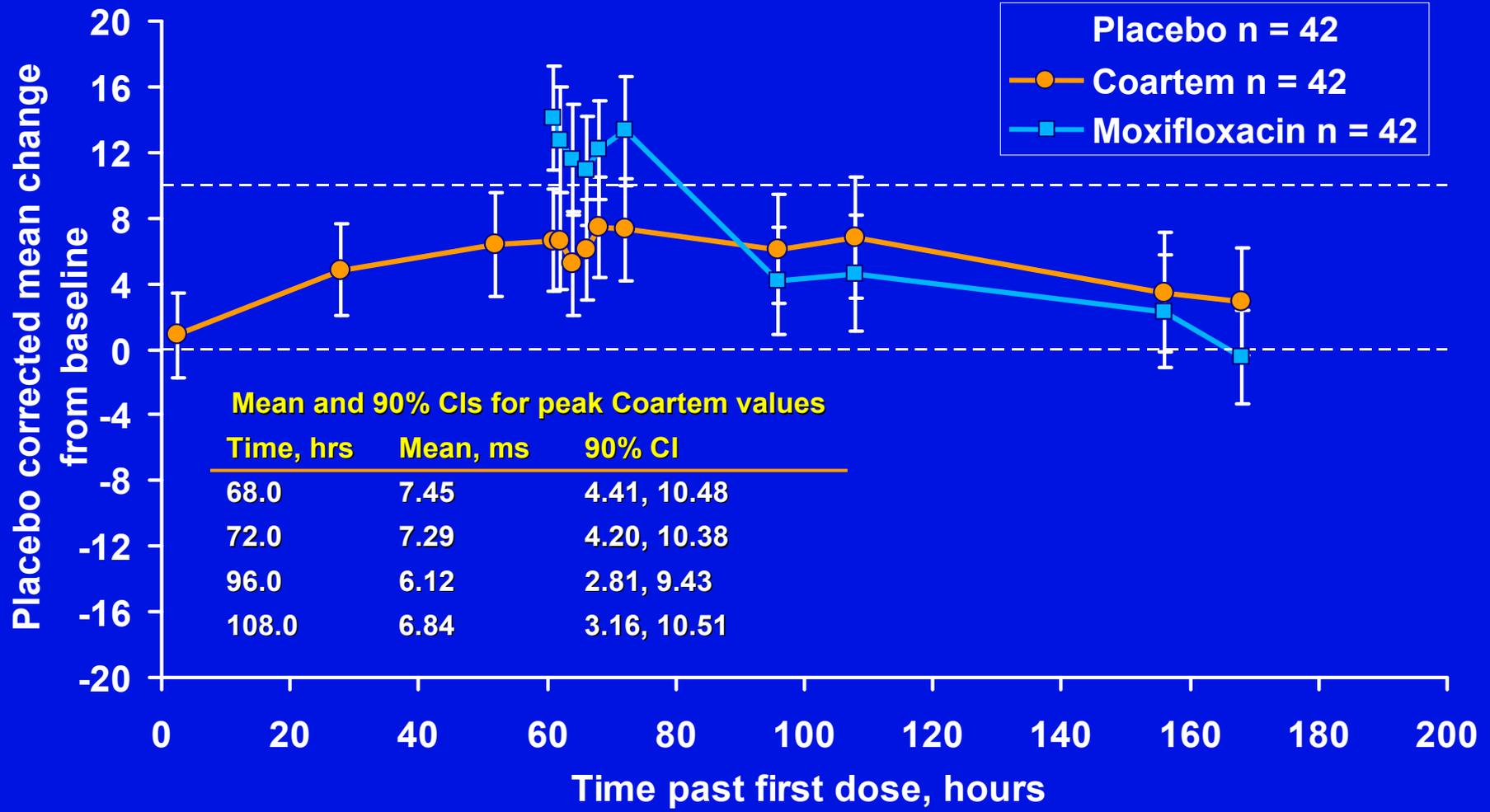
# In Vitro hERG Channel Assay Using HEK 293: Antimalarial Drugs

<b>Agent</b>	<b>IC<sub>50</sub>- IKr in <math>\mu\text{M}</math></b>	<b>IC<sub>50</sub>/therapeutic free plasma concentration<sup>a</sup></b>
Halofantrine	0.04	0.07
Chloroquine	2.5	6.3
Mefloquine	2.6	50
Lumefantrine	8.1	48
Desbutyl-lumefantrine	5.5	~2900

<sup>a</sup> Cardiac safety index (> 30 = cardiotoxicity unlikely).

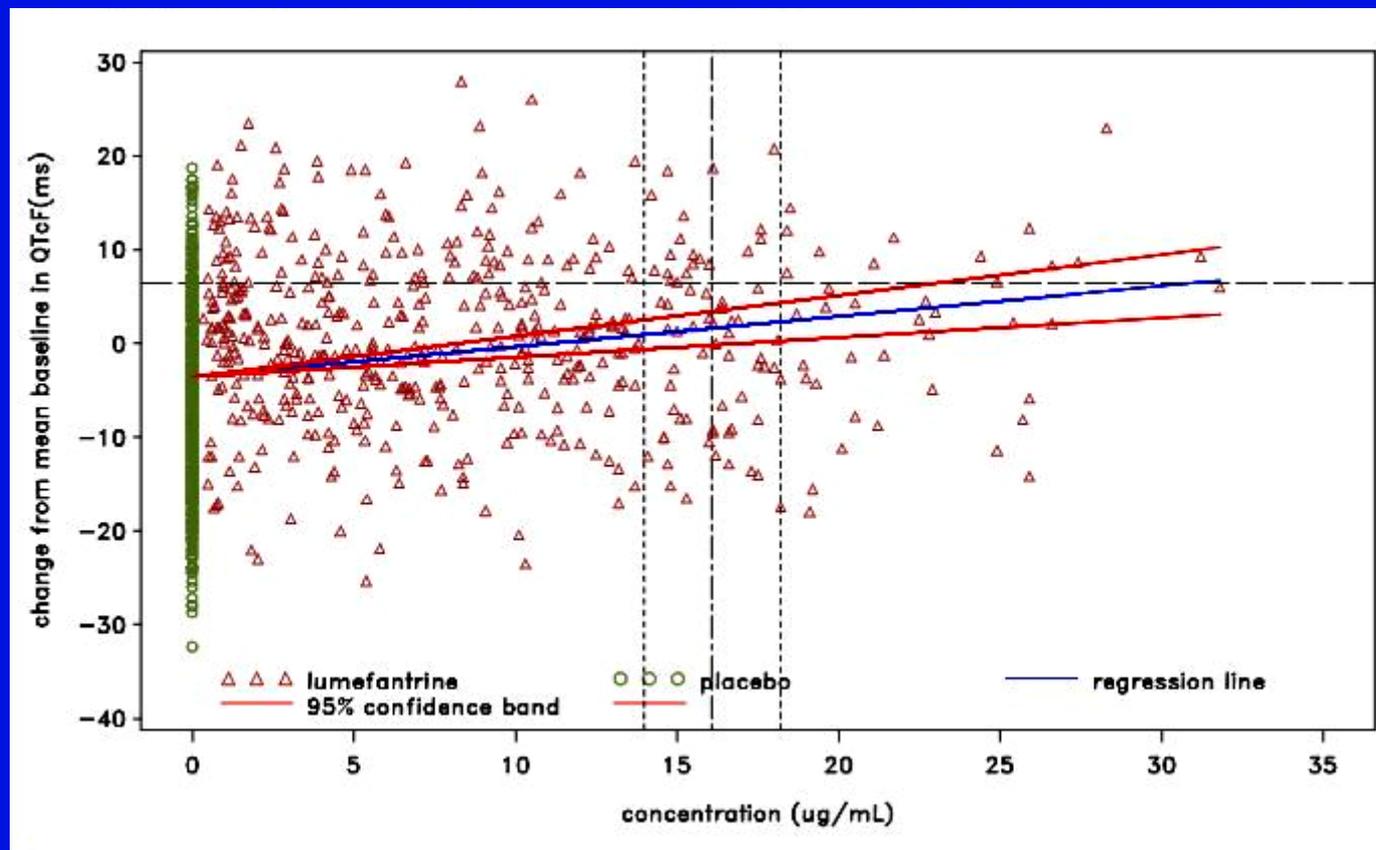
# Placebo-Corrected Mean Change From Time-Averaged Baseline QTc(F)

## Study A2101 (ICH E14)–Healthy Volunteers



# QTc(F) and Lumefantrine Exposure or $C_{max}$ Study A2101 (ICH E14)–Healthy Volunteers

- At the mean  $C_{max}$ , a 10-msec increase versus placebo is excluded



# Summary of Safety Results

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- ✦ Safety and tolerability assessed in nearly 3600 patients
- ✦ Majority of AEs likely associated with malaria or concomitant infections
- ✦ Few deaths or SAEs occurred and likely not associated with Coartem
- ✦ Vast majority of nervous system and ear/labyrinth disorders were of mild intensity and reversible
- ✦ No AEs related to QTc prolongation
- ✦ No new safety signals from spontaneous reporting apart from hypersensitivity reactions

# **Coartem Tablets**

## **Benefit/Risk Assessment**

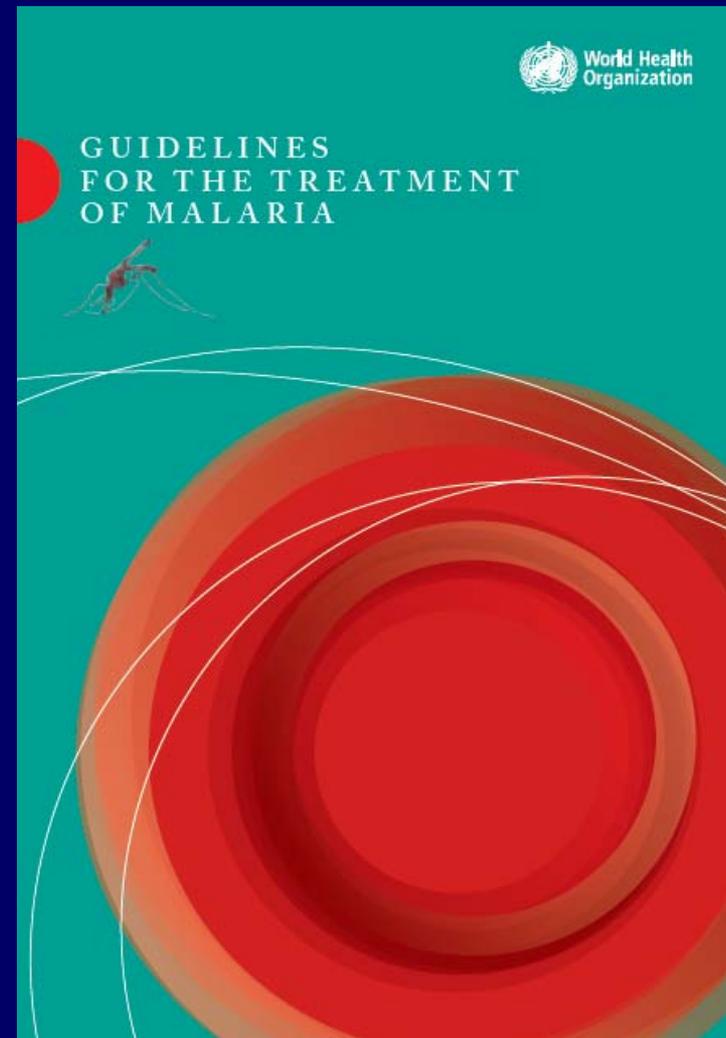
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**Philip Rosenthal, MD**

**Professor, Department of Medicine  
University of California, San Francisco,  
School of Medicine**

# WHO Treatment Guidelines—2006

- ACTs first line
- Aim for 95% cure rates at day 28\*
- Change policy if  $< 90\%$  cure rate
- Minimum duration of follow-up should be 28 days



\* Evaluable population; PCR-corrected.  
[www.who.int/malaria/docs/TreatmentGuidelines2006.pdf](http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf)

# Summary of Antimalarial Efficacy Meta-Analysis of 32 Published Studies

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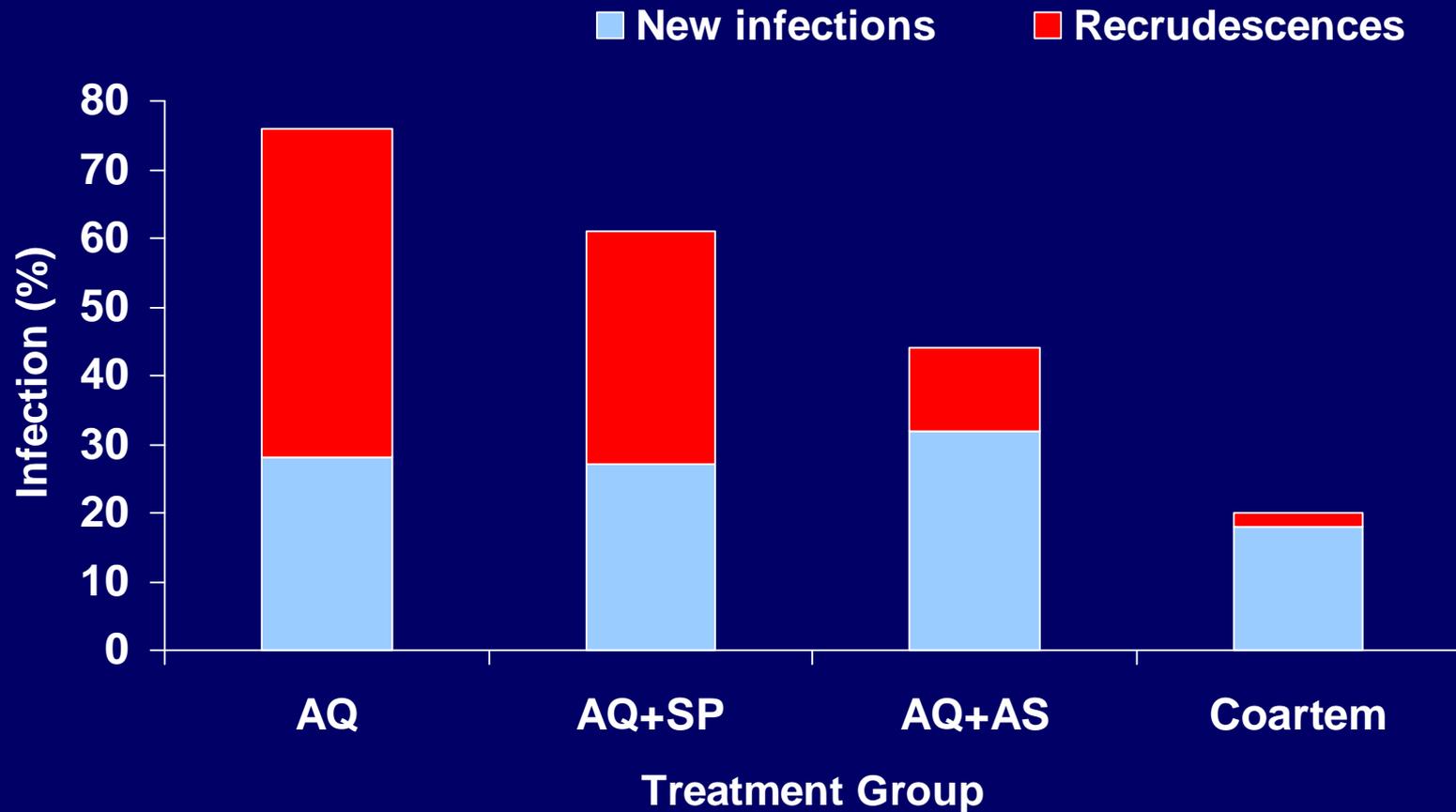
<b>Treatment combination</b>	<b>28-day PCR-corrected cure rate<sup>a</sup>, %</b>
<b>Coartem</b>	<b>97.4</b>
<b>Mefloquine + artesunate</b>	<b>96.9</b>
<b>Amodiaquine + artesunate</b>	<b>88.5</b>
<b>Amodiaquine + sulfadoxine-pyrimethamine</b>	<b>85.7</b>
<b>Sulfadoxine-pyrimethamine + artesunate</b>	<b>82.6</b>
<b>Chloroquine + sulfadoxine-pyrimethamine</b>	<b>72.1</b>
<b>Chloroquine + artesunate</b>	<b>45.8</b>

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<sup>a</sup> Evaluable population.

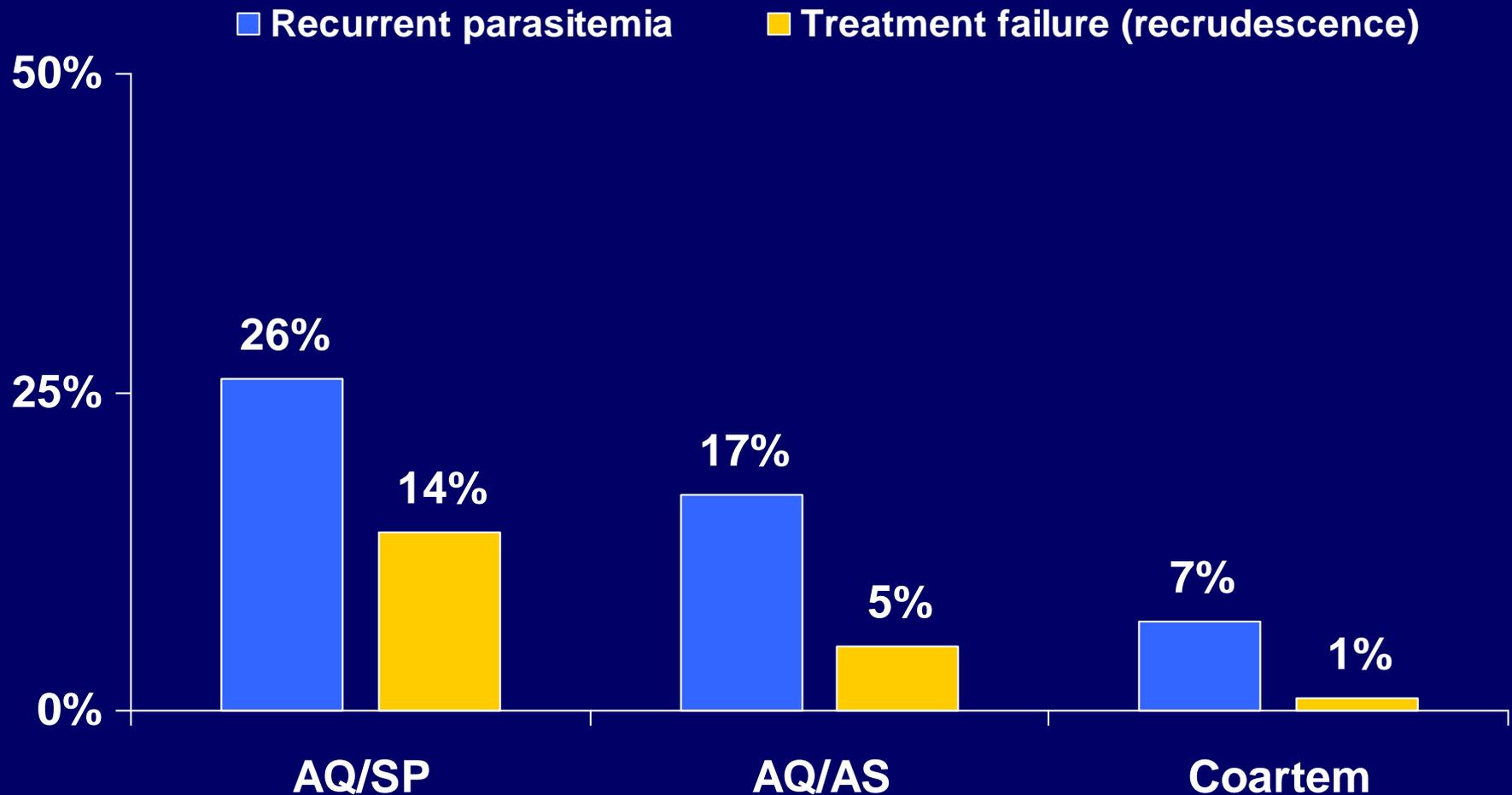
Jansen FH, et al. *Am J Trop Med Hyg.* 2007; 77:1005-9.

# Drug Effectiveness in Coastal Tanzania



# Antimalarial Efficacy of Combination Therapies in Kampala

## 28-day Outcomes From a Longitudinal Study



# Trials of Coartem

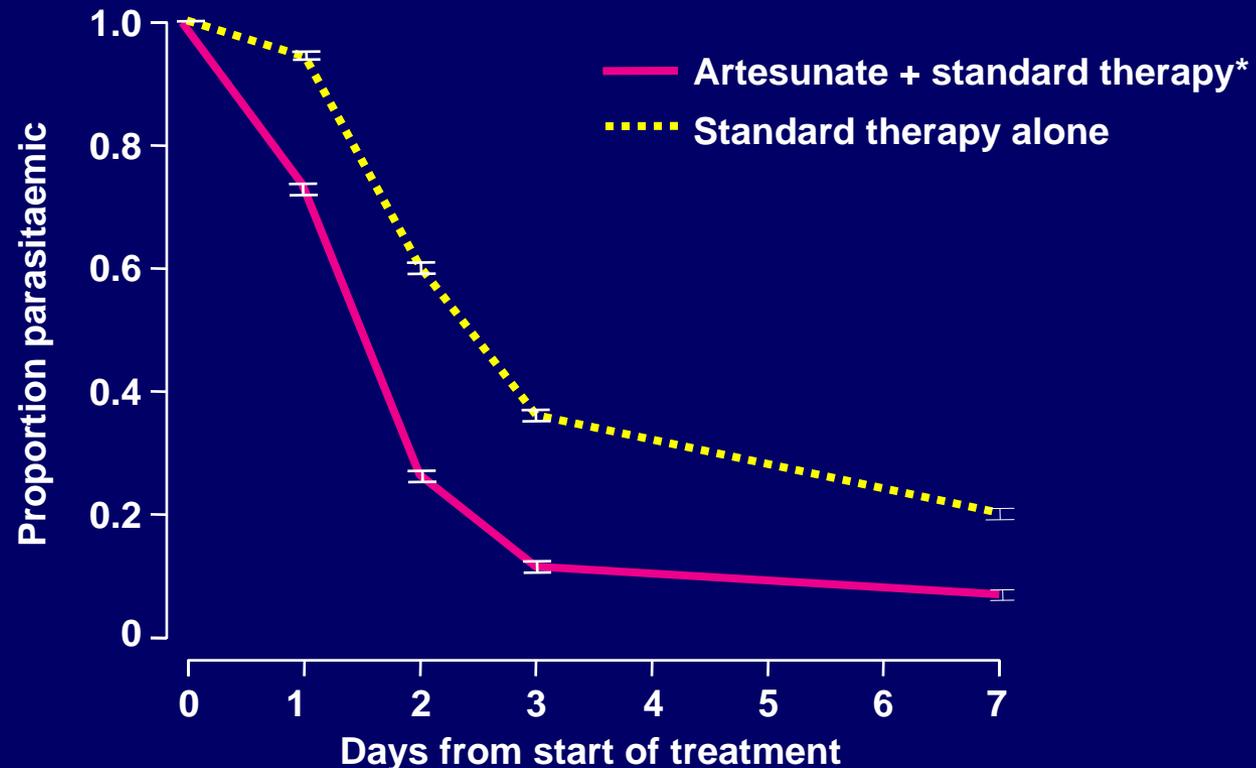
## Efficacy

Study site	Date	Transmission intensity	Drugs	Failure rate	Reference
Tororo, Uganda	2004-05	Very high	AL	1.0%	Bukirwa, et al.: PLoS Clin Trials, 2006
			AS+AQ	0%	
Kampala, Uganda	2004-06	Moderate	AL	1.0%	Dorsey, et al.: JAMA, 2007
			AS+AQ	4.6%	
			AQ+SP	14.1%	
Apac, Uganda	2006	Very high	AL	8.9%	Kanya, et al.: PLoS Clin Trials, 2007
			DP	1.9%	
Kanungu, Uganda	2006-07	Moderate	AL	3.2%	Yeka, et al.: PLoS One, 2008
			DP	0.9%	
Bobo-Dioulasso, Burkina Faso	2005	Moderate	AL	1.6%	Zongo, et al: Lancet, 2007
			AQ+SP	0.4%	
Bobo-Dioulasso, Burkina Faso	2006	Moderate	AL	3.4%	Zongo, et al: Clin Inf Dis, 2007
			AQ+SP	3.9%	
			DP	2.2%	

All outcomes are PCR-corrected at 28 days.

# Addition of Artesunate Achieves Faster Parasite Clearance

Meta-Analysis: (*Lancet* 2004)



Numbers of patients who have not cleared their parasites

Combination	1935	1201	329	134	—	—	—	89
Standard drug	1969	1695	1176	653	—	—	—	269

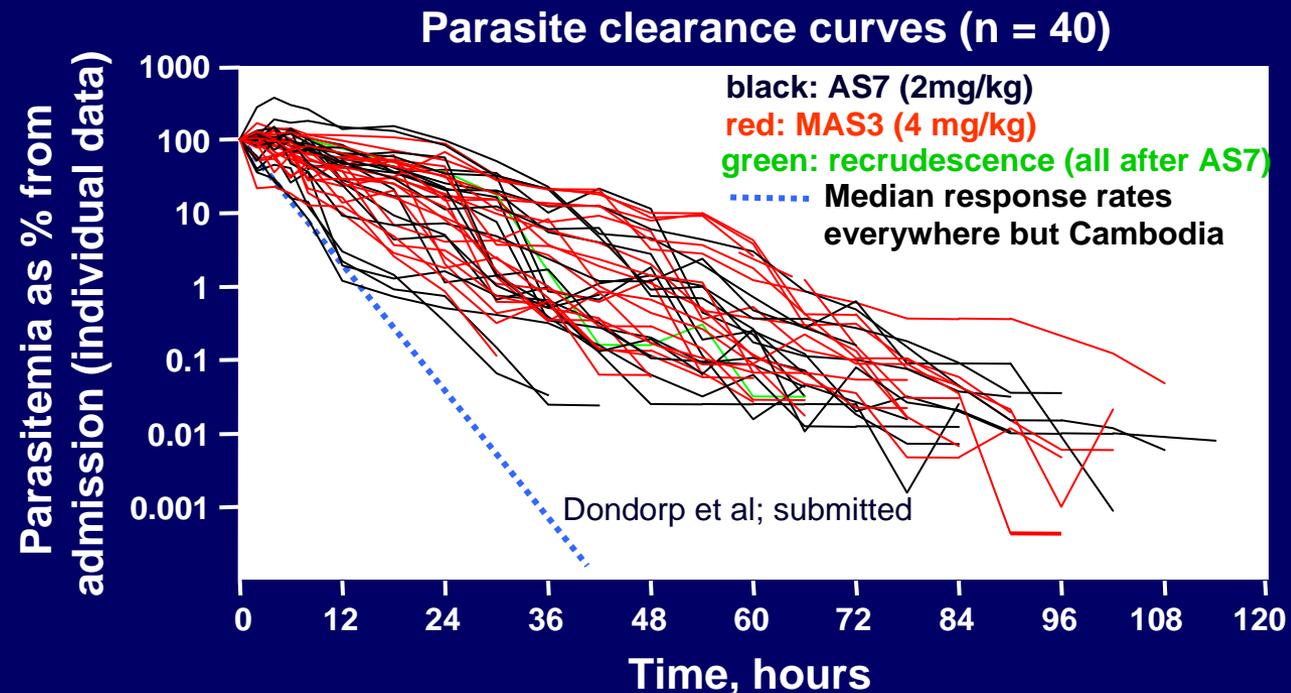
\* Standard therapy was either chloroquine, amodiaquine, sulfadoxine-pyrimethamine, or mefloquine.

International Artemisinin Study Group. *Lancet*. 2004; 363: 9-17.

# Resistance to Coartem Has Not Emerged as a Clinical Problem

- Sensitivity to lumefantrine varies by region;  $IC_{50}$  is higher in some regions (eg, Asia and French Guiana)
- Main identified determinant of lumefantrine resistance is *Pfmdr* copy number

Resistance to artemisinins may be emerging in Cambodia but is not yet a clinical problem



# Safety Considerations

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- **Potential risks are minimal versus known risks of untreated malaria**
- **Majority of AEs likely a result of malaria or concomitant infections**
- **Few deaths or SAEs reported- likely not associated with Coartem**
- **Nervous system and ear & labyrinth disorders are transient and mild**
- **No AEs related to QTc prolongation**
- **Large worldwide postmarketing experience has not indicated any particular safety signals apart from a few cases of hypersensitivity or skin reactions**

# Rationale for Availability of Coartem in US

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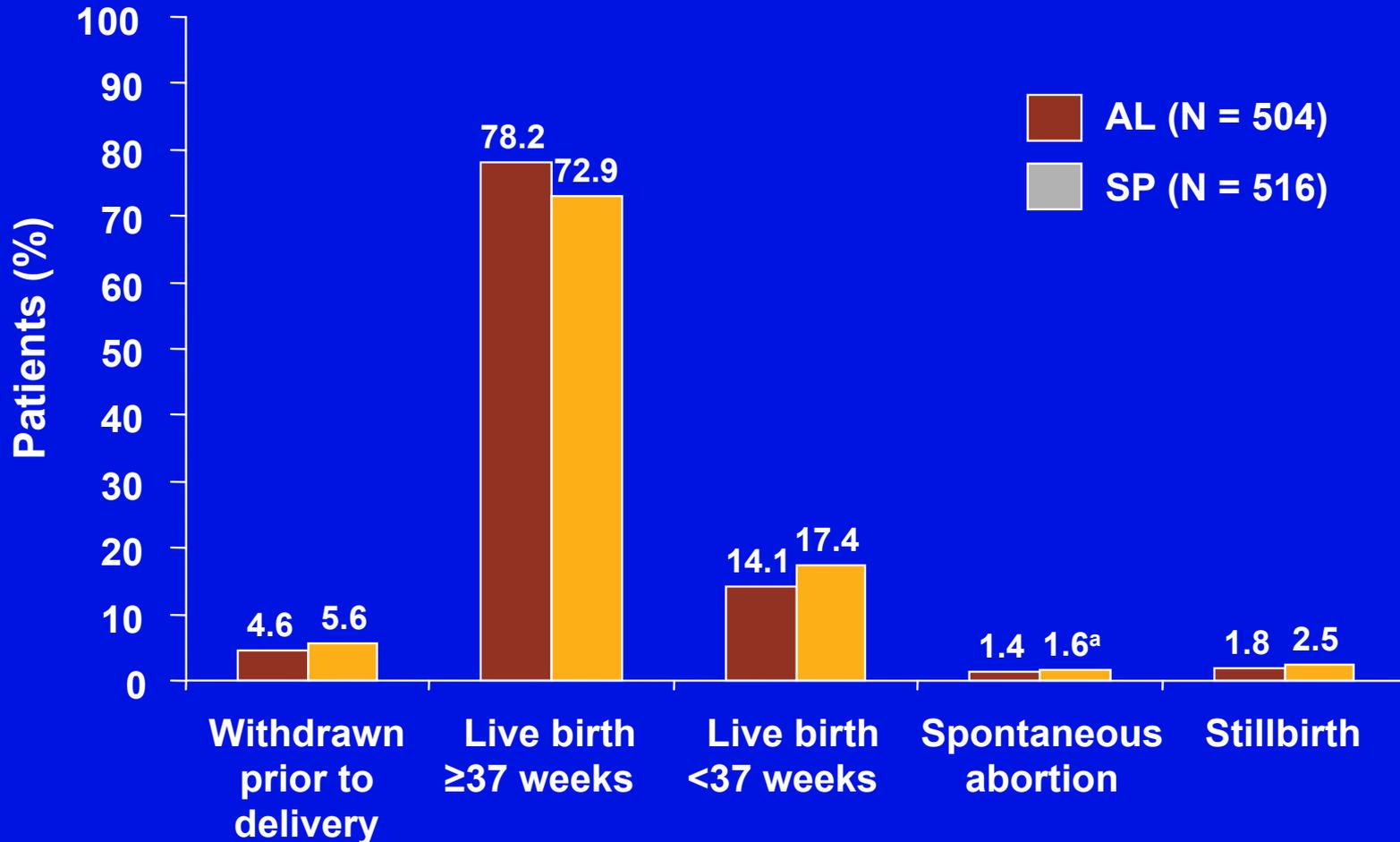
- International standard to treat *P falciparum* malaria
- Meets WHO criteria for efficacy against *P falciparum*
  - > 95% efficacy (28 day; evaluable; PCR-corrected)
- Additional treatment option in patients intolerant of other drugs or who have received other drugs for chemoprophylaxis
- Resistance has not emerged as a clinical problem
- Favorable safety profile in ~ 3600 patients in Novartis-sponsored trials, many others in > 40 studies, and extensive clinical use

# Backup

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# Safety of Coartem in Pregnancy

## Study 2407–Perinatal Mortality



<sup>a</sup> Includes 1 set of twins and 1 set of triplets.

# Safety of Coartem in Pregnancy

## Study 2407–Incidence of Malformations

	<b>Coartem</b> <b>n = 465</b>	<b>SP</b> <b>n = 466</b>
<b>Total number of newborns with birth defects</b>	<b>23 (4.9%)</b>	<b>13 (2.8%)</b>
<b>Umbilical hernia</b>	<b>17 (3.7%)</b>	<b>7 (1.5%)<sup>a</sup></b>
<b>Polydactyly</b>	<b>3 (0.7%)</b>	<b>4 (0.9%)<sup>a</sup></b>
<b>Trisomy 21</b>	<b>1 (0.2%)</b>	<b>0 (0.0%)</b>
<b>Small labia</b>	<b>1 (0.2%)</b>	<b>0 (0.0%)</b>
<b>Hyperextensibility of joints</b>	<b>1 (0.2%)</b>	<b>0 (0.0%)</b>
<b>Ears – malformed</b>	<b>0 (0.0%)</b>	<b>1 (0.2%)</b>
<b>Inguinal hernia</b>	<b>0 (0.0%)</b>	<b>1 (0.2%)</b>

<sup>a</sup> One newborn had umbilical hernia and polydactyly.

# Nervous System and Ear/Labyrinth Disorders

## Studies A026 & A028: Coartem vs MAS

Preferred term	Patients, n (%)	
	Coartem 6-dose n = 314	MAS n = 105
<b>Nervous system disorders</b>		
Headache	166 (52.9)	46 (43.8)
Dizziness	123 (39.2)	37 (35.2)
Fine motor delay	2 (0.6)	0
Hypoaesthesia	2 (0.6)	0
Ataxia	1 (0.3)	0
Coma <sup>a</sup>	1 (0.3)	0
Nystagmus	1 (0.3)	0
Tremor	1 (0.3)	1 (1.0)
<b>Ear and labyrinth disorders</b>		
Tinnitus	1 (0.3)	0
Ear pruritus	0	1 (0.1)

<sup>a</sup> Day of onset = 14.

# Exposure (AUC) Changes Following Drug-Drug Interactions

## Change in exposure (AUC)

Coartem +	Artemether	Lumefantrine	Co-medication <sup>a</sup>	Clinical implications
Mefloquine	Unchanged	↓ 32%	Unchanged	Dose with food to increase lumefantrine bioavailability
Quinine	↓ 46%	Unchanged	Unchanged	Quinine associated peak QTc prolongation enhanced from 6 msec to 15 msec
Ketoconazole	↑ 2.5 fold	↑ 1.7 fold	Not measured	Dose adjustment unnecessary when administered with CYP3A4 inhibitors

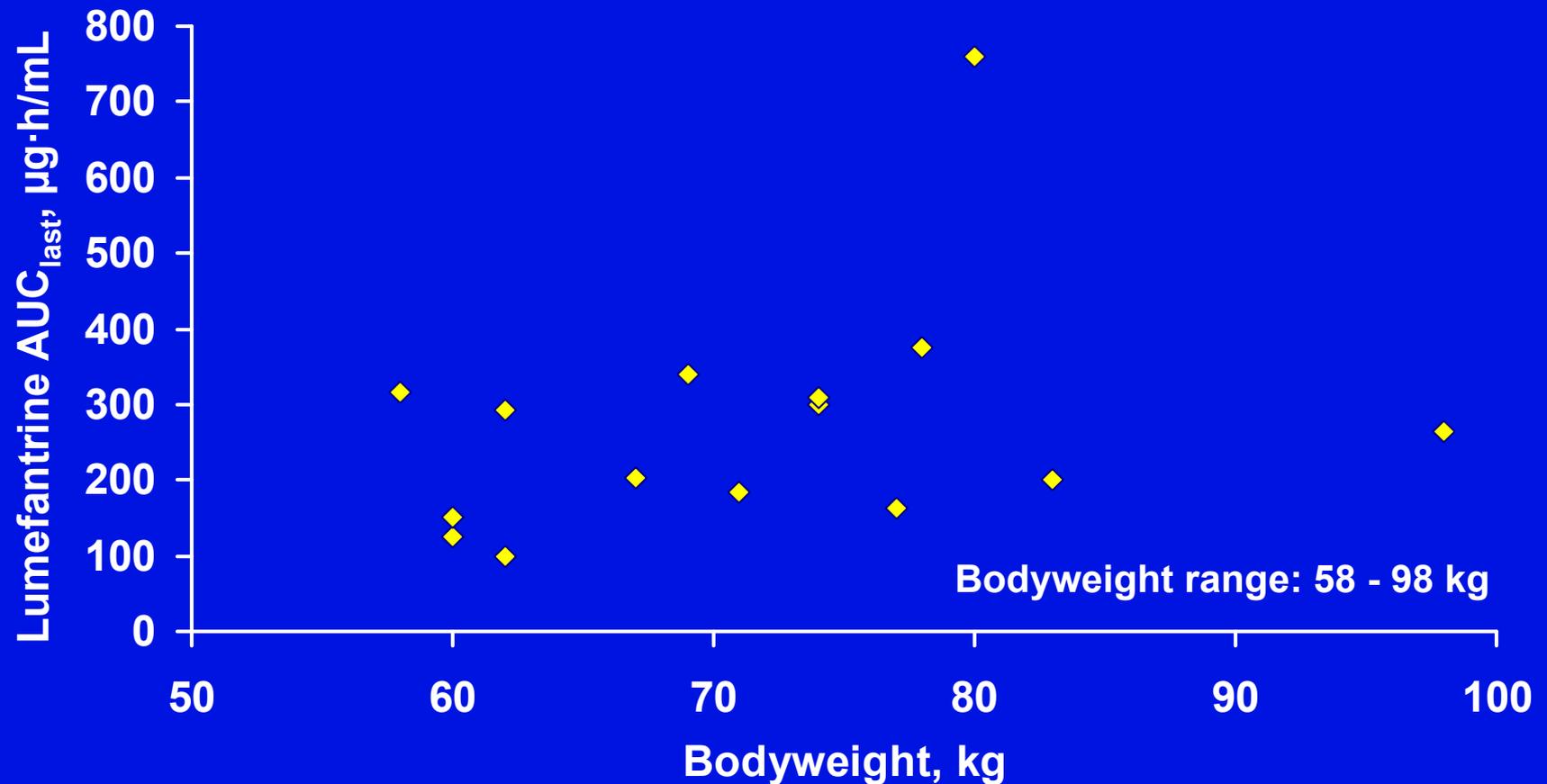
<sup>a</sup> Mefloquine or ketoconazole or quinine.

# **C<sub>max</sub> and AUC<sub>last</sub> by Bodyweight—Less Than Versus Greater Than 70 Kg**

**Study A2401**

	<b>&lt; 70 kg (n = 7)</b> <b>Mean: 62.6 kg (range 58 – 68)</b>		<b>&gt; 70 kg (n = 8)</b> <b>Mean: 79.4 kg (range 71 – 98)</b>	
	<b>C<sub>max</sub></b> <b>(µg/mL)</b>	<b>AUC<sub>last</sub></b> <b>(µg·h/mL)</b>	<b>C<sub>max</sub></b> <b>(µg/mL)</b>	<b>AUC<sub>last</sub></b> <b>(µg·h/mL)</b>
<b>Mean ± SD</b>	<b>4.73 ± 2.49</b>	<b>218 ± 98.2</b>	<b>6.59 ± 3.13</b>	<b>320 ± 192</b>
<b>CV (%)</b>	<b>52.6</b>	<b>45.1</b>	<b>47.6</b>	<b>60.1</b>
<b>Min</b>	<b>2.12</b>	<b>98.8</b>	<b>2.50</b>	<b>164</b>
<b>Max</b>	<b>8.03</b>	<b>339</b>	<b>11.2</b>	<b>761</b>

# Lumefantrine Exposure Not Correlated With Body Weight



# Similar Efficacy in Malaria Patients $\geq 70$ kg Body Weight (Study A2417)

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- ✦ 51 patients enrolled in Colombia and treated with 6-dose regimen
  - 35% female
  - Age 14-56 years (mean,  $33.8 \pm 11.1$  years)
  - Body weight 70-110 kg (mean,  $78.5 \pm 8.3$  kg)
  
- ✦ All were cured at day 28

# Efficacy: Day 42 Cure Rate

## Study B2303—Africa

### All patients

#### 42-day parasitological cure rates, no PCR correction

mITT population, n/M (%) patients  
95% CI

318/427 (74.5%)  
70.3, 78.6

Evaluable patients, n/M (%) patients  
95% CI

315/407 (77.4%)  
73.3, 81.5

#### 42-day PCR-corrected parasitological cure rates

mITT population, n/M (%) patients  
95% CI

347/372 (93.3%)  
90.7, 95.8

Evaluable patients, n/M (%) patients  
95% CI

344/355 (96.9%)  
95.1, 98.7

## **Exclusion Criteria 2401**

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- ✦ Having received halofantrine or any other drug known to influence cardiac function within 4 weeks prior to Screening visit or taking other drugs that are known to prolong the QT interval, including class IA and III antiarrhythmics, neuroleptics, antidepressive agents, certain antibiotics (including some macrolides, fluoroquinolones, imidazole, and triazole antifungal agents), certain non-sedating antihistaminics (terfenadine, astemizole) and cisapride.**