

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-799

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-799/N_000

Drug Name: Quinine Sulfate, USP 324 mg capsules

Indication(s): Treatment of uncomplicated *Plasmodium falciparum* malaria

Applicant: Mutual Pharmaceutical Company, Inc.

Date(s): Application: October 13, 2004
Received: October 13, 2004
User Fee: August 12, 2005

Review Status: Standard (10-month review)

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Keywords: NDA Review, clinical studies, meta-analysis, class antimalarial, indication malaria treatment

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

An extensive clinical history, spanning over 200 years, of quinine therapy for treatment of *Plasmodium (P.) falciparum* malaria obviates the need for additional clinical studies to assess the safety and efficacy of this therapy. Among the copious amount of information, randomized, clinical trials published in the worldwide literature between 1974 and 2005 served as the primary NDA data for oral quinine sulfate capsules. Not considered during this review is the large body of information in the literature from non-randomized studies or patient case reports. A systematic review of identifying, reviewing, summarizing, and assessing each available published study occurred resulting in 22 randomized, active-controlled, studies including approximately 2,495 patients of which 1,456 were randomized to an oral quinine regimen. For purposes of a systematic review, the reviewer considered ten of these studies primary. Among five primary studies, evaluating a quinine 10 mg/kg tid x 7 day monotherapy regimen, four had cure rates of 82-87% (61-70%) in the evaluable (ITT) populations and one study of 48 patients had a cure rate of 100% in both populations. In seven primary studies, evaluating quinine 10 mg/kg tid in combination with tetracycline for 7 days the cure rates were 94-100% (68-95%) in the evaluable (ITT) populations (one study not reporting ITT rates). Cure, defined as parasite clearance by day 7 without recrudescence at day 28, varied due to drug resistance patterns across malaria endemic study regions. Lost to follow-up led to the observed lower cure rates in the ITT population.

Although the quality and design of the available published randomized studies varies from poor to average, the totality of data and clinical experience provides sufficient evidence to conclude that oral quinine 10 mg/kg tid x 7 days is effective for treatment of uncomplicated *P. falciparum* malaria in adults. Additionally, this regimen in combination with tetracycline for seven days demonstrated effectiveness based on seven randomized published studies. Insufficient data exists from randomized clinical studies to estimate the overall treatment effect of other quinine combination therapies or shortened quinine durations.

1.2 Brief Overview of Clinical Studies

The Sponsor submitted 21 published randomized clinical studies that evaluated the efficacy of an oral quinine regimen for treatment of uncomplicated *P. falciparum* malaria. Additionally, the reviewer located an additional study during an independent literature search. Detailed summaries of these publications are in Appendix A and B and in Tables 2.2-2.3. As supportive data, the Sponsor also provided 14 published randomized clinical studies evaluating parenteral quinine for treatment of complicated or severe *P. falciparum* malaria. These studies are briefly summarized in Table 2.4.

1.3 Statistical Issues and Findings

The clinical efficacy data provided in this submission consists of published clinical trials identified through database searches performed by the Sponsor and the reviewer. Databases searched include MEDLINE® (1966 to present), EMBASE® (1974 to present), JICST-Eplus (1985 to present) and Biosis

Previews® (1969 to present). Although these databases are quite extensive providing access to numerous published studies, they are not void of potential biases including publication bias, time lag bias, multiple publication bias, citation bias, language bias and selection bias. These are discussed in detail in section 3.1.3.

The reviewer conducted numerous meta-analyses, which support the conclusion of efficacy of quinine for treatment of uncomplicated *P. falciparum* malaria.

2. INTRODUCTION

2.1 Overview

2.1.1 Malaria incidence in the United States

The incidence of new malaria cases reported annually in the United States is approximately 1,200. These cases are mostly due to imported malaria from travelers or immigrants returning from malaria endemic countries. In 2003, the CDC received reports of 1,278 cases of malaria. Of these, seven were fatal and 53.3%, 22.9%, 3.6%, and 2.6% cases were *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* respectively (Eliades et al., 2005).

2.1.2 History of Quinine

The history of quinine dates back to the early 17th century when Jesuit Priests, returning to Europe after working in Peru, first introduced it. Quinine occurs naturally in the bark of cinchona trees, which are high-altitude evergreen trees native to South America. To prevent shivering while working in cold streams, Peruvian Indians often chewed on the bark. Physicians reasoned that this physiological effect was due to quinine's effect on skeletal muscle and neuromuscular junctions. In 1820, French chemists isolated quinine from the cinchona bark to use to treat intermittent fever, which often was the diagnosis for a variety of conditions understood today. Quinine remained the standard therapy for intermittent fever throughout the world into the 20th century at which time alternative therapies were developed. It is worth noting that the discovery of malaria came many years after the discovery of quinine, however the symptoms of malaria were likely the primary uses of quinine all along.

2.1.3 Regulatory History of Oral Quinine

Prior to 1938, quinine was marketed in the United States as an over-the-counter therapy (OTC), however in 1994 following review of a citizens petition and other data, the FDA issued a final rule stating that OTC sales of quinine for nocturnal leg cramps (a common use of quinine) is not generally recognized as safe and effective. In 1998, the FDA issued another rule restricting quinine to prescription only status for treatment or prevention of malaria due to safety concerns with the drug requiring monitoring by healthcare providers. Currently, several manufacturers throughout the United States market quinine; however, none of these products has undergone the formal FDA review process to determine efficacy and safety.

During the pre-NDA meeting with the Sponsor, it was agreed that the regulatory requirement for labeling of quinine for the indication of 'treatment of uncomplicated *P. falciparum* malaria' would likely be met

30 languages (40 languages for older journals that date back to 1966). Roughly, 52% of current cited articles are published in the United States and 86% are published in English.

- EMBASE® (1974 to present): This database is a comprehensive index of the world's literature on human medicine and related disciplines (more comprehensive with respect to European studies than is MEDLINE). It includes citations from approximately 3700 primary journals, 110 countries, and 39 languages (about 77% published in English).
- JICST-Eplus (1985 to present): This database covers Japanese and Asian literature in the fields of science, technology, and medicine. It includes citations from 6,000 journals and serials in addition to conference papers, technical reports, and other non-periodicals published by the Japanese government. The majority of articles are in Japanese (85%), with 14% in English, and 1% in other languages.
- Biosis Previews® (1969 to present): This database contains a worldwide coverage of research in the biological and biomedical sciences (primarily identifies abstracts from meetings and symposia). It includes citations from over 6000 journals, books, reports, patents, and meetings representing about 100 countries and 57 languages (86% are in English).
- OLDMEDLINE (1951-1965) (pre-MEDLINE)

Note: This database search yielded no useful references as per the Sponsor.

Additionally, the Sponsor manually searched the literature for references preceding electronic databases and searched older editions of selected standard medical textbooks.

Summarized in the following table are the Sponsor's searches performed along with the search strategy used.

Table 2.1: Summary of Sponsor's Literature Searches

Date of Search	Strategy	No. of Unique Citations
5 December 2002	Quinine sulfate reviews	59
10 January 2003	Quinine sulfate and malaria (no reviews)	135
16 July 2003	Quinine and malaria (no reviews), randomized, placebo, controlled, efficacy, or trial	1226
1 July 2004	Quinine and malaria (no reviews), randomized, placebo, controlled, efficacy, or trial in 2003 and 2004 (update of 16 July 03 search)	110

Obtained from ISE.pdf, page 21

The Sponsor's search located 11 publications that evaluated a quinine monotherapy regimen for treatment of uncomplicated *P. falciparum* malaria, however one (*de Vries et al., 2000*) consisted of data previously published by *Bich et al. (1996)*. Therefore, 10 unique studies were identified. The Sponsor also provided 16 publications that discuss a quinine-combination regimen (of which six included a quinine monotherapy group and one includes the study by *de Vries et al., 2000*). The reviewer identified an additional combination study (*Ramharter et al., 2005*). In addition, as supportive information, the Sponsor provided 14 randomized, active-controlled studies evaluating parenteral quinine for treatment of severe or

complicated malaria. Brief descriptions of these studies are given below in Tables 2.2-2.4. Details of all publications on oral quinine are provided in Appendices A&B.

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Table 2.2: Table of Published Oral Quinine Monotherapy Studies

Oral Quinine monotherapy									
<u>Author, Year</u>	<u>No. Patients Enrolled/Completed</u>	<u>M/F</u>	<u>Q Pts Enrolled/Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
Watt <i>et al.</i> , 1988 (Mono Study 1)	20 / 20	20 / 0	10/10	male pts ≥16 y.o	Philippines (SE Asia)	NS	No	Compared E of Q vs. CQ	DB design with matched placebo tablet for both groups, small sample
Pukrittayakamee <i>et al.</i> , 2004 # (Mono Study 2)	176 / 142	176 / 0	126/96	male pts ages 14-62 yrs	Thailand (SE Asia)	NS	No	Determined if addition P to Q or A is as effective as Q + T, or Q alone	Well summarized publication- primary Q7
Mueller <i>et al.</i> , 2004 (Mono Study 3)	132 / 98	N/A	48/43	adults ≥18 y.o	Rep. of Congo (Africa)	NS	No	Compared E of Artemisia tea with Q control	Limited summary of outcomes, however included in primary Q7 analysis
Aché <i>et al.</i> , 2002 (Mono Study 4)	165 / 165	121 / 44	48/48	≥6 months	Venezuela (South America)	Stratified by weighted proportion of malaria cases in each community conducted	Yes, detailed along with formal hypothesis	Evaluated the growing resistance to CQ and S/P in that region, Q served as control	Well designed and summarized field study- primary Q7
Rahman <i>et al.</i> , 2001 #* (Mono Study 5)	425 / 413	380 / 33	/194	12-60 yrs	Bangladesh (SE Asia)	Codes prepared in blocks and provided in envelopes	Yes-expected failure rates,	Compared nationally recommended treatment	Interim analysis performed resulting in regimen &

Oral Quinine monotherapy									
<u>Author, Year</u>	<u>No. Patients Enrolled/Completed</u>	<u>M/F</u>	<u>Q Pts Enrolled/Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
McGready <i>et al.</i> , 2000 (Mono Study 6)	115/108	0 / 115	/42	<u>Pregnancy</u> women in 2 nd or 3 rd trimester	Thailand (SE Asia)	2 blocks of 100 codes prepared	power and type I error	regimens CQ vs. Q vs. M vs. QS/P	sample size change-randomization flawed Statistical design appropriate, however unable to calculate ITT cure rates- primary study in pregnancy
Pukrittayakamee <i>et al.</i> , 2000 # (Mono Study 7)	204 / 161	204 / 0	204 / 161	adult male pts	Thailand (SE Asia)	'simple'	No	Compared E Q+C vs. Q+T or Q alone	Provides a robust summary and description of results- primary Q7
De Vries <i>et al.</i> , 2000#^ (Mono Study 8)	268/221	216/52	268/221	Ages 8-65 yrs	Vietnam (SE Asia)	computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion	No	Compared E of AQ3, AQ5 and Q7	Results include those previously published by Bich <i>et al.</i> , 1996 along with new information from modified study design. Original randomization flawed by changes in treatments and sample size-study eliminated due to multiple

Oral Quinine monotherapy

<u>Author, Year</u>	<u>No. Patients Enrolled/Completed</u>	<u>M/F</u>	<u>Q Pts Enrolled/Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
Bich <i>et al.</i> , 1996 # (Mono Study 9)	157 ² / 118 ³	128 / 29 ⁴	59/44	Ages 8-65 yrs	Vietnam (SE Asia)	computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion	Partially-only discussed expected drop-out rate-no expected failure rates discussed	Compare A+Q and A+D vs. standard Q (control)	publication Study stopped and analyzed at 161 patients- primary Q7
Metzger <i>et al.</i> , 1995 # (Mono Study 10)	120 / 108	57 / 51 ⁴	120/108	Age ≥15	Gabon (Africa)	NS	No	Compare Q (1.5d) + D (+C) vs. Q (1.5d) alone	Limited detail provided on population and results
Segal <i>et al.</i> , 1974 (Mono Study 11)	51 / 47	51 / 0	26/22	Thai males ≥15 yrs	Thailand (SE Asia)	NS	No	Compared E of WR vs. Q (control)	Limited detail on study design, population, and findings

Study includes a quinine monotherapy and combination therapy group

* Study considered supportive only due to design/randomization issues identified by the reviewer and only phase I of this study will be used

^ Multiple publication, study removed from review

¹ Of the 268 patients enrolled, 5 were not evaluable (early dropouts), 5 were lost before Day 7 after initial recovery and parasitic clearance, and 37 were lost between Day 7 and 28

² Data analysis comprised 157 cases (161 patients enrolled; however, four cases were *P. vivax* infection)

³ Of the 157 patients enrolled, 6 were not evaluable (early dropouts), 6 were lost before Day 7 after initial recovery and parasitic clearance, and 27 were lost between Day 7 and 28

⁴ Demographic data provided only for patients completing follow-up

NS=not specified

Q=quinine, T=tetracycline, A=artesunate, P=primaquine, CQ=chloroquine, M=mefloquine, A/P=atovaquone + proguanil, S/P=sulfadoxine/pyrimethamine, Amo=amodiaquine, C=clindamycin, D=doxycycline, E=efficacy, S=safety

Table 2.3: Table of Published Oral Quinine Combination Therapy Studies

Oral Quinine Combination									
<u>Author, Year</u>	<u>No. Patients Enrolled/Completed</u>	<u>M/F</u>	<u>Q Pts Enrolled/Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
Pukrittayakamee <i>et al.</i> , 2004 # (Combo Study 1)	176 / 142	176 / 0	126/96	male pts ages 14-62 yrs	Thailand (SE Asia)	NS	No	Studied if the addition P to Q or A is as effective as Q + T or Q alone	Well described study- primary Q7T7 study
Rahman <i>et al.</i> , 2001 #* (Combo Study 2)	425 / 413	380 / 33	/194	12-60 yrs	Bangladesh (SE Asia)	Codes prepared in blocks and provided in envelopes	Yes- provided expected failure rates, power and type I error	Compared nationally recommended treatment regimens CQ vs. Q vs. M vs. QS/P	Interim analysis performed resulting in regimen & sample size change- randomization flawed- supportive only
Pukrittayakamee <i>et al.</i> , 2000 # (Combo Study 3)	204 / 161	204 / 0	204 / 161	adult male pts	Thailand (SE Asia)	'simple'	No	Compared E of Q+C vs. Q+T or Q alone	Provides a robust summary and description of results- primary Q7T7 study
De Vries <i>et al.</i> , 2000#^ (Combo Study 4)	268/221	216/52	268/221	Ages 8-65 yrs	Vietnam (SE Asia)	computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion	No	Compared E of AQ3, AQ5 and Q7	Results include those previously published by Bich <i>et al.</i> , 1996 along with new information from modified study design. Original randomization flawed by changes in

Oral Quinine Combination

<u>Author, Year</u>	<u>No. Patients Enrolled/Completed</u>	<u>M/F</u>	<u>O Pts Enrolled/Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
Bich <i>et al.</i> , 1996 #* (Combo Study 5)	157 ² / 118 ³	128 / 29 ⁴	59/44	Ages 8-65 yrs	Vietnam (SE Asia)	computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion	Partially-only discussed expected drop-out rate-no expected failure rates discussed	Compare A+Q and A+D vs. standard Q (control)	treatments and sample size-study eliminated due to multiple publication Study stopped and analyzed at 161 patients-supportive study
Metzger <i>et al.</i> , 1995 # (Combo Study 6)	120 / 108	57 / 51 ⁴	120/108	Age ≥15	Gabon (Africa)	NS	No	Compare Q (1.5d) + D (+C) vs. Q (1.5d) alone	Limited detail provided on population and results
Duarte <i>et al.</i> , 1996 (Combo Study 7)	176/167	145/31	88/82	Pts ≥14 yrs	Brazil (Amazon) (South America)	Table of random numbers	Yes-based on expected cure rate and 15% difference	Compare E&S of A+T vs. Q+T (control)	Triple-blind, well described study
Fungladda <i>et al.</i> , 1998 (Combo Study 8)	137/114	120/17	60/56	Pts ages 15-60 yrs	Thailand (SE Asia)	'simple' noted only	Yes-but driven by expected compliance/AE rates and not on E	Primary obj. to evaluate compliance of two treatment regimens, cure was secondary Q+T vs. A	E was secondary endpoint and therefore study should serve as supportive

Oral Quinine Combination									
<u>Author, Year</u>	<u>No. Patients Enrolled / Completed</u>	<u>M/F</u>	<u>Q Pts Enrolled / Completed</u>	<u>Population</u>	<u>Endemic Area</u>	<u>Randomization Method</u>	<u>Sample size justification</u>	<u>Study Objective</u>	<u>Reviewer's Comment</u>
Salcedo <i>et al.</i> , 1997* (Combo Study 9)	42/26	35/7	14/	Pts ages 8-64 yrs	Brazil (Amazon) (South America)	NS	No	Compared E of A with Q and M	E rates pooled by regimen-results uninterrupted-supportive study
De Alencar <i>et al.</i> , 1997 (Combo Study 10)	175/154	154/0	7/7	Adult men 18-65 yrs	Brazil (Amazon) (South America)	NS	No	Compared A/P vs. Q+T (control)	In-patient only study- primary Q7T7 study
Bunnag <i>et al.</i> , 1996 (Combo Study 11)	90/86	90/0	90/86	Thai adult men ages 16-54 yrs	Thailand (SE Asia)	NS	No	Compared E&S of 5&7d Q+T regimens (7d served as control)	In-patient only study- primary Q7T7 study
Vanijanontia <i>et al.</i> , 1996 (Combo Study 12)	50/36	50/0	50/36	Thai adult men	Thailand (SE Asia)	NS	No	Compare Q+C vs. Q+T (control)	Q+C ineffective (44% cure rate in ITT) In-patient only study- primary Q7T7 study
Loareesuwan <i>et al.</i> , 1994 (Combo Study 13)	102/93	75/27	50/46	Pts ages 16-60 yrs	Thailand (SE Asia)	NS	No	Compare E of M+T vs. Q+T (control)	In-patient only study- primary Q7T7 study
Karbwang <i>et al.</i> , 1994 (Combo Study 14)	64/60	64/0	33/30	Thai male pts ages 15-35 yrs	Thailand (SE Asia)	NS	Yes-based on previous data to detect a 35% faster clearance rate in A group compared to Q+T	Compared E of A vs. Q+T (control)	Detailed description of design and results In-patient only study. Primary Q7T7 study

Oral Quinine Combination									
Author, Year	No. Patients Enrolled/Completed	M/F	Q Pts Enrolled/Completed	Population	Endemic Area	Randomization Method	Sample size justification	Study Objective	Reviewer's Comment
Kremsner <i>et al.</i> , 1988 (Combo Study 15)	115/95	74/20 ⁴	86/70	Pts ≥14 yrs of age	Brazil (Amazon) (South America)	Age-dependant schedule (categories not given)	No	Compared Q+S/P and Q+CQ vs. Amo (control)	Amo dropped after 25 pts due to lack of E
de Souza <i>et al.</i> , 1985 (Combo Study 16)	100/99	100/0	50/50	Males 18-55 yrs old	Brazil (Paragominas) (South America)	NS	No	Compared E of M vs. Q+S/P (control)	Older study
Ramharter <i>et al.</i> , 2005 (Combo Study 17)	100/94	50/48	53/47	Gabonese children ages 3-11 yrs	Gabon (Africa)	Computer generated codes in blocks of 10	Yes, based on 98% cure rate assumption in control and 7% NI margin, 10 LTF rate	Compared A+C vs. Q+C (control)	Well designed and described study, which should serve as primary for pediatric population and secondary for adult.

Study includes a quinine monotherapy and combination therapy group

* Study considered supportive only due to design/randomization issues identified by the reviewer

^ Multiple publication, study removed from review

¹ Of the 268 patients enrolled, 5 were not evaluable (early dropouts), 5 were lost before Day 7 after initial recovery and parasitic clearance, and 37 were lost between Day 7 and 28

² Data analysis comprised 157 cases (161 patients enrolled; however, four cases were *P. viva* infection)

³ Of the 157 patients enrolled, 6 were not evaluable (early dropouts), 6 were lost before Day 7 after initial recovery and parasitic clearance, and 27 were lost between Day 7 and 28

⁴ Demographic data provided only for patients completing follow-up

NS=not specified

Q=quinine, T=tetracycline, A=artesunate, P=primaquine, CQ=chloroquine, M=mefloquine, A/P=atovaquone + proguanil, S/P=sulfadoxine/pyrimethamine, Amo=amodiaquine, C=clindamycin, D=doxycycline, E=efficacy, S=safety

Table 2.4: Table of Published Studies Evaluating Parenteral Quinine (supportive only)

Parenteral Quinine									
Author, Year	No. Randomized	M/F	Q Pts Randomized	Endemic Area	Population Studied	Route (Duration in Days)	Quinine Mortality Rate	Comparator Mortality Rate	
Singh <i>et al.</i> , 2000	52	33/19	26	India	Adults ≥ 15 yrs	IV (7)	4/26 (15%)	AM5: 2/26 (8%)	
Sattu <i>et al.</i> , 2002	77	NR	39	Sudan	Children ages 1-15 yrs (cerebral)	IV/ORAL (7)	2/39 (5%)	AM4: 3/38 (8%)	
Adam <i>et al.</i> , 2002	41	20/21	21	Sudan	Children	IV/ORAL (7)	1/21 (5%)	AM5: 0/20 (0%)	
Faiz <i>et al.</i> , 2001	105	78/27	54	Bangladesh	Ages 14-50 yrs (cerebral)	IV/ORAL (7)	10/54 (19%)	AM5: 9/51 (18%)	
Thuma <i>et al.</i> , 2000	92	47/45	44	Zambia	Children ages 0-10 yrs (cerebral)	IV/ORAL (7)	9/44 (21%)	AE5: 10/48 (21%)	
Moyou-Somo <i>et al.</i> , 2001	106	49/43	51	Cameroon	Children ages 0-10 yrs (cerebral)	IV/ORAL (7)	14/51 (28%)	AM5: 8/51 (16%)	
Olumese <i>et al.</i> , 1999	103	NR	49	Nigeria	Children 1-5 yrs (cerebral)	IV/ORAL (7)	14/49 (29%)	AM5: 11/54 (20%)	
Karbwang <i>et al.</i> , 1995	102	92/10	52	Thailand	Adults ≥ 15 yrs	IV/ORAL (7)	19/50 (38%) ³	AM7: 5/46 (11%)	
Karbwang <i>et al.</i> , 1992	26	25/1	12	Thailand	Adults and children ≥ 10 yrs	IV/ORAL (7)	5/12 (42%)	AM7: 1/14 (7%)	
Van Hensbroeck <i>et al.</i> , 1996	288	143/145	288	Gambia	Children (cerebral)	IV/ORAL (5)	62/288 (22%)	AM4: 59/288 (20%)	
Tran <i>et al.</i> , 1996*	561	425/135	276	Vietnam	Adults ≥ 15 yrs	IM/ORAL (7)	47/276 (17%)	AM3: 36/284 (13%)	
Newton <i>et al.</i> , 2003*	113	79/34	54	Thailand	Adults ≥ 15 yrs	IV/ORAL (7)	12/46 (26%) ¹	AS7: 6/54 (11%)	
Taylor <i>et al.</i> , 1998*	183	39/42	88	Malawi	Children	IV/ORAL (7)	12/81 (15%) ²	AM3: 11/83 (13%)	

Parenteral Quinine								
Author, Year	No. Randomized	M/F	O Pts Randomized	Endemic Area	Population Studied	Route (Duration in Days)	Quinine Mortality Rate	Comparator Mortality Rate
Murphy <i>et al.</i> , 1996*	160	80/80	71	Kenya	(cerebral) Children 5-12 yrs (cerebral)	IV	8/71 (12%)	AM3: 18/89 (20%)

AM=artemether, AS=artesunate, AE=arteether-number following comparator represents the number of treatment days

*Treatment was in combination with another antimalarial

¹ Only 46 of the 54 patients randomized to quinine and 54 of 59 randomized to artesunate did not have severe malaria

² 12 artemether patients and 7 quinine patients removed from study due to not meeting entry criteria

³ 2 quinine and 3 artemether patients excluded due to co-infections

2.2 Data Sources

This submission relies solely on available randomized studies published in the worldwide literature. The Sponsor submitted the relevant studies to the following EDR links:

[\\Cdsub1\21799\N_000\2004-10-13](#)

[\\Cdsub1\21799\N_000\2005-06-17](#)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Sponsor did not perform a formal analysis of the data but rather provided summary tables with parasitological response rates, fever and parasite clearance rates for the intent-to-treat (ITT) and evaluable populations (if data were available). The reviewer performed a more thorough review of the literature, evaluating each study's quality in terms of randomization method, sample size estimation, study population and data analysis. The reviewer concluded that ten out of the 22 studies were suitable for inclusion into meta-analyses. Among five studies that evaluated a quinine 10 mg/kg tid x 7 day monotherapy regimen, cure (parasite clearance by day 7 without recrudescence by day 28) rates were 82-87% (61-70%) in the evaluable (ITT) populations and one study of 48 patients had a cure rate of 100% in both populations. In seven primary studies, evaluating quinine 10 mg/kg tid in combination with tetracycline for 7 days the cure rates were 94-100% (68-95%) in the evaluable (ITT) populations (one study did not provide information to calculate ITT rate). Cure rates, particularly among the quinine monotherapy studies, varied due to drug resistance patterns across malaria endemic study regions. A large number of patients lost to follow-up at the day 28 follow-up drove lower cure rates in the ITT populations.

The remainder of this section discussed methods and results of the reviewer's systematic review of all available publications relevant to quinine monotherapy and combination therapy clinical studies.

3.1.1 Methodology

The reviewer performed a detailed review and summary of each published, randomized study provided in the submission (publication details for the oral quinine studies are in Appendices A & B). The reviewer also performed independent searches for relevant publications using MEDLINE®, EMBASE® and The Cochran Database of Systematic Reviews available through the FDA online medical library.

Following a thorough selection of relevant studies, the reviewer performed meta-analyses of integrated published data according to quinine regimen, comparator type, and study location.

In studies using oral quinine to treat uncomplicated *P. falciparum* malaria, the primary endpoint was cure defined as parasitological cure by day 7 without recrudescence by day 28. Cure rates in the ITT population were calculated as the number of patients cured over the number randomized. In the evaluable population, cure rates were calculated as the number of patients cured over the number of patients completing the 28-day follow-up. The publications provided usually presented the evaluable population cure rates, however if the number of randomized patients was given, the reviewer also calculated the ITT

population cure rates, assuming patients lost to follow-up were treatment failures. The statistic used to measure treatment effect was the odds ratio (OR), i.e. the relative odds of the event in both groups. An odds ratio greater than one suggests an increased probability of cure in the quinine group compared to the control. Statistical significance within a level of 5% is attained when the 95% CI around the estimated odds ratio excludes one.

In studies using parenteral forms of quinine to treat severe malaria (*supportive information*), the primary endpoint was death. The odds ratio was also used as the statistic to evaluate treatment effect of quinine versus artemether; however, the interpretation differs from the oral quinine data analyses. Given that the primary outcome is negative, an odds ratio greater than one suggests an increased probability of death in the quinine treated groups and conversely for odds ratios less than one.

Forest plots were created to graphically display individual study treatment effects along with the estimated combined treatment effect (using fixed or random effects modeling) and respective 95% confidence intervals. Solid squares represent treatment effects, with larger squares representing studies with greater weight (inverse variance) or contribution to the integrated analysis. A solid diamond shapes represent the weighted combined effect estimate.

The combined treatment effect obtained in a meta-analysis is the weighted average of the individual treatment effects where each treatment effect serves as an observation (similar to a patient outcome in a clinical study). This process of pooling data from multiple clinical trials required methods to tests for study heterogeneity (i.e. tests to determine if the data are similar enough to combine). The chi-square test for homogeneity, derived from the Q statistic (*DerSimonian & Laird, 1986*), was used to test for between-study heterogeneity. When the Q statistic was significant, implying heterogeneity, a random effects model was used; otherwise, the fixed effect model was used. The fixed effect model (Mantel-Haenszel method) assumes that all studies come from a common population such that the only source of variance is the within-study variance. The fixed effect estimate is the sum of each study's treatment effect times the weight (inverse variance) divided by the sum of the weights. Under the random effects model (*DerSimonian and Laird method*), one assumes that studies did not originate from the same population and therefore variance comes from both the within-study differences as well as the between-study variance. The random effects estimate is calculated as the sum of each study's treatment effect times the weight divided by the sum of the weights where weight is the inverse of the sum of the within study and between study variances. The test of difference in treatment rate for both fixed effect and random effects uses the Z-value (combined effect rate/standard error).

Funnel plots (*Egger, Davey, Schneider, & Minder, 1997a*), which are simple scatter plots of a study's effect estimates (x-axis) against its precision (y-axis), were analyzed to test selection bias among selected studies. This plotting method applies a hypothesis that precision will increase as sample size increases when estimating the underlying treatment effect. The spread will narrow as precision increases among larger studies. In the absence of bias, the plot likely resembles a symmetrical inverted funnel; otherwise, the plot shows an asymmetrical and skewed shape. A method referred to as 'The Trim and Fill method' (*Duval & Tweedie, 2000*) essentially trims off the asymmetrical right side of the funnel plot after estimating which studies are in this outlying part. Using the symmetrical remainder of the plot the true 'center' of the funnel plot is identified and then the 'trimmed' studies are placed along with imputed 'missed counterpart studies' around the center. The 'filled' funnel plot is the basis for an estimate of the true overall effect and variance. The key to this method is estimating the number of missed studies due to

publication bias. The reviewer applied these methods, as diagnostic, during the initial evaluation of the published data. Results are not reported in this review.

Although visually useful, funnel plots alone are not ‘proof’ of bias. For instance, funnel plot asymmetry may occur (and often does in studies with high-risk patients due to difficulty in recruitment) if the true treatment effect is larger in the smaller trials leading to an association between treatment effect size and its standard error. The regression method (Egger *et al.*, 1997a) and rank correlation test (Begg & Mazumdar, 1994) are two proposed methods to test for association between treatment effect size and its variance. The rank correction test is based on Kendall’s tau, derived by enumerating the numbers of pairs of studies that are ranked in the same order with respect to adjusted effect size and variance. The regression method proposes a linear regression of the standard normal deviate (effect size/standard error) against the precision (1/standard error). This review employed both methods when feasible.

Due to the variation in available fever and parasite clearance rates (i.e. mean, median or range provided) analyses of these data are not feasible.

The software used in the meta-analyses was *Comprehensive Meta-Analysis version 2.2.020* and *RevMan 4.2.8*.

3.1.2 Results

The reviewer performed a literature search using key words, “malaria” and “oral quinine”, which resulted in two additional published studies, one in children evaluating a six day combination treatment of quinine and clindamycin (Ramharter *et al.*, 2005) and one in adult travelers (Parola *et al.*, 2001) of which the former was included in the review. The study by Parola *et al.* was excluded on the basis that it included a different patient population from the other studies included. A search using key words, “malaria” and “quinine” resulted in several systematic reviews, none of which evaluated oral quinine. There were however two useful systematic reviews located of parenteral quinine for treatment of severe malaria, one by *The Artemether-Quinine Meta-analysis group (2001)* and another by Pittler and Ernst (1999). Both are briefly discussed in 3.1.2.3, which discusses parenteral quinine.

3.1.2.1 Oral Quinine Monotherapy

The Sponsor identified 11 publications, dated from 1974 and 2004, of randomized studies that evaluated oral monotherapy quinine for treatment of uncomplicated *P. falciparum* malaria. These studies are discussed, in detail, in Appendix A and in Table 2.2. Publications excluded from all meta-analyses include de Vries *et al.* (2000) and Rahman *et al.* (2001). De Vries *et al.* published results previously summarized in Bich *et al.* (1996) as well as modified the treatment assignments. Due to the concern of multiple publication bias and well as flawed randomization, the reviewer eliminated this study. The study by Rahman *et al.* discussed a change in treatment in one group and sample size adjustment following an interim analysis invalidating the original randomization. The authors did not provide any valid statistical justification for these changes.

Among the remaining nine published studies, the most commonly administered quinine dose was 10 mg (sulfate salt)/kg given three times daily for seven days. Five studies compared quinine monotherapy

versus a synthetic antimalarial or artesunate. Four studies compared a quinine monotherapy versus a quinine-containing combination regimen. All studies had the inclusion criteria of confirmed uncomplicated *P. falciparum* malaria by either *Giesma*-stained thick/thin smear and/or parasite density count within a specified range. Patients with severe malaria, inability to take oral medication, recent use of antimalarials, and pregnancy (except *McGready et al. (2000)*) were excluded. While only six of the nine studies confirmed that the study population was semi-immune, it is reasonable to assume that all studies included semi-immune patients given that the locations of the studies were in malaria endemic regions. The common primary endpoint was initial parasite clearance by day 7 without recrudescence at day 28. An estimated 1,140 patients participated in these studies, of which approximately 371 were randomized to receive quinine monotherapy. Adult and adolescent men were the common population studied.

Quinine 10 mg/kg tid x 7 days monotherapy

Six studies (*Ache et al., 2002; McGready et al., 2000; Mueller et al., 2004; Pukrittayakamee et al., 2004; Pukrittayakamee et al., 2000; Bich et al., 1996*) were identified, which evaluated a quinine 10 mg/kg tid (approximately 500-600 mg/day for an average size patient) x 7 days monotherapy regimen (Q7). All five studies had a 28-day follow-up assessment, except the study by *McGready et al.*, which evaluated patients at 63 days. Due to the longer follow-up assessment, the review eliminated this study from the analysis.

Four studies (*Ache et al., 2002; Bich et al., 1996; Mueller et al., 2004; Pukrittayakamee et al., 2004*) evaluated a Q7 regimen versus a non-quinine regimen and were therefore considered in a meta-analysis. Among these studies, 630 patients were randomized, 185 received the Q7 regimen and 153 (82.7%) were evaluable. Q7 cure rates in the evaluable and ITT populations ranged from 82% to 100% and 61% to 100% respectively. Variation in observed cure rates is likely due to variation in drug resistance by study region [SE Asia (2), Africa (1), and South America (1)], however due to the limited number of studies in all locations, a sub-group analysis by location is not feasible.

In a meta-analysis of the **evaluable** population, using comparators with similar durations, (i.e. the comparator with a duration close to 7-days used in studies with more than one comparator), the test for heterogeneity was significant (p-value = 0.023). Both the rank correlation and regression tests were insignificant for an association between small study treatment effect and variance. The random effects model calculated an overall odds ratio of 6.11, 95% CI [1.56, 24.00], 99% CI [1.01, 36.9], p-value=0.010. This estimated odds ratio suggests that the odds of cure is 6.11 times greater with Q7 versus a non-quinine control. There is some evidence of Q7 effectiveness, especially against chloroquine regimens; however, given the variation in comparators studied, these results should be interpreted with caution. The forest plot, with 95% CIs, of this analysis appears in Figure 1.

Figure 1: Meta-Analysis of Q7 Studies (Evaluable)

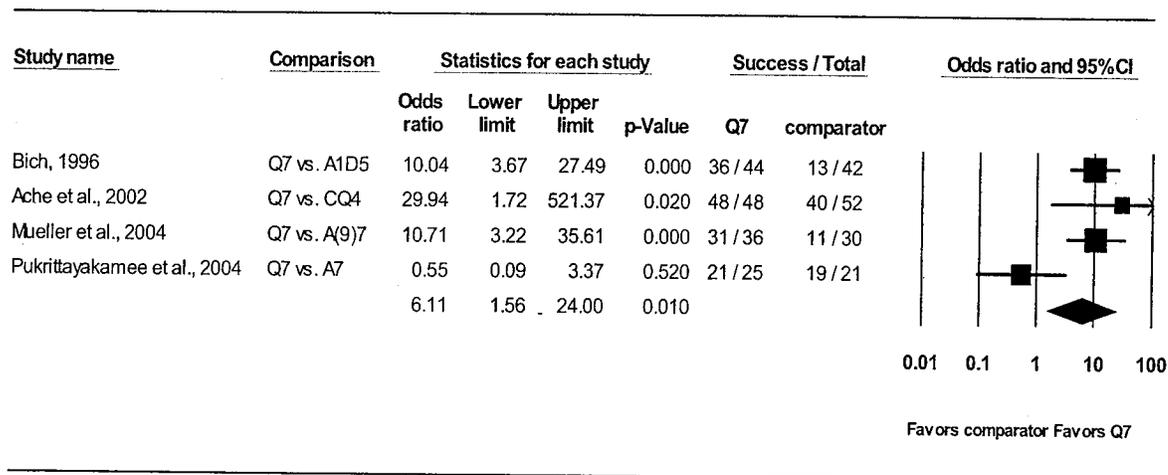


Figure Footnote: Black squares represent OR estimates with size directly proportional to amount of information provided by respective study in the combined analysis. The black diamond represents the overall OR estimate and 95% confidence interval. An OR greater than one suggest a greater probability of cure in the quinine regimen versus comparator and conversely for odds ratios less than one. Q7=oral quinine x 7 days, A1D5=artemisinin x 1 day plus doxycycline x 5 days, CQ4=chloroquine x 4 days, A (9)7=Artemisia tea (9g herb/l) x 7 days, A7=artesunate x 7 days

In a meta-analysis of the ITT population of these four studies using comparators with similar durations, the test for heterogeneity was significant (p-value =0.009). Both the rank correlation and regression tests were insignificant for an association between small study treatment effect and variance. The random effects model resulted in an overall odds ratio of 3.31, 95% CI [1.00, 10.97], 99% CI [0.68, 16.00], p-value=0.051 suggesting a trend in favor of the quinine monotherapy regimen albeit not statistically significant. Again, these results, shown in Figure 2 should be interpreted with caution given the variation in comparators studied.

Figure 2: Meta-Analysis of Q7 Studies (ITT)

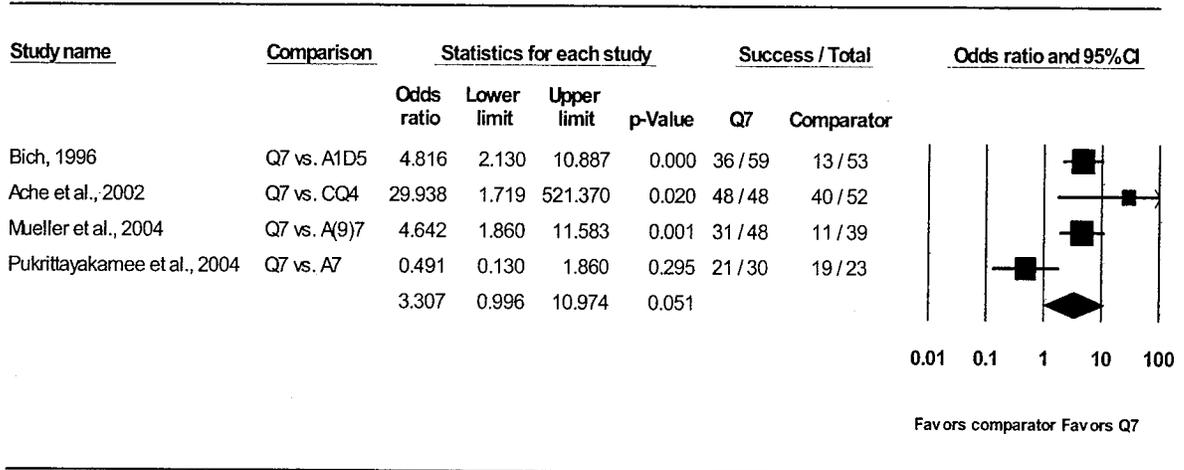


Figure Footnote: Black squares represent OR estimates with size directly proportional to amount of information provided by respective study in the combined analysis. The black diamond represents the overall OR estimate and 95% confidence interval. An OR greater than one suggest a greater probability of cure in the quinine regimen versus comparator and conversely for odds ratios less than one. Q7=oral quinine x 7 days, A1D5=artemisinin x 1 day plus doxycycline x 5 days, CQ4=chloroquine x 4 days, A (9)7=Artemisia tea (9g herb/l) x 7 days, A7=artesunate x 7 days

Three additional studies (*Watt et al., 1988; Metzger, Mordmuller, Graninger, Bienzle, & Kremsner, 1995; Segal et al., 1974*) that evaluated a quinine monotherapy regimen were not used in the analysis due to variation in quinine dose or duration (see summaries in Appendix A). The *Watt et al.* study evaluated quinine 10 mg/kg tid x 5 days, *Metzger et al.* evaluated quinine 12 mg/kg x 1.5 days, and *Segal et al.* evaluated quinine 10 mg/kg tid x 6 days.

In summary, it is evident that given the few valid randomized studies, using quinine monotherapy, and the variation among these studies in terms of location and comparator used, these results lack robustness. Few randomized studies using quinine monotherapy are available mainly because the evaluation and universal acceptance of this regimen occurred prior to the era of randomized clinical trials. For this reason, the evaluation of quinine monotherapy occurs more frequently in non-randomized studies (not discussed within review) such as case or observational studies. Among the randomized studies available in the literature, oral quinine commonly served as the active control. Because of this, publication bias is possible given that studies with unfavorable results for a new treatment versus quinine (i.e. quinine treatment was better) are less likely to be published compared to studies with results favoring a new treatment. Among the available publications using a Q7 regimen, there is evidence that this regimen is as

effective, in terms of a 28-day cure rate, versus an artemisinin comparator or possibly more effective versus chloroquine or a modified artemisinin regimen (Artemisia tea or shorter durations of artemisinin).

3.1.2.2 Oral Quinine Combination Therapy

The Sponsor identified 16 randomized clinical studies published between 1974 and 2004 using oral quinine in combination with another antimalarial or an antimicrobial (clindamycin, tetracycline, doxycycline, sulfadoxine/pyrimethamine, primaquine, or artemisinin derivative). The study by *De Vries et al. (2000)* was excluded due to replication and the study by *Rahman et al. (2001)* excluded due to methodological issues discussed in the study summary. Four studies included a quinine monotherapy arm and therefore included in the monotherapy study review. The reviewer located one additional study (*Ramharter et al., 2005*), which is included in the summary and analysis. Quinine was generally administered as quinine sulfate 10 mg/kg or 600 mg of base q8hrs (tid) for 7 days although there were some studies that evaluated a shorter quinine regimen. The inclusion/exclusion criteria were generally the same as those described for the monotherapy studies, however some studies required patients to remain hospitalized for the 28-day study duration. Among all 15 (14 from Sponsor and one additional from reviewer) studies, 1,808 patients were randomized of which 1,005 received a quinine-combination regimen. The patient population consisted mainly of adult men; however, some children were included, and most of the studies occurred in Southeast Asia. Six studies required that patients remain hospitalized during the study; seven studies allowed patients to leave the hospital following initial parasite clearance and return for the follow-up visit, and two studies were entirely outpatient field studies.

Quinine 10 mg/kg tid x 7 days combination therapy

In combination with oral tetracycline:

The literature search identified ten randomized studies (*Bunnag et al., 1996; Karbwang et al., 1994; de Alencar et al., 1997; Fungladda et al., 1998; Looareesuwan et al., 1994; Pukrittayakamee et al., 2004; Pukrittayakamee et al., 2000; Vanijanonta et al., 1996; Duarte, Fontes, Gyorkos, & Abrahamowicz, 1996; Salcedo, Camargo, Braga, de Maria, & Macedo, 1997*) evaluating quinine in combination with tetracycline. The study by *Salcedo et al.* was difficult to interpret and therefore removed from analysis (see summary in Appendix B). The study by *Fungladda et al.* was removed due to lack of a follow-up (i.e. day 28) assessment because it was designed as a compliance study. The remaining eight studies evaluated a quinine 10 mg/kg tid plus tetracycline x 7 days (Q7T7) regimen except *Duarte et al.* that evaluated quinine 10 mg/kg tid x 3 day plus tetracycline x 7-days (Q3T7).

The following analysis focuses on the seven studies (*Bunnag et al., 1996; de Alencar et al., 1997; Karbwang et al., 1994; Looareesuwan et al., 1994; Pukrittayakamee et al., 2004; Pukrittayakamee et al., 2000; Vanijanonta et al., 1996*) that evaluated a Q7T7 regimen with a 28-day study endpoint. Of the 861 patients randomized into the studies, approximately 325 received a Q7T7 regimen. Cure rates ranged from 94% to 100% in the evaluable populations and between 68% and 95% in the ITT populations (one study not reporting ITT rate).

Given that the comparators varied among these studies, the reviewer performed an analysis grouping studies according to whether or not the comparator contained quinine and type (i.e. non-quinine, quinine-combination and quinine monotherapy). This analysis evaluated the treatment effect in each group and overall. Three studies (*de Alencar et al., 1997; Karbwang et al., 1994; Looareesuwan et al., 1994*) had a

non-quinine containing comparator, two studies (*Bunnag et al., 1996; Vanijanonta et al., 1996*) utilized a quinine-combination comparator, other than Q7T7, and two studies (*Pukrittayakamee et al., 2004; Pukrittayakamee et al., 2000*) used Q7 as a comparator.

The fixed effect and mixed effects models yielded the same results. The mixed effects model combines studies within each sub-group to estimate an overall treatment effect for each sub-group and a fixed effect model combines sub-groups to yield an overall treatment effect. In the evaluable analysis, the test for heterogeneity among these seven studies was insignificant (p-value of 0.971). Both the rank correlation and regression tests were expectedly insignificant given the insignificant test for heterogeneity. Using the fixed effect model, the overall estimated effect size was 6.26 (OR), 95% CI [2.34, 16.75], 99%CI [1.72, 22.83], p-value =0.0003. The estimated fixed effect within studies having a non-quinine comparator was 3.07 (OR), 95% [0.61, 15.5], p-value=0.18. Between the two studies having a quinine-combination comparator, the estimated fixed effect was 11.6 (OR), 95% CI [1.97, 67.91], p-value=0.007. Between the two studies using a Q7 comparator, the estimated fixed effect was 7.85 (OR), 95% CI [1.38, 44.52], p-value=0.020. The sub-group estimated effect sizes have large confidence intervals due to less information provided and thus should prompt the use of caution when interpreting results. Also, meta-analytic sub-group analysis are prone to bias and therefore should be interpreted with caution (*Davey, Egger, & Phillips, 1997*). The forest plot of this analysis appears in Figure 3 below.

Figure 3: Meta-Analysis of Q7T7 Studies Sub-Grouped by Comparator Type (Evaluable)

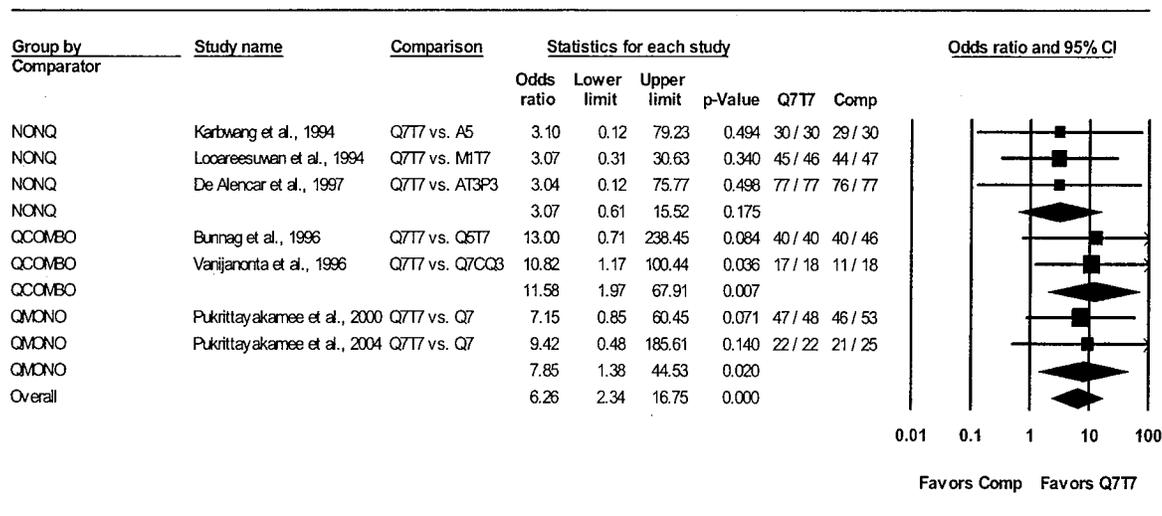


Figure Footnote: Black squares represent OR estimates with size directly proportional to amount of information provided by respective study in the combined analysis. Each diamond represents the overall OR estimate and 95% confidence interval for the respective sub-group analysis. The bottom row diamond represents the overall

estimate. An OR greater than one suggest a greater probability of cure in the quinine regimen versus comparator and conversely for OR less than one. NONQ=comparator did not contain quinine, QCOMBO=quinine combination comparator, QMONO=quinine monotherapy, A6=oral artesunate x 6 days, MIT7=mefloquine x 1 days plus tetracycline x 7 days, AT3P3=atovaquone plus proguanil x 3 days, Q5T7=quinine x 5 days plus tetracycline x 7 days, Q7CQ3=quinine x 7 days plus chloroquine x 3 days, Q7T7=quinine plus tetracycline x 7 days

In the ITT analysis, the overall, and within comparator sub-group, trends favor the Q7T7 regimen; however, the differences were not statistically significant.

The studies occurred in Thailand except the *De Alencar et al* study (1997), which occurred in Brazil. Removal of this study does not significantly affect the estimated effect size of the treatment effect.

In summary, published data on randomized clinical studies, evaluating quinine 10 mg/kg tid in combination with a second antimicrobial (tetracycline, doxycycline, or clindamycin) are limited. Among seven studies, that compared a Q7T7 regimen to other regimens, an overall trend in favor of the Q7T7 was shown. No significant difference was observed among the sub-set of studies that compared a Q7T7 regimen to a non-quinine containing regimen. Differences were observed in the evaluable analysis; however, when the comparator was either Q7 alone or sub-optimal quinine combinations (i.e. shorter durations or using a second treatment such as chloroquine). These results are driven in large part to the fact that all but one of these studies occurred in Thailand, which is an area with known quinine resistance where quinine monotherapy is less effective. Insufficient data exists to evaluate, in a systematic fashion, quinine in combination with clindamycin or doxycycline or to evaluate shorter durations of combination regimens.

3.1.2.3 Parenteral Quinine Therapy (*supportive*)

Parenteral forms of quinine are the choice of drug in many parts of the world for treatment of severe and complicated cases of *P. falciparum* malaria, including cerebral malaria (*World Health Organization, 2000*).

Providing a comprehensive summary of quinine efficacy, the Sponsor submitted 14 published randomized studies comparing parenteral [intravenous (i.v.) or intramuscular (i.m.)] quinine to an artemisinin derivative (artemether, n=12; or arteether, n=2) for treatment of severe malaria. Two studies had a double blind design and the rest were open-label. Seven studies were conducted in Asia (four in Southeast Asia, one in India and one in Bangladesh) and seven in Africa. Ten studies evaluated an intravenous quinine monotherapy regimen and four other studies allowed for additional antimalarials once patients were able to take oral medication. The patient populations were adults (4 studies), children (8 studies) and children & adults (2 studies). There were approximately 1,125 children or adults from ages 0 to 78 (average of mean or median of 12 yrs) years old reportedly enrolled. Patients randomized to parenteral quinine (intravenous in 12 studies and intramuscular in 2) received an initial loading dose of 20 mg dihydrochloride salt over four hours in 12 studies followed by a maintenance dose of 10 mg/kg salt q8 hours. The common treatment duration among these studies was seven days and given the high mortality rate of severe or complicated malaria, mortality was the primary endpoint. Table 2.4 summarizes these studies.

Parenteral Quinine Monotherapy Studies

As presented in Table 2.4, the mortality rates of the ten parenteral quinine monotherapy studies ranged from 5% (2/39) to 42% (5/12). The largest study (*van Hensbroek et al., 1996*) resulted in a 22% (62/288) mortality rate in the quinine group and a similar mortality rate of 21% (59/288) in the artemether comparator group. There were 140/621 deaths in the quinine group and 108/627 in the artemisinin group.

Among the eight studies that compared parenteral quinine to artemether (*Adam, Idris, Mohamed-Ali, Aelbasit, & Elbashir, 2002; Faiz et al., 2001; Karbwang et al., 1995; Karbwang et al., 1992; Olumese, Bjorkman, Gbadegesin, Adeyemo, & Walker, 1999; Satti, Elhassan, & Ibrahim, 2002; Singh, Bhagyabati, Singh, Singh, & Singh, 2001; van Hensbroek et al., 1996*) heterogeneity was not observed (p-value=0.10). The overall fixed effect estimate was 1.39, 95% CI [1.02, 1.89], p-value=0.04 suggesting an increased probability of death, albeit not highly significant, in the quinine group. These results are shown in Figure 4 below.

Figure 4: Meta-Analysis of Parenteral Quinine vs. Artemether Studies

Review: Parenteral Quinine for Severe Malaria (Version 01)
Comparison: 01 Mortality in Parenteral Monotherapy Studies
Outcome: 01 Mortality

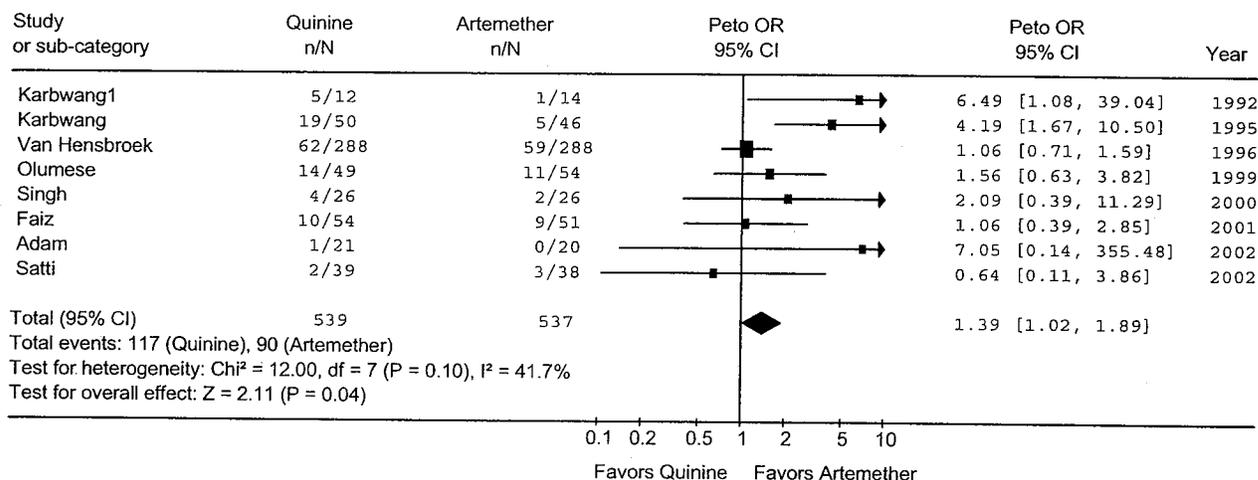


Figure Footnote: Squares represent odds ratio (OR) estimates with size directly proportional to amount of information provided by respective study in the combined analysis. The diamond represents the fixed effect estimate with the width corresponding to the 95% CI. An OR greater than one suggests a greater probability of death in the quinine regimen versus comparator and conversely for OR less than one.

The reviewer located a published meta-analysis, by *Pittler and Ernst (1999)* that assessed the evidence regarding clinical effectiveness of artemether (i.m.) versus quinine (i.v. or i.m.) for severe malaria. The authors located nine published randomized clinical studies via a computerized literature search for independent review. The author concluded that there was no significant mortality difference between artemether (14.6%) and quinine (17.6%) with an odds ratio of 0.76, 95% CI [0.50, 1.14].

The reviewer located a second meta-analysis, which utilized actual patient data and therefore considered

by the reviewer as a more robust analysis. This meta-analysis, published by The Artemether-Quinine Meta-analysis study group (2001), compared parenteral quinine and artemether regimens for treatment of severe malaria in terms of rate of mortality. The authors obtained individual patient data from seven published studies comprising 1,947 patients and conducted independent review and analyses. The authors identified 164/958 (17%) and 136/961 (14%) deaths among parenteral quinine and artemether treated patients respectively resulting in a summary odds ratio of 0.8, 95% [0.62, 1.02], p-value=0.08. The authors concluded that the central result of their meta-analysis was that artemether treatment is associated with a trend towards a lower mortality compared to quinine but that this result was not significant at the 5% level. The authors also performed sub-group analysis by age and geographical region suggesting that in adults and Asian patients, artemether was significantly more effective than quinine in reducing mortality while emphasizing that lack of a statistical significance in the overall results. The authors reasoned that these sub-group mortality differences favoring artemether may be due to increased effectiveness in areas of quinine resistance or an age-specific variation in efficacy.

Sub-Group Meta-Analyses by Geographical Region

There is a difference in the clinical presentation of severe malaria between sub-Saharan Africa and Asia (especially Southeast Asia) due large in part to the rate of transmission. In parts of tropical Africa, malaria transmission is intense and therefore the rate of severe malaria is less, especially in adults, due to malaria-specific immunity. In Africa, children between ages 1-3 remain at risk for severe malaria due to the lack of established immunity. In contrast is Asia where malaria transmission is sporadic, severe malaria affects both adults and children due to decreased or lack of immunity. Therefore, on a population level, the clinical presentation of severe malaria differs between that observed in Africa and in Asia largely. To understand the geographical factor, the reviewer performed a meta-analysis, sub-grouping studies by geographical region (Africa or Asia) of the eight studies using artemether as a comparator. Four studies were in Africa and four in Asia. All four studies conducted in Africa treated children, whereas the four studies in Asia treated adults and children. This is expected given that, as stated above, the risk of severe malaria in adults is low in Africa but high in Asia. Given that all studies conducted in Africa were in children and those in Asia in children and adults, an analysis by patient population is identical to the analysis by geographical region.

The analysis sub-grouping by geographical region resulted in fixed effect estimates of 2.53, 95% CI [1.36, 4.72], 99% CI [1.12, 5.74] and 1.12, 95% CI [0.79, 1.61], 99% CI [0.70, 1.80] for studies performed in Asia and Africa respectively. The sub-group results from the Asian studies suggest a statistically significant increase in the risk of mortality in the parenteral quinine group compared to parenteral artemisinin. A trend in favor of artemisinin was found in African studies, although not statistically significant. These results are consistent with the overall results; however, sub-group p-values in a meta-analysis generally lack in power and therefore should be interpreted with caution. Figure 5 illustrates the sub-group findings.

Figure 5: Sub-group Meta-analysis of Parenteral Quinine Monotherapy Studies by Geographical Region

Review: Parenteral Quinine for Severe Malaria (Version 01)
Comparison: 02 Mortality by Geographical Region
Outcome: 01 Mortality

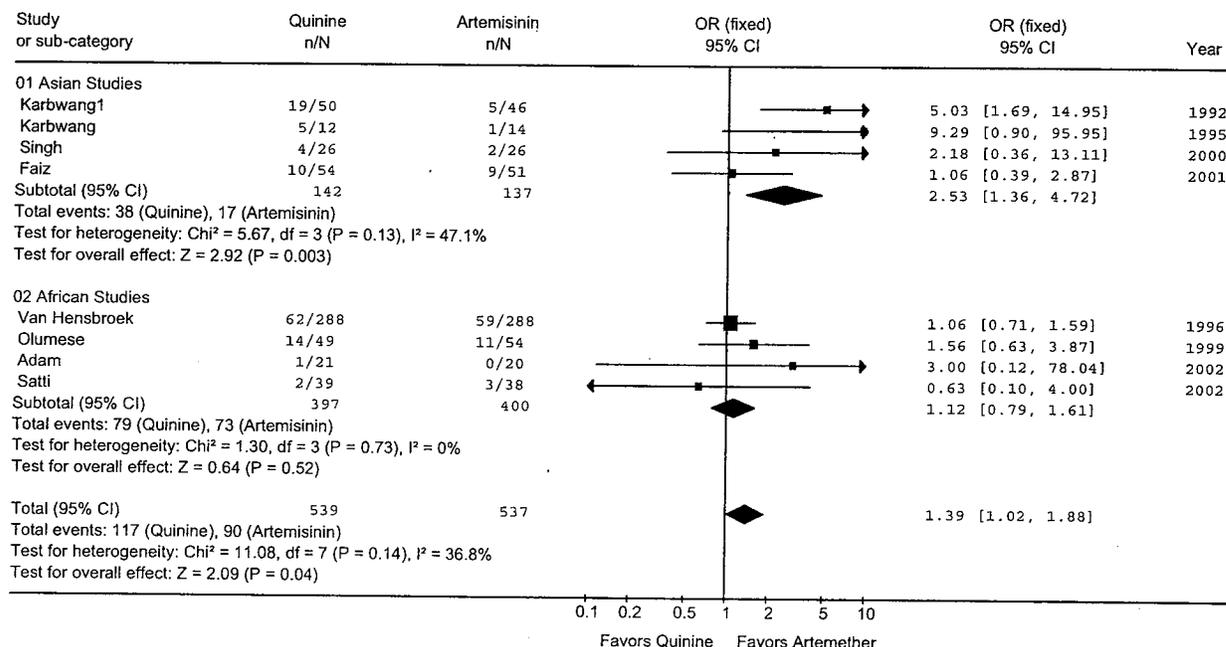


Figure Footnote: Squares represent odds ratio (OR) estimates with size directly proportional to amount of information provided by respective study in the combined analysis. Each diamond represents the overall OR estimate and 95% confidence interval for the respective sub-group analysis or the overall analysis (bottom estimate). An OR greater than one suggests a greater probability of death in the quinine regimen versus comparator and conversely for OR less than one.

Parenteral Quinine Combination Studies

Four studies (Murphy et al., 1996; Newton et al., 2003; Taylor, Wills, Courval, & Molyneux, 1998; Tran et al., 1996) utilized a second antimalarial once patients were able to take oral medications. Mortality rates in quinine combination studies ranged from 12% (8/71) to 26% (12/46). The largest combination therapy study (Tran et al., 1996) resulted in a mortality rate of 17% (47/276) in the quinine group and a rate of 13% (36/284) in the comparator group. Given variability in treatment regimens and a limited number of studies, the reviewer did not perform a meta-analysis of these studies. See Table 2.4 for details of studies.

In summary, the overall meta-analysis of the parenteral quinine monotherapy studies showed an increase in mortality rate compared to artemether comparator. Sub-group analysis by geographical region showed

a difference between treatment groups, favoring artemether in Asian studies more so than in African studies. These sub-group differences could be due to patterns of quinine resistance occurring in parts of Southeast Asia or due to age variation among patients studied. Though these meta-analyses point to increased efficacy of artemether compared to quinine, artemether is currently unapproved in the United States and overall quinine showed a survival rate significantly larger than what should be expected with no treatment, i.e. mortality close to 100%. Therefore, these data on parenteral quinine for treatment of severe malaria are supportive.

3.1.3 Statistical Issues with the Use of Published Data and Meta-Analysis

Given the nature of this review, it is necessary to discuss the issues/biases associated with the use of published data to evaluate quinine's safety and efficacy.

Publication bias (*Easterbrook, Berlin, Gopalan, & Matthews, 1991; Dickersin, 1997; Dickersin, Min, & Meinert, 1992; Begg & Berlin, 1989*), or the likelihood that studies with statistically significant 'positive' results are often published more than those with 'negative' results, is a major concern when obtaining primary data from literature databases. Negative or inconclusive results typically are unpublished, as they are perceived as uninteresting to the medical community. The publication of only positive results is likely to result in an inaccurate or over-estimated overall treatment effect. Given that quinine was generally the control treatment in the available published studies, there is great potential for this bias. Consideration of this bias should be used when interpreting results.

Time lag bias (*Stern & Simes, 1997; Ioannidis, 1998*) is the concern that studies with 'positive' results are much more likely to be published within a shorter time than studies with 'negative' results leading to bias in the availability and interpretation of results from clinical studies.

Multiple publication bias (*Tramer, Reynolds, Moore, & McQuay, 1997; Gotzsche, 1987; Gotzsche, 1989; Huston & Moher, 1996*) addresses the concern of published data occurring more than once in the literature without acknowledgement by the author(s). Duplication, which is sometimes deliberate, can result in analysis of patient data (in a meta-analysis) more than once leading to an overestimated treatment effect. Many examples of this bias exist in the literature including multiple publications in different languages, presenting analysis in different populations (intent-to-treat, per protocol) in different publications, combining duplicated data from another trial and reporting a combined analysis, or adding further data to data previously published (i.e. adding data to an interim analysis previously published). This bias was present in two of the studies provided in this submission.

Citation bias (*Gotzsche, 1987; Ravnskov, 1992; Begg et al., 1989*) includes the citation or non-citation of clinical studies results depending on the type and direction of these results.

Language bias (*Gregoire, Derderian, & Le, 1995; Egger et al., 1997b*) addresses the reporting of statistically significant results in English speaking journals while insignificant results may occur in non-English speaking journals. Investigators working in non-English speaking countries may prefer to present only positive findings in English journals to achieve recognition. To avoid this bias, systematic review should include database searched in English and non-English speaking journals if possible.

Selection bias describes the bias associated with ‘apple-picking’ results that favor the overall objective. This bias can occur in what data an author submits for publication as well in the studies chosen in a systematic review by a meta-analyst.

Aside from the multiple issues just discussed regarding the quality and consistency of published studies, several issues exist that are germane to meta-analysis. For instance, the inclusion of randomized studies in a meta-analysis does not imply that comparisons between studies are also random. This assumption is made in error much too often when interpreting results from a meta-analysis. An assumption in meta-analysis is that each independent data set has an unbiased estimate of the treatment effect. The only expected variability is that which is random in nature and tends to zero as the sample size increases. Similarly, variability between studies in a meta-analysis is attributable to random variation such that the overall effect obtained from a set of independent studies should provide an unbiased treatment effect estimate with increased precision. This is true when studies are homogeneous in nature, however when heterogeneity is present the overall estimate of the treatment effect can be misinterpreted. Forest plots and tests for heterogeneity are necessary to investigate any possible heterogeneity; however, these methods are unable to explain sources of heterogeneity.

Additionally, meta-analysis of clinical studies may increase the precision of the overall treatment effect estimate, possibly leading to reduced probability of false-negative results. Additionally, the quality of a meta-analysis is only as good as the quality of the individual studies. All clinical trials suffer from the risk of biases that threaten the validity of results, such as selection bias (baseline imbalances more present in non-randomized studies), performance bias (unequal care between treatment groups present in unblinded studies), detection bias (biased assessment of outcomes), and attrition bias (biased exclusion of randomized patients). In light of the concerns that occur when aggregating multiple studies, meta-analysis should be performed only within the context of a systematic review (*Egger, Smith, & Sterne, 2001*), i.e. reviews prepared using a systematic approach to minimize bias and explicitly address issues regarding the completeness, quality and combinability of the data available.

3.2 Evaluation of Safety

Due to limitations in data from the identified published randomized clinical studies, the reviewer did not perform a formal safety review. Clinical perspectives on the safety of oral quinine, gathered from available published studies, product labels, and spontaneous adverse reactions reports via FDA’s Adverse Events Reports System, are in the medical officer’s review (Mary Singer, MD) as well as in reviews by the Office of Drug Safety and the pregnancy labeling group (via consults).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Given the overall quality of the available published randomized studies, which lack in efficacy details by demographic and more importantly lack individual patient data, sub-group analysis are not feasible. Furthermore, sub-group analysis within a meta-analysis are often prone to bias (*Davey et al., 1997*) due to an over or under representation of a particular sub-group in one or more studies that can influence the overall comparison.

4.2 Other Special/Subgroup Populations

Limited demographic characteristics exist in the available studies thus preventing sub-group analyses.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Refer to section 3.1.3, and throughout the results section 3.1.2 for a summary of the multiple statistical issues or warnings specific to meta-analyses of published studies.

Unlike a standard NDA, which bases safety and efficacy on two well-controlled, randomized clinical studies, this submission relies on a large body of clinical experience summarized in the worldwide literature. Although each identified clinical study offers information, not one single study is robust enough to represent the total experience with oral quinine. For this reason, this review considered all studies in an integrated fashion.

The integration of randomized oral quinine monotherapy studies was limited largely to the evolution of quinine therapy prior to modern randomized clinical studies. Experience with oral quinine monotherapy is based more on case study reporting than on randomized clinical studies. Among the few studies of oral quinine monotherapy, quinine serves as the active control, which introduces some bias against quinine. The small number of studies, however, significantly limits any meaningful meta-analysis. Due to a growing resistance to quinine monotherapy throughout many parts of the world, particularly in Southeast Asia, studies that are more recent have evaluated quinine combinations rather than monotherapy. Because of this, more data from randomized clinical studies exists on the use of oral quinine in combination with other antimalarials or with antimicrobials. The information from the literature suggests that a quinine plus tetracycline regimen has at least a 90% cure rate. Most data on this regimen comes from studies conducted in Southeast Asia and therefore one should use caution when making generalities across countries. Some data exists directly comparing a quinine combination regimen with a quinine monotherapy regimen. These data suggest an added benefit with the combination regimen; however, these data are limited in size. Less information exists regarding quinine combination with clindamycin or doxycycline and pertaining to shorter treatment durations of quinine.

Supportive data from studies of parenteral quinine versus intramuscular artemether for treatment of severe or complicated malaria show a higher mortality rate for quinine. Given that artemether is unapproved in the US for this indication, and given that the overall quinine survival rate is much larger than what would be expected with no treatment, these data are supportive.

5.2 Conclusions and Recommendations

An extensive clinical history, spanning over 200 years, of quinine therapy for treatment of *Plasmodium (P.) falciparum* malaria obviates the need for additional clinical studies to assess the safety and efficacy of this therapy. Among the copious amount of information, randomized, clinical trials published in the worldwide literature between 1974 and 2005 served as the primary NDA data for oral quinine sulfate capsules. Not considered during this review is the large body of information in the literature from non-randomized studies or patient case reports. A systematic review of identifying, reviewing, summarizing, and assessing each available published study occurred resulting in 22 randomized, active-controlled, studies including approximately 2,495 patients of which 1,456 were randomized to an oral quinine regimen. For purposes of a systematic review, the reviewer considered ten of these studies primary. Among five primary studies, evaluating a quinine 10 mg/kg tid x 7 day monotherapy regimen, four had cure rates of 82-87% (61-70%) in the evaluable (ITT) populations and one study of 48 patients had a cure rate of 100% in both populations. In seven primary studies, evaluating quinine 10 mg/kg tid in combination with tetracycline for 7 days the cure rates were 94-100% (68-95%) in the evaluable (ITT) populations (one study not reporting ITT rates). Cure, defined as parasite clearance by day 7 without recrudescence at day 28, varied due to drug resistance patterns across malaria endemic study regions. Lost to follow-up led to the observed lower cure rates in the ITT population.

Although the quality and design of the available published randomized studies varies from poor to average, the totality of data and clinical experience provides sufficient evidence to conclude that oral quinine 10 mg/kg tid x 7 days is effective for treatment of uncomplicated *P. falciparum* malaria in adults. Additionally, this regimen in combination with tetracycline for seven days demonstrated effectiveness based on seven randomized published studies. Insufficient data exists from randomized clinical studies to estimate the overall treatment effect of other quinine combination therapies or shortened quinine durations.

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APPENDIX A-SUMMARY OF QUININE MONOTHERAPY PUBLICATIONS

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Mono Study 2: Pukrittayakamee S, Chotivanich K, Chantra A, et al. Activities of artesunate and primaquine against asexual and sexual stage parasites in *falciparum* malaria. *Antimicrob Agents Chemother* 2004; 48:1329-1334..... 37

Mono Study 3: Mueller MS, Runyambo N, Wagner I, et al. Randomized controlled trial of a traditional preparation of *Artemisia annua* L. (Annual Wormwood) in the treatment of malaria. *R Soc Trop Med Hyg* 2004; 98:318-321..... 38

Mono Study 4: Aché A, Escorihuela M, Vivas E, et al. In vivo drug resistance of *falciparum* malaria in mining areas of Venezuela. *Trop Med Int Health* 2002; 7:737-743..... 40

Mono Study 5: Rahman MR, Paul DC, Rashid M, et al. A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated *falciparum* malaria in a multi drug resistant *falciparum* area of Bangladesh—narrowing the options for the National Malaria Control Programme? *Trans R Soc Trop Med Hyg* 2001; 95:661-667..... 41

Mono Study 6: McGready R, Brockman A, Cho T, et al. Randomized comparison of Mefloquine artesunate versus quinine in the treatment of multidrug-resistant *falciparum* malaria in pregnancy. *Trans Roy Soc Trop Med Hyg* 2000; 94:689-693..... 43

Mono Study 7: Pukrittayakamee S, Chantra A, Vanijanonta S, et al. Therapeutic responses to quinine and clindamycin in multidrug-resistant *falciparum* malaria. *Antimicrob Agents Chemother* 2000; 44:2395-8..... 44

Mono Study 8: De Vries PJ, Bich NN, Thien HV, et al. Combinations of artemisinin and quinine for uncomplicated *falciparum* malaria: efficacy and pharmacodynamics. *Antimicrob Agents Chemother* 2000;44:1302-1308..... 46

Mono Study 9: Bich NN, de Vries PJ, Thien HV, et al. Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated *falciparum* malaria. *Am J Trop Med Hyg* 1996; 55:438-443..... 48

Mono Study 10: Metzger W, Mordmüller B, Graninger W, et al. High efficacy of short-term quinine antibiotic combinations for treating adult malaria patients in an area which malaria is hyperendemic. *Antimicrob Agents Chemother* 1995; 39:245-246..... 50

Mono Study 11: Segal HE, Chinvanthananond P, laixuthai B, et al. Preliminary study of WR 33063 in the treatment of *falciparum* malaria in northeast Thailand. *Am J Trop Med Hygiene* 1974;23:560-564..... 51

SUMMARY OF QUININE MONOTHERAPY PUBLICATIONS

Mono Study 1: Watt G, Long GW, Padre LP, et al. Chloroquine and quinine: a randomized, double-blind comparison of efficacy and side effects in the treatment of *Plasmodium falciparum* malaria in the Philippines. *Trans R Soc Trop Med Hyg* 1988; 82:205-208.

Note: Double blind design with matched placebo but small sample size lacking statistical power.

Design: R, DB, AC

Location: Manila, Philippines

Patient Population: Male patients 16 years or older

Inclusion Criteria: >1000 asexual *P. falciparum* parasites per μ l of blood

Exclusion Criteria: Severe malaria, malaria acquired outside of Philippines, history of vomiting, antimalarials within past 3 weeks

Randomization Method: not specified

Treatment Groups:

- Experimental: Oral quinine 648 mg tid x 5d with matched placebo (Q5)
- Active Control: Chloroquine phosphate (300 mg base/tablet) 3 tablets on day 1, 1 tablet on days 1-2, matched placebo on days 3-5 (CQ3)

Study Procedures: quantitative parasite counts twice daily, oral temperature q4hrs

Primary Endpoint: Not explicitly specified

Results:

Characteristic	Q5	CQ3
Randomized/Completed	10/10	10/10
Mean Age (yrs) \pm SD (range)	28 \pm 11 (16-49)	30 \pm 11 (18-49)
Mean Baseline Parasite count \pm SD (range)	8,710 \pm 2,754 (1,500-26,381)	9,333 \pm 3,020 (1,323-33,900)
Mean FCT (hrs) \pm SD	43.2 \pm 20.0	46.3 \pm 24.7
Mean PCT (hrs) \pm SD	60.3 \pm 12.5	76.1 \pm 29.3
Cure rate (ITT)*	10/10	10/10
Cure rate (Eval)*	10/10	10/10

*by day 6

Mono Study 2: Pukrittayakamee S, Chotivanich K, Chantra A, et al. Activities of artesunate and primaquine against asexual and sexual stage parasites in falciparum malaria. *Antimicrob Agents Chemother* 2004; 48:1329-1334.

Note: Study objective was to determine if the addition of primaquine to either artesunate or quinine is as effective as standard 7-day quinine + tetracycline. Sample size justification not provided.

Design: R, OL, AC

Location: Thailand

Patient Population: Adult male patients

Inclusion Criteria: acute uncomplicated *P. falciparum* malaria confirmed by thick/thin blood smear

Exclusion Criteria: severe malaria, primary mixed malaria infection, antimalarial within 48 hrs, G6PD deficiency

Randomization Method: not specified

Treatment Groups:

- Experimental:
 - Quinine sulfate 10 mg/kg tid + tetracycline 4 mg/kg qid x 7d (Q7T7)
 - Quinine sulfate 10 mg/kg tid + primaquine 0.25 mg base/day x 7d (QP(.25)7)
 - Quinine sulfate 10 mg/kg tid + primaquine 0.50 mg base/day x 7d (QP(.50)7)
 - Artesunate 200 mg on day 1, 100 mg on days 2-7 (A7)
 - Artesunate 200 mg on day 1, 100 mg on days 2-7 + primaquine 0.50 mg base/day x 7d (A7P7)
- Active Control: Quinine sulfate (300 mg of salt/tablet) at 10 mg of salt/kg tid x 7d (Q7)

Study Procedures: vital signs q4hrs, parasite count q12hrs until clearance and daily for 28 days

Primary Endpoint: Not explicitly specified

Sample Size justification: Not provided

PCT: interval from the start of therapy until undetectable asexual parasite count

FCT: defined as time taken for temperature to fall below 37.5° Celsius for > 48 h

F/U: 28 days

Results:

Characteristic	Q7	Q7T7	QP(.25)7	QP(.50)7	A7	A7P7
Randomized/Completed	30/25	30/22	29/18	37/31	23/21	27/25
Mean Age (yrs) ± SD	24 ± 8	27 ± 9	25 ± 9	24 ± 10	23 ± 8	24 ± 8
Median Baseline Parasite count (range)	9,004 (234-116,054)	14,066 (630-231,104)	10,306 (168-229,094)	17,637 (405-200,458)	64,449 (321-569,722)	26,566 (800-350,173)
Median FCT (h) (range)	63 (7-152)	33 (8-117)	48 (8-152)	60 (7-154)	34 (7-180)	32 (8-164)
Median PCT (h) (range)	80 ± 26	81 ± 19	78 ± 23	79 ± 19	69 ± 19	63 ± 18
Cure rate (ITT)*	21/30	22/30	13/29	23/37	19/23	21/27
Cure rate (Eval)*	21/25	22/22	13/18	23/31	19/21	21/25

*up to day 28

Mono Study 3: Mueller MS, Runyambo N, Wagner I, *et al.* Randomized controlled trial of a traditional preparation of *Artemisia annua* L. (Annual Wormwood) in the treatment of malaria. *R Soc Trop Med Hyg* 2004; 98:318-321.

Note: The study objective was to evaluate the efficacy of *Artemisia annua* tea preparation vs. quinine active control. Study described as pilot. Sample size justification not provided. Detailed summary provided of patient disposition and limited summary of clinical/parasitological outcomes.

Design: R, OL, R

Location: Democratic Republic of the Congo

Patient Population: adult patients ≥ 18 yrs

Inclusion Criteria: *P. falciparum* malaria with parasitemia $> 2,000$ ul, permanent resident for at least five years, and at least one clinical sign of malaria

Exclusion Criteria: pregnancy, antimalarial treatment within past 2 weeks, current treatment for other diseases

Randomization Method: Not specified

Treatment Groups:

- Experimental:
 - Artemisia tea 5g herb/l, 1 liter/day x 7d (ATEA5)
 - Artemisia tea, 9g herb/l, 1 liter/day x 7d (ATEA9)
- Active Control:
 - Quinine sulfate 500 mg tid x 7 days (Q7)
 - Chloroquine-group dropped from analysis due to poor efficacy by day 3

Study Procedures: days 3 and 7 vitals and temperature, parasitemia measured (frequency unspecified)

Primary Endpoint: Cure rate on day 7 defined as negative blood film on day 7

Secondary Endpoints: Cure rate on days 14, 28, and 35 and change in clinical symptoms as measured by patient questionnaire

Sample Size justification: Not provided

Efficacy Failure: severe malaria, parasitemia on day 3 equal or higher than baseline, parasitemia on day 7, malaria recurrence up to day 35 in patients who were cleared on day 7

F/U: day 35

Results:

Characteristic	Q7	ATEA5	ATEA9
Randomized/Completed	48/43	45/39	39/33
M/F	Not provided		
Age (yrs)	Not provided		
Baseline Parasite count	Not Provided		
FCT	Not Provided		
PCT	Not Provided		
Cure rate (ITT)-day 7	39/48	30/45	23/39
Cure rate (Eval)-day 7	39/43 (91%)	30/39 (77%)	23/33 (70%)
Cure rate (ITT)-day 14	35/48	20/45	18/39
Cure rate (Eval)-day 14	35/39 (90%)	20/35 (57%)	18/31 (58%)
Cure rate (ITT)-day 28	31/48	12/45	11/39
Cure rate (Eval)-day 28	31/36 (86%)	12/32 (38%)	11/30 (37%)
Cure rate (ITT)-day 35	27/48	11/45	9/39
Cure rate (Eval)-day 35	27/34 (79%)	11/32 (34%)	9/30 (30%)

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Mono Study 4: Aché A, Escorihuela M, Vivas E, *et al.* In vivo drug resistance of falciparum malaria in mining areas of Venezuela. *Trop Med Int Health* 2002; 7:737-743.

Note: The study objective was to evaluate the increased drug resistance to chloroquine and S/P in regions of Venezuela. Detailed sample size justification provided along with formal hypothesis, detailed summary of study population and results. This study should serve as a primary study.

Design: R, OL, AC

Location: Venezuela

Patient Population: patients ≥ 6 months

Inclusion Criteria: mono-infection with *P. falciparum* with parasitemia in the range of 500-5000 parasites per μL , absence of fever in the 72h before exam, temperature $< 39.5^\circ$ Celsius

Exclusion Criteria: severe malaria, febrile conditions, severe malnutrition

Randomization Method: stratified according to weighted proportion of falciparum malaria cases in each community in which study was conducted

Treatment Groups:

- Chloroquine 25 mg/kg x 3d (CQ3)
- Chloroquine 40 mg/kg x 4d (CQ4)
- S/P 1.25 mg single dose (SP1)
- Quinine 10 mg/kg tid x 7 day (Q7)

Primary Endpoint: Adequate clinical response (ACR) defined as absence of parasitemia on days 3, 7, 14, 21, 28 (description of endpoint is confusing and a bit unclear)

Secondary Endpoints: Early treatment failure (ETF) signs of symptoms or malaria on day 3 $>25\%$ of day 0, late treatment failure (LTF) defined as signs or symptoms of malaria on days 7, 14, 21, and 28

One hundred sixty-five patients enrolled; all completed follow-up. There were 121 males and 44 females with an average age of 28.5 years. Mean baseline parasite counts ranged from 1799/ μL to 3065/ μL . Malaria history was not reported but study areas are considered malaria endemic. Only quinine resulted in ACR in all patients. Low-dose chloroquine was ineffective. The higher dose of chloroquine and the sulfadoxine/pyrimethamine regimens produced ACR in 77% of patients. Combined efficacy data for the treatment groups from the three different sites are summarized in the table below. Adverse effects were not reported.

Treatment	No. of Patients	Clinical Response		
		ACR	ETF	LTF
CQ3	12	0 (0%)	12 (100%)	0 (0%)
CQ4	52	40 (77%)	4 (8%)	8 (15%)
SP1	53	41 (77%)	7 (13%)	5 (9%)
Q7	48	48 (100%)	0 (0%)	0 (0%)

ACR=adequate clinical response, ETF=early treatment failure, LTF=late treatment failure

Note: Text and table obtained from Sponsor's ISE, page 76

Mono Study 5: Rahman MR, Paul DC, Rashid M, et al. A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated falciparum malaria in a multi drug resistant falciparum area of Bangladesh—narrowing the options for the National Malaria Control Programme? *Trans R Soc Trop Med Hyg* 2001; 95:661-667.

Note: Purpose of this study was to compare and evaluate the nationally recommended treatment regimens for uncomplicated malaria in Bangladesh. The original sample size was justified by providing expected failure rates in each treatment group, power and type I error rates, however an interim analysis was performed followed by a regimen change in one of the treatment arms and a new sample size.

Design: R, OL, AC

Location: Bangladesh

Patient Population: male and female patients aged 12-60 years

Inclusion Criteria: fever of history in previous 48 hrs, blood slide confirmed parasitemia of 500-250,000/mm³

Exclusion Criteria: pregnancy, antimalarial therapy in past week, severe malaria, co-infection

Randomization Method: codes for treatment prepared in blocks of eight and placed each in a separate envelope

Treatment Groups:

- Oral chloroquine phosphate tablets 10 mg/kg day 0, 7.5 mg/kg days 1 and 2 (CQ3)
- Oral quinine sulphate tablets 10 mg/kg tid x 3d + S/P 25 mg/kg on day 3 (Q3SP3)
- Oral quinine sulphate tablets 10 mg/kg tid x 7d (Q7)*
- Oral mefloquine 20 mg/kg single dose (M1)*

Note: A single dose of primaquine 45 mg base was given to all patients on last day of treatment according to national guidelines.

**Q7 discontinued following 9-mo interim analysis. Author described results at interim analysis as phase I results. New patients then randomized to M1 during the second 'phase' of the study. The paper does not provide rationale for change in treatment arm and in sample size. Therefore, only phase I results were considered.*

Study Procedures: daily clinical assessments and blood-slide exam days 0-7, slide exam and clinical f/u on days 14, 21, and 28

Primary Endpoint: Not explicitly stated

Endpoints: Early treatment failure (ETF) defined as parasitemia or persistent fever from day 3 on or worsening conditions by day 3, late treatment failure (LTF) defined as initial clearance by day 3 but with recurrent/persistent parasitemia and fever at a later time in the study, adequate clinical response (ACR) defined as not being classified as ETF or LTF, recrudescence rates (RI: negative on day 7 and positive anytime thereafter, RII: positive on day 2 with < 25% of parasite density on day 0, and either positive on day 7 or alternative antimalarial therapy was required anytime between days 2 and 7, RIII: if parasite density on day 2 was >25% of baseline density or alternative antimalarial therapy was required on or before day 2

Sample Size Justification: Based on expected failure rates in all four treatment groups

PCT: time between admission and first of two consecutive negative blood slides

FCT: time from admission to the start of at least 48 hrs when the temperature remained < 37.8° Celsius

F/U: 28 days

Results: PHASE I ONLY

Characteristic	Q7 (phase I)	Q3SP3 (phase I)	CQ3 (phase I)
Randomized/Completed	NP/49	NP/76	NP/79
Male	Demographic and baseline information, by treatment group, not provided for phase I		
Mean Age (yrs)			
Baseline Parasite count			
FCT (h)			
PCT (d)			
ACR	48/49 (98%)	58/76 (76.3%)	23/79 (29.1%)

NP=not provided

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Mono Study 6: McGready R, Brockman A, Cho T, et al. Randomized comparison of Mefloquine artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. *Trans Roy Soc Trop Med Hyg* 2000; 94:689-693.

Note: Study objective to evaluate efficacy and safety of 3-day artesunate regimen with 7-day quinine monotherapy regimen in pregnant women. Sample size justified based on expected cure rates. An interim analysis was performed; however, no statistical plan was provided.

Design: R, OL, AC

Location: Thailand

Patient Population: pregnant women in their 2nd or 3rd trimester with

Inclusion Criteria: microscopy confirmed uncomplicated *P. falciparum* infection

Exclusion Criteria: severe malaria, co-infection, less than 12 weeks gestation, history of mental disorder

Randomization Method: two blocks of 100 treatment codes

Treatment Groups:

- Experimental: Mefloquine 25 mg/kg + artesunate 4 mg/kg x 3d (MT3A3)
- Active Control: Oral quinine 10 mg/kg tid x 7d (Q7)

Study Procedures:

Primary Endpoint: treatment failure defined as a positive malaria smear for *P. falciparum* or mixed infection before 63 days of follow-up

Sample Size Justification: based on study design to show a difference in cure rates from 70% with Q to 90% with MA by day 63, 95% CI, 90% power and 20% dropout rate

PCT: not specified

FCT: not specified

F/U: day 63

Results:

Characteristic	Q7	MT3A3
Randomized*/Completed	NP/42	NP/66
Median Age (yrs) (range)	23 (16-36)	25 (15-37)
Median Gestational Age at Baseline (range)	24 (15-38)	24 (12-40)
Baseline Parasite count (median)	19,086 (79-149,389)	11,651 (32-241,127)
FCT (h)	Not reported	
PCT (h)	Not reported	
Cure rate (Eval) *	27/41 (67%)	64/65 (98%)

115 patients randomized and 7 excluded (breakdown of no. randomized by treatment not provided)
*only 19 women were febrile on admission and all were afebrile by 48hrs. Proportion of patients negative for parasitemia by 48hrs were 18/42 (43%) in the quinine group and 54/66 (82%) in the mefloquine-artesunate group. Cure rates not reported by treatment groups; however, the authors reported that 13 of 108 women had reappearance of parasites. PCR revealed that nine of these (all in the quinine group) had true recrudescence prior to delivery, two women (1/group) had new infections and two women in the Mefloquine-artesunate group had indeterminate samples and were assumed recrudescence. Therefore, rates above are based on PCR confirmation with the unknown cases considered failures.

Mono Study 7: Pukrittayakamee S, Chantira A, Vanijanonta S, et al. Therapeutic responses to quinine and clindamycin in multidrug-resistant falciparum malaria. *Antimicrob Agents Chemother* 2000; 44:2395-8.

Note: This study evaluated the efficacy of clindamycin in combination with quinine in comparison with those of quinine-tetracycline and quinine alone in a known multi-drug resistant P. falciparum endemic area of Thailand. The authors concluded that quinine continues to show efficacy against the multi-drug-resistant P. falciparum parasites prevalent in Thailand. They further concluded that clindamycin is an effective and well-tolerated alternative to tetracycline in combination with quinine. Sample size justification not provided.

The authors provided a robust summary and description of the study results. For these reasons, this publication should serve as primary during this meta-analyses review of the literature.

Design: R, OL, AC

Location: Thailand

Patient Population: adult male patients

Inclusion Criteria: acute *P. falciparum* malaria confirmed via thick/thin blood smear

Exclusion Criteria: severe malaria, mixed infection, antimalarial use within past 48h

Randomization Method: simple randomization

Treatment Groups:

- Experimental:
 - Quinine 10 mg/kg tid + tetracycline 4 mg/kg qid x 7d (Q7T7)
 - Quinine 10 mg/kg tid + clindamycin 5 mg base/kg qid x 7d (Q7C7)
- Active Control: Quinine 10 mg/kg tid x 7d (Q7)

Study Procedures: vital signs q4hrs until resolution and q6-12hrs thereafter, parasite counts q12hrs until clearance and daily for 28 days thereafter

Primary Endpoint: Not explicitly specified

PCT: time taken for parasite count to drop below specified amount, i.e. PCT₅₀=time to drop below 50%, etc.

FCT: time for temperature to drop below 37.5° Celsius and remain below this value for >48h

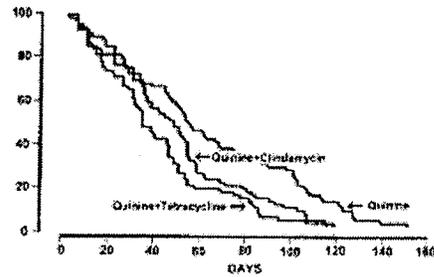
F/U: 28 days

Results:

Characteristic	Q7	Q7C7	Q7T7
Randomized/Completed	68/53	68/60	68/48
Mean Age (yrs) ±SD	24.6 ± 8.9	25.6 ± 9.3	27.3 ± 10.2
Mean Baseline Parasite count	9,493	17,155	9,352
Median FCT (h) (range)	56 (4-152)	47 (8-120)	36 (8-117)
Mean PCT (h) (± SD)			
50% decrease from baseline	21 ± 17	21 ± 14	21 ± 14
90% decrease from baseline	57 ± 15	58 ± 19	61 ± 19
Below detectable level	77 ± 25	79 ± 20	77 ± 23
Cure rate (ITT)	46/68 (68%)	60/68 (88%)	47/68 (69%)
Cure rate (Eval)	46/53 (87%)	60/60 (100%)	47/48 (98%)

Mean PCT did not significantly differ among the three treatment group, however median FCT (56 h, 47h, 36h for Q, Q+C, and Q+T respectively) was significantly longer in the quinine monotherapy group ($p=0.004$).

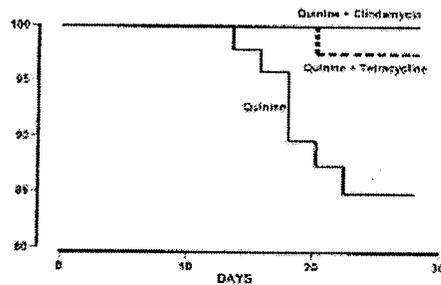
Cumulative Fever Clearance Rates by Treatment in Patients with Uncomplicated *P. falciparum* Malaria (Pukrittavakamee et al., 2000)



Source: Figure 1, Pukrittavakamee et al., 2000

The cure rates at day 28 of follow-up were 100%, 98% and 87% ($p \leq 0.04$) for quinine + clindamycin, quinine + tetracycline and quinine along respectively. Recrudescence of *P. falciparum* malaria at day 28 was reported in patients who received quinine monotherapy ($n=7$, 13%) and in one patient who received the quinine + tetracycline regimen.

Cumulative Cure Rates by Treatment in Patients with Uncomplicated *P. falciparum* Malaria (Pukrittavakamee et al., 2000)



Source: Figure 2, Pukrittavakamee et al., 2000

Mono Study 8: De Vries PJ, Bich NN, Thien HV, et al. Combinations of artemisinin and quinine for uncomplicated falciparum malaria: efficacy and pharmacodynamics. *Antimicrob Agents Chemother* 2000;44:1302-1308.

Note: The authors note that this study was a continuation of a study published by *Bich et al. (1996)*. The publication by *Bich et al.* discussed results of an open-label, randomized, study comparing quinine monotherapy with artemisinin+quinine for 3 days and artemisinin + doxycycline for 3 days. Results of an interim analysis suggested poor efficacy in the artemisinin + doxycycline group and the authors then decided to analyze and then publish the data of the patients evaluated up to that point. Due to the observed poor efficacy in the artemisinin + doxycycline group, the authors state that doxycycline in combination with artemisinin was replaced with quinine in combination with artemisinin and extended treatment to 5 days. They further note that patients previously treated with Q and AQ3 as summarized by *Bich et al.*, were included in this analysis citing the reasons being that the numbers of patients in these groups had increased since previously reported and the interpretation of the kinetic data of the parasite clearance had not been performed. They further note that the change of treatment regimens was considered not to have introduced bias because the procedures for inclusion did not change.

Lastly, the authors state that toward the end of the study, the Q and AQ3 regimens were discontinued and the study continued only with the AQ5 regimen for the last 36 patients.

This unplanned treatment change and premature termination of two treatment groups invalidates the original treatment randomization. This study should serve as supportive only.

Design: R, OL, AC

Location: Vietnam

Patient Population: patients aged from 8 to 65 years

Inclusion Criteria: uncomplicated *P. falciparum* malaria with parasite density between 1,000 and 100,000/ul

Exclusion Criteria: quinine use in previous 12hrs, artemisinin or derivatives in past 24hrs, or tetracycline in past 7 days

Randomization Method: computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion

Treatment Groups:

- Experimental:
 - Artemisinin 20 mg/kg one time followed by quinine 10 mg/kg tid x 3d (AQ3)
 - Artemisinin 20 mg/kg one time followed by quinine 10 mg/kg tid x 5d (AQ5)
- Active Control: Oral quinine 10 mg/kg tid x 7d (Q7)

Study Procedures: vital signs q8hrs, parasite count q8h until three negative smears then 7, 14, 21 and 28 days

Primary Endpoint: Not explicitly stated

Clinical failure defined as no improvement, necessitating additional treatment within the first 48hrs of treatment (early failure) or after 48hrs of therapy (late failure).

PCT: time to initiation of treatment to the first of three consecutive negative blood smears

FCT: time to initiation of treatment to the first of three consecutive normal temperatures (<37° Celsius)

F/U: 28 days

Results:

Characteristic	Q7	AQ3	AQ5
Randomized/Completed	84/69	96/74	88/78
Male/females	70/14	76/20	70/18
Median Age (yrs) (range)	26 (7-60)	26 (7-64)	26 (7-60)
Mean Baseline Parasite count (range)	16,157 (12,642-20,646)	16,123 (12,611-20,611)	23,202 (17,888-30,091)
Mean FCT (h) [95%]	47 [41-53]	41 [37-46]	43 [38-47]
Mean PCT (h) [95%]	62 [57-67]	41 [38-44]	42 [39-46]
Recrudescence rate* (%)	11/69 (16)	28/74 (38)	12/78 (15)
Cure rate (ITT)	56/84 (67%)	46/96 (48%)	66/88 (75%)
Cure rate (Eval)	56/69 (81%)	46/74 (62%)	66/78 (85%)

* $P < 0.001$ (χ^2 test)

95% CIs around the differences in the evaluable population are: Q vs. AQ3: 8-36%, Q vs. AQ5: -11-13%, AQ3 vs. AQ5: 9-37% (Bich et al., 1996)

**APPEARS THIS WAY
ON ORIGINAL**

Mono Study 9: Bich NN, de Vries PJ, Thien HV, *et al.* Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated falciparum malaria. *Am J Trop Med Hyg* 1996; 55:438-443.

Note: Differences between the regimens were noted while the study was on going and therefore the investigators decided to analyze the data of 161 patients (45% of the intended sample size of 120/group) entered.

Patients who received quinine alone or quinine + artemisinin were included in the results published by De Vries *et al* (2000). As discussed in the De Vries *et al.* study, the artemisinin plus doxycycline regimen appeared unsatisfactory (as discussed in Bich *et al.*) and therefore this regimen was changed to quinine x 5 days plus single day of artemisinin.

Comment: This publication along with De Vries *et al* (2000) demonstrates the concern with multiple publication bias, i.e. multiple publications of the same data. Only data published in the Bich *et al.* study will be considered in the analysis.

Design: R, OL, AC

Location: Vietnam

Patient Population: patients aged from 8 to 65 years

Inclusion Criteria: uncomplicated *P. falciparum* malaria with parasite density between 1000 and 100,000/ul

Exclusion Criteria: pregnancy, mixed-infection, quinine use in previous 12h, artemisinin or derivatives in past 24h, or tetracycline in past 7d

Randomization Method: computer generated randomization codes (120 per treatment) provided in closed envelopes consecutively drawn after inclusion

Treatment Groups:

- Experimental:
 - Artemisinin 20 mg/kg one time followed by quinine 10 mg/kg tid x 3d (AQ3)
 - Artemisinin 20 mg/kg one time followed by doxycycline 4 mg/kg tid x 5d (AD5)
- Active Control: Oral quinine 10 mg/kg tid x 7d (Q7)

Study Procedures: vital signs q8hrs, parasite count q8h until three negative smears then 7, 14, 21 and 28 days

Primary Endpoint: Not explicitly stated

Clinical failures defined as no improvement, necessitating additional treatment within the first 48h of treatment (early failure) or after 48h of therapy (late failure).

Radical cure defined as parasite clearance by day 7 w/o recrudescence up to day 28

PCT: time to initiation of treatment to the first of three consecutive negative blood smears

FCT: time to initiation of treatment to the first of three consecutive normal temperatures (<37° Celsius)

F/U: 28 days

Results:

Characteristic	Q7	AQ3	AD5
Randomized/Completed	59/44	45/32	53/42
Male/female	47/12	34/11	47/6
Mean Age (yrs) \pm SD (range)	25 \pm 12 (14-66)	27 \pm 13 (12-64)	26 \pm 13 (9-63)
Mean Baseline Parasite count \pm SD	29,636 \pm 39,720	21,321 \pm 21,877	46,088 \pm 91,523
Mean FCT (h) \pm SD	41 \pm 23	34 \pm 19	31 \pm 23
Mean PCT (h) \pm SD	66 \pm 24	43 \pm 14	41 \pm 19
Cure rate (ITT)	36/59 (61%)	23/45 (51%)	13/53 (24%)
Cure rate (Eval)	36/44 (82%)	23/32 (72%)	13/42 (31%)

**APPEARS THIS WAY
ON ORIGINAL**

Mono Study 10: Metzger W, Mordmüller B, Graninger W, et al. High efficacy of short-term quinine antibiotic combinations for treating adult malaria patients in an area which malaria is hyperendemic. *Antimicrob Agents Chemother* 1995; 39:245-246.

Note: The study objective was to determine if the addition of clindamycin or doxycycline to 1.5d quinine regimen is more effective than a 1.5d quinine alone regimen (a 3d quinine regimen previously shown ineffective in Gabonese children). Authors conclude that the 1.5d quinine monotherapy regimen is inefficient to cure uncomplicated *P. falciparum* malaria in Gabonese adults while the addition of clindamycin or doxycycline to 1.5d quinine is effective. Publication is limited in detail regarding study design, population and results.

Design: R, OL, AC

Location: Gabon, Africa

Patient Population: patients 15 years of age or older, semi-immune (all previously infected)

Inclusion Criteria: mono-infection with *P. falciparum* with parasitemia > 200/ul

Exclusion Criteria: antimalarials with past 7d, pregnancy

Randomization Method: Not described

Treatment Groups:

- Experimental:
 - Quinine 12 mg/kg three doses (one every 12h) + clindamycin 5 mg/kg six doses (one every 12h) (Q1.5C3)
 - Quinine 12 mg/kg three doses (one every 12h) + doxycycline 2 mg/kg six doses (one every 12h) (Q1.5D3)
- Active Control: Quinine 12 mg/kg three doses (one every 12h) (Q1.5)

Study Procedures: blood smears q12h until parasite free for 24h thereafter on days 14, 21, and 28

Primary Endpoint: Not explicitly stated

Cure defined as negative blood smear after treatment and remaining until day 28

Sample Size Justification: Not provided

PCT: Not defined

FCT: Not defined

F/U: 28 days

Results:

Characteristic	Q1.5	Q1.5C3	Q1.5D3
Randomized/Completed	40/37	40/36	40/35
Male/female	21/16	15/21	21/14
Median Age (yrs) (range)	32 (15-70)	35 (15-71)	28 (16-70)
Mean Baseline Parasite count	5,515	10,642	7,807
FCT (h)	Not reported		
PCT (h)	Not reported		
Cure rate (ITT)	14/40 (35%)	33/40 (82%)	32/40 (80%)
Cure rate (Eval)	14/37 (38%)	33/36 (92%)	32/35 (91%)

Mono Study 11: Segal HE, Chinvanthananond P, laixuthai B, et al. Preliminary study of WR 33063 in the treatment of falciparum malaria in northeast Thailand. Am J Trop Med Hygiene 1974;23:560-564.

Note: The study objective was to evaluate efficacy and toxicity of WR 33063 in Thai male adults. Quinine served as the active control. Sample size unjustified.

Design: R, OL, AC

Location: Thailand (northeast)

Patient Population: Thai males aged 15 years or older with symptomatic falciparum infection

Inclusion Criteria: parasitemia of 1000-100,000/mm³

Exclusion Criteria: antimalarials with past 4d, renal or cerebral complications

Randomization Method: Not described

Treatment Groups:

- Experimental: WR 33063 600 mg tid x 6d (WR6)
- Active Control: quinine 540 mg base tid x 6d (Q6)

Study Procedures: temperature q6h, blood smears q12hrs and on days 14, 21, and 28

Primary Endpoint: Not explicitly stated

Failures defined as un-cleared parasitemia or recrudescence

PCT: time to clear parasitemia

FCT: time to reach temperature less than 99° Fahrenheit for 48hrs

F/U: 28 days

Results:

Characteristic	Q6	WR6
Randomized/Completed	26/22	25/25
Median Age (yrs) (range)	23 (15-53)	23.5 (15-53)
Mean Baseline Parasite count	13,500	20,400
Mean FCT (h) (range)	59.7 (12-126)	58.5 (16-112)
Mean PCT (h) (range)	65.1 (21-103)	66.3 (21-113)
Cure rate (ITT)	21/26 (81%)	23/25 (92%)
Cure rate (Eval)	21/22 (95%)	23/25 (92%)

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SUMMARY OF QUININE COMBINATION THERAPY PUBLICATIONS

The Sponsor identified 16 publications of randomized clinical studies evaluating quinine in combination with other antimalarials. Six of these studies (*Bich et al., 1996; de Vries et al., 2000; Metzger et al., 1995; Pukrittayakamee et al., 2004; Pukrittayakamee et al., 2000; Rahman et al., 2001*) are summarized in Appendix A and therefore will not be summarized here (link to summary in Appendix A provided). The following is summary of the remaining 10 studies.

Combo Study 1: Pukrittayakamee S, Chotivanich K, Chantra A, et al. Activities of artesunate and primaquine against asexual and sexual stage parasites in falciparum malaria. *Antimicrob Agents Chemother* 2004; 48:1329-1334.

See Summary in Appendix A [Mono Study 2]

Combo Study 2: Rahman MR, Paul DC, Rashid M, et al. A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated falciparum malaria in a multi drug resistant falciparum area of Bangladesh—narrowing the options for the National Malaria Control Programme? *Trans R Soc Trop Med Hyg* 2001; 95:661-667.

See Summary in Appendix A [Mono Study 5]

Combo Study 3: Pukrittayakamee S, Chantra A, Vanijanonta S, et al. Therapeutic responses to quinine and clindamycin in multidrug-resistant falciparum malaria. *Antimicrob Agents Chemother* 2000; 44:2395-8.

See Summary in Appendix A [Mono Study 7]

Combo Study 4: De Vries PJ, Bich NN, Thien HV, et al. Combinations of artemisinin and quinine for uncomplicated falciparum malaria: efficacy and pharmacodynamics. *Antimicrob Agents Chemother* 2000; 44:1302-1308.

See Summary in Appendix A [Mono Study 8]

Combo Study 5: Bich NN, de Vries PJ, Thien HV, et al. Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated falciparum malaria. *Am J Trop Med Hyg* 1996; 55:438-443.

See Summary in Appendix A [Mono Study 9]

Combo Study 6: Metzger W, Mordmüller B, Graninger W, et al. High efficacy of short-term quinineantibiotic combinations for treating adult malaria patients in an area which malaria is hyperendemic. *Antimicrob Agents Chemother* 1995; 39:245-246.

See Summary in Appendix A [Mono Study 10]

Combo Study 7: Duarte EC, Fontes CJF, Gyorkos TW, et al. Randomized controlled trial of artesunate plus tetracycline versus standard treatment (quinine plus tetracycline) for uncomplicated Plasmodium falciparum malaria in Brazil. Am J Trop Med Hyg 1996; 54:197-202.

Note: This study assessed the efficacy and safety of artesunate + tetracycline compared with quinine + tetracycline (control). The study was conducted in an area where the standard treatment for drug-resistant falciparum malaria was quinine (3-days) + tetracycline (7-days), however due to quinine-associated side effects alternate therapies, particularly artemisinins were being considered. In general, this study was well designed and described and should serve as primary.

Design: R, triple-blind (patients, physicians, lab technicians), AC

Note: Drugs provided in envelopes indicating administration timetable.

Location: Brazilian Amazon

Patient Population: patients aged 14 years or older

Inclusion Criteria: uncomplicated *P. falciparum* malaria

Exclusion Criteria: antimalarials for current infection, pregnancy, mixed infection

Randomization Method: table of random numbers

Sample Size: Designed with 80% power to detect a significant (at alpha=0.05) difference b/t two groups of equal size. Provided expected cure rates and minimum clinically important difference of 15%; however, the reference provided to justify the assumed cure rate is Spanish written.

Treatment Groups:

- Experimental: oral artesunate 100 mg initial dose, 50 mg q12h x 6d + tetracycline 500 mg q8h x 7d (A1T7)
- Active Control: oral quinine 1g q12h x 3d + tetracycline 500 mg q8h x 7d (Q3T7)

Study Procedures: clinical exam and blood smears performed on day 0, 2, 4, 7, 14 and 28,

Primary Endpoint: Not explicitly stated

Effectiveness was measured using cure rates (WHO criteria for S, RI, RII, and RIII) and parasite clearance at day 2. Results of the ITT population were primary with loss to follow-up counted as failure.

PCT: Not provided

FCT: Not provided

F/U: 28 days

Results:

Characteristic	Q3T7	A1T7
Randomized/Completed	88/82	88/85
Male/female	73/15	72/16
Mean Age (y) (range)	30.9 (14-70)	32.2 (15-57)
Median Baseline Parasite count	6,670	5,174
Mean FCT (h) (range)	Not Provided	
Mean PCT (h) (range)	Not Provided	
Cure rate (ITT)	68/88 (77%)	70/88 (79%)
Cure rate (Eval)	Not Provided	

**APPEARS THIS WAY
ON ORIGINAL**

Combo Study 8: Fungladda W, Honrado ER, Thimsam K, et al. Compliance with artesunate and quinine plus tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bulletin of WHO 1998; 76: 59-66.

Note: The primary goal of this study was to compare the compliances with the standard 7-day quinine + tetracycline regimen with a 5-day 700 mg oral artesunate regimen for treatment of uncomplicated *P. falciparum* malaria. The sample size driven by compliance rates based on adverse reaction rate and not on efficacy rates. Cure rate considered a secondary objective of this study and only evaluated on the final day of treatment, i.e. no follow-up assessments performed. Given these issues, the use of this study to assess the efficacy of oral quinine for treatment of uncomplicated *P. falciparum* malaria up to the typical 28-day follow-up time point is not possible. The reviewer considers this study as supportive only.

Design: R, AC

Location: Thailand

Patient Population: patients aged 15-60 years

Inclusion Criteria: uncomplicated *P. falciparum* malaria

Exclusion Criteria: pregnancy, severe or complicated malaria, history of renal/hepatic disease

Randomization Method: simple randomization

Treatment Groups:

- Experimental: oral artesunate 300 mg on day 1, 100 mg days 1-4 (A4)
- Active Control: oral quinine 600 mg tid + tetracycline 500 mg bid x 7d (Q7T7)

Study Procedures: clinical exam and blood smears performed on day 0, 2, 4, 7, 14 and 28,

Primary Endpoint: Not explicitly stated

Compliance stated as a study objective

Curative effectiveness was evaluated by bloods smear on day 5 (A4) and 7 (Q7T7)

Note: study did not evaluate effectiveness at day 28

PCT: Not provided

FCT: Not provided

F/U: none

Results:

Characteristic	Q7T7	A4
Randomized/Completed	60/53	77/61
Male/female	59/1	61/16
Mean Age (y) ± SD	31.9 ± 11.5	30.8 ± 9.4
Baseline Parasite count	Not provided	
Mean FCT	Not Provided	
Mean PCT	Not Provided	
Cure rate (ITT)	41/60 (68%)	61/77 (79%)
Cure rate (Eval)*	41/53 (77%)	61/61 (100%)

*p<0.05

Combo Study 9: Salcedo JMV, Camargo LMA, Braga, MFV, et al. Evaluation of the efficacy of artesunate associated with tetracycline in the therapy of falciparum malaria. Brazil Soc Trop Med J 1997; 30:215-222. [English Translation]

Note: This publication presents cure rates for mefloquine, quinine + tetracycline and artesunate + tetracycline pooling the intravenous data with the oral data. It is difficult to interpret the efficacy of the quinine combination (oral) regimen from these data and therefore the review considers this study as supportive only.

Design: R, AC

Location: Brazil

Patient Population:

Inclusion Criteria: uncomplicated *P. falciparum* malaria

Exclusion Criteria: pregnancy, severe or complicated malaria, antimalarial use in past 15d

Randomization Method: simple randomization

Treatment Groups:

- Oral artesunate 100 mg initial dose, 50 mg q12h x 5 day + tetracycline 500 mg tid x 7d (OAT)
- IV artesunate 1.5 mg/kg at 0, 4, 24 and 48h + tetracycline 500 mg tid x 7d (IAT)
- Mefloquine single dose of 15 mg/kg (M)
- IV quinine 10 mg/kg tid x 3 d + tetracycline 500 mg tid x 7d (IQT)
- Oral quinine 10 mg/kg tid x 3d + tetracycline 500 mg tid x 7d (OQT)

Study Procedures: temperature q6h, clinic f/u on days 7, 14, 21 and 28, parasite count q12hrs and days of follow-up

Primary Endpoint: Not stated

PCT: Not provided

FCT: Not provided

F/U: none

Results:

Characteristic	OAT	IAT	M	IQT	OQT
Randomized/Completed	8	8	2	6	8
Male/female	7/1	5/3	10/2	6/0	7/1
Mean Age (y)	28 (15-43)	38 (8-64)	32 (12-54)	29 (10-53)	37 (22-57)
Baseline Parasite count (mean)	31,732	56,825	57,550	2,774	88,424
Mean FCT (h) (range)	Not Provided				
Mean PCT (h) (range)	Not Provided				
Cure rate (ITT) *	Not provided by treatment group				
Cure rate (Eval)*	Not provided by treatment group				

* This publication presented cure rates by pooled treatment groups, i.e. pooled oral and IV data for each treatment. Efficacy can not be interpreted from these results.

Combo Study 10: De Alencar FE, Cerutti C, Durlacher RR, et al. Atovaquone and proguanil for the treatment of malaria in Brazil. *J Inf Dis* 1997; 175:1544-1547.

Note: The purpose of this in-patient study was to evaluate an experimental regimen of atovaquone + proguanil versus the standard regimen of quinine + tetracycline. Study performed entirely as an in-patient study thus avoiding the difficulty of lost to follow-up. Study does not provided the numbers randomized by treatment group thus preventing the calculation of ITT cure rates.

Location: Brazil

Design: R, OL, AC

Patient Population: adult men (ages 18-65 years)

Inclusion Criteria: parasitemia of 1000-100,000/mm³

Exclusion Criteria: refusal to stay in hospital for 28 days, missed doses of study drug

Randomization Method: Not described

Treatment Groups:

- Experimental: atovaquone 1 g + proguanil 400 mg qd x 3d (AP3)
- Active Control: quinine 600 mg tid + tetracycline 250 mg qid x 7d (Q7T7)

Study Procedures: blood smears q6h until three consecutive negative smears, daily clinical assessment during first week and weekly thereafter

Primary Endpoint: Not explicitly stated

PCT: time to clear parasitemia

FCT: time to reach temperature less than 99° for 48hrs

F/U: 28 days

Results:

Characteristic	Q7T7	AP3
Randomized*/Completed	NP/77	NP/77
Mean Age (yrs) ± SD	28.2 ± 1.2	30.2 ± 1.1
Mean Baseline Parasite Count ± SD	9589 ± 1357	12059 ± 1696
Mean FCT (h) ± SD	18.8 ± 17.7	28.5 ± 19.8
Mean PCT (h) ± SD	56.1 ± 14.1	64.5 ± 23.1
Cure rate (ITT)	Not provided	Not provided
Cure rate (Eval)	77/77 (100%)	76/77 (99%)

* Publication does not provided number of patient randomized by treatment group (total n=175).

Combo Study 11: Bunnag D, Karbwang J, Na-Bangchang K, Thanavibul A, Chittamas S, Harinasuta T. Quinine-tetracycline for multidrug resistant falciparum malaria. Southeast Asian J Trop Med Public Health 1996; 27:15-18.

Note: The objective of this study was to compare the efficacy and toxicity of 5- and 7-day quinine + tetracycline regimens. A shorter quinine dose was sought to reduce quinine-related toxicity. Authors conclude that quinine on the last 2 days (i.e. day 6-7) had an influence on the clearing of remaining parasites and that the results support previous findings on the importance of maintaining quinine concentrations above the MIC throughout 7 day of treatment. They further suggest that in areas of decreased quinine sensitivity that the quinine course should be 7 days. **Comment:** The caveat to this study is that it was an in-patients study and therefore patient compliance was above average thus increasing the rate of efficacy. In field settings, the known toxicity of quinine could lead to decreased compliance thus decreased efficacy. One should use caution when drawing conclusions regarding the efficacy of a 7-day course of quinine from this study given that this was an in-patient study.

Design: R, OL, AC, in-patient (IP)

Location: Thailand (in-patient for full 28 days of study)

Patient Population: adult men (ages 16-54 years)

Inclusion Criteria: acute uncomplicated *P. falciparum* malaria

Exclusion Criteria: history of hepatic/renal disease

Randomization Method: Not described

Sample Size justification: Not provided

Treatment Groups:

- Experimental: oral quinine 600 mg tid x 5d + tetracycline 250 qid x 7d (Q5T7)
- Active Control: oral quinine 600 mg tid x 7d + tetracycline 250 qid x 7d (Q7T7)

Study Procedures: parasite count q6hrs until negative and then daily for 28d

Primary Endpoint: Not explicitly stated

Cure rate

PCT: time for parasite count to fall below detection level

FCT: time to reach temperature below 37.3° Celsius

F/U: 28 days

Results:

Characteristic	Q5T7	Q7T7
Randomized*/Completed	48/46	42/40
Median Age (y) (range)	24 (17-40)	25 (16-54)
Median Parasitemia (range)	23,424 (159-292,432)	24,542 (630-343,800)
Median FCT (h) (range)	75 (4-136)	75 (12-132)
Median PCT (h) (range)	88 (45-159)	90 (45-135)
Cure rate (ITT)	40/48 (83%)	40/42 (95%)
Cure rate (Eval)	40/46 (87%)	40/40 (100%)

Combo Study 12: Vanijanonta S, Chantra A, Phophak N, et al. Therapeutic effects of chloroquine in combination with quinine in uncomplicated falciparum malaria. *Ann Trop Med Parasitol* 1996; 90:269-275.

Note: The objective of this study was to determine if the addition of chloroquine to quinine had any antimalarial or anticytokine effects on chloroquine-resistant falciparum malaria. Sample size justification not provided.

Design: R, OL, AC, IP

Location: Thailand (in-patient for full 28 days of study)

Patient Population: adult men

Inclusion Criteria: uncomplicated *P. falciparum* malaria

Exclusion Criteria: severe malaria, antimalarials in past 24h

Randomization Method: Not described

Sample Size justification: Not provided

Treatment Groups:

- Experimental: oral quinine 10 mg/kg tid x 7d + chloroquine x 3d (Q7C3)
- Active Control: oral quinine 10 mg/kg tid x 7d + tetracycline 4 mg/kg qid x 7d (Q7T7)

Study Procedures: temperature q4hrs, parasite count q12hrs until clearance then daily for 28 days, baseline and 48hr ECG

Primary Endpoint: Not explicitly stated

Cure rate

PCT: time for treatment initiation to undetectable parasite count

FCT: time to reach temperature below 37.5° Celsius

F/U: 28 days

Results:

Characteristic	Q7T7	Q7C3
Randomized*/Completed	25/18	25/18
Age	Not provided	
Mean Parasitemia (range)	18,197 (9,550-34,670)	19,498 (10,710-35,480)
Mean FCT (h) ± SD	41 ± 27	51 ± 33
Mean PCT (h) ± SD	83 ± 21	80 ± 25
Cure rate (ITT)	17/25 (68%)	11/25 (44%)
Cure rate (Eval)	17/18 (94%)	11/18 (61%)

Combo Study 13: Looareesuwan S, Vanijanonta S, Viravan C, *et al.* Randomised trial of mefloquine+tetracycline and quinine-tetracycline for acute uncomplicated falciparum malaria. *Acta Tropica* 1994; 57: 47-53.

Note: This study was conducted to assess whether or not mefloquine + tetracycline is similar in effectiveness to quinine + tetracycline in treatment of uncomplicated *P. falciparum* malaria in Thailand where quinine + tetracycline is the standard regimen. The authors note explicitly that the decrease of quinine efficacy in the 1980s led to the addition of tetracycline, however due to known quinine-related toxicities other combination therapies were needed. The authors conclude that mefloquine + tetracycline is 'equally effective' to quinine + tetracycline and can be used as an alternate treatment of acute uncomplicated drug-resistant *P. falciparum* malaria in Southeast Asia.

No sample size calculation or formal hypothesis testing provided.

Design: R, OL, AC, IP

Location: Thailand (in-patient for full 28 days of study)

Patient Population: patients aged 16-60 years

Inclusion Criteria: acute uncomplicated *P. falciparum* malaria, parasite counts of 100-400,000/ul

Exclusion Criteria: pregnancy, severe malaria, antimalarials in past week

Randomization Method: Not described

Sample Size justification: Not provided

Treatment Groups:

- Experimental: Mefloquine 750 mg initial, 500 mg 6h later + tetracycline 250 mg qid x 7d (MT1T7)
- Active Control: quinine 600 mg tid + tetracycline 250 mg qid x 7d (Q77)

Study Procedures: vital signs q4hrs for first week and then weekly thereafter, blood smears q6hrs until negative and then daily thereafter

Primary Endpoint: Not explicitly stated

PCT: time from treatment to first negative blood smear

FCT: time from treatment to temperature below 37.5° Celsius for at least 48hrs

F/U: 28 days

Results:

Characteristic	Q7T7	MT1T7
Randomized*/Completed	50/46	52/47
Male/female	36/16	39/11
Mean Age (y) (range)	31.1 (17-67)	27.8 (16-51)
Mean Parasitemia (range)	12, 638 (200-367,770)	10, 607 (267-183,300)
Mean FCT (h) (range)	61.8 (4-156)	47.8 (4-128)
Mean PCT (h) (range)	73.9 (23-128)	64 (26-127)
Cure rate (ITT)	45/50 (90%)	44/52 (85%)
Cure rate (Eval)	45/46 (98%)	44/47 (94%)

Combo Study 14: Karbwang J, Na-Bangchang K, Thanavibul A, *et al.* Comparison of oral artesunate and quinine plus tetracycline in acute uncomplicated falciparum malaria. Bull World Health 1994; 72:233-238.

Note: The study objective was to evaluate the efficacy (including recrudescence rate) of oral artesunate with the standard quinine + tetracycline regimen. Sample size estimation provided. High cure rates observed due to in-patient design (lower rates expected in field study/clinical practice due to decrease patient compliance). Study should serve as primary.

Design: R, OL, AC, IP

Location: Thailand (in-patient for full 28 days of study)

Patient Population: Thai male patients aged 15-35 yrs

Inclusion Criteria: acute uncomplicated *P. falciparum* malaria, weight

Exclusion Criteria: history of liver/kidney disease, antimalarial for current infection, severe malaria

Randomization Method: not described

Sample Size: determined based on previous data (not referenced) to detect a 35% faster clearance rate from artesunate than from quinine + tetracycline (at a 95% confidence level)

Treatment Groups:

- Experimental: Artesunate 200 mg initial dose, 100 mg 12h later, 100 mg qd x 4d (A4)
- Active Control: Quinine sulfate 600 mg tid + tetracycline 250 mg qid x 7d (Q7T7)

Study Procedures: blood smears q6h for 7d, ECG daily in artesunate group

Primary Endpoint: Not explicitly stated but sample size based on expected rate of parasite clearance Rate of treatment failure (RI, RII, RIII)

PCT: time for undetectable parasite count

FCT: time from treatment to temperature below 37.3° Celsius for at least 24hrs

F/U: 28 days

Results:

Characteristic	Q7T7	A4
Randomized*/Completed	33/30	31/30
Mean Age (y) (range)	23 (17-35)	25 (15-35)
Mean Parasitemia (range)	35,188 (351-175,010)	50,206 (504-292,560)
Mean FCT (h) (range)*	73.2 (36-135)	36.5 (24-52)
Mean PCT (h) (range)*	55.4 (4-104)	36.5 (24-52)
Cure rate (ITT)	30/33 (91%)	29/31 (93%)
Cure rate (Eval)	30/30 (100%)	29/30 (97%)

*p<<0.01

Combo Study 15: Kremsner PG, Zotter GM, Feldmeier H, et al. A comparative trial of three regimens for treating uncomplicated falciparum malaria in Acre, Brazil. *J Infect Dis* 1988;158:1368-1371.

Note: Results showed that amodiaquine and the combination of quinine + S/P were inadequate to treat multi-drug-resistance *P. falciparum* malaria in Brazil. Sample size justification not provided.

Design: R, OL, AC

Location: Brazil

Patient Population: patients ≥14 yrs of age

Inclusion Criteria: parasitologically proven *P. falciparum* infection

Exclusion Criteria: sever illness, chronic diarrhea, pregnancy, antimalarial within past 7d

Randomization Method: age-dependent randomization schedule (age groupings/categories not provided)

Sample Size justification: Not provided

Treatment Groups:

- Experimental:
 - Quinine 15 mg/kg bid x 3d + S/P x 2d (Q3SP2)
 - Quinine 15mg/kg bid x 3d + clindamycin 10 mg/kg x 3d (Q3C3)
- Active Control: amodiaquine 10 mg/kg initial followed by 7.5 mg x 2d (AM2)

Study Procedures: daily clinical and parasitological assessments until resolution, blood smear on days 14 and 28

Primary Endpoint: cure defined negative blood smear by day 7 and remained parasite free on day 14 and 28 of follow-up

PCT: not defined

FCT: not defined

F/U: 28 days

Results:

Characteristic	AM2	Q3SP2	Q3C3
Randomized/Completed	29/25*	40/30	46/40
Male/female	20/5	22/7	32/8
Age	Not provided		
Median Parasitemia (range)	5,360 (500-68,000)	3,630 (500-58,500)	6,989 (500-56,200)
Mean FCT (h)	Not provided		
Mean PCT (h)	82.7	78.2	86.4
Cure rate (ITT)	1/29 (3%)	9/40 (22%)	36/46 (78%)
Cure rate (Eval)	1/25 (4%)	9/30 (30%)	36/40 (90%)

* The authors indicate that due to bad response this group closed after 25 patients were monitored. Patients not included in the evaluable population were lost to follow-up.

Combo Study 16: De Souza JM, Sheth UK, De Oliveira MG, et al. An open, randomized, phase III clinical trial of mefloquine and of quinine plus sulfadoxine-pyramethamine in the treatment of symptomatic falciparum malaria in Brazil. Bulletin of WHO 1985; 63:603-609.

Note: The study objective was to evaluate the safety, efficacy and tolerability of mefloquine versus standard regimen of quinine + S/P x 3d in an area of Brazil with increased quinine and S/P resistance pattern. No sample size justification or primary hypothesis provided.

Design: R, OL, AC, IP

Location: Brazil

Patient Population: male patients aged 18-55 years

Inclusion Criteria: symptomatic *P. falciparum* malaria

Exclusion Criteria: none listed

Randomization Method: Not provided

Sample Size justification: Not provided

Treatment Groups:

- Experimental: mefloquine 1000 mg base single dose (MT1)
- Active Control: quinine 600 mg + S/P day 0, quinine 600 mg tid x 2d (Q2SP1)

Study Procedures: daily clinical assessment for first week and weekly thereafter until day 42, blood smears daily x 42 days

Primary Endpoint: Not explicitly stated

PCT: not defined

FCT: not defined

F/U: 42 days

Results:

Characteristic	Q2SP1	MT1
Randomized/Completed	50/50	50/49
Age	Not provided	
Mean Parasitemia	19,628	19,490
Mean FCT (h)	Not provided	
Mean PCT (h)	Not provided	
Cure rate (ITT)	46/50 (92%)	49/50 (98%)
Cure rate (Eval)	46/50 (92%)	49/49 (100%)

Fever cleared by day 3 in 96% of M treated patients and in 98% of QSP treated patients. The four failures in the QSP were RI failures (between days 16 and 21).

Combo Study 17: Ramharter M, Oyakhirome S, Klouwenberg PK, et al. Artesunate-clindamycin versus quinine-clindamycin in the treatment of Plasmodium falciparum malaria: a randomized controlled trial. Clin Infect Dis 2005; 40:1777-94

The reviewer while scanning the literature located this additional publication using oral quinine in combination with clindamycin. This publication summarizes a well-controlled clinical study in children. Given the recent publication of this study and thorough summary of design and findings, it is included in this review as supportive information.

Note: This study evaluated the efficacy and tolerability of oral artesunate+clindamycin versus standard quinine+clindamycin for the treatment of uncomplicated *P. falciparum* malaria in children in sub-Saharan Africa. The mainstay treatment is artemisinin-based combinations as advocated by WHO.

This study was well designed and described, providing thorough detail regarding sample size determination, efficacy assessment and safety findings. Due to the population studied (children) this study serves as supportive.

Design: R, OL, AC

Location: Gabon, Africa

Patient Population: children between the ages of 3 and 12

Inclusion Criteria: confirmed uncomplicated *P. falciparum* mono-infection, asexual parasitemia of 1,000-100,000/ul, weight of 10-70kg

Exclusion Criteria: severe malaria, current antibiotic treatment or antimalarial use in past 7 days, low hematocrit <23% and WBC count > 15 x 10⁹ cells/L, severe disease

Randomization Method: computer generated codes in blocks of 10 placed in sealed envelopes, physicians opened sealed envelope only after patient deemed eligible to participate in study

Treatment Groups:

- Experimental: oral artesunate 2 mg/kg + clindamycin 7 mg/kg q 12h x 6d (A6C6)
- Active Control: oral quinine 15 mg/kg + clindamycin 7 mg/kg q12h x 6d (Q6C6)

Study Procedures: Twice-daily assessments for 3 days or until resolution of clinical signs and 2 consecutive negative blood smears, follow-up at days 7, 14, and 28

Primary Endpoint: cure rate, defined as the proportion of patients who presented without reappearance of asexual parasitemia during the 28-day follow-up after initial clearance of parasites as corrected by PCR genotyping

Sample size: n=50/goup based on assumption of 98% efficacy in standard treatment and cure rate of the experimental group within 7% of the control, a LTF rate of 10%, 80% power and 0.05 error rate
ITT and PP populations well defined

Missing or premature withdrawal due to non-AE related reasons were counted as failures in the ITT analysis

Secondary endpoint: PCT and FCT

PCT: time to clearance

FCT: time to first of two subsequent measurements of a tympanic temperature < 37.5° Celsius

F/U: 42 days

Results:

Characteristic	A6C6	Q6C6
Randomized/Completed	50/46	50/48
Mean Age (y) ± SD	7.1 ± 2.6	7.7 ± 3.3
Median Parasitemia (range)	12,000 (1,100-96,000)	19,750 (1,200-96,000)
Mean PCT (h) [95% CI]	21.2 [16.3-26.1]	30.2 [23.5-36.8]
Mean FCT (h) [95% CI]	29.3 [26.4-32.1]	46.0 [41.0-51.0]
Cure rate (ITT) [95% CI]	40/50, 80% [67-89]	45/50, 90% [79-96]
Cure rate (Eval) [95% CI]	40/46, 87% [74-94]	45/48, 94% [93-98]

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APPENDIX C: LIST OF ABBREVIATIONS

<u>Abbreviation</u>	<u>Definition</u>
FCT	fever clearance time
PCT	parasite clearance time
F/U	follow-up visit
LTF	late treatment failure
ETF	early treatment failure
ACR	adequate clinical response
RI	clearance of asexual parasitemia within 7 days of the first day of treatment followed by recrudescence
RII	marked reduction of asexual parasitemia but no clearance
RIII	no marked reduction of asexual parasitemia
R	randomized
OL	open-label
AC	active-control
DB	double blind
IP	in-patient
ITT	intent-to-treat population
EVAL	evaluative/per protocol population
Q	quinine
CQ	chloroquine
A	artemisinin (artesunate, artemether)
ATP	atovaquone + proguanil
T	tetracycline
D	doxycycline
C	clindamycin
Amo	amodiaquine
M	mefloquine
S/P	sulfadoxine-pyrimethamine
P	primaquine
E	efficacy
S	safety
qd	quaque die (once daily)
bid	bis in die (twice a day)
tid	ter in die (three times a day)
qid	quarter in die (four times a day)

APPENDIX D: REFERENCES

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