

al., 2001		51 AE	old		then 10 mg/kg q 8 h IV then PO for total of 7 days	then 1.6 mg/kg IM daily for 5 days total	reported
Taylor, et al., 1998	Randomized, open-label	183 88 Q 95 AR	Children	Malawi	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV then PO for total of 7 days, followed by single dose SP (1.25 mg/kg pyramethamine- 25 mg/kg sulfadoxine	AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for a minimum of 3 doses, followed by single dose SP (1.25 mg/kg pyramethamine- 25 mg/kg sulfadoxine)	Adverse events not reported
Olumese, et al., 1999	Randomized, open-label	108 49 Q 54 AR	Children 6 months-5 years old	Nigeria	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV then PO for total of 7 days	AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 4 days (5 days total)	Adverse events not reported
Murphy, et al., 1996	Randomized, open-label	200 97 Q 103 AR	Children	Kenya	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV (minimum of 3 doses) followed by single dose SP (1.25 mg/kg pyramethamine- 25 mg/kg sulfadoxine	AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 4 days (5 days total)	Adverse events reported
Karbwang, et al., 1995	Randomized, open-label	102 52 Q 50 AR	Patients 15-65 years old	Thailand	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV then PO for total of 7 days.	AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 6 days (7 days total)	Some adverse events reported
Karbwang, et al., 1992	Randomized, open-label	26 12 Q 14 AR	Patients 15-45 years old	Thailand	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV then PO for total of 7 days	AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 6 days (7 days total)	Some adverse events reported
Hien, et al., 1996	Randomized, open-label	560 276 Q 284 AR	Patients > 14 years old	Vietnam	20 mg/kg IM loading dose, then 10 mg/kg IM q 8 h ††	AR: 4 mg/kg IM loading dose, then 2 mg/kg IM q 8h ††	Some adverse events reported
Van Hensbroek, et al., 1996	Randomized, open-label	576 288 Q 288	Children 1-9 years old	Gambia	20 mg/kg IM loading dose, then 10 mg/kg q 12 h IM, then	AR: AR: 3.2 mg/kg IM loading dose, then 1.6 mg/kg	Some adverse events reported

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		AR			PO for 5 days#	IM daily for 4 days #	
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Q= quinine; AR= artemether; AS= artesunate; AML= artemotil; AE= arteether; SP= sulfadoxine-pyrimethamine
 IV= intravenous; IM= intramuscular; PO= per os (by mouth)
 *standard dose of quinine is 10 mg/kg 3 x daily; and it is not clear if this was a publication error or actual dose
 **comparator was changed to oral artesunate + mefloquine, then artesunate +tetracycline or doxycycline after an unspecified period of time
 † 80 mg/kg artemether is probably an error in publication; more likely dose was 80 mg daily.
 †† In both treatment arms, when patient could take oral medication, a second randomization to mefloquine (single dose 15 mg/kg PO), or quinine 10 mg/kg 3 x daily for up to 4 days (to complete 7 days treatment)
 # In both treatment arms, SP (single dose 1.25 mg/kg pyrimethamine-25 mg/kg sulfadoxine) was given after study treatment in second and third year of study.

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7.2.1.2 Demographics

In the pharmacokinetic studies sponsored by the applicant, healthy male and female volunteers between the ages of 18 and 61 were included.

The randomized, controlled studies with oral quinine monotherapy for treatment of uncomplicated malaria included both children and adults, and efficacy and safety were not analyzed separately by age. Most of these studies were in young men. The table below shows the patient demographics in these studies.

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Table 87: Patient Demographics in Randomized Controlled Trials of Oral Quinine Monotherapy for Treatment of Uncomplicated Malaria (source: dataset created by Statistical Reviewer)

Study	Treatment	N	Mean Age ± S.D. (years)	Median Age (years) (age range)	Gender # male/# female	Country where study was performed
Segal, et al., 1974	Quinine	26	--	23 (15-53)	26/0	Thailand
	WR33063	25		23 (25-53)	26/0	
Watt, et al., 1988	Quinine	10	28 ± 11	-- (16-49)	10/0	Phillipines
	Chloroquine	10	30 ± 11	-- (18-49)	10/0	
Metzger, et al., 1995	Quinine	40	--	32 (15-70)	21/16	Gabon
	Quinine + clindamycin	40	--	35 (15-71)	15/21	
	Quinine + doxycycline	40	--	28 (16-70)	21/14	
Bich, et al., 1996	Quinine	59	25 ± 12	-- (14-66)	47/12	Vietnam
	Quinine + artemisinin	45	27 ± 13	-- (12-64)	34/11	
	Artemisinin+doxycycline	53	26 ± 13	-- (9-63)	47/6	
Pukrittayakamee, et al., 2000	Quinine	68	24.6 ± 8.9	--	68/0	Thailand
	Quinine + clindamycin	68	25.6 ± 9.3	--	68/0	
	Quinine + tetracycline	68	27.3 ± 10.2	--	68/0	
De Vries, et al., 2000	Quinine + artemisinin (3 days)	96	--	26 (7-60)	70/14	Vietnam
	Quinine + artemisinin (5 days)	88	--	26 (7-64)	76/20	
	Quinine	84	--	26 (7-60)	70/14	
McGready, et al., 2000	Quinine	42	--	23 (16-36)	0/42*	Thailand
	Mefloquine + artesunate	66	--	24 (15-37)	0/66*	
Rahman, et al., 2001	Quinine	49	24.7 ± 8.5	--	45/4	Bangladesh
	Quinine + SP	145	26.3 ± 9.8	--	136/9	
	Chloroquine	149	26.1 ± 9.9	--	138/11	
	Mefloquine	70	27 ± 9.4	--	61/9	
Ache, et al., 2002	Quinine	16	27.3 ± 7.3	--	9/7	Venezuela (Ikabaru)
	SP	16	28.7 ± 19		11/5	
	Chloroquine (25 mg/kg)	0				
	Chloroquine (40 mg/kg)	16	30 ± 11.3	--	15/1	
	Quinine	16	30.4 ± 8.5	---	13/3	Venezuela (Km88)
	SP	11	27 ± 8.5	--	8/3	
	chloroquine (25 mg/kg)	6	31.3 ± 8.2	--	4/2	
	chloroquine (40 mg/kg)	13	28.6 ±	--	11/2	

			7.7			
	Quinine	16	28.5 ± 18.1	--	11/5	Venezuela (Maripa)
	SP	26	22 ± 20.6	--	17/9	
	Chloroquine (25 mg/kg)	6	33 ± 24.4	--	4/2	
	chloroquine (40 mg/kg)	23	26.7 ± 19.8	--	18/5	
Mueller, et al., 2004	Quinine	48	--	--	--	Congo
	Artemisia tea (5 g/day)	45	--	--	--	
	Artemisia tea (9 g/day)	39				
Pukrittayakamee, et al., 2004	Quinine	30	24 ± 8	--	30/0	Thailand
	Quinine + tetracycline	30	27 ± 9	--	30/0	
	Quinine + Primaquine (0.25 mg)	29				
	Quinine + Primaquine (0.5 mg)	37				
	Artesunate	23	23 ± 8	--	23/0	
	Artesunate + Primaquine	27				

SP= sulfadoxine-pyrimethamine

* All pregnant females enrolled

A total of 504 patients received quinine alone, 624 received a non-quinine comparator, and 686 received a quinine combination regimen. Among patients who received oral quinine monotherapy for treatment of uncomplicated malaria in these studies, 350/456 (77%) patients (not including 48 patients whose gender was not specified) were male, and 106/456 (23%) were female; while among patients who received a non-quinine comparator, 420/540 (78%) patients (not including 84 patients whose gender was not specified) were male and 120/540 (22%) were female. Among patients who received quinine combination therapy, 514/686 (75%) were male, and 172/686 (25%) were female.

Medical Officer Comments: Most of these studies were performed in Southeast Asia, which is where the incidence of mefloquine-resistant P. falciparum is rising, and some quinine resistance has been reported. Most patients were young males, based on mean and median age of patients, when reported in the studies. The gender disparity in these studies probably reflects the disproportionate incidence of malaria in young men in these countries in which agricultural workers (mainly young men) who spend most of their time outdoors in the fields, are affected. In one of these studies, McGready, et al., 2000, only pregnant women were enrolled. Pediatric patients (≤ 15 years old) were enrolled in several of these studies, but the numbers of pediatric patients enrolled were not specified in the individual studies.

Of the studies provided on quinine combination therapy for treatment of uncomplicated malaria, several had a quinine monotherapy treatment arm, and were included in the table above. These studies, not included in the table below, include Metzger, et al. (1995), Bich, et al. (1996), Pukrittayakamee, et al. (2000), De Vries, et al. (2000), Rahman, et al. (2001), and Pukrittayakamee, et al. (2004). Not including the studies shown in the table above, 582/1010

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(58%) % received quinine in combination with another antimalarial drug, and 428/1010 (42%) % received another comparator. Overall, 858/1010 (85%) of patients were male, and 185/1010 (15%) were female.

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Table 88: Patient Demographics in Randomized Controlled Trials of Oral Quinine Combination Therapy for Treatment of Uncomplicated Malaria (source: Statistical Reviewer's dataset)

Study	Treatment	N	Mean Age ± S.D. (years)	Median Age (years) (age range)	Gender # male/# female	Country where study was performed
Kresmer, et al., 1988	Quinine + clindamycin	40	--	--	32/8	Brazil
	Quinine + SP	30	--	--	22/7	
	Amiodaquine	25	--	--	20/7	
Karbwan, et al., 1994	Quinine + tetracycline	33	23	-- (17-35)	33/0	Thailand
	Artesunate	31	25	-- (15-35)	35/0	
Looareesuan, et al., 1994	Quinine + tetracycline	50	31.1 ± 12.3	-- (17-67)	39/11	Thailand
	Mefloquine + tetracycline	52	27.8 ± 10.1	-- (16-51)	36/16	
Bunnag, et al., 1996	Quinine (5 days) + tetracycline	48	--	24 (17-40)	48/0	Thailand
	Quinine (7 days) + tetracycline	42	--	25 (16-54)	42/0	
Duarte, et al., 1996	Quinine + tetracycline	88	30.9 ± 11.8	-- (14-70)	73/15	Brazil
	Artesunate + tetracycline	88	32.3 ± 11.5	-- (15-57)	72/16	
Vanijanonta, et al., 1996	Quinine + chloroquine	25	23 ± 7	--	25/0	Thailand
	Quinine + tetracycline	25	27 ± 9	--	25/0	
Salcedo, et al., 1997	Quinine (po) + tetracycline	8	37 ± 10.3	-- (22-57)	7/1	Brazil
	Quinine (IV) + tetracycline	6	29 ± 14.6	--(10-53)	6/0	
	Artesunate (po) + tetracycline	8	28 ± 9.8	-- (15-43)	7/1	
	Artesunate (IV) + tetracycline	8	38 ± 8.7	--(8-64)	5/3	
	Mefloquine	12	32 ± 12.1	--(12-54)	10/2	
De Alencar, et al., 1997	Quinine + tetracycline	77	28.2 ± 1.2	--	77/0	Brazil
	Atovaquone- proguanil	77	30.2 ± 1.1	--	77/0	
Fungladda, et al., 1998	Quinine + tetracycline	60	31.9 ± 11.5	--	59/1	Thailand
	Artesunate	77	30.8 ± 9.4	--	61/16	
DeSouza, et al., 1985	Quinine+SP	50	--	--	50/0	Brazil
	Mefloquine	50	--	--	50/0	

Medical Officer's Comments: Most patients in these studies were young males, so whether the data on adverse events can be generalized to female or elderly patients is not known. Pediatric patients were enrolled in several of these studies, although the number of pediatric patients enrolled was not specified in the publications.

The demographic data from the pediatric studies of oral quinine mono- or combination therapy included in this review is shown in the table below. A total of 230 children were enrolled in these two studies, 132/230 (57%) were male, and 98/230 (43%) were female. A total of 31/230 (13%) received quinine alone, 84/230 (37%) received quinine plus clindamycin, and 115/230 (50%) received a non-quinine regimen.

Table 89: Demographic Data from Pediatric Studies of Oral Quinine Mono- or Combination Therapy

Study	Treatment	N	Mean Age ± S.D. (years)	Median Age (years) (age range)	Gender # male/# female	Country where study was performed
Ramharter, et al., 2005	Quinine-Clindamycin	50	7.7 ± 3.3	--	30/20	Gabon
	Artesunate+Clindamycin	50	7.1 ± 2.6	--	23/27	
Kremsner, et al., 1994	Quinine	31	--	10	22/9	Gabon
	Quinine + clindamycin	34	--	9	21/13	
	Chloroquine	32	--	10	18/14	
	Chloroquine + clindamycin	33	--	10	18/15	

Demographic data from the studies of parenteral quinine therapy are shown in the table below. Overall, 1116/2268 (49%) patients were treated with parenteral quinine alone and 1152/2268 (51%) patients were treated with an artemisinin derivative for severe malaria, and 60% patients were male and 40 % were female.

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Table 90: Patient Demographics in Randomized Controlled Trials of Parenteral Quinine for Treatment of Severe Malaria

Study	Treatment	N	Mean Age ± S.D. (years)	Median Age (years) (age range)	Gender # male/# female	Country where study was performed
Singh, et al., 2000	Quinine	26	--	(15->60)	--	Manipur.
	A	26	--	-(15->60)	--	
Tran Hien, et al., 1996	Quinine	276	--	30 (15-78)	213/63	Vietnam
	A	284	--	30 (15-79)	212/72	
Newton, et al., 2003	Quinine	54	--	25 (15-59)	40/14	Thailand
	A	59	--	25 (15-66)	39/20	
Satti, et al., 2002*	Quinine	39	--	-- (-15)	--	
	A	38	--	-- (-15)	--	
Adam, et al., 2002*	Quinine	21	3.59 ± 3.2	--	10/11	Sudan
	A	20	4.1 ± 2.5	--	11/9	
Faiz, et al., 2001	Quinine	54	30 ± 10	-- (14-50)	42/12	Bangladesh
	A	51	28 ± 10	-- (14-50)	36/15	
Thuma, et al., 2000*	Quinine	44	3.3 ± 1.8	-- (0-10)	27/17	Zambia
	A	48	3.9 ± 2.3	-- (0-10)	20/28	
Moyou-Somo, et al., 2001*	Quinine	51	3.25	-- (0-10)	33/18	Cameroon
	A	51	3.4	-- (0-10)	26/25	
Taylor, et al., 1998*	Quinine	81	3.21 ± 1.98	--	39/42	Malawi
	A	83	2.94 ± 1.97	--	44/39	
Olumese, et al., 1999*	Quinine	49	3.1	-- (1-5)	--	Nigeria
	A	54	--	-- (1-5)	--	
Murphy, et al., 1996*	Quinine	71	--	2.5 (0.4-12)	36/35	Kenya
	A	89	--	2.2 (0.4-9)	44/45	
Karbwan, et al., 1995	Quinine	50	--	28 (15-54)	--	Thailand
	A	47	--	25 (15-55)	--	
Karbwan, et al., 1992	Quinine	12	31.7 ± 10.4	--	--	Thailand
	A	14	30.4 ± 10	--	--	
Van Hensbroek, et al., 1996*	Quinine	288	3.83 ± 1.78	-- (1-9)	143/145	Gambia
	A	288	4 ± 1.8	-- (1-9)	152/136	

*Studies that enrolled only pediatric patients
 A= artemisinin derivative used as comparator

Medical Officer Comments: As noted in the table above, several of these studies enrolled only pediatric patients, with a total of 410 pediatric patients who received parenteral quinine; while all of these studies enrolled patients who were 14 or 15 years old.

However, from the individual study publications, we were not able to determine the specific numbers of pediatric (< 16 years old) and adult patients enrolled as separate entities. These studies encompass a wider range of malarious regions including Africa, and SE Asia, than did the studies with oral quinine for treatment of uncomplicated malaria, however, no studies from South America were included.

7.2.1.3 Extent of exposure (dose/duration)

Clinical Studies with oral Quinine Monotherapy

In the randomized, controlled trials of oral quinine monotherapy for treatment of uncomplicated malaria, most studies used a dosing regimen of 10 mg/kg 3 times daily (or every 8 hours) for 7 days, as shown in the following table. In the study performed by Watt, et al. (1988), a quinine dose of 648 mg would be equivalent to 9.25 to 10.8 mg/kg for a 60- or 70 kg adult, respectively. The dosing regimen of quinine sulfate, 648 mg every 8 hours, is proposed in this NDA. In the study by Segal, et al. (1974), a quinine dose of 540 mg would be equivalent to 7.7 to 9.0 mg/kg in a 60- or 70 kg adult, respectively, somewhat lower than the proposed dose of quinine sulfate for this NDA. The study by Metzger, et al. (1995) used a quinine dosing regimen of 12 mg/kg every 12 hours for a total of 3 doses only, a regimen which is significantly different from that in the other studies submitted, and from the proposed dosing regimen.

Table 91: Dosing and Duration of Quinine in RCT or Oral Quinine for Treatment of Uncomplicated Malaria (Applicant's Table 3.66, Summary)

Author (year) Country	Quinine Dosage Regimen	Duration (Days)	No. Patients Completed / Randomized (% Completed)
RANDOMIZED, DOUBLE-BLIND STUDIES (N=1)			
Watt et al., 1988 (Philippines)	648 mg (sulfate salt) every 8 hours	5	10/10 (100%)
RANDOMIZED, OPEN-LABEL STUDIES (N=10)			
Pukrittayakamee et al., 2004 (Thailand)	10 mg/kg (sulfate salt) 3 times daily	7	25/30 (83%)
Mueller et al., 2004 (Congo)	500 mg (sulfate salt) 3 times daily	7	36/48 (75%)
Ache et al., 2004 (Venezuela)	10 mg/kg (sulfate salt) every 8 hours	7	48/48 (100%)
Rasman et al., 2004 (Bangladesh)	10 mg/kg (sulfate salt) every 8 hours	7	49/49 (100%)
McGrandy et al., 2000 (Thailand)	10 mg/kg (sulfate salt) every 8 hours	7	27/42* (67%)
Pukrittayakamee et al., 2008 (Thailand)	10 mg/kg (sulfate salt) 3 times daily	7	53/68 (82%)
de Vries et al., 2000 (Vietnam)	10 mg/kg (sulfate salt) 3 times daily	7	69/84 (82%)
Bich et al., 1996 (Vietnam)	10 mg/kg (sulfate salt) 3 times daily	7	44/59 (75%)
Metzger et al., 1995 (Gabon)	12 mg/kg every 12 hours ²	1.5 ³	37/40 (92%)
Segal et al., 1974 (Thailand)	2 tablets sulfate salt (540 mg base) every 8 hours	6	22/26 (85%)
TOTAL			407/504 (81%)

*36 patients completed Day 28 follow-up and 34 patients completed Day 35 follow-up. No efficacy summary was provided for Day 28 therefore Day 35 data are used in this document

²Not specified to be dosed as the salt or base

³This three-dose regimen was commonly given in Central Africa at the time

⁴Duration of follow-up was 63 days

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Clinical studies of Oral Quinine Combination Therapy

In the studies of oral quinine combination therapy for treatment of uncomplicated malaria, the quinine dosing regimen was generally 10 mg/kg 3 times daily (or every 8 hours), or 600-650 mg every 8 hours; and duration of quinine treatment ranged from 3-7 days, as summarized in the table below.

Table 92: Dosing and Duration of Quinine in Studies of oral Quinine Combination Therapy for Uncomplicated Malaria

Study	Quinine Combination and Duration Code*	Quinine Dosing Regimen	Number of Patients Completed/number Randomized (%)
Duarte, et al., 1996	Q3T7	1000 mg q 12h	69/88 (78.4)
Pukrittayakamee, et al., 2004	Q7T7	10 mg/kg tid	22/30 (73.3)
	Q7	10 mg/kg tid	25/30 (83.3)
Rahman, et al., 2001	Q3SP1	10 mg/kg or 600 mg q8h	145/145 (100)
	Q7	10 mg/kg tid or q8h	49/49 (100)
Pukrittayakamee, et al., 2000	Q7C7	10 mg/kg tid	60/68 (88.2)
	Q7T7	10 mg/kg tid	48/68 (70.6)
	Q7	10 mg/kg tid	53/68 (77.9)
De Vries, et al., 2000	A1Q3	10 mg/kg tid	74/96 (77.1)
	A1 Q5	10 mg/kg tid	78/88 (88.6)
	Q7	10 mg/kg tid	69/84 (82.1)
Fungladda, et al., 1998	Q7T7	600 mg tid	53/60 (88.3)
Salcedo, et al., 1997	Q3T7	600 mg or 10 mg/kg q8h	--/14
De Alencar, et al., 1997	Q7T7	600-650 mg tid or q8h	77/77 (100)
Bunnag, et al., 1996	Q5T7	600-650 mg tid or q8h	46/48 (95.8)
	Q7T7	600-650 mg tid or q8h	40/42 (95.2)
Vanijanonta, et al., 1996	Q7T7	10 mg/kg tid	18/25 (72.0)
	Q7CQ3	10 mg/kg q8h	18/25 (72.0)
Bich, et al., 1996	ART1Q3	10 mg/kg tid	32/45 (71.1)
	Q7	10 mg/kg tid or q8h	44/59 (74.5)
Metzger, et al., 1995	Q1.5C3	12 mg/kg q 12h	36/40
	Q1.5D3	12 mg/kg q	35/40

		12h	
Looareesuwan, et al., 1994	Q7T7	600-650 mg tid or q8h	46/50 (92.0)
Karbwang, et al., 1994	Q7T7	600-650 mg tid or q8h	30/33 (90.9)
De Souza, et al.,	Q3SP1	10 mg/kg or 600 mg q8h	50/50 (100)
Kresmer, et al.,	Q3C	15 mg/kg q12h	40/46 (86.9)
	Q3SP	15 mg/kg q12h	30/40 (75.0)

*Code is treatment abbreviation (see below), followed by treatment duration in days for each component of the combination. q=every; h= hours; tid= 3 times a day
 Q=quinine; T= tetracycline; D= doxycycline; C= clindamycin; CQ= chloroquine; A=artesunate
 ART = artemisinin; SP = sulfadoxine-pyrimethamine

Medical Officer Comments: Two of these studies used a different quinine dosing regimen than that proposed in this NDA (648 mg every 8 hours), 12 mg/kg every 12 hours in Metzger, et al. (1995), and 15 mg/kg every 12 hours in Kresmer, et al. (1988). Quinine dosing in most of the other studies was similar to the proposed dose.

Clinical Studies of Parenteral Quinine Therapy

In most of the parenteral quinine studies submitted, a loading dose of 20 mg/kg quinine was infused (or injected) prior to the maintenance dose of quinine, 10 mg/kg every 8 hours. In most of these studies, oral quinine at the same maintenance dose was substituted for the parenteral preparation, as soon as the patient could take oral medications. Parenteral quinine dosing and duration is summarized in the following table. In each of these studies, except for that by Van Hensbroek, et al. (1996), the total duration of quinine dosing was 7 days.

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Table 93: Dosing and Duration of Quinine in RCT of Parenteral Quinine for Treatment of Severe P. falciparum malaria (Applicant's Table 3.70, summary)

Author, year (Country)	Quinine Dosage Regimen	Route (Duration [Days])	No. Patients Randomized
RANDOMIZED, DOUBLE-BLIND STUDIES			
INTRAVENOUS QUININE			
Singh <i>et al.</i> , 2000 (India)	IV loading dose: None IV dose: 10 mg/kg every 8 hours ¹ Oral maintenance dose: None	IV (7)	26
INTRAMUSCULAR QUININE			
Tran <i>et al.</i> , 1996 (Vietnam)	IM loading dose: 20 mg salt/kg IM maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IM ² /ORAL ^{1,4} (7)	376
RANDOMIZED, OPEN-LABEL STUDIES			
INTRAVENOUS QUININE			
Newton <i>et al.</i> , 2003 (Thailand)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg/kg every 8 hours	IV/ORAL ⁴ (7)	54
Satti <i>et al.</i> , 2002 (Sudan)	IV loading dose: None IV dose: 10 mg/kg every 8 hours Oral maintenance dose: 10 mg/kg every 8 hours	IV/ORAL (7)	39
Adam <i>et al.</i> , 2001 (Sudan)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg Oral maintenance dose: 10 mg/kg	IV ³ /ORAL (7)	21
Faiz <i>et al.</i> , 2001 (Bangladesh)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV/ORAL (7)	54
Thama <i>et al.</i> , 2000 (Zambia)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV/ORAL (7)	44
Mouou-Somo <i>et al.</i> , 2001 (Cameroon)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV ³ /ORAL (7)	51
Taylor <i>et al.</i> , 1998 (Malawi)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV ³ /ORAL ⁴ (7)	88
Olumese <i>et al.</i> , 1994 (Nigeria)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg/kg every 8 hours	IV/ORAL (7)	49
Murphy <i>et al.</i> , 1996 (Kenya)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: None	IV ^{4,5,6}	71
Karbwang <i>et al.</i> , 1995 (Thailand)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV/ORAL (7)	52
Karbwang <i>et al.</i> , 1992 (Thailand)	IV loading dose: 20 mg salt/kg IV maintenance dose: 10 mg salt/kg every 8 hours Oral maintenance dose: 10 mg salt/kg every 8 hours	IV/ORAL (7)	12
INTRAMUSCULAR QUININE			
Van Hensbroek <i>et al.</i> , 1996 (Gambia)	IM loading dose: 20 mg salt/kg IM maintenance dose: 10 mg salt/kg every 12 hours Oral maintenance dose: 10 mg salt/kg every 12 hours	IV/ORAL (5)	288
Total			1125

¹Publication error likely – dosing cited as 10 mg/kg per day but as they are using quinine as the standard of care, the dose was likely given every 8 hours

²Parenteral quinine was to be administered for a minimum of 3 days

Medical Officer Comments: Parenteral quinine dosing regimens were far more uniform than for quinine monotherapy or combination therapy regimens described in the tables above.

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7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The applicant also provided quinine product labels from 11 countries where quinine is marketed for malaria, and/or for nocturnal leg cramps, or for myotonia. A review of these labels for safety information, including recommended dose, indications, and adverse events is included in section 7.1.4 above.

7.2.2.2 Postmarketing experience

The applicant provided a summary of the postmarketing experience obtained from the FDA and from the World Health Organization (WHO). The FDA databases included the Spontaneous Reporting System (from 1969 to October 31, 1997), and the Adverse Event Reporting System (AERS), from November, 1997 to June 30, 2003. The 120-day safety update extended the AERS data through December, 2003. The WHO database included reports from 1968 through March, 2004, and the safety update extended the information through November, 2004. For the FDA postmarketing data, the applicant did not address possible relationship of adverse events to quinine in the ISS or in the safety update because individual MedWatch reports were not provided by the Agency as of March, 2005. These data are summarized in this section, but postmarketing data on specific adverse events is included in sections 7.1.5 and 7.1.17 above.

Additionally, the Office of Drug Safety (ODS) was consulted by the Division to review postmarketing adverse events reported to the FDA, and to comment on a possible causal relationship of specific adverse events to quinine, as well as to make recommendations regarding final product labeling. The ODS Consultation Report has been appended to this review (section 10 3).

FDA Postmarketing Data Summary Provided by the Applicant

As of December, 2003, 487 adverse events were reported in either the Spontaneous Adverse Event Reporting System, or AERS database, naming quinine as a suspect medication. Outcomes from these adverse events are shown in the following table, which includes data through June 2003 presented in the ISS and through December, 2003, provided in the safety update. A table of the most common postmarketing adverse events was shown above.

Table 94: Outcome Summary for Postmarketing Adverse Events reported to the FDA from 1969 through December, 31, 2003 (Applicant's Table 7, 120-day safety update)

Adverse Event Outcome	Count	
	NDA 21-799 1969 to Jun 2003 ¹	Update 1969 to 31 Dec 2003 ²
Hospitalization, initial or prolonged	234	256
Other	68	76
Death	54	80
Required intervention to prevent permanent impairment	52	56
Life-threatening	51	56
Treated with prescription drug	38	38
Recovered	32	32
None	25	25
Disability	17	20

1. Source: FOI Report of Adverse Events with Quinine, 9 June 2004
2. Source: FOI Report of Adverse Events with Quinine Outcome Summary through 31 December 2003, the most current information available publicly as of 31 December 2004

Medical Officer Comments: Note that the total number of outcomes reported here (619) is greater than the total number of adverse events reported through December, 2003 (487 events). Presumably, adverse events may have been associated with more than one outcome (e.g. hospitalization and death).

WHO Postmarketing Data Summary Provided by the Applicant

The initial NDA 21-799 reported 1195 adverse events in 504 reports from 15 countries worldwide, including the U.S. through March, 2004. The 120-day safety update reported 4191 adverse events from 1908 reports, from 27 countries worldwide through November, 2004. A table of the most common postmarketing events was shown above.

7.2.2.3 Literature

This NDA is a 505(b) 2 application, and is supported only by data on the safety and efficacy of quinine from published literature. The applicant's initial literature search for the original NDA included the following databases: MEDLINE® (1966 through February 2004), EMBASE (1974-February 2004), JICST-Eplus (1985-February 2004), and Biosis Previews (1969-February 2004). A search for all side effects, adverse reactions, and drug reactions reported with quinine in humans returned 2601 citations at that time. The search was further limited to non-review articles published between 1993 and 2004, resulting in 841 unique citations, 146 of which were fully reviewed based on titles and abstract. An additional search of the same databases was performed in June, 2004, resulting in 417 unduplicated citations, 108 of which were fully reviewed. Overall, 192 publications and one review article provided the information included in the NDA submission.

For the 120-day safety update, another search of the same databases was performed in December, 2004. Another 859 unique citations were obtained, and only 11 publications were identified which provided additional safety data.

Literature cited in this review other than that provided by the applicant with the original NDA submission or the 120-day safety update was obtained by search of PubMed for additional

publications related to quinine safety. These literature citations are found in the References section of this review.

Medical Officer Comments: The literature searches performed by the applicant appear to have captured most of the relevant safety data on quinine published after 1992. Some additional case reports (mostly published prior to 1993), additional reviews on quinine toxicity, and a few clinical studies relative to quinine safety were identified by the Medical Officer and included in this review.

7.2.3 Adequacy of Overall Clinical Experience

Adequacy of Quinine Exposure

Quinine has been used to treat malaria since the 17th century, and adverse events associated with quinine treatment for malaria or other indications are well known. However, clinical studies which specifically addressed quinine safety, particularly in comparison to other antimalarial drugs, are lacking. Two pharmacokinetic studies sponsored by the applicant evaluated single-dose quinine safety in 50 healthy subjects. The applicant also provided 11 primary studies from the literature which evaluated efficacy of oral quinine monotherapy for uncomplicated malaria, which enrolled 504 patients (adults and children) who were randomized to quinine. Additionally, 16 primary studies from the literature which evaluated oral quinine in combination with another antimalarial agent for treatment of uncomplicated malaria, which enrolled (975) patients (adults and children) randomized to quinine combination therapy (some of these studies overlap because there is a quinine monotherapy arm). The applicant also provided 14 randomized studies from the literature which evaluated the use of parenteral quinine in patients with severe malaria in support of the NDA. These studies included 1125 adults and children who received intravenous or intramuscular quinine.

Medical Officer Comments: The overall number of patients exposed to quinine in these studies appears adequate to make a safety evaluation. However, significant safety data was found in only some of the studies on quinine monotherapy, combination therapy and parenteral quinine. In many cases adverse events were not reported systematically, and in many cases, not by treatment group, or not quantitatively. In most studies, there was no discussion on how adverse events were monitored. Thus, the quantitative safety data obtained from these studies is limited. However, because the safety profile of quinine is fairly well-known because of its use for centuries, as well as from published reviews of quinine toxicity and because many years of quinine postmarketing safety data were obtained from two separate sources (FDA and WHO), the quinine exposure could be considered adequate.

Few of these studies, however, provided safety data on use of quinine in pregnancy, in patients with renal or hepatic insufficiency or with other underlying diseases. Although some elderly patients were included in these studies, safety and efficacy data were not provided separately for elderly and younger patients. Additionally, most of the studies for oral quinine mono- or combination therapy, combined adult and pediatric patients, so conclusions regarding pediatric safety of quinine cannot be drawn. Several of the

parenteral quinine studies were conducted only in pediatric patients. These studies included 410 pediatric patients who received parenteral quinine therapy, so preliminary on the safety of parenteral quinine in pediatric patients is available.

We would agree with the applicant that the final product labeling at this time states that "the safety and efficacy of quinine in pediatric patients has not been established".

Adequacy of Quinine Doses and Durations

Details regarding quinine dosing and duration in the studies submitted for this NDA were discussed previously. The quinine doses used in the primary studies of oral quinine mono- or combination therapy were similar to or higher than the proposed dose of oral quinine for treatment of uncomplicated *P. falciparum* malaria is 648 mg every 8 hours in this NDA

most patients in the studies which evaluated quinine monotherapy received 7 days of quinine (10 received 5 days, and 40 received 1.5 days),

For safety evaluation however, the incidence of adverse events would be expected to be higher with the longer course of therapy. Adverse event data was limited in these studies, so no estimate on relative incidence of adverse events with quinine sulfate duration was attempted. The efficacy of the 3, 5, and 7 day quinine combinations was evaluated in the ISE, section 6 above. However, for safety evaluation, the incidence of adverse events was reported in this review from combined study data.

Among the studies which evaluated parenteral quinine for severe falciparum malaria, quinine dosing and duration was fairly uniform among studies (20 mg/kg loading dose, followed by 10 mg/kg every 8 hours for 7 days, with exceptions as previously described. Parenteral quinine is assumed to have 100% bioavailability; while that of oral quinine is approximately 80%, thus total peak plasma concentrations of quinine administered parenterally would most likely be somewhat higher than those of orally-administered quinine. The cardiovascular and visual toxicity of quinine has been related to plasma quinine concentrations (Taylor and White, 2004). Thus, the incidence of adverse events in patients who received parenteral quinine might be expected to exceed that of patients treated with oral quinine.

Medical Officer Comments: Despite the fact that this NDA was submitted for use of oral quinine, including the studies on parenteral quinine for treatment of severe malaria in this NDA was useful because drug reactions associated with quinine are potentially more common in patients treated with parenteral rather than oral quinine, and could represent the worst case scenario. However, the patients treated with parenteral quinine all had severe malaria, and because of overlap in the signs and symptoms of malaria with the known toxic effects of quinine, drug-related adverse events were difficult to ascertain.

Adequacy of Study Design

Most of the studies submitted for this NDA were randomized, but only a few were blinded, as outlined in section 6.1.3 above. In the studies of oral monotherapy, the comparator was an

antimalarial agent approved by the FDA for treatment of malaria (chloroquine, or sulfadoxine-pyrimethamine), newer, currently unapproved antimalarial drugs (artemisinin derivatives), or quinine combination therapy. In the studies of quinine combination therapy, comparators included quinine alone, atovaquone-proguanil (FDA-approved for malaria), newer unapproved drugs (artemisinin derivatives alone or in combination with another antimalarial agent), or other quinine combinations. The studies of parenteral quinine treatment for severe malaria compared quinine to the currently unapproved artemisinin derivatives in each case. The non-randomized studies submitted were not evaluated for efficacy in this review, because of the potential for bias in such studies. Some of these studies, however, provided additional safety information regarding quinine.

Medical Officer Comments: Because of the open-label study design in most cases, there may have been reporting bias with regards to adverse events. Additionally, because multiple antimalarial agents were used as comparators, the usefulness of the comparative safety data from the combined studies is limited.

Evaluation of Potential Class Effects

The most important class effect of quinine is shared by its diastereomer, quinidine. Both drugs have antiarrhythmic properties, and are known to affect cardiac conduction, resulting in QTc prolongation, and potentially serious cardiac arrhythmias such as torsades de pointes. In the pharmacokinetic studies sponsored by the applicant, which included 50 healthy subjects, electrocardiograms were obtained at baseline, 2-, 4-, 6-, 12- and 24 hours after a single quinine dose, as reviewed in section 7.1.9. ECG data revealed QTc prolongation (>450 msec) in 7 of 23 (30.4%) subjects in the dose-proportionality study. The maximum Δ QTc was 10-12 msec after a single 324mg or 648 mg dose of quinine sulfate. None of the subjects were noted to have significant cardiac arrhythmias or other serious cardiac events during these studies.

Medical Officer Comments: The potential of quinine for QTc prolongation is well known (from preclinical studies, clinical trials, case reports, and with quinine overdose). Although the pharmacokinetic studies were not formal QT studies, the potential for QT prolongation was suggested, even after single-dose quinine. Additional studies from the literature which included QT data in healthy subjects and in patients with malaria provided confirmatory evidence for QT prolongation with quinine sulfate. We have proposed a Warning regarding potential QT prolongation with quinine in the final proposed label. Additionally, we have proposed a Contraindication against quinine use with baseline prolonged QTc, and a Warning for use of quinine with concomitant drugs known to prolong the QTc interval (e, g. astemizole, terfenadine, cisapride, antiarrhythmic drugs, and others), and for use in patients with other risk factors for torsades de pointes. Other proposed Warnings include use of quinine concomitantly with mefloquine or halofantrine, and with erythromycin.

Exclusion of Special Populations

Most of the studies submitted were performed in young men, presumably without significant underlying concomitant illnesses. Pregnant women were excluded from most of the trials, with the exception of the study reported by McGready, et al., 2000, which included only pregnant

women, except for those in the first trimester of pregnancy. Patients with renal or hepatic insufficiency were excluded from 3 of the studies with quinine combination therapy, but from none of the studies with a quinine monotherapy arm. Patients with severe malnutrition or obesity were excluded from several studies. None of the studies specifically excluded patients with HIV disease, AIDS, or diabetes.

Table 95: Exclusions in Studies on Treatment of Uncomplicated Malaria with oral Quinine Monotherapy

Study	N	Exclusion based on Age	Exclusion based on gender	Exclusion based on pregnancy	Exclusion based on other underlying illness
Watt, et al., 1998	20	< 16 years old	Female	NA	no
Pukrittayakamee, et al., 2004	176	"adults only"	Female	NA	Severe malnutrition
Mueller, et al., 2004	132	< 18 years old	No	Yes	No
Ache, et al., 2002	136	< 6 months	No	No	Severe malnutrition
Rahman, et al., 2001	413	< 12 > 60 years old	No	Yes	No
Pukrittayakamee, et al., 2000	204	"adults only"	Female	NA	Severe malnutrition
McGready, et al., 2000	108	No	Male	First trimester of pregnancy	Mental disorder
De Vries, et al., 2000*	268	< 8 > 65 years old	No	No	No
Bich, et al., 1996	157	< 8 > 65 years old	No	Yes	No
Metzger, et al., 1995	120	< 15 years old	No	Yes	No
Segal, et al., 1974	51	< 15 years old	Female	NA	No

N= number of patients enrolled in study (all treatment groups); NA= not applicable

*Note that this study was a continuation of the study reported by Bich, et al., 1996, so there is some duplication of patients between the 2 studies

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Table 96: Patient Exclusions in Studies on Treatment of Uncomplicated Malaria with oral Quinine Combination Therapy*

Study	N	Exclusion based on Age	Exclusion based on gender	Exclusion based on pregnancy	Exclusion based on other underlying illness
Duarte, et al., 1996	176	< 14 years old	No	Yes	No
Pukrittayakamee, et al., 2004*	176	“adults only”	Female	NA	Severe malnutrition
Rahman, et al., 2001*	413	< 12 > 60 years old	No	Yes	No
Pukrittayakamee, et al., 2000*	204	“adults only”	Female	NA	Severe malnutrition
De Vries, et al., 2000*	268	< 8 > 65 years old	No	No	No
Fungladda, et al., 1008	137	<15 > 60 years old	No	Yes	Renal or hepatic disease
De Alencar, et al., 1997	154	< 18 > 65 years old	Female	NA	Not specifically
Bunnag, et al., 1996	90	< 16 > 54 years old	No	No	Liver or kidney disease
Vanijanonta, et al., 1996	50	No	Female	NA	No
Bich, et al., 1996*	157	< 8 > 65 years old	No	Yes	No
Metzger, et al., 1995*	120	< 15 years old	No	Yes	No
Looareesuwan, et al., 1994	102	< 16 > 60 years old	No	Yes	Weight < 45 or > 60 kg
Karbwang, et al, 1994	34	< 15 > 35 years old	Females	NA	Weight < 45 or > 65 kg Liver or kidney disease
Kresmer, et al., 1988	95	< 14 years old	No	Yes	Chronic diarrhea
De Souza, et al., 1985	100	< 18 > 55 years old	Female	No	No

N=number of patients enrolled in study (all treatment groups); NA= not applicable

*Studies with combination therapy include some of the studies on monotherapy listed in table _ - above, because they contain a quinine combination therapy arm in addition to quinine monotherapy arm.

Medical Officer Comments: Because of the preponderance of patients in these studies were young men, cardiovascular effects, such as QTc prolongation, may not have been observed as often as expected if women or more older men were included in these studies. Additionally, safety information regarding use of quinine in pregnancy is limited. Although most studies did not exclude patients with renal or hepatic impairment, quinine safety in patients with liver or kidney disease who may have been included in these studies was not provided separately. Additionally, no information regarding concomitant medication use was provided in the studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The applicant provided sufficient preclinical data to confirm the potential of quinine for QTc prolongation, as discussed in detail in the Pharmacology/Toxicology Review by Dr. Steven Kunder. The pharmacology summary provided by the applicant also included information on quinine ototoxicity and hypoglycemia in animals. Repeat-dose toxicity studies were summarized, and included evaluation of ophthalmology, hematology and biochemistry profiles in rats. The applicant also reported results of single-dose toxicity and chronic toxicity studies in rats. Genotoxicity studies included *in vitro* tests in non-mammalian cells, and *in vivo* tests in rodents. Specific carcinogenicity testing was not performed in animals because the clinical use of quinine is expected to be short-term (7 days) for treatment of malaria. Reproductive and developmental toxicity in animals was summarized by the applicant; however, no specific fertility studies in animals were identified. See Dr. Kunder's review for further details on the preclinical testing data.

7.2.5 Adequacy of Routine Clinical Testing

For the pharmacokinetic studies sponsored by the applicant, monitoring of electrocardiographic data, vital signs, and laboratory tests were adequate. For most of the studies which evaluated oral quinine use as monotherapy or in combination with other antimalarial agent, routine ECG testing was not performed or not reported. Similarly, specific data on vital signs or laboratory tests were not reported except in the case of adverse events. In studies with parenteral quinine for treatment of severe malaria, ECG and laboratory monitoring were done in a number of studies.

Medical Officer Comments: Although the lack of monitoring or reporting laboratory data, ECGs and vital signs is a limitation of the published studies on oral quinine use, these studies also have limitations in adverse event reporting. In addition to the applicant's pharmacokinetic studies, we can rely to some degree on laboratory, ECG, and vital sign data, where available from studies of parenteral quinine and in the available postmarketing data to determine the relative frequency of serious adverse events, laboratory adverse events, and ECG abnormalities with quinine use.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant adequately characterized quinine's absorption, metabolism and excretion, as summarized in the Clinical Pharmacology review by Dr. Gerlie Gieser. Quinine is metabolized almost exclusively in the liver, mainly by CYP3A4, and to a lesser extent by CYP2C19.

The applicant summarized the published data on drug interactions with quinine, noting increased quinine metabolism with rifampin, a potent inducer of CYP3A4. Quinine inhibits CYP2D6, a cytochrome P450 isoenzyme involved in the metabolism of many drugs. Formal drug interaction studies have not been performed with drugs metabolized by CYP2D6 other than with debrisoquine. However, a table of potential quinine drug interactions was provided by the applicant, as shown below.

Table 97: Drugs metabolized by cytochrome P450 CYP2D6 isoenzyme

Substrates of Cytochrome P450 CYP2D6

Drug Class	Drugs
Antidepressants	Amitriptyline, clomipramine, imipramine, desipramine, nortriptyline, trazodone, fluoxetine, paroxetine, fluvoxamine, citalopram, venlafaxine, mianserin, mirtazapine
Antipsychotics	Thioridazine, perphenazine, haloperidol, risperidone, clozapine, olanzapine, sertindole
Opiates	Codeine, dextromethorphan, tramadol
Beta-blockers	Metoprolol, timolol, pindolol
Antiarrhythmics	Eucainide, flecainide, propafenone
Miscellaneous	Debrisoquine, sparteine, phenformin

Source: *Spina et al. 2003* Table 1

Other drug-interaction studies provided included one which showed a CYP1A2-mediated interaction between quinine and cimetidine, but not ranitidine (Wanwimolruk, et al., 1986). Additionally, one study noted that quinine concentrations were approximately 2-fold higher in patients treated with quinine plus tetracycline than with quinine alone (Karbwang, et al., 1991). The mechanism of this interaction is unknown. One study was cited showing increased systemic exposure to carbamazepine and phenobarbitone, but not to phenytoin with administration of a single oral dose of quinine (Amabeoku, et al., 1993). Two studies were provided showing increased digoxin serum levels in the presence of quinine (1990; Pedersen et al., 1985), and one study which demonstrated quinine inhibition of amantidine renal tubular transport in men (Gaudry, et al., 1993).

Medical Officer Comments: Other potential pharmacodynamic interactions such as that of quinine with astemizole, which resulted in QT prolongation and torsades des pointe in a patient reported by Martin, et al. (1997) were not further discussed by the applicant. Although astemizole (Hismanol®) has been removed from the U.S. market, no information was provided on whether the newer non-sedating antihistamines have the potential for a similar interaction with quinine.

We have proposed a Warning in the final product label regarding the potential of quinine for QTc prolongation and state that use of concomitant medications known to have the potential for QTc prolongation should be avoided.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As discussed above, many of the studies from the published literature provided in support of this application did not systematically monitor or report adverse events. Thus, a quantitative determination of adverse events from these studies was not possible, and only rough estimates of incidence are provided in this review. Additionally, routine ECG, laboratory and vital signs monitoring and/or reporting were not performed in studies with oral quinine, so this information was obtained mostly from studies with parenteral quinine or from postmarketing surveillance data.

***Medical Officer Comments:** Quinine has been used for centuries for the treatment of fevers, and later for malaria, and more recently for treatment of nocturnal leg cramps. The significant adverse effects associated with quinine are well-known and have been summarized in reviews on quinine toxicity (Taylor and White, 2004; Bateman and Dyson, 1986; Jaeger, et al., 1987). Because determining the incidence of adverse events in the randomized studies from the literature provided only a rough estimate of incidence, we have proposed a listing of potential adverse events without reference to incidence in the final product labeling.*

7.2.8 Assessment of Quality and Completeness of Data

Except for two pharmacokinetic studies sponsored by the applicant, the safety data submitted for this 505(b) 2 application is limited to the safety data in the published literature. The applicant provided safety data from the studies submitted for evaluation of quinine efficacy, and from review of the literature on quinine toxicity. However, additional safety data was available in the form of clinical information on quinine toxicity obtained by hundreds of years of quinine use, in published reviews on quinine toxicity, and in the postmarketing surveillance data submitted to the FDA and to the WHO for evaluating quinine safety.

7.2.9 Additional Submissions, Including Safety Update

In the 120-day Safety Update, submitted on 25 March, 2005, the ECG data from the pharmacokinetic study, R04-0376, was summarized, and reviewed. In addition, the applicant provided another search of the medical literature for new safety information since the previous searches in February and June, 2004. No new non-clinical safety information was found in this search, but eleven additional publications were identified, including review articles, clinical case reports on quinine adverse events and further information on quinine overdose. The only new adverse events noted were one case of esophagitis and one case of suicide with quinine ingestion. These additional references were incorporated into the organ system review (section 7.1.3.3 above) and the section on quinine overdosage (section 7.1.16). In addition, labeling for oral quinine was provided from Australia, Denmark, Sweden, The Netherlands, France, Germany, and New Zealand.

Additionally, the 120-day Safety Update included updated AERS data received by the applicant as of December, 2004. This updated information has been incorporated into 7.1.9 above. The applicant concluded that no new safety concerns were identified in the medical literature or in the U.S. and WHO postmarketing safety data.

Additional submissions by the applicant, on 17 June, 2005, and 22 June, 2005, were in response to specific questions regarding NDA 21-799.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Most of the studies provided for review of efficacy and safety of quinine did not specify whether adverse events were considered drug-related or related to the underlying disease. In the pharmacokinetic studies sponsored by the applicant, drug-related adverse events as assessed by the investigator are reviewed above. However, these single-dose quinine studies may not reflect adverse events which occur in a treatment setting. For these, we have relied on reviews of quinine toxicity, and case series and case reports to identify those adverse events which are possibly, probably or definitely related to quinine. Those adverse events of concern include QTc prolongation, with the potential with serious cardiac arrhythmias, including torsades de pointes, hypotension, hypoglycemia, cinchonism in all of its manifestations, including tinnitus, vertigo, hearing impairment, visual impairment or blindness, gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain, and neurological manifestations including impaired consciousness and coma.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Adverse event data from the two pharmacokinetic studies sponsored by the applicant was pooled to estimate incidence of specific adverse events in these studies by quinine dose. However, the number of subjects in these studies was small, and subjects received only a single dose of quinine, so these data cannot readily be generalized to malaria patients receiving quinine treatment, nor can a dose-response relationship be established.

The applicant did not combine safety data across studies in the literature to estimate incidence of adverse events. In fact, the study designs, and adverse event reporting varied so widely, pooling of study data may not be valid. Nevertheless, for this review, studies which reported adverse events were pooled separately for quinine monotherapy, quinine combination therapy, and quinine parenteral therapy, in an attempt to roughly estimate the incidence of adverse events.

7.4.1.2 Combining data

Adverse event data from studies which reported adverse events were combined by adding the numerators for specific adverse events and adding the denominators (number of enrolled patients) for each treatment. As mentioned above, the validity of combining studies with diverse study design, or drug dosage and duration is questionable.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In one pharmacokinetic study sponsored by the applicant, R04-376, the dose proportionality study, adverse events were reported by quinine dose. However, the total number of subjects in the study was 23, and determining a clear dose-relationship for adverse events was not possible. Among the studies from the published literature submitted to evaluate the efficacy and safety of oral quinine monotherapy, most used the standard (10 mg/kg 3 times daily or 648 to 650 mg 3 times daily) quinine dose, for 7 days. Among the studies of quinine combination therapy, most studies used standard quinine dosing, but some of the studies compared different durations of quinine treatment, as discussed below.

7.4.2.2 Explorations for time dependency for adverse findings

For studies from the literature which evaluated oral quinine monotherapy, the treatment duration was generally 7 days, with a few exceptions. Watt, et al., (1988) evaluated 5 days of quinine monotherapy, and Segal, et al, (1974) evaluated 6 days of quinine therapy. Metzger et al.(1995) used a higher than standard quinine dose , 12 mg/kg administered every 12 hours for 3 doses. However, adverse events were not reported by treatment group in this study. In studies submitted for evaluation of quinine combination therapy, only one directly compared different durations of quinine therapy (Bunnag et al., 1996). Additionally, adverse events were not reported by day of onset in most cases. Thus, no explorations for time dependency were performed for this review.

7.4.2.3. Explorations for drug-demographic interactions

None of the studies provided for evaluation of quinine efficacy and safety analyzed safety information by age, race, or gender.

7.4.2.4 Explorations for drug-disease interactions

None of the studies provided for evaluation of quinine efficacy and safety analyzed safety information by patient co-morbidities. Some overlap between symptoms of malaria, particularly severe malaria in the case of parenteral quinine use, and adverse events associated with quinine is expected.

7.4.2.5 Explorations for drug-drug interactions

Except for the antimalarial drugs used with quinine for combination therapy, concomitant medications were not reported or discussed in the studies provided for evaluation of quinine efficacy and safety.

Medical Officer Comments: Several studies compared the efficacy quinine monotherapy with quinine in combination with tetracycline, doxycycline, or clindamycin. Although no

apparent differences were noted adverse event incidence or safety profile of quinine alone in comparison to quinine combination regimens, safety data was limited, and definitive conclusions could not be drawn from these studies.

7.4.3 Causality Determination

Only a few of the published studies provided for this NDA specifically reported drug-related adverse events. In the other studies, no attempt was made to attribute adverse events to study drugs. In the pharmacokinetic studies sponsored by the applicant, the investigator assessed the relationship of adverse events to quinine sulfate. There were no serious adverse events or deaths in these studies, and case report forms were further reviewed by the medical officer for two subjects who experienced syncope in these studies. It was determined that these events were probably not related to quinine.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen of quinine sulfate 648 mg every 8 hours for 7 days appears to be appropriate for the treatment of uncomplicated *P. falciparum* malaria based on the studies of oral quinine monotherapy and combination therapy submitted for this NDA.

Quinine has a low therapeutic index, and plasma concentrations > 10 mg/L have been associated with toxicity. However, as shown in these studies, serious quinine toxicity appears to be relatively uncommon in patients with malaria. Most patients with malaria who receive quinine experience some degree of cinchonism, which is usually reversible. Hypersensitivity reactions are unpredictable and idiosyncratic, and may occur with low or single doses of quinine; while serious cardiovascular adverse events may be dose-related, occurring at higher plasma quinine concentrations.

*Medical Officer Comments: The proposed dose of quinine sulfate for treatment of uncomplicated *P. falciparum* malaria is similar to that recommended by the CDC treatment guidelines for chloroquine-resistant (or unknown resistance) *P. falciparum* malaria (quinine sulfate 650 mg salt or 542 mg base po tid for 3-7 days in combination with an antimicrobial agent, doxycycline, tetracycline, or clindamycin (CDC 2004 Guidelines for Treatment of Malaria in the U.S.). The studies submitted for this NDA support a 7-day duration for quinine monotherapy or combination therapy with an antimicrobial agent.*

Based on pharmacokinetic studies in otherwise healthy patients with mild to moderate hepatic impairment, no dosage adjustment is necessary for quinine sulfate; however, in patients with severe chronic renal failure AUC and C_{max} for quinine is increased, and dosage adjustment is required (see Clinical Pharmacology review). Similar pharmacokinetic studies were not done in patients with severe hepatic dysfunction, or in patients with uncomplicated malaria with renal or

hepatic disease. The following labeling recommendations were proposed regarding quinine sulfate dosing in patients with renal or hepatic impairment:

“For patients with hepatic impairment:

In otherwise healthy subjects with Child-Pugh B hepatic impairment, the AUC of quinine increased by 55% compared to subjects with normal liver function. In patients with mild to moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively), dosage reduction is not warranted but patients should be monitored closely for adverse reactions associated with quinine (See CLINICAL PHARMACOLOGY /Special Populations.) The effects of severe hepatic impairment (Child-Pugh C) on the safety and pharmacokinetics of quinine sulfate are not known.”

“For patients with renal impairment:

In otherwise subjects with severe chronic renal failure not receiving any form of dialysis (mean serum creatinine = 9.6 mg/dL), the median plasma quinine exposure (AUC) increased by 195% compared to subjects with normal renal function. In patients with severe chronic renal failure,

Although the pharmacokinetics of quinine are similar in adults and children, ages 1.5 to 12 years old, pediatric dosing recommendations were not made in the proposed label because further information on the safety and efficacy of quinine sulfate for treatment of *P. falciparum* malaria is required to approve a pediatric indication. The following dosage recommendations on quinine sulfate dosage and administration were proposed for the final product labeling:

*“For treatment of uncomplicated *P. falciparum* malaria in adults, the dosage is 648 mg (two capsules) every 8 hours for 7 days. (See Clinical Studies)”*

8.2 Drug-Drug Interactions

Quinine is metabolized by the cytochrome P450 system in the liver, mainly via CYP3A4, and to a less extent CYP 2C19. Thus, drugs that affect the activity of CYP3A4 may alter plasma quinine concentrations. Additionally, *in vitro* and *in vivo* evidence collectively suggests that quinine has the potential to influence the metabolism of many other drugs that are substrates of CYP3A4 and CYP2D6. See Clinical Pharmacology Review by Dr. Gerlie Gieser for further details.

Drugs known to interfere with quinine sulfate absorption include antacids containing aluminum or magnesium. Drugs known to increase quinine exposure include cimetidine, ketoconazole, tetracycline, troleandomycin, and the urinary alkalizers, acetazolamide, and sodium bicarbonate; while rifampin, a potent CYP3A4 inducer, is known to decrease quinine exposure. Quinine sulfate is known to increase levels of carbamazepine, and phenobarbital, astemizole,

cisapride, digoxin, and desipramine. We have proposed changes to the proposed label, expanding the section on drug interactions to describe these interactions or potential interactions in detail.

Important pharmacodynamic interactions with quinine have also been reported. Quinine, like its diastereomer, quinidine, has antiarrhythmic properties, and has been shown to prolong the QT interval when administered orally or parenterally, in healthy individuals, in patients with malaria, and in patients receiving quinine for other indications. Clinical studies have demonstrated increased QT intervals in patients who received concomitant quinine and mefloquine (Na-Bangchang, et al., 1999). *In vitro* studies demonstrated that quinine inhibited the metabolism of halofantrine via cytochrome P450 CYP 3A4 (). Therefore, quinine could potentiate the cardiotoxic effects of halofantrine, including QT prolongation and potentially fatal cardiac arrhythmias such as torsades de pointes and ventricular fibrillation. We have proposed a WARNING in the final product label regarding concomitant use of mefloquine or halofantrine with quinine sulfate.

Although not specifically studied, quinine use should also be avoided with concomitant class I antiarrhythmic agents, such as quinidine, procainamide, or disopyramide and III antiarrhythmic agents, such as amiodarone, sotalol, and dofetilide), and with any medication known to cause QT prolongation. Case reports in the published literature and from the AERS database describe QT prolongation and torsades de pointes associated with quinine with concomitant astemizole. As noted above, there is a pharmacokinetic interaction between quinine and astemizole, resulting in increased plasma levels of astemizole. Similar interactions of quinine with other drugs known to cause QT prolongation, such as cisapride, terfenadine, and others could potentially result in serious or potentially fatal ventricular dysrhythmias. We have proposed a statement in the PRECAUTIONS section of the final product label regarding concomitant use of quinine sulfate with drugs known to cause QT prolongation.

Quinine has effects on skeletal muscle, namely, neuromuscular blocking activity, and could potentiate the activity of neuromuscular blocking agents, such as tubocurarine, succinylcholine, pancuronium, and others. We have proposed wording in the Warnings section of the final product label regarding concomitant administration of drugs with neuromuscular blocking activity and quinine sulfate.

8.3 Special Populations

Pregnancy

P. falciparum malaria can cause substantial morbidity and mortality in pregnant women and the fetus. Infection in non-immune pregnant women can result in spontaneous abortion or fetal loss, with a maternal mortality of approximately 10%, as reviewed by Phillips-Howard and Wood (1996). The applicant submitted one randomized, controlled, open-label study which compared efficacy of quinine monotherapy to a combination of mefloquine plus artesunate in Thai women in the second or third trimester of pregnancy (McGready, et al 2000). Cure was assessed at day 63 of follow-up, rather than the 28 day endpoint used in most of the other studies. Cure rates were 98% for the mefloquine-artesunate group (N=65 evaluable patients), and 67% for the quinine treatment group (N=41 evaluable patients). Patients were followed until delivery, and of

92 births, there were no stillbirths, congenital abnormalities, or differences in mean birthweight or estimated gestational age between treatment groups. There were no serious adverse events reported in the study, but the incidence of tinnitus and dizziness were higher in the quinine treatment group. The efficacy of quinine monotherapy in this study would be unacceptable for treatment of pregnant women with malaria. This is probably due to two factors, namely, the 63 day rather than 28 day endpoint used in this study could result in lower efficacy due to late recrudescence or reinfection, although the latter, as confirmed by polymerase chain reaction (PCR) was reported only in 2 patients. Secondly, the study was performed in an area of Thailand, known to have increased quinine (and mefloquine) resistance of *P. falciparum*.

A second randomized, controlled study performed in Thailand was identified in the published literature, which compared oral quinine sulfate to oral artesunate plus mefloquine (Bounyasong, 2001). In this study, pregnant women (at least 28 weeks gestational age) were treated with oral quinine 10 mg/kg q8h for 7 days (N=29), or 5 days oral artesunate plus 25 mg/kg mefloquine on day 6 (N=28). None of the evaluable patients had recrudescence within 28 days. Fever and parasite clearance times were significantly shorter in the mefloquine+artesunate group, and neonatal birthweight, Apgar score at 1 minute were significantly lower in the quinine treatment group. There was no difference between treatment groups in the incidence of intrauterine growth retardation, or the gestational age at birth, and no congenital abnormalities were reported in either group. Adverse events were more frequent in the quinine treatment group. Those events more common in women treated with quinine than those treated with mefloquine+artesunate were nausea, vomiting, vertigo, tinnitus, and hypoglycemia. Additionally, the mean hematocrit at the end of treatment was significantly lower in patients who received quinine than the comparator regimen.

An additional randomized, controlled study (McGready, et al., 2001), which evaluated oral quinine plus clindamycin (7 days treatment) in comparison to oral artesunate (7 days treatment), was identified in a literature search by the medical officer. In this study, pregnant women in the second or third trimester of pregnancy were evaluated for efficacy and safety of the antimalarial treatments. Treatment failed, defined as parasite (*P. falciparum*) recrudescence (confirmed by parasite genotyping), at the time of delivery or 42 days after treatment. There were no treatment failures in evaluable patients in either treatment group. No serious adverse events were reported for either treatment group, and there was no significant difference in the adverse event profile, except for more tinnitus in the quinine-clindamycin group (45%) compared to the artesunate group (9%). Pregnancy outcomes were also evaluated in this study. Among the 115 singleton pregnancies followed, there was one stillbirth in each treatment group. There was one report of a congenital abnormality (midline epidermoid cyst) in the quinine-clindamycin group, and none in the artesunate group. There was no difference in mean birthweight, estimated gestational age, or proportion of infants with low birthweight.

Safety issues with quinine in pregnancy include hypoglycemia, caused by increased insulin secretion by pancreatic beta cells. Pregnant women, many of whom have altered glucose homeostasis, appear to be particularly vulnerable to quinine's effect on insulin production. Earlier literature suggested that quinine was associated with increased stillbirths, spontaneous abortion, intrauterine growth retardation, low-birthweight, or congenital abnormalities (mainly

deafness and optic nerve hypoplasia). Additionally, as described by the Pharmacology/Toxicology reviewer, Dr. Steven Kunder, teratogenic effects have been reported in several animal species (rabbits, guinea pigs, and chinchillas), but not in others (mice, rats, dogs, and monkeys). However, as reviewed by Dr. Gerard Nahum, a Medical Officer with the Pregnancy and Lactation Team, recent epidemiological studies did not show any increased increased of these events in women who had received quinine at some time during pregnancy. The following statement regarding the use of quinine in pregnancy is proposed for the final product labeling:

“Quinine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The risks and benefits of alternative treatments should be considered. If quinine sulfate is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus”.

Quinine crosses the placenta and gives measureable blood levels in the fetus. In 8 women who delivered live infants 1 to 6 days after starting quinine therapy, placental cord plasma quinine concentrations were between 1.0 and 4.6 mg/l (mean 2.4 mg/l) and the mean (\pm SD) ratio of cord plasma to maternal plasma quinine concentrations was 0.32 ± 0.14 . Quinine levels in the fetus may not be therapeutic. If congenital malaria is suspected after delivery, the infant should be evaluated and treated appropriately. We have proposed this information be stated in the Pregnancy section of the proposed label as follows:

*“Quinine crosses the placenta and gives measurable blood concentrations in the fetus. In 8 women who delivered live infants 1 to 6 days after starting quinine therapy, placental cord plasma quinine concentrations were between 1.0 and 4.6 mg/l (mean 2.4 mg/l) and the mean (\pm SD) ratio of cord plasma to maternal plasma quinine concentrations was 0.32 ± 0.14 . (See **CLINICAL PHARMACOLOGY**).”*

“Quinine levels in the fetus may not be therapeutic. If congenital malaria is suspected after delivery, the infant should be evaluated and treated appropriately.”

At doses several times the proposed dose for treatment of malaria, quinine has been shown to may stimulate the pregnant uterus. However, there is no evidence that quinine causes uterine contractions at the doses used for treatment of malaria. This is stated in the proposed label under the heading, Labor and Delivery, as follows:

“Labor and Delivery: There is no evidence that quinine causes uterine contractions at the doses recommended for the treatment of malaria. In doses several-times higher than those used to treat malaria, quinine may stimulate the pregnant uterus.”

The applicant has proposed that quinine sulfate receive a pregnancy category C in the product label. After consultation with the Pregnancy and Lactation Team, we have proposed that quinine sulfate receive a pregnancy category C based on our risk/benefit assessment. The risks associated with quinine treatment appear relatively low in comparison to the risk of significant morbidity

and mortality associated with *P. falciparum* malaria in non-immune pregnant women and fetus. Additionally, in areas of multidrug parasite resistance, there are few treatment options, and quinine is still effective in some locations.

Quinine is also secreted in the breast milk of women. There is limited information on the safety of quinine in breastfed infants. In one pharmacokinetic study, quinine levels in breast milk were approximately 30% of the maternal plasma concentration; and it was estimated that infants received 1.5 to 3 mg per day of quinine via breast milk. No quinine-associated toxicities were reported in the 25 infants in this study. We have proposed the following statement in the final product labeling under PRECAUTIONS:

“Nursing Mothers: There is limited information on the safety of quinine in breastfed infants. No toxicity was reported in infants in a single study where oral quinine sulfate (10 mg/kg every 8 hours for 1 to 10 days) was administered to 25 lactating women. It is estimated from this study that breastfed infants would receive less than 2 to 3 mg per day of quinine base (< 0.4% of the maternal dose) via breast milk. (See CLINICAL PHARMACOLOGY.)”

“Although quinine is generally considered compatible with breastfeeding, the risks and benefits to infant and mother should be assessed”.

“If malaria is suspected in the infant, appropriate evaluation and treatment should be provided. Plasma quinine levels may not be therapeutic in infants of nursing mothers receiving quinine.”

Pediatrics

P. falciparum malaria causes substantial morbidity and mortality in children, particularly those who are non-immune, i.e. younger children, and those who do not live in hyperendemic areas. Many of the studies submitted for this NDA which evaluated oral quinine sulfate for the treatment of uncomplicated *P. falciparum* malaria included pediatric patients; however efficacy and safety results in these studies were not reported separately for children and adults. Two pediatric studies of oral quinine monotherapy or combination therapy for uncomplicated *P. falciparum* malaria were identified in the literature by the medical officer, and were included in this review. Additionally, several of the supportive studies on treatment of severe malaria with parenteral quinine were pediatric studies.

The safety and efficacy of oral quinine sulfate for treatment of uncomplicated *P. falciparum* malaria in children ≥ 16 years of age can be extrapolated from adult data. Additionally, although the dosing of quinine sulfate may be similar to adult dosing based on pharmacokinetic studies in the literature, the current formulation of quinine sulfate (capsules for oral administration) may not be appropriate for young children, and a specific pediatric formulation may be required. Alternatively, bioequivalence studies may be required to evaluate effects of providing quinine sulfate capsule contents with food or liquid.

Elderly Patients

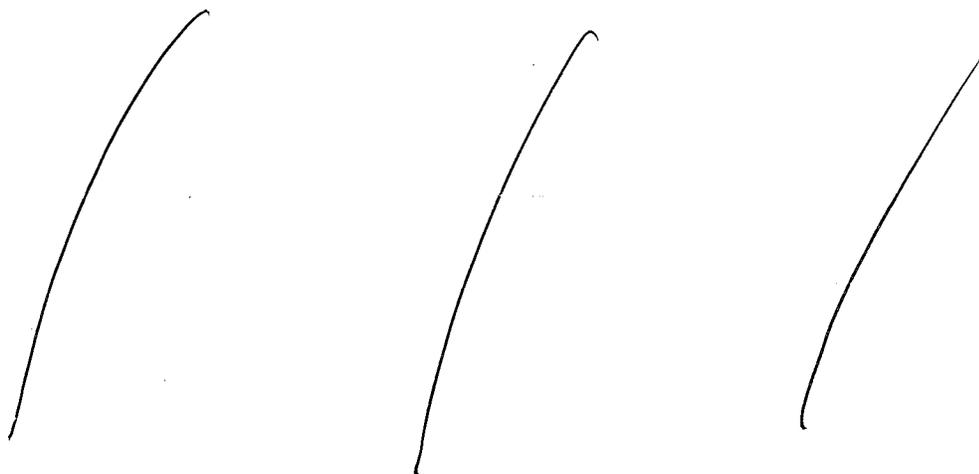
None of the studies submitted for this application evaluated efficacy and safety of quinine sulfate in elderly patients separately from younger patients. Pharmacokinetic studies revealed some differences in quinine clearance between elderly and younger patients; however, as reviewed by Clinical Pharmacology, no dosage adjustment is necessary in the elderly. In order to further evaluate the safety of quinine sulfate in elderly patients, the applicant has agreed to perform a twice-yearly analysis of reported postmarketing adverse events by age, indication for quinine use, and potential relationship to quinine, as part of the postmarketing commitments. The following statement has been proposed regarding geriatric use for the final product labeling:

“Geriatric Use: Clinical studies of quinine sulfate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.”

8.4 Pediatrics

Although quinine sulfate has been used for hundreds of years worldwide to treat *P. falciparum* malaria in adults and children, and some of the studies submitted for this application included pediatric patients, sufficient information was not available in the submission to determine the safety and efficacy of quinine sulfate oral capsules for the treatment of *P. falciparum* malaria in children. The following wording regarding pediatric use was proposed for the final product labeling:

“Pediatric Use: The safety and efficacy of quinine sulfate in pediatric patients under the age of 16 has not been established.”



8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

This submission was a 505 (b) 2 application, and the applicant provided a review of efficacy from the published clinical studies of oral quinine monotherapy and combination therapy in the treatment of uncomplicated *P. falciparum* malaria, and a literature review on quinine safety. The applicant's information was supplemented by literature reviews performed by the medical officer and statistical reviewer, and has been incorporated into this review. See References section for listing of specific references included in this review.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan. See section 9.3.1 below for the Division's recommended risk management plan.

8.8 Other Relevant Materials

See consultations from ODS, DSRCS, DDMAC, DMETS, and the Pregnancy Labeling Team attached to this review in Appendix, section 10. 3.

9 OVERALL ASSESSMENT

9.1 Conclusions

In areas where multi-drug resistance of *P. falciparum* is increasing, such as Southeast Asia, cure rates with 7 days of oral quinine monotherapy were at least 80%; while cure rates for 7 days of oral quinine combined with an antimicrobial agent (tetracycline or clindamycin) were greater than 90%. In areas where resistance of *P. falciparum* was not as widespread, cure rates with 7 days of quinine monotherapy ranged from 86 to 100%.

Completion of a 7 day oral quinine treatment regimen may be limited by drug intolerance, and shorter courses (3 days) of quinine combination therapy have been used. However, the published data from randomized, controlled clinical trials for shorter regimens of oral quinine in conjunction with tetracycline, doxycycline, or clindamycin for treatment of uncomplicated *P. falciparum* malaria is limited, and the shorter course combination regimens may not be as effective as the longer treatment regimens.

The safety of quinine sulfate is reviewed in the Integrated Summary of Safety, in section 7 of this review. In brief, quinine has a well-known toxicity profile. The most common adverse events with quinine are a cluster of symptoms, referred to as cinchonism. Symptoms of mild cinchonism

include headache, vasodilatation, sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, and visual disturbances. More severe symptoms of cinchonism are vomiting, diarrhea, abdominal pain, deafness, blindness, and disturbances of cardiac rhythm or conduction. Most symptoms of cinchonism are reversible and resolve with quinine discontinuation.

Quinine, like quinidine, its diastereomer, has antiarrhythmic properties, and can cause QT prolongation, which can increase the risk of potentially fatal cardiac arrhythmias such as torsades de pointes and ventricular fibrillation. Other significant safety concerns with quinine are hypersensitivity reactions, hypoglycemia and drug interactions. Hypotension appears to be associated mainly with parenteral quinine administration. These issues are described in detail in the ISS, section 7. Appropriate Warnings, Precautions, and Contraindications have been proposed for the final product label

9.2 Recommendation on Regulatory Action

APPROVAL is recommended for quinine sulfate oral capsules for the treatment of uncomplicated *P. falciparum* malaria.

P. falciparum malaria is a serious infection, particularly in non-immune individuals such as travelers to endemic areas. Severe or complicated *P. falciparum* malaria is associated with significant morbidity and mortality. Non-immune patients with uncomplicated *P. falciparum* malaria can rapidly progress to severe or complicated infection if not treated appropriately. *P. falciparum* malaria also results in significant morbidity and mortality in pregnant women and children, particularly in endemic areas. Resistance of this parasite to other antimalarial drugs is increasing worldwide. Resistance to chloroquine and sulfadoxine-pyrimethamine is now widespread, and resistance to mefloquine is well-documented in some parts of the world, especially Southeast Asia. Quinine resistance has also been described in some areas of South America, Southeast Asia and Bangladesh.

Most patients treated with quinine experience cinchonism, a symptom complex including headache, nausea, tinnitus, vertigo or dizziness, mild hearing impairment, and visual disturbances. These symptoms usually resolve after quinine discontinuation. More severe symptoms of cinchonism can also occur, usually with higher doses of quinine than those used for treatment of malaria, including vomiting, diarrhea, abdominal pain, disturbances of cardiac rhythm or conduction, blindness and deafness. Quinine is also associated with QT prolongation, and rarely with torsades de pointes and other serious cardiac arrhythmias. Serious hypersensitivity reactions to quinine include anaphylaxis, angioedema, serious skin reactions, as well as a number of idiosyncratic reactions thought to be due to development of quinine-dependent antibodies. These include thrombocytopenia, thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, disseminated intravascular coagulation, granulomatous hepatitis, and others. Quinine also has a number of important drug-drug interactions. The proposed label clearly states the indications for use of quinine sulfate as well as Contraindications, Warnings, Precautions, Drug-Interactions, Adverse Events (see Proposed Label in section 10.2)

For patients with *P. falciparum* malaria, the benefit of treatment with quinine is likely to outweigh the risk of serious adverse reactions associated with this drug. In this country, most cases of *P. falciparum* malaria occur in returned travelers, most of whom are healthy adults under the age of 65, and the risks of quinine sulfate use in patients with malaria are addressed in the proposed label. However, the use of quinine sulfate for off-label use such as nocturnal leg cramps cannot be supported based on the current risk/benefit assessment. Many, if not most patients who receive quinine for leg cramps are elderly, have multiple co-morbidities, or take multiple concomitant medications. All these factors potentially put them at increased risk for quinine toxicity. Additionally, the efficacy of quinine sulfate in the treatment of nocturnal leg cramps has not been established by adequate and well-controlled studies. Thus, we have proposed a CONTRAINDICATION and WARNING for use of quinine sulfate for treatment or prevention of nocturnal leg cramps. This issue was addressed previously by the Agency in a 1994 final rule and a Federal Register notice in 1995, prohibiting the marketing of quinine for treatment and/or prevention of leg cramps (21 CFR 310.546).

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Division has proposed the following Risk Management Plan to ensure the safe and effective use of quinine sulfate. This plan includes proposed postmarketing commitments detailed further in section 9.3.2.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 NDA 21-799}
 Quinine Sulfate Capsules USP, 324 mg

Table 98: Proposed Risk Management Program

Safety Issues	Risk Management Plan
Quinine for Treatment/prevention of Nocturnal Leg Cramps	Warning in Label, Patient Package Insert
	Educational Program
	“Dear Doctor” Letter
	Postmarketing surveillance: twice-yearly analysis of adverse event reports
QT prolongation, torsades de pointes, ventricular arrhythmias	Contraindications, Warning Postmarketing surveillance
Myasthenia gravis	Contraindications, Warning
G6PD deficiency	Contraindications, Warning
Optic neuritis	Contraindications, Adverse Events
Quinine use in elderly patients, or conditions known to cause QT prolongation	Warning
Hypersensitivity (including anaphylaxis, angioedema, serious rashes, thrombocytopenia, TTP-HUS, blackwater fever, and other events)	Contraindications, Warnings, Precautions Postmarketing surveillance
Drug Interactions: Mefloquine , halofantrine, rifampin, macrolide antibiotics such as erythromycin, neuromuscular blocking agents, astemizole, antiarrhythmic agents, and others	Warnings, Precautions/Drug Interactions
Atrial fibrillation and flutter	Precaution
Hypoglycemia	Precaution
Additional Drug Interactions: antacids, H2-receptor blockers, anticonvulsants, desipramine and CYP2D6 substrates, digoxin, warfarin	Precaution/Drug Interactions
Pregnancy	Labeled as Pregnancy Category C Postmarketing surveillance for congenital abnormalities
Labor and Delivery (abortifacient)	Label states that in doses several times higher than those used to treat malaria, quinine may stimulate the pregnant uterus. Postmarketing surveillance for spontaneous abortions in pregnant women
Nursing Mothers	Label notes estimated dose of quinine received by nursing infants (<2-3 mg per day) Postmarketing surveillance for serious adverse events in infants of nursing mothers receiving quinine
Additional Serious Adverse Reactions (e.g. renal failure, hepatitis, blindness, deafness, and other serious adverse events)	Postmarketing surveillance

9.3.2 Required Phase 4 Commitments

The following postmarketing commitments have been proposed by DSPIDP and accepted by Applicant:

- 1. Develop a Risk Management Plan** to be implemented within one year of NDA approval that includes the following elements:

- An educational program directed at physicians and other health care providers regarding the safe and effective use of quinine sulfate for treatment of *Plasmodium falciparum* malaria.
- A written "Dear Doctor" Letter to physicians describing the favorable risk/benefit ratio of oral quinine sulfate for treatment of *P. falciparum* malaria; in contrast with the unfavorable risk/benefit ratio for treatment of nocturnal leg cramps.

2. Post-marketing Surveillance for Adverse Events:

Provide twice-yearly analysis of postmarketing adverse event data, including assessment of possible causal relationship of adverse events to quinine sulfate, analysis of adverse events by age (< 16, 16 to 65 and > 65 years old) and by indication for quinine use. These analyses are requested in addition to the required 15-day reporting for all serious adverse events and the required quarterly updates of post-marketing adverse events associated with oral quinine sulfate.

9.3.3 Other Phase 4 Requests

/ / / /

9.4 Labeling Review

We have proposed extensive changes in the following sections of the product label proposed by the applicant with the NDA submission on 13 October, 2004. These changes included the sections on Clinical Pharmacology, Microbiology, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage and Administration. We have also included a Clinical Studies Section, and created a Patient Package Insert. The final product label agreed upon with the applicant is shown in the Appendix, section 10.2. Additionally, DDMAC and DMETS were consulted regarding the proposed package insert and patient package insert, and made labeling recommendations. Consultations from these divisions are included in the Appendix, section 10. 3.

Some of the major changes to the proposed label include the following:

/ / /

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 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Review of Individual Randomized, Controlled Studies of Oral Quinine Monotherapy

Study 1: Watt G., Long GW, Padre LP, Alban P., Sangalang R., and Ranoa CP. Chloroquine and quinine: a randomized, double-blind comparison of efficacy and side effects in the treatment of Plasmodium falciparum malaria in the Phillipines. Trans. Royal Soc. Trop. Med. And Hygeine 1988; 82: 205-208

Study design: Randomized, double-blind study comparing 5 days of oral quinine (648 mg every 8 hours) to chloroquinine (600 mg first dose, then 300 mg 6 hours later, then 300 mg/day for 2 more days)

Study Location and Dates: Phillipines, study dates not specified

Study Objectives: To compare efficacy and "side effects" of oral quinine and chloroquine in adult Filipino males

Study Endpoints:

1. Fever clearance time
2. Parasite clearance time
3. Adverse event rates

Treatment Groups:

1. Chloroquine plus quinine placebo
2. Quinine plus chloroquine placebo

Inclusion Criteria:

1. Male patients \geq 16 years old with $>$ 1000 asexual P. falciparum parasites per μ l of blood
2. Informed consent

Exclusion Criteria:

1. Seriously ill patients
2. Acquisition of malaria outside the Phillipines
3. History of vomiting
4. Receipt of antimalarial drugs within the 3 weeks prior to hospital admission

Drug Product:

- Quinine was supplied as quinine sulfate, 324 mg per capsule (Henry Schein, Inc.).

- Chloroquine was supplied as chloroquine phosphate 300 mg base/tablet (Aralen®, Winthrop Laboratories).
- Quinine Placebo: gelatin capsules filled with sodium bicarbonate
- Chloroquine Placebo: Multivitamin tablets resembling chloroquine

Dosage Regimens:

Quinine: Quinine sulfate (648 mg orally every 8 hours) for 5 days, plus chloroquine placebo (2 tablets first dose, then one tablet 6 hours later, and one tablet daily for 2 more days).

Chloroquine: 600 mg first dose, then 300 mg 6 hours later, then 300 mg/day for 2 more days), plus quinine placebo (2 capsules every 8 hours for 5 days)

Concomitant Therapy:

Primaquine was given before hospital discharge (dose not specified). Other concomitant medications were not discussed in the publication.

Medical Officer Comments: The authors stated that primaquine was given before hospital discharge to prevent the possible transmission of chloroquine resistant strains. Presumably primaquine was given to patients of both treatment groups, although this was not specifically stated. Since primaquine has little effect on the asexual stage of P. falciparum, and because this species has no hepatic stage, the use of primaquine should not affect efficacy evaluation. Primaquine may reduce P. falciparum gametocytemia, thus reducing transmission.

Baseline Assessments:

- Routine biochemistry, hematology, and quantitative parasite counts
- History and physical examination
- *In vitro* sensitivity to chloroquine and quinine (defined as no parasite maturation to schizonts in the presence of 5-7 pmol of chloroquine and 64 pmol of quinine).

On Treatment Evaluation:

- Quantitative parasite counts twice daily
- Oral temperature recorded every 4 hours
- Physical examination daily
- Patients questioned about side effects daily
- Patients were discharged from the hospital if there was an absence of asexual parasitemia on 2 days, if they were afebrile and if they felt well enough to return home.

Determination of Efficacy:

Time to fever resolution was defined as time from the first dose of study medication to the time when the temperature dropped and remained below 37.6°C.

Parasite clearance time was defined as number of hours between the smear taken on entry and the first smear demonstrating absence of asexual parasitemia.

Safety Evaluation:

Symptoms which occurred during treatment but not during the illness preceding hospital admission were considered side effects of study medication.

Statistical Methods: The two-tailed t-test was used to analyze data at baseline and for endpoints (fever and parasitological clearance time).

Results

Baseline Patient Demographic and Clinical Characteristics

Ten patients were enrolled in each treatment group. The baseline patient characteristics were similar between treatment groups, as shown in the following table. According to the authors, pretreatment laboratory values were comparable between treatment groups, but these data were not shown.

Table 1. Baseline Patient Characteristics (from Table 1, Watt, et al., 1988)

Patients Characteristic	Chloroquine N=10	Quinine sulfate N=10
Age (years) \pm SD (range)	30 \pm 11 (18-49)	28 \pm 11 (16-49)
Admission temperature ($^{\circ}$ C) \pm SD (range)	38.9 \pm 0.8 (37.6-40.0)	39.4 \pm 0.8 (37.7-40.4)
Mean weight (kg) \pm SD (range)	56 \pm 7 (46-68)	52 \pm 4 (47-57)
Mean parasite count (per μ l blood) \pm SD (range)	9333 \pm 3020 (1323-33900)	8710 \pm 2754 (1500-26381)

SD= standard deviation

Medical Officer Comments: The two treatment groups were similar relative to age, weight, baseline temperature, and mean parasite count. Notably, none of the patients had high levels of parasitemia (> 100,000 parasites/ μ l).

Baseline *in vitro* Sensitivity of *Plasmodium* isolates

Parasite growth was adequate to determine *in vitro* susceptibility to quinine in isolates from only 4/10 (40%) patients, and to chloroquine in isolates from only 5/10 (50%) patients. All 4 isolates from quinine-treated patients were quinine-sensitive *in vitro*; while only 1 of 5 isolates from chloroquine-treated patients was sensitive to chloroquine *in vitro*.

Patient Disposition: The authors did not discuss patient exclusion or withdrawal from the study.

Clinical Outcomes

Table 2. Fever and Parasite Clearance Time

Outcome Measure	Chloroquine	Quinine	p-value
Fever clearance time (hours) \pm SD	46.3 \pm 24.7	43.2 \pm 20.0	0.76
Parasite clearance time (hours) \pm SD	76.1 \pm 29.3	60.3 \pm 12.5	0.13

SD= standard deviation

Medical Officer Comments: *Although the time to fever resolution was similar for both treatment groups, the time to parasitological clearance was somewhat shorter in patients treated with quinine. Because the treatment groups were small, statistically significant differences between groups would not necessarily be expected.*

Although in vitro sensitivity does not necessarily predict in vivo drug efficacy, it is notable that efficacy (based on the fever and parasitological clearance times) did not differ significantly between the two treatment groups, even though only 20% of the Plasmodium isolates obtained from patient in the chloroquine treatment group were resistant to chloroquine at baseline; while all of those isolated from patients in the quinine treatment group were sensitive to quinine at baseline. However, if the parasites were chloroquine-resistant, as suggested by the in vitro susceptibility data, the parasite and fever clearance times observed in this study in the chloroquine treatment group may have been longer than if the parasites had been chloroquine sensitive. In other words, this wasn't really a fair comparison of treatments- quinine treatment for quinine-sensitive parasites, versus chloroquine treatment for parasites which were mostly chloroquine resistant in vitro. According to the authors, approximately 6% of P. falciparum isolates in the Phillipines were found to be chloroquine-resistant in vitro in the early 1980's ; while only 1.5% of isolates were quinine resistant.

Efficacy Conclusions

1. Fever clearance time was similar among patients who received quinine or chloroquine.
2. Parasite clearance time was somewhat shorter among patients who received quinine than those who received chloroquine. This difference was not statistically significant, however.
3. Because of differences in baseline *in vitro* sensitivity to quinine and chloroquine, conclusions regarding comparative efficacy of these two drugs may be limited.
4. No conclusions can be drawn regarding cure for this NDA review, because these patients were not followed for 28 days to evaluate recrudescence.

Safety Data

Adverse events were reported for 4/10 (40%) patients in each treatment group. Adverse events reported in patients who received quinine included vomiting (1 patient), dizziness (1 patient), tinnitus (2 patients), diarrhea (2 patients). Adverse events reported in patients who received chloroquine included vomiting (1 patient), diarrhea (2 patients), and pruritus (1 patient).

Medical Officer Comments: *Although the number of patients and adverse events were small, tinnitus occurred only in the quinine treatment group; while pruritus was reported only in the chloroquine group.*

Safety Conclusions: Because the number of patients was so small in this preliminary study, conclusions regarding comparative safety are limited.

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

Study Design: Randomized, open-label study of efficacy of primaquine in combination with quinine or artesunate.

Study Location and Dates: Thailand; dates not specified

Study Objectives: To assess the value of adding primaquine to artesunate or quinine compared with the standard 7-day oral quinine-tetracycline regimen.

Study Endpoints:

- Fever clearance time
- Parasite clearance time
- Parasite reduction ratio at 48 hours
- Gametocyte clearance time
- Clinical outcome at 28 days (overall cure rate)
- Time to onset of recrudescence or to onset of *P. vivax* infection

Inclusion Criteria:

- Adult, male patients hospitalized with acute uncomplicated *P. falciparum* malaria.
- Informed consent

Exclusion Criteria:

- Severe malaria
- Patients with mixed malaria infections at baseline
- History of drug hypersensitivity
- Receipt of antimalarial medications within previous 48 hours
- Positive urine screening test for sulfonamides or 4-aminoquinolones
- G6PD deficiency (excluded from treatment with primaquine)

Drug Products:

Quinine: Quinine sulfate, 300 mg (salt)/tablet (Thai Government Pharmaceutical Organization)

Tetracycline: Tetracycline 250 mg/tablet (Thai Government Pharmaceutical Organization)

Primaquine: primaquine 15 mg (base)/tablet (Thai Government Pharmaceutical Organization)
 Artesunate 50 mg (salt)/table (Guilin No. 1 Factory, Guangxi, People's Republic of China)

Table. 1. Treatment Groups and Dosing Regimens

Treatment Group	Antimalarial drugs	Dose	Frequency of doses	Duration of treatment
A	Quinine sulfate	10 mg (salt)/kg	3 times daily	7 days
B	Quinine sulfate+ tetracycline	10 mg (salt)/kg quinine + 4 mg/kg tetracycline	3 times daily (Q) 4 times daily (T)	7 days
C	Quinine sulfate + primaquine	10 mg (salt)/kg quinine + 0.25 mg (base)/kg primaquine	3 times daily (Q) Once daily (P)	7 days
D	Quinine sulfate + primaquine	10 mg (salt)/kg quinine + 0.50 mg (base)/kg primaquine	3 times daily (Q) Once daily (P)	7 days
E	Artesunate	3.3 mg/kg first day, then 1.65 mg/kg/day	Once daily	7 days
F	Artesunate +primaquine	3.3 mg/kg first day, then 1.65 mg/kg/day artesunate +0.50 mg (base)/kg primaquine	Once daily	7 days

Q= quinine sulfate; T= tetracycline; P= primaquine

Concomitant Therapy

Acetaminophen (0.5 to 1.0 grams every 4 hours) was administered for fever > 38°C. No other concomitant medications were discussed.

Medical Officer Comments: Routine use of acetaminophen could affect the fever clearance time. Presumably all patients with fever received acetaminophen, although this is not specifically stated in the publication.

Baseline Assessments:

- Diagnosis confirmed with thick and thin smears
- Routine serum biochemistry and hematology tests

On-Treatment Evaluation:

- Vital signs were recorded every 4 hours until fever resolution, then every 6-12 hours
- Parasite and gametocyte counts were measured every 12 hours in thin or thick films until clearance, then daily for 28 days.
- Routine biochemical and hematological tests were repeated on day 7, 14, 21, and 28.

Determination of Efficacy

- Fever clearance time was defined as time for temperature to fall and remain below 37.5°C for 48 hours.
- Parasite clearance time was defined as time for interval from the start of antimalarial treatment until the asexual parasite count fell below detectable levels on a peripheral blood smear.
- Parasite reduction ratio was defined as parasite count on admission/parasite count at 48 hours.
- Gametocyte clearance time was the interval from the first detection to the last detection of gametocytes on a peripheral blood smear. If gametocytemia was intermittent, then intervals without gametocytes were subtracted from the gametocyte clearance time.
- Gametocyte carriage was defined as the total number of hours for each patient during which gametocytemia was detectable.
- Reappearance of infection was determined for patients who remained in Bangkok (in hospital or at home) for at least 28 days.

Safety Evaluation

Methods for obtaining safety data were not described in the publication.

Statistical Analysis

Data from treatment groups were compared by one-way analysis of variance with post-hoc adjustment for multiple comparisons using the Bonferroni correction. Nonparametric data were compared by the Kruskal-Wallis test. Categorical data were compared by Fisher's exact test or the chi-square test with Yates' correction. Cumulative cure rates were determined by Kaplan-Meier survival analysis and were compared with the log rank test. Gametocytemia rates were compared by stratified analysis with the Mantel-Haenszel test.

Study Results

Baseline Patient Characteristics

Only adult male (ages 14-62 years old for all treatment groups combined) patients were enrolled in this study. No significant difference in patient age was noted; however the level of baseline parasitemia was significantly higher in the artesunate treatment group, as shown in the following table.

Table 2. Baseline Patient Demographics and Parasite Count

Parameter	Quinine N=30	Quinine + tetracycline N=30	Quinine + primaquine (0.25 mg/day) N=29)	Quinine + primaquine (0.5 mg/day) N=37	Artesunate N=23	Artesunate + primaquine N=27
Mean age ± SD (years)	24 ± 8	27 ± 9	25 ± 9	24 ± 10	23 ± 8	24 ± 8
Geometric Mean Parasite Count Count/μl (range)	9,004 (234- 116,054)	14,006 (630- 231,104)	10,306 (168- 229,094)	17,637 (405- 200,458)	64,449 (321- 569,722)	26,566 (800- 350,173)

SD = standard deviation

Medical Officer Comments: These patients had a wide range of baseline parasite counts. The actual distribution of parasite counts or standard deviation of the mean count within each treatment group was not provided, so whether the higher mean count for the artesunate group was due to a single outlier is not known. The authors note, however, that the difference in baseline parasite count for the artesunate group was statistically significant in comparison to the other treatment groups.

Clinical Outcomes

As shown in the following table, for the quinine-containing regimens, fever clearance time was shorter with quinine plus tetracycline than with quinine alone, or quinine plus primaquine. This difference was statistically significant for the quinine plus tetracycline group (p value = < 0.001). The mean parasite clearance time was similar for all the quinine-containing regimens; while the PCT was significantly shorter for the combined artesunate groups (65 ± 18 hours) in comparison to the combined quinine treatment groups (79 ± 21 hours) (p-value = < 0.001). The parasite reduction ratio at 48 hours was significantly higher for the combined artesunate groups than the combined quinine groups (p=< 0.001); while there was no significant difference between the quinine subgroups or the artesunate subgroups.

Table 3. Fever and Parasite Clearance Times

Endpoint	Quinine N=30	Quinine + tetracycline N=30	Quinine + primaquine (0.25 mg/day) N=29)	Quinine + primaquine (0.5 mg/day) N=37	Artesunate N=23	Artesunate + primaquine N=27
Median FCT (hours)(range)	63 (7-152)	33 (8-117)	48 (8-152)	60 (7-154)	34 (7-180)	32 (8-164)
Mean PCT ± SD (hours)	80 ± 26	81 ± 19	78 ± 23	79 ± 19	69 ± 19	63 ± 18
Median PRR48 (range)	35 (<1-3,38)	176 (<1-8,895)	139 (1.3-4,270)	221 (<1-2,052)	759 (59-5,801)	1,374 (108- 12,521)

FCT = fever clearance time; PCT = parasite clearance time; PRR48 = parasite reduction ratio at 48 hours

SD= standard deviation

Medical Officer Comments: As expected, the addition of primaquine did not affect parasite clearance time when combined with either quinine or artesunate. Primaquine is not considered to have a significant effect on the asexual blood stage of P. falciparum. Primaquine, however, was shown in this study to shorten the duration of gametocyte carriage in combination with either quinine or artesunate in this study, and may decrease transmission of the parasite.

In this study, clinical cure rates were assessed by parasitological data alone, although the authors state that clinical recovery followed treatment in all patients and none developed severe malaria. Patients who did not have recrudescence of *P. falciparum* by day 28 were considered cured. Rates of *P. falciparum* recrudescence and cure, as well as the rate of *P. vivax* emergence post-treatment are shown in the table below.

Table 4. Study Completion, Cure Rates and Recrudescence of *P. falciparum* or occurrence of *P. vivax* within 28 days of starting Treatment (Evlauable Population)

Parameter	Quinine N=30	Quinine + tetracycline N=30	Quinine + primaquine (0.25 mg/day) N=29	Quinine + primaquine (0.5 mg/day) N=37	Artesunate N=23	Artesunate + primaquine N=27
Study Completion n (%)	25 (83.3)	22 (73.3)	18 (62.1)	31 (83.8)	21 (91.3)	25 (92.6)
<i>P. falciparum</i> recrudescence n (%)*	4 (16.0)	0	5 (28.0)	8 (25.8)†	2 (9.5)	4 (14.8)
<i>P. falciparum</i> cure rate n (%)**	21 (84.0)	22 (100)	13 (72.2)	23 (74.2)	19 (90.5)	21 (84.0)
<i>P. vivax</i> appearance n (%)*	2 (8.0)	4 (18.2)	3 (17)	5 (16)	5 (23.8)	3 (12.0)

* calculated using number of patients who completed 28 day study as denominator

** cure rate was defined as no subsequent appearance of *P. falciparum*, calculated using number of patients who completed 28 day study as denominator and number of patients with recrudescence minus number of patients who completed study as cured (full data not shown in publication)

†The authors reported 8 patients (7%) with recrudescence, which was most likely an error.

Medical Officer Comments: *It would have been useful to know if P. falciparum recurrence was early or late, but that information was not provided. Additionally, patients lost to follow-up should have been counted as treatment failures, rather than being excluded, as they were in this analysis. If patients lost-to-follow-up are counted as failures, the cure rates would be 21/30 (70%) for quinine alone, 22/30 (73.3%) for quinine plus tetracycline, 13/29 (44.8%) for quinine plus primaquine 0.25 mg/kg/day, 23/37 (62.2%) for quinine plus primaquine 0.5 mg/kg/day, 19/23 (82.6%) for artesunate alone, and 21/27 (77.8%) for artesunate plus primaquine. In this analysis, the P. falciparum cure rates were similar with quinine alone or quinine plus tetracycline, and lower with the quinine plus primaquine regimens. Interestingly, the use of primaquine in combination with quinine did not reduce the incidence of P. vivax emergence during the 28 day follow-up period. Primaquine is active against the hepatic phase (hypnozoite phase) of P. vivax, preventing recurrence. Patients with P. vivax infection at baseline were to have been excluded from the study, so whether these data indicate a new infection or recurrence of an occult P. vivax infection, is not clear.*

Gametocyte Clearance Time and Duration of Carriage

Although these endpoints were evaluated in this study, they are not discussed further for this review because gametocytemia is more relevant to malaria transmission than to primary treatment.

Clinical Outcomes- Conclusions

1. Among the quinine-containing regimens, clinical cure (assessed by parasitological cure) was highest with quinine plus tetracycline as determined by the authors, excluding patients lost to follow-up. However, when patients who were lost to follow-up were counted as treatment failures, cure rates for quinine alone, and quinine plus tetracycline were similar.
2. When quinine-containing regimens were compared to the artesunate treatment groups, no significant differences in cure rates were observed.
3. Fever clearance time was shortest with quinine plus tetracycline or the artesunate-containing regimens.
4. Parasite clearance time was similar among all the quinine-containing regimens, and was shortest with the artesunate treatment regimens. Parasite reduction ratios at 48 hours were also highest for the artesunate-containing regimens.

Safety Data

As stated in the publication, none of the patients developed rashes or other serious adverse events. No further safety data was provided.

Study 3: Mueller MK, Runyambo N, Wagner I, Borrmann S, Dietz K, Heide L. 2004. Randomized controlled trial of a traditional preparation of *Artemisia annua* (annual wormwood) in the treatment of malaria. R. Soc. Trop. Med Hg 2004; 98:318-321.

Study Design: Randomized open-label pilot study comparing oral quinine to *Artemisia* tea preparations for treatment of uncomplicated *P. falciparum* malaria

Study Objectives: To evaluate safety and efficacy of *Artemisia* tea preparations in treatment of *P. falciparum* malaria

Study Location and Dates: Democratic Republic of Congo; February, 2001 to December, 2001

Study Endpoints

Primary Endpoint: Cure rate on day 7 (proportion of patients with negative blood films on day 7)

Medical Officer Comments: Note that the primary endpoint is parasitological cure in this study.

Secondary Endpoints:

Cure rates on day 14, 28, and 35

Change in clinical symptoms

Treatment Groups:

1. A5 group: *Artemisia annua* tea 5 g herb/L (1 liter per day for 7 days)
2. A9 group: *Artemisia annua* tea 9 g herb/L (1 liter per day for 7 days)
3. Quinine group: quinine sulfate tablets (500 mg salt) 3 times daily for 7 days

Inclusion Criteria:

- *P. falciparum* parasitemia > 2000/ μ l
- Age \geq 18 years
- Residence in South Kivu Province for \geq 5 years
- At least one on the following symptoms: fever, chills, fatigue, vertigo, nausea, joint pain, vomiting, headache, abdominal pain, or diarrhea

Exclusion Criteria:

- Pregnancy or lactation
- Treatment for malaria within 2 weeks prior to recruitment
- Current treatment (modern or traditional) for other diseases
- Chronic and progressive or life-threatening diseases
- Positive urine test for chloroquine or quinine

Drug Products:

Artemisia tea: *Artemisia annua* L. cv. *Artemis* was cultivated, harvested, and dried at Tübingen University, Germany. Leaves were packaged, and sealed in plastic bags in doses of 5g or 9g. The artemisinin content of the dried plant material was 1.4%. The tea was prepared daily by the medical staff using standardized procedures.

Quinine: quinine sulfate tablets, 500 mg. No further information was provided in the publication.

Dosage Regimens:

See treatment groups above. The liter of *Artemisia* tea was divided into 4 doses of 250 mL each per day.

Concomitant Therapy

The authors did not discuss concomitant therapy.

Baseline Assessments:

- Parasite count
- Symptom assessment (see inclusion criteria)

On Treatment Evaluation:

- Pulse, blood pressure, temperature on days 3 and 7
- Assessment for clinical symptoms and adverse events on days 3 and 7, 14, 28 and 35
- Parasite count day 7, 14, 28, and 35

Determination of Efficacy:

- Cure rate (parasite-negative blood smear) on days 7, 14, 28, and 35
- Symptoms were assessed by standardized questionnaire
- Treatment failure was defined as development of severe malaria or danger signs, parasitemia on day 3 equal or higher than on day 0, parasitemia on day 7, and initial parasite clearance, followed by recurrence up to day 35.

Safety Evaluation

Adverse events were assessed using a standardized questionnaire on days 3, 7, 14, 28, and 35.

Statistical Methods:

The authors did not discuss statistical methods in the publication, although, confidence intervals were provided for day 7 cure rates.

Study Results

Baseline Patient Demographics and Clinical Characteristics

This data was not provided in the publication

Patient Disposition

Table 1. Patient Disposition in Study

Patient Disposition	A5 Group	A9 Group	Quinine
Enrolled	45	39	48
Excluded*	6	6	5
Evaluable day 7	39	33	43
Evaluable day 14	35	31	39
Evaluable day 28	32	30	36
Evaluable day 35	32	30	34

*reasons for exclusion urine test positive for quinine or chloroquine on day 0 (2 in A5, 4 in A9); parasite count < 2000/ μ l (2 in A5, 2 in A9, 2 in quinine); withdrawal of consent (3 in quinine); diagnosis of typhus (3 in A5); did not return to study site (1 in A5)

Table 2. Reasons for Patient Non-Evaluability

Reason (study day)	A5 Group N=45	A9 Group N=39	Quinine N=48
	n	n	n
Lost to follow-up:			
(by day 14)	4	2	4
(by day 28)	3	1	3
(by day 35)	0	0	2
Total lost to follow-up	7 (15.5%)	3 (7.7%)	9 (18.8%)
Treatment failure:			
(by day 7)	9	10	4
(by day 14)	6	3	0
(by day 28)	5	6	1
(by day 35)	1	2	2
Total treatment failure	21 (46.7%)	21(53.8%)	7 (14.6%)

n= number of patients

Medical Officer Comments: Presumably patients considered treatment failures were not considered evaluable because they received an alternative treatment for malaria; however, this is not stated specifically in the publication. Notably, treatment failure was considerably higher in the Artemisia treatment groups than in the quinine group.

Efficacy Outcomes

Table 3. Parasitological Cure Rates (Evaluable Population)

Study Day	A5 group n/N (%)	A9 group n/N (%)	Quinine n/N (%)
Day 7	30/39 (77)	23/33 (70)	39/43 (91)
Day 14	20/35 (57)	18/31 (58)	35/39 (90)
Day 28	12/32 (38)	11/30 (37)	31/36 (86)
Day 35	11/32 (34)	9/30 (30)	27/34 (79)

n/N= number of patients with parasitological cure/ number of evaluable patients

Medical Officer Comments: In the author's analysis above, patients lost to follow-up and those with treatment failure were excluded from the analysis. These data are reanalyzed below using the ITT population (all treated patients) as the denominator. Although cure rates were higher for quinine than for Artemisia in this study, statistical analysis (confidence interval around treatment difference) was not performed to determine if quinine was actually superior to Artemisia.

In the following analysis of efficacy, patients who were excluded, or failed or were lost to follow-up were included in the denominator. The quinine cure rates were 81% at 7 days, 73% at 14 days, 65% at 28 days and 56% for 35 days in this analysis.

Table 4. Parasitological Cure Rates (ITT population) (Medical Officer's Analysis)

Study Day	A5 group	A9 group	Quinine
	n/N (%)	n/N (%)	n/N (%)
Day 7	30/45 (67)	23/39 (59)	39/48 (81)
Day 14	20/45 (44)	18/39 (46)	35/48 (73)
Day 28	12/45 (27)	11/39 (28)	31/48 (65)
Day 35	11/45 (24)	9/39 (23)	27/48 (56)

Medical Officer Comments: In this analysis, parasitological cure rates were higher for the quinine than the Artemisia groups at all time points. The 28 day cure rate most likely represents recrudescence rather than reinfection because the rates are different for the Artemisia and quinine treatment groups. If reinfection was responsible for declining rates of cure over time, similar rates of reinfection would be expected regardless of treatment group.

Efficacy Conclusions

1. Quinine efficacy was 81% at 7days, and 65% at 28 days in the ITT analysis based on parasitological cure.
2. Quinine cure rates were 91% at 7 days, and 86% at 28 days in the evaluable population.
3. Cure rates at all time points were higher with quinine than with *Artemisia* tea.

Safety Evaluation

The authors stated that adverse events were similar in all treatment groups except for tinnitus which occurred in 27% of patients treated with quinine. Other adverse events were not reported.

Study 4: Ache A., Escorihuela M, Vivas E., Paez E., Miranda L, Matos A., Perez W, Diaz O, and Izarra E. *In vivo* drug resistance of falciparum malaria in mining areas of Venezuela. Trop. Med. And Int. Health. 2002. 7:737-743.

Study Design: Randomized, open-label study

Study Location and Dates: Venezuela (3 sites in Bolivar state, including Kilometro 88, Maripa, and Ikabaru); 1996-1998

Study Objective: to assess efficacy of antimalarials used routinely by the Venezuela Malaria Programme

Study Endpoints: Therapeutic response categorized as early treatment failure (ETF), late treatment failure (LTF), and adequate clinical response (ACR)

Treatment Groups:

First line therapy: chloroquine

Second line therapy: sulfadoxine-pyramethamine

Third line therapy: quinine

Each of these antimalarial drugs was given jointly with primaquine

Inclusion Criteria:

- Age > 6 months
- Infection with *P. falciparum* alone
- Parasitemia 500-5000 asexual parasites/ μ l
- Absence of fever in the 72 hours before examination
- Axillary temperature < 39.5°C
- No general danger signs or signs of severe and complicated falciparum malaria according to WHO definition
- Ability to come for follow-up visits
- Easy access to the health facility
- Absence of febrile conditions caused by diseases other than malaria
- Absence of severe malaria
- Informed consent
- Absence of hypersensitivity reactions to sulfonamides or any other drugs
- Absence of skin conditions which could increase risk of severe adverse reactions to study drug
- Hemoglobin value > 5.0 g/dL or hematocrit above 15%

Exclusion Criteria: none listed

Drug Products:

- Chloroquine was supplied as chloroquine phosphate 150 mg base tablets (Pharma®, Milan, Italy)
- Sulfadoxine-pyrimethamine was supplied as tablets of 500 mg sulfadoxine plus 25 mg pyrimethamine (Pharma®, Milan, Italy)
- Quinine was supplied as quinine sulfate 500 mg salt tablets (Pharma®, Milan, Italy)

Dosage Regimens:

1. Chloroquine 25 mg/kg body weight daily for 3 days
2. Chloroquine 40 mg/kg body weight daily for 4 days
3. Sulfadoxine-pyrimethamine single dose given as 1.25 mg pyrimethamine/kg body weight
4. Quinine 30 mg/kg body weight daily, divided into 3 doses (every 8 hours) for 7 days

Concomitant Therapy

Primaquine 0.75 mg base/kg was used jointly with each regimen, but whether this was a single or daily dose was not specified. Additional concomitant medications, if any, were not reported.

Medical Officer Comments: Since primaquine has little effect on the asexual stage of P. falciparum, and because this species has no hepatic stage, the use of primaquine should not affect efficacy evaluation. Primaquine may reduce P. falciparum gametocytemia, thus reducing transmission.

Baseline Assessments:

- Clinical assessment, body temperature, parasitemia, and body weight were obtained on day 0.
- Hemoglobin and hematocrit were obtained at baseline at only 2 sites, Kilmetro 88 and Ikabaru.

On-Treatment Evaluations:

- Clinical assessment and body temperature on days 1, 2, 3, 7, 14, 21, 28
- Parastiological evaluation on days 3, 7, 14, 21, and 28

Determination of Efficacy:

- **Early treatment failure (ETF):** development of danger signs of severe malaria on days 1, 2, or 3 in the presence of parasitemia on day 2 > day 0, or parasitemia on day 3 < 25% of day 0 count
- **Late treatment failure (LTF):** development of danger signs of severe malaria in the presence of parasitemia on day 3, or earlier return of patients because of the development of danger signs in the presence of parasitemia, or presence of parasitemia on days 7, 14, 21, or 28
- **Adequate clinical response (ACR):** absence of ETF or LTF during follow-up period

Safety Evaluation: not reported

Statistical Methods

Sample sizes were too small to provide confidence intervals.

Study Results

Baseline Patient Demographics and Clinical Characteristics

These data were provided separately by study site, as shown in the tables below.

Table 1. Baseline Patient Characteristics (Maripa)

Parameter	Chloroquine 25 mg/kg N=6	Chloroquine 40 mg/kg N=23	Sulfadoxine – pyrimethamine N=26	Quinine N=16
Mean age (years) ± SD	33.0 ± 24.4	26.7 ± 19.8	22.0 ± 20.6	28.5 ± 18.1
Gender	4M/2F	18M/5F	17M/9F	11M/5F
Mean Parasite density ± SD (parasite count/μl)	1860 ± 594	1930 ± 963	1799 ± 764	2195 ± 969

SD= standard deviation

Medical Officer Comments: At this site, mean age parasite densities at baseline were similar between groups. Additionally, more male than female patients were enrolled at each site.

Table 2. Baseline Patient Characteristics (Kilmetro 88)

Parameter	Chloroquine 25 mg/kg N=6	Chloroquine 40 mg/kg N=13	Sulfadoxine – pyrimethamine N=11	Quinine N=16
Mean age (years) ± SD	31.1 ± 8.2	28.6 ± 7.7	27.0 ± 8.5	30.4 ± 8.5
Gender	4M/2F	11M/2F	8M/3F	13M/3F
Mean Parasite density ± SD (parasite count/μl)	2880 ± 873	2707 ± 974	2404 ± 707	2260 ± 1053
Mean hemoglobin ± SD (g/dL)	12.0 ± 1.0	11.4 ± 1.4	11.2 ± 1.2	11.4 ± 1.4
Mean hematocrit (%) ± SD	39.5 ± 3.0	37.6 ± 4.4	36.9 ± 3.3	35.1 ± 5.0

SD = standard deviation

Medical Officer Comments: Although the mean age is similar at this site to that of Maripa, the standard deviation of the mean is lower at this site. Mean parasite count at baseline was similar for all treatment groups at this site, and similar to that of the other sites. Mean hemoglobin and hematocrit were similar across treatment groups. In this study, patients with a hemoglobin of < 5 g/dL or hematocrit < 15% were appropriately excluded. Severe anemia is a marker for severe malaria.

Table 3. Baseline Patient Characteristics (Ikabaru)

Parameter	Chloroquine 40 mg/kg N=16	Sulfadoxine – pyrimethamine N=16	Quinine N=16
Mean age (years) ± SD	30.0 ± 11.3	28.7 ± 19.0	27.3 ± 7.3
Gender	15M/1F	11M/5F	9M/7F
Mean Parasite density ± SD (parasite count/μl)	2190 ± 1110	2999 ± 1183	3065 ± 1644
Mean hemoglobin ± SD (g/dL)	11.4 ± 1.4	11.3 ± 1.2	11.0 ± 1.4
Mean hematocrit (%) ± SD	37.7 ± 3.8	37.0 ± 4.0	36.4 ± 5.6

SD = standard deviation

Medical Officer Comments: At this site, the lower dose of chloroquine, 25 mg/kg/day for 3 days was not used, in favor of the higher dosage regimen of 40 mg/kg/day for 4 days because chloroquine resistance was assumed. Mean age and parasite counts were similar to the other two sites, and likewise, more males than females were enrolled. Mean

hemoglobin and hematocrit were similar across treatment groups, and to the Kilometro 88 site.

Patient Disposition: The authors stated that there were no patients lost to follow-up.

Efficacy Outcomes

No patients developed signs or symptoms of severe or complicated malaria. The following table shows the combined clinical responses for all 3 sites, because baseline demographics and clinical characteristics were similar.

Table 4. Therapeutic Response for Combined Study Sites (ITT= Evaluable Populations)

Response	Chloroquine 25 mg/kg N=12	Chloroquine 40 mg/kg N=52	Sulfadoxine- pyrimethamine N=53	Quinine N=48
	n (%)	n (%)	n (%)	n (%)
ETF	12 (100)	4 (7.7)	7 (13.2)	0
LTF	0	8 (15.4)	5 (9.4)	0
ACR	0	40 (76.9)	41 (77.4)	48 (100)

ETF= early treatment failure; LTF= late treatment failure; ACR= adequate clinical response (See definitions in determination of efficacy section above.)

***Medical Officer Comments:** All patients who received quinine had an adequate clinical response; while all patients who received chloroquine 25 mg/kg/day for 3 days had early treatment failure. The small numbers of patients who received the chloroquine 25 mg/day dosage regimen at the 2 sites where it was included as a treatment group (Maripa and Kilmetro 88), was likely a result of the treatment protocol which specified that once treatment failures exceeded 25% enrollment in that treatment arm ceased.*

Adequate clinical response was similar in patients who received chloroquine 40 mg/kg/day for 4 days or single dose sulfadoxine-pyrimethamine. It should be noted that 100% of patients at the Ikabaru site had an adequate clinical response regardless of treatment group.

Efficacy Conclusions:

1. Quinine efficacy was 100% in this study; while approximately 25% patients failed therapy (early or late) in the chloroquine 40 mg/kg and single dose sulfadoxine-pyrimethamine group.
2. All patients who were treated with chloroquine 25 mg/kg for 3 days had early treatment failure.
3. Failures with chloroquine and sulfadoxine-pyrimethamine treatment are presumably due to parasite resistance to those agents.
4. The authors concluded that chloroquine 40 mg/kg/day for 4 days should be the standard first line treatment regimen for malaria in Venezuela; and sulfadoxine-pyrimethamine + amiodaquine, as second-line therapy at this time. They envisioned that quinine would be used in the future as a second-line therapy once the failure rate reaches a pre-determined level.

***Medical Officer Comments:** This study was used as a survey to evaluate efficacy of antimalarial drugs in different regions of Venezuela for public health reasons, to monitor changes in susceptibility of *P. falciparum* to first, second- and third-line drugs (by determination of clinical response), and to aid in modification of national drug policies.*

Safety Data: Safety data was not reported in this study.

Study 5: Rahman MR, Paul DC, Rashid M, Ghosh A, Bangali AM, Jalil MA, and Faiz MA. A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated malaria in a multidrug-resistant falciparum area of Bangladesh-narrowing the options for the National Malaria Control Programme? *Trans. Roy. Soc. Trop. Med and Hyg.* 2001; 95:661-667.

Study Design: Randomized, open-label, controlled study

Study Location and Dates: Bangladesh; July, 1996 to December, 1997

Study Objective: To compare the efficacy of the recommended first-, second-, and third-line antimalarial regimens, as well as mefloquine for treatment of uncomplicated falciparum malaria.

Study Endpoints: (Primary endpoint was not defined.)

1. Clinical Response defined as follows:

- **Early treatment failure (ETF):** parasitemia and persistent fever from day 3 onwards, or patients with worsening condition prior to day 3
- **Late treatment failure (LTF):** initial clearance of fever ($< 37.8^{\circ}\text{C}$) by day 3, but with persistent/recurrent parasitemia and fever ($< 37.8^{\circ}\text{C}$) at a later time over the observation period.
- **Adequate clinical response (ACR):** patients with neither ETF or LTF

2. Parasitological Response categorized as follows:

- **RIII:** density of parasite on day 2 more than 25% of density on day 0; or alternative antimalarial therapy required on or before day 2.
- **RII:** positive on day 2, with a density of $< 25\%$ of density on day 0, and either positive on day 7, or alternative antimalarial therapy required on any days of day 2-7.
- **RI:** Negative or positive ($< 25\%$ day 0) on day 2 and negative on day 7, but positive anytime thereafter up to 28 days.
- **S:** Negative or positive ($< 25\%$ day 0) on day 2, but negative thereafter.

3. **Fever clearance time:** time from admission to start of the time when temperature was $< 37.8^{\circ}\text{C}$ for at least 48 hours.

4. Parasite clearance time: time between admission and first 2 consecutive negative blood smears.

5. Hematological response: hemoglobin on day 0, 14, and 28.

Treatment Groups:

Group I. Chloroquine

Group II Quinine + sulfadoxine-pyramethamine

Group III. Quinine

Group IV. Mefloquine (added in place of group III) after interim analysis at 9 months

Inclusion Criteria:

- 12-60 years old
- fever or history of fever in previous 48 hours
- Confirmed *P. falciparum* asexual forms on blood smear with parasite density of 500-250,000/mm³
- Informed consent

Exclusion Criteria:

- Pregnant and lactating women
- History of antimalarial use in previous week
- Manifestations of severe malaria
- Other infections
- Co-infection with *P. vivax*
- Hypersensitivity to sulfonamides or other antimalarial drugs

Drug Products:

- Chloroquine and quinine were obtained from local distributors and were pre-tested from a WHO reference laboratory. Both drugs had content above the minimal acceptable levels.
- Sulfadoxine-pyrimethamine was supplied as Fansidar® (F. Hoffman-LaRoche, Basel, Switzerland)
- Mefloquine was supplied as Eloquine® (Medochemie Ltd, Limassol, Cyprus)

Dosage Regimens:

Group I. Oral chloroquine phosphate tablets 10 mg base/kg single dose on day 0, and 7.5 mg base/kg single doses on days 1 and 2.

Group II. Oral quinine sulfate tablets 30 mg/kg daily given as 10 mg/kg every 8 hours on days 0, 1, and 2, followed by a single tablet of sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine)

Group III. Oral quinine sulfate tablets 10 mg/kg every 8 hours for 7 days

Group IV. Oral mefloquine single dose 20 mg/kg

Concomitant therapy

Patients in each of the treatment groups also received a single dose of primaquine (45 mg base) according to national guidelines. Other concomitant medications were not discussed in the publication.

Medical Officer Comments: *Since primaquine is thought to have little effect on the asexual stage of P. falciparum, and because this species has no hepatic stage, the use of primaquine should not affect efficacy evaluation. Primaquine may reduce P. falciparum gametocytemia, thus reducing transmission.*

Baseline and On-Treatment Assessments: Patients had daily clinical follow-up and blood smear evaluation for parasitemia for 8 days (day 0-7) during their hospital stay, and again on days 14, 21, and 28.

Determination of efficacy: See section above on Study Endpoints.

Safety Evaluation: Methods for safety evaluation were not described in this publication.

Statistical Methods:

Statistical tests included χ^2 for frequency, ANOVA (t-test) for continuous variables, and Kruskal-Wallis for non-parametric tests. Confidence intervals were determined by exact binomial distributions.

Study Results

Baseline Patient Demographic and Clinical Characteristics

The study was performed in 2 phases. The first phase included treatment groups I, II and III and included 212 patients over a 9 month period. The second phase included treatment groups I, II and IV, and included 210 patients. The study populations were similar with respect to mean age, and mean weight for the 2 treatment phases. However, patients enrolled during phase 1 were less likely to be female (10/203, 4.9% in phase 1 and 24/210, 11.4% in phase 2, p-value = 0.02); and differed in baseline hemoglobin, hepatomegaly and splenomegaly during these time periods. Patients enrolled during phase 1 had higher mean hemoglobin (9.25 ± 1.32 g/dL in phase 1 and 8.84 ± 1.11 g/dL in phase 2, p-value = < 0.001), were more likely to have hepatomegaly (66/203 in phase 1 and 12/210 in phase 2, p-value = < 0.001), and were less likely to have splenomegaly (30/203 in phase 1 and 93/203 in phase 2, p-value = < 0.001)

Medical Officer Comments: *Because treatment groups were changed after the interim analysis, randomization may not have been valid. Therefore this study is not considered primary for determination of quinine efficacy for this NDA.*

Baseline characteristics were similar between the treatment groups for mean age, gender, use of antimalarials over previous 2-4 weeks, and weight. Mean hemoglobin, parasite counts, and temperature were similar, but some differences were noted in hepatomegaly, splenomegaly, and regular use of mosquito nets. Selected baseline data are summarized in the table below.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Group I Chloroquine	Group II Quinine + SP	Group III Quinine	Group IV Mefloquine
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	N=149	N=145	N=49	N=70
Male n (%)	138 (93)	136 (94)	45 (92)	61 (87)
Mean age ± SD	26.1 ± 9.9	26.3 ± 9.8	24.7 ± 8.5	27.0 ± 9.4
Median* parasite count (per µl) (range)	15,000 (500- 149,000)	11,550 (480- 154,560)	10,940 (500- 250,000)	11,500 (97,000)
Hemoglobin ± SD (g/dL)	9.0 ± 1.2	9.0 ± 1.3	9.0 ± 1.2	8.8 ± 1.1
Splenomegaly n (%)	113 (76)	115 (79)	42 (86)	44 (63)
Hepatomegaly n (%)	29 (19)	27 (19)	18 (37)	4 (6)

*table 4 in reference says mean parasite count, but text says median (range)
 SD= standard deviation; SP= sulfadoxine-pyrimethamine
 N= number of evaluable patients; n = number of patients with characteristic

Medical Officer Comments: Most patients enrolled were male, and were relatively young (although age range was not provided). Mean hemoglobin levels were similar between treatment groups. Although the median baseline parasite counts were similar between treatment groups, the range of parasitemia was wide. Hepatomegaly and splenomegaly are not necessarily signs of severe malaria; nor have they been shown to portend a poor outcome with treatment, so the differences noted between the groups for these 2 physical findings is probably not clinically significant.

Patient Disposition

Patient disposition was not provided by treatment group in the publication. Overall, 12 patients were excluded from analysis, 1 patient developed hypersensitivity, 4 had vivax malaria, 2 left the hospital after 2 days, and 5 were lost to follow-up. A total of 413 patients were considered evaluable.

Efficacy Outcomes

Clinical and parasitological responses are summarized in the following table.

Table 2. Response to Antimalaria Therapy (from table 5 Rahman, et al., 2001)

Response	Group I Chloroquine N=149	Group II Quinine + SP N=145	Group III Quinine N=49	Group IV Mefloquine N=70
	n (%)	n (%)	n (%)	n (%)
Clinical Response:				
ACR	50 (34)	114 (79)	48 (98)	62 (89)
ETF	50 (34)	0	0	0
LTF	49 (33)	31 (21)	1 (2)	8 (11)
Parasitological Response:				
S (radical cure)	34 (23)	96 (66)	40 (82)	51 (73)
RI	32 (21)	32 (22)	5 (10)	9 (13)
RII	24 (16)	5 (3)	1 (2)	3 (4)
RIII	59 (40)	12 (8)	3 (6)	7 (10)
Mean PCT (days) ± SD	2.87 ± 1.48	2.35 ± 1.13	2.27 ± 0.91	2.38 ± 1.21
Mean FCT (hours) n (%) SD	33.5 ± 29.0	35.1 ± 24.7	33.9 ± 27.6	25.5 ± 26.5

SP= sulfadoxine-pyrimethamine; SD= standard deviation

ACR= adequate clinical response; ETF= early treatment failure; LTF= late treatment failure (see section above on study endpoints for definitions)

S, RI, RII, and RIII are defined in the section on Study Endpoints above.

PCT= parasite clearance time; FCT= fever clearance time

Medical Officer Comments: Quinine monotherapy for 7 days resulted in an adequate clinical response in 98% patients. ACR was somewhat lower in the groups which received quinine for 3 days followed by a single dose of sulfadoxine-pyrimethamine or mefloquine alone. All treatment failures in the quinine monotherapy or the quinine + sulfadoxine-pyrimethamine group were late failures. The ACR was low in the chloroquine group, 34%, a finding not unexpected given known chloroquine resistance in this geographical area. As cited in this publication, the in vitro sensitivity of P.falciparum isolates from Bangladesh between before 1993 was 15% for chloroquine, 63% for sulfadoxine-pyrimethamine, and 100% for mefloquine and quinine. At the same time, in vivo cure rates in this region were 41% for chloroquine, 56% for sulfadoxine-pyrimethamine, and 100% for quinine. Mefloquine had not been used previously in this geographical area.

When determined by parasitological response, radical cure (S) was achieved in 82% of those who received quinine alone in comparison to 66% of those who received the quinine combination therapy. Cure rates were lower for mefloquine than for quinine

monotherapy, and were significantly lower for chloroquine. The difference in cure as determined parasitologically differed from clinical cure (adequate clinical response) in this study, presumably due to the definition of adequate clinical response, which was not very specific.

Parasite clearance time (reported as the mean) did not differ significantly between treatment groups. Fever clearance time was somewhat shorter with mefloquine than with the other treatments, but this difference was not statistically significant.

Efficacy Conclusions

The 7 day oral quinine regimen had better clinical and parasitological outcomes than the 3 day quinine plus sulfadoxine-pyrimethamine regimen, and than the other antimalarial regimens used in this study.

Safety Data: No safety data was reported in this study.

Study 6: McGready R, Brockman A, Cho T, Cho D., van Vugt M, Luxemburger C, Chongsuphajaisiddhi T, White NJ, and Nosten F. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. *Trans. Royal Soc. Trop. Med. and Hyg.* 2000; 94:689-693.

Study Design: Randomized, open-label, controlled study

Study Objectives: To compare the standard 3 day artesunate-mefloquine regimen with 7 days quinine monotherapy in the treatment of uncomplicated *P. falciparum* malaria in women in the second and third trimesters of pregnancy.

Study Location and Dates: Northwestern border of Thailand; October, 1995-July, 1997

Study Endpoints:

Clinical failure was defined as a positive malaria smear before 63 days of follow-up.

Medical Officer Comments: Study endpoints, other than clinical failure were not described; however, other end-point evaluated included pregnancy outcome and proportion of patients with anemia on follow-up.

Treatment groups:

1. Mefloquine plus artesunate
2. Quinine

Inclusion criteria:

- Pregnant women in second or third trimester of pregnancy
- Microscopically-confirmed *P. falciparum* infection
- Informed consent

Exclusion criteria:

- Severe or complicated malaria
- Intercurrent infection requiring hospitalization
- Allergy to quinine or mefloquine
- < 12 weeks gestation
- History of mental disorder or mefloquine-induced psychosis

Drug Products:

- Mefloquine: Lariam®, (Hoffman La Roche, Basel, Switzerland)
- Artesunate: (Guilin no. 1 factory, People's republic of China)
- Quinine: quinine sulfate

Dosage Regimens:

1. Mefloquine 15 mg base/kg on day 1 and 10 mg/kg on day 2 plus artesunate 4 mg/kg/day on days 0, 1, and 2
2. Quinine sulfate 10 mg salt/kg every 8 hours for 7 days

Concomitant therapy: none reported

Baseline Assessments:

- Physical examination
- Malaria smear
- Hematocrit
- Blood samples for parasite genotyping (using 3 polymorphic markers, merozoite surface proteins -1 and -2 (MSP-1 and MSP-2), and the glutamate rich protein (GLURP) in the *P. falciparum* genome to detect recrudescence versus reinfection)

On-Treatment Assessments:

Women were followed on a weekly basis until delivery or until 63 days post-treatment. Specific assessments during treatment were not reported in the publication.

Determination of Efficacy:

- Clinical failure was defined as a positive blood smear for *P. falciparum* or mixed *P. falciparum* and *P. vivax* infection before 63 days of follow-up.
- Gametocyte positivity rate was defined as the proportion of women who did not have gametocytes on admission, but became gametocyte positive after treatment.
- The person-gametocyte-weeks were calculated by dividing the number of weeks the patient had gametocytes after treatment by the number of weeks they were followed.
- Prematurity was defined as delivery before 37 weeks estimated gestational age.

Safety Evaluation:

Adverse events were checked daily until patient was blood smear-negative for parasites. Symptoms present at baseline were considered disease-attributable; while symptoms that were not present on admission, but appeared up to 28 days post-treatment prior to reappearance of parasitemia, were considered possibly drug-related.

Statistical Methods: Rates of failure by day 63 of follow-up were analyzed by the χ^2 test.

Study Results

Baseline Patient Demographics and Clinical Characteristics

Table 1. Baseline Patient Characteristics

Characteristic	Quinine N=66	Mefloquine-artesunate N=42
Median age (range)	23 (16-36)	24 (15-37)
Mean gestational age (range)	24 (15-38)	24 (12-40)
Mean parasite count/ μ l (range)	19,086 (79-149,389)	11,651 (32-241,127)
Number of patients with gametocytes (%)	5 (12)	7 (11)
Mean Hematocrit (%) (range)	28.7 (21.0-37.2)	29.4 (17.5-39)

N=number of evaluable patients

Medical Officer Comments: The treatment groups appeared to be fairly closely matched for these parameters. The number of gametocytes reflects infectivity, or ability to transmit the parasite to the mosquito host where the life cycle can begin again, but does not reflect severity of disease at baseline.

Patient Disposition:

The authors note that 115 patients were recruited, and of these, 7 patients were not-evaluable, leaving 108 evaluable patients (66 in the mefloquine-artesunate group and 42 in the quinine group). Six patients delivered prior to completion of drug treatment, and 1 patient required parenteral treatment for hyperparasitemia and severe malaria after the first quinine dose.

Medical Officer Comments: The patient that developed severe malaria and hyperparasitemia after the first oral quinine dose should have been counted as a treatment failure. Likewise, the 6 patients who delivered prior to completion of malaria treatment should have been followed for efficacy and pregnancy outcome.

Efficacy Outcomes

All treated patients were afebrile by 48 hours; however, only 19 patients were febrile on study entry. At 48 hours, 18/42 (43%) patients treated with quinine, and 54/66 (82%) of patients treated with mefloquine-artesunate were negative for parasitemia. Day 63 cure rates were 98.2% (95% confidence interval 94.7-100) for the mefloquine-artesunate group (N=65); and were 67% (95% confidence interval 43.3-90.8) for quinine monotherapy (N=41). Note that 1 patient from each treatment group had reappearance of parasitemia that was considered reinfection rather than recrudescence by genotyping, and thus the denominators differ from the number of evaluable patients in each group.

*Medical Officer Comments: Only a small proportion of patients were febrile on study entry, and whether those without fever had asymptomatic parasitemia rather than acute malaria was not discussed. However, pregnant women with asymptomatic parasitemia may also be at risk for anemia and low birthweight infants. Mefloquine-artesunate resulted in higher 63 day cure rates than quinine in this setting, an area of known multi-drug resistance of *P. falciparum*. However, this is concern regarding a potential for increased stillbirths with mefloquine (Nosten, et al., 1999), and this may not be the preferred antimalarial agent for treatment of pregnant women.*

Pregnancy Outcomes

Among the 108 evaluable patients, there were 91 singleton births and 1 set of twins reported. In the 16 remaining pregnancies, there were 13 (12%) lost to follow-up, 2 (1.9%) mid-trimester abortions, and 1 maternal death, reportedly unrelated to malaria. The patients with mid-trimester abortions were both primagravidas with their first episode of documented malaria in the mefloquine-artesunate treatment group. No stillbirths or congenital abnormalities were reported among the 92 documented births. The following table shows additional data obtained from the singleton infants at birth.

Table 2. Pregnancy outcomes at time of delivery (adapted from author's table 3)

Parameter	N	Mefloquine-artesunate	N	Quinine
Mean birthweight (g)± SD	54	2877 ± 459	34	2844 ± 479
Mean placental weight (g) ± SD	30	466 ± 94	22	468 ± 85
Estimated gestational age, weeks ± SD	50	39 (1.8)	29	39 ± 2.0
Number of low birthweight* infants	53	9 (17 %)	33	6 (18 %)

SD= standard deviation; N= number of singleton infants evaluated for these parameters

*low birthweight was not defined

Medical Officer Comments: Mean birth weight, placental weight, and estimated gestational age were similar for both treatment groups. The number and proportion of premature births was not reported; however, the proportion of low birth weight infants was similar for both groups.

Neonatal and Infant Outcomes

A total of 65 of 91 (71%) singleton infants were followed after birth, most (70%) for at least 12 months. The time to reach developmental milestones was similar for infants of mothers treated with quinine or mefloquine-artesunate with the exception of one infant whose mother had received quinine, who was blind due to retinopathy of prematurity. The estimated gestational age for that infant was 31 weeks.

There were a total of 5 deaths, in infants or neonates born to mothers treated for malaria in this study, as outlined in the table below.

Table 3. Infant and neonatal deaths in this study (adapted from author's table 4)

Mother's Treatment Group	EGA (weeks)	Age at death	"Details related to death"*
Quinine	36.5	23 days	Symptomatic <i>P. falciparum</i>
Quinine	36.2	6 weeks	Infantile beri-beri
Mefloquine-artesunate	32.5	1 day	Symptomatic <i>P. falciparum</i>
Mefloquine-artesunate	31.8	6 days	Symptomatic <i>P. vivax</i>
Mefloquine-artesunate	37.6	7 months	Dehydration and malnutrition

*the author did not specify these as cause of death
 EGA= estimated gestational age

Medical Officer Comments: Untreated malaria causes significant morbidity and mortality in both pregnant women and the unborn child. In this study, 1 neonate, whose mother had received quinine, died, presumably due to P. falciparum infection and/or complications thereof. In infants of mothers treated with mefloquine-artesunate, 2 neonates died, presumably due to malaria, one falciparum, and one vivax. Whether these neonates received antimalarial therapy is not discussed in this publication.

Efficacy Conclusions:

1. At the 63 day post-treatment follow-up, cure rates were higher for the mefloquine-artesunate than the quinine group, 98% and 67% respectively.
2. Among the 92 documented birth outcomes, there were no stillbirths or congenital abnormalities reported.
3. There was no apparent difference in neonatal and infant outcomes between the two treatment groups.

Safety Data

Adverse Events

No drug-related serious adverse events were reported in either treatment group. Adverse events were reported by percentage of treated patients, as shown in the following table. The rates of both dizziness and tinnitus were significantly higher in the quinine treatment group.

Table 4. Adverse Events Reported in Study (from author's Figure 2)

Adverse Event	Quinine	Mefloquine-artesunate
	N=66	N=42
	%	%
Headache	50	21
Muscle/joint pain	28	32
Abdominal pain	50	29
Anorexia	48	34
Nausea	50	47
Vomiting	2	0
Dizziness	87	45
Tinnitus	66	17
Abnormal neuro*	5	1

*author did not state if this meant neurological sign or symptom

Medical Officer Comments: Presumably these adverse events were considered drug-related, based on the definitions for drug-attributable and disease-attributable events, described above. On a qualitative basis, the safety profile of quinine appears similar in pregnant women to that described for patients in other clinical studies and in the literature.

Study 7: Pukrittayakamee S, Chantira A, Vanijanonta S, Clemens R, Looareesuwan S, and White NJ. Therapeutic Responses to quinine and clindamycin in multidrug-resistant falciparum malaria. *Antimicrob. Agents and Chemotherapy* 2000; 44: 2395-2398.

Study Design: Randomized, open-label, active-controlled study

Study Objectives: To determine efficacy of clindamycin in combination with quinine in comparison to quinine alone, and quinine in combination with tetracycline, for treatment of falciparum malaria.

Study Location and Dates: Bangkok, Thailand; 1995-1997

Study Population: Adult males

Study Endpoints: (Primary endpoint was not specified.)
Fever clearance time

Parasite clearance time
Parasite reduction rates

Treatment Groups:

1. Quinine alone
2. Quinine plus tetracycline
3. Quinine plus clindamycin

Inclusion Criteria:

- Adult male patients with acute *P. falciparum* malaria admitted to Bangkok hospital between 1995 and 1997
- Informed consent

Exclusion Criteria:

- Severe malaria
- Mixed malaria parasite infections
- History of drug hypersensitivity
- Antimalarial drug use within 48 hours prior to study entry
- Positive urine test for sulonamides, or 4-aminoquinonlines
- Patients who were unable to stay in the hospital until clearance of fever and parasites.

Drug Product:

Quinine was supplied as quinine sulfate (Thai Government Pharmaceutical Organization).
Tetracycline was supplied by Thai Government Pharmaceutical Organization.
Clindamycin was supplied as Dalacin C (Pharmacia % Upjohn Pharmaceuticals).

Dosage Regimens:

Quinine: 10mg salt/kg 3 times daily for 7 days (oral)

Quinine plus tetracycline: quinine as above, plus tetracycline 4 mg/kg four times daily for 7 days.

Quinine plus clindamycin: quinine as above, plus clindamycin 5 mg base/kg four times daily for 7 days.

Concomitant therapy:

Oral acetaminophen (0.5 to 1 g every 4 hours) was given for temperature > 38°C. No other concomitant medications were reported.

Medical Officer Comments: Receipt of acetaminophen may change the fever clearance time, reported as a study endpoint.

Baseline Assessments:

Clinical assessment and confirmation of diagnosis

Baseline blood samples obtained for hematology and biochemistry

On-Treatment Assessments:

- Vital signs were recorded every 4 hours until fever resolution, then every 6-12 hours.
- Parasite counts were measured every 12 hours until clearance, then daily for 28 days.
- Routine biochemical and hematological tests were obtained on days 7, 14, 21, and 28

Determination of Efficacy:

- Fever clearance time (FCT) was expressed as FCTA, the time required for temperature to first fall below 37.5°C; and FCTB, the time for temperature to remain below 37.5°C for 48 hours.
- Parasite density: number of parasites per μ l of blood
- Parasite clearance time: time required for parasite count to fall below 50% (PC50) or 90% (PC90) of the value at the time of admission; or PCT, the time taken for parasite levels to fall below detectable levels
- Reappearance of infection was assessed in patients who remained in Bangkok (outside a malarious area) at home or in the hospital for at least 28 days.

Safety Evaluation:

Adverse events were not reported.

Statistical Methods:

Data for each treatment group were compared by one-way analysis of variance with Bonferroni correction for multiple comparisons. Nonparametric data were compared by the Kruskal-Wallis test. Cumulative FCTs, PC rates and cure rates were calculated by Kaplan-Meier survival analysis with comparison by the log-rank test. Associations between FCT, PC rate and PRR were measured with Spearman's rank correlation coefficient.

Study Results

Baseline Patient Demographics and Clinical Characteristics

A total of 204 patients were randomized into the 3 treatment groups. Most patients (77%) reportedly came from the western border of Thailand, where the prevalence of multi-drug resistant *P. falciparum* is high. There were no significant differences in age, number of patients with previous episodes of malaria, or geographic distribution, or baseline parasite count between the treatment groups, as shown in the table below. Additionally, there was no difference between treatment groups for baseline hematocrit, white blood cell count, platelet count, serum creatinine, or AST level. Elevated total bilirubin was reported in 26 patients at baseline, 13/68 (19.1%) in the quinine monotherapy group, 10/68 (14.7%) in the quinine+clindamycin group, and 3/68 (4.4%) in the quinine+tetracycline group. No patients had severe anemia (hematocrit < 15%) or elevated serum creatinine (> 3 mg/dL).

Table 1. Baseline Patient Characteristics (adapted from author's table 1)

Characteristic	Quinine N=68	Quinine + clindamycin N=68	Quinine +tetracycline N=68
Mean age ± SD (years)	24.6 ± 8.9	25.6 ± 9.3	27.3 ± 10.2
Number (%) patients with previous malaria	31 (46)	29 (43)	32 (47)
Number (%) patients from western Thailand	57 (84)	60 (88)	40 (59)
Geometric mean Parasite count (number/μl)	9,493	17,155	9,352

SD= standard deviation

Medical Officer Comments: Patients were fairly closely matched between treatment groups, except for total bilirubin at baseline, which was higher in the quinine monotherapy and quinine + clindamycin group than in the quinine + tetracycline group. Elevated bilirubin could represent baseline liver dysfunction, although AST levels were similar for each of the treatment groups, or hemolysis, which can be an indicator of more severe malaria. Although the mean hematocrits were similar across treatment groups, ranges were not shown, so a few patients with a decreased hematocrit due to significant hemolysis would not be detected in this analysis.

Patient Disposition:

Overall, 161 of 204 (79%) patients completed follow-up at least 28 days or remained hospitalized until clearance of fever and parasites. In the quinine monotherapy group, 53/66 (80.3%) completed the study in comparison to 60/66 (90.9%) in the quinine+ clindamycin group, and 48/66 (72.7%) in the quinine+tetracycline group. Reasons for not completing the study were not provided.

Efficacy Outcomes:

Outcomes are shown in the table below. FCTA was similar for all treatment groups, while FCTB was significantly higher in the quinine monotherapy group. Parasite clearance times (PCT50, PCT90, and PCTT) were similar for each of the treatment groups. Recrudescence rates were highest in the quinine monotherapy group for the evaluable population.

Table 2. Clinical and parasitological Responses (adapted from author's table 2)

Response Parameter	Quinine N=68	Quinine + clindamycin N=68	Quinine + Tetracycline N=68
Median FCTA (hours) (range)	10 (2-100)	8 (2-95)	8 (3-36)
Median FCTB (hours) (range)	56 (4-152)	47 (8-120)	36 (8-117)
Mean PCT50 (hours) ± SD	21 ± 17	21 ± 14	21 ± 14
Mean PCT90 ±SD	57 ± 25	58 ± 19	61 ± 19
Mean PCTT ± SD	77 ±25	79 ± 20	77 ± 23
Number (%) patients with subsequent appearance of <i>P.</i> <i>falciparum</i> or <i>P.</i> <i>vivax</i> / number of patients who completed follow- up	7/53 (13.2) (<i>P. falciparum</i>) 12/53 (22.6) (<i>P. vivax</i>)	0/60 (0) (<i>P. falciparum</i>) 12/60 (20.0) (<i>P. vivax</i>)	1/48 (2.1) (<i>P. falciparum</i>) 9/48 (18.8) (<i>P. vivax</i>)

SD= standard deviation

FCT= fever clearance time (see above for definitions)

PCT= parasite clearance time (see above for definitions)

Medical Officer Comments: *If the cure rate is considered the proportion of patients who did not have recrudescence of P. falciparum during the 28 day follow-up period, 46/68 (68%) patients treated with quinine monotherapy, 60/68 (88.2%) patients treated with quinine + clindamycin, and 47/68 (69%) patients treated with quinine + tetracycline were cured, in the ITT population. For the evaluable population, cure rates were 46/53 (87%) for quinine, 60/60 (100%) for quinine + clindamycin, and 47/48 (98%) quinine + tetracycline. The P. vivax infections noted during the follow-up period were probably cryptic infections at the time of enrollment which recurred because none of these antimalarial drugs has activity against the latent hepatic stage of that organism.*

Efficacy Conclusions:

1. The overall cure rates at 28 days were higher for the quinine combination therapies (clindamycin or tetracycline) than for quinine monotherapy.
2. The rate of efficacy of quinine monotherapy was 68% for the ITT population, and 87% for the evaluable population during the time period studied, 1995-1997, so significant quinine resistance did not appear to be an issue.
3. Patients with *P. falciparum* recrudescence were subsequently treated with quinine + tetracycline, and were successfully treated. Potential quinine resistance in these isolates was not evaluated.

Safety Data

The authors noted that the majority of all patients (193/204, 93.7%) developed transient tinnitus, most often after 3 days of treatment. There was no difference in incidence of cinchonism between the 3 treatment groups, and none of the patients developed rashes, or serious adverse events (data not shown).

Study 8: DeVries PJ, Nguyen NB, Van ThienH, Hung LN, Anh TK, Kage, PA, and Heisterkamp SH. Combinations of artemisinin and quinine for uncomplicated falciparum malaria: efficacy and pharmacodynamics. *Antimicrob. Agents Chemother.* 2000; 44:1302-1308.

Study Design: Randomized, open-label, active-controlled study

Medical Officer Comments: This study was a continuation of the study by Bich, et al., 1996, which compared single dose artemisinin combined with quinine or doxycycline to quinine monotherapy. The doxycycline-artemisinin treatment arm proved unsatisfactory and doxycycline was replaced with quinine for 3 or 5 days as reported in this publication. Patients treated with quinine or artemisinin-quinine (3 days) in the previous study (Bich, et al., 1996) were included in this analysis. Because of randomization and duplication issues, this study was not considered primary for evaluation of quinine efficacy in this review.

Study Location and Dates: Vietnam; dates not specified.

Study Objectives: Comparison of quinine monotherapy to two combination regimens of artemisinin plus quinine for treatment of uncomplicated *P. falciparum* malaria

Study Endpoints:

- Primary endpoint was not stated in the publication.
- Fever clearance time
- Parasite clearance time
- Clinical failure
- Parasitological response

Treatment Groups:

1. Quinine monotherapy
2. Single dose artemisinin followed by quinine for 3 days
3. Single dose artemisinin followed by quinine for 5 days

Inclusion Criteria:

- Patients admitted to hospital for uncomplicated malaria
- Ages 8-65 years old
- Parasite density between 1000 and 100,000/ μ L

Exclusion Criteria:

Inability to take oral medications

Allergy to one of study drugs

Quinine use in previous 12 hours; artemisinin or derivatives in previous 24 hours, and mefloquine, tetracycline, or doxycycline in previous 7 days

Drug Products:

- Quinine was supplied as quinine sulfate 250-mg tablets (Pharmaceutical Factory n. 24, Hanoi, Vietnam)
- Artemisinin was supplied as 250-mg capsules (ACE Chemie, Maarssen, The Netherlands)

Dosage Regimens:

1. Quinine 10 mg/kg 3 times daily of 7 days
2. Artemisinin 20 mg/kg single dose, followed after 6 hours by quinine 10 mg/kg 3 times daily for 3 days (AQ3)
3. Artemisinin 20 mg/kg single dose, followed after 6 hours by quinine 10 mg/kg 3 times daily for 5 days (AQ5)

Medical Officer Comments: the quinine monotherapy and artemisinin-quinine (3 day) treatment groups were discontinued before the end of the study and the last 36 patients received artemisin+quinine (5 days), which invalidates randomization.

Concomitant Therapy: not reported in publication

Baseline Assessments:

All patients were hospitalized until full clinical recovery, parasite clearance and completion of study drug treatment

Vital signs, physical examination

CBC and liver tests

Thick and thin blood smears for malaria

On-Treatment Assessments:

Vital signs every 8 hours

Daily physical examination

CBC and liver tests on third day

Blood smears for malaria every 8 hours until 3 negative smears obtained, then on days 7, 14, 21, and 28 days post-treatment

Determination of Efficacy:

- Fever clearance time was defined as the time from initiation of treatment to the first of 3 consecutive normal temperature readings ($< 37^{\circ}\text{C}$) axillary temperature.
- Parasite clearance time was defined as the time from initiation of treatment to the first of 3 consecutive negative blood smears.

- Clinical failure was defined as no improvement, necessitating additional treatment within the first 48 hours (early failure) or after 48 hours (late failure).
- Parasitological Response was defined as follows:
 - Radical cure: parasite clearance by day 7 without recrudescence up to day 28.
 - R1: initial disappearance of parasites with recrudescence before day 14 (early R1), or from day 14 to 28 (late R1)
 - R2: initial decrease of parasite count to < 25% of initial value, followed by resurgence, without clearance by day 7
 - R3: no response or small decrease in parasitemia, to more than 25% of initial value, assessed at 48 hours after initiation of therapy

Safety Evaluation: Adverse event monitoring was not described in the publication.

Statistical Methods: Clinical outcome was analyzed with contingency tables and χ^2 tests with continuity correction for categorical parameters and with analysis of variance or nonparametric tests for numerical parameters.

Study Results

Baseline Patient Demographic and Clinical Characteristics

No significant differences were noted between treatment groups for age, gender, or baseline parasitemia, as shown in the following table.

Table 1. Baseline Patient Characteristics (adapted from author's table 1)

Characteristic	Quinine N=84	AQ3 N=96	AQ5 N=88
Median age (year) (range)	26 (7-60)	26 (7-64)	26 (7-60)
Gender (M/F)	70/14	76/20	70/18
Geometric mean parasite count/ μ l	16,157	16,123	23,202

AQ3= artemisinin+quinine (3 days)

AQ5= aremisinin +quinine (5 days)

N= number of patients enrolled

Patient Disposition

Study completion (up to 28 days follow-up) was similar for each of the 3 treatment groups, as shown in the table below.

Table 2. Patient Disposition (adapted from author's table 2)

Patient disposition	Quinine N=84	AQ3 N=96	AQ5 N=88
Early dropout (not evaluable)	3	1	1
Lost to follow-up before day 7	2	3	0
Lost to follow-up days 7-28	10	18	9
Completed 28 day follow-up (total evaluable)	69 (82%)	74 (77%)	78 (89%)

AQ3= artemisinin+quinine (3 days)

AQ5= aremisinin +quinine (5 days)

N= number of patients enrolled

Treatment Outcomes

Radical Cure rates defined as clearance of parasites by day 7 with no recurrence by day 28 were similar in the quinine monotherapy or artemisinin+quinine (5 days); but was significantly lower in the artemisinin +quinine (3 days) group, using either the ITT or evaluable population. There was not significant difference in fever clearance time; but mean parasite clearance time was longest in the quinine monotherapy group.

Table 3. Clinical and Parasitological Outcomes

Patient Outcome	Quinine N=84	AQ3 N=96	AQ5 N=88
28 day cure rate (ITT)	56/84 (67%)	46/96 (48%)	66/88 (75%)
28 day cure rate (Evaluable)	56/69 (81%)	46/74 (62%)	66/78 (85%)
R1 recrudescence rate (evaluable)	11/69 (16%)	28/74 (38%)	12/78 (15%)
Mean fever clearance time (hours)	47	41	43
Mean parasite clearance time (hours)	62	41	42

AQ3= artemisinin+quinine (3 days)

AQ5= aremisinin +quinine (5 days)

N= number of patients enrolled

Medical Officer Comments: This study does not support the use of a 3 day quinine combination regimen in this geographical area of Southeast Asia which may have some level of quinine resistance, although this is not well-documented.

Efficacy Conclusions:

1. Quinine monotherapy and the combination of quinine+artemisinin (5days quinine) treatment groups had similar efficacy outcomes; while the quinine+artemisinin (3 days quinine) group had lower rates of cure.
2. Because this study was a continuation of the study by Bich, et al., 1996, and because 2 treatment arms were discontinued previously in this study, invalidating randomization, this study should be considered as supportive only for this NDA.

Safety Data

The authors noted that hemoglobinuria was noted in 2 patients after 24 hours of treatment, but the treatment group was not specified. These patients were withdrawn from the study and treated with artesunate. Presumably, these patients had received quinine alone, because this adverse effect was considered quinine-related. Cinchonism was reported in all 3 treatment groups, but the incidence was not reported.

Study 9: Bich NN, DeVries PJ, Van Thien H, Phong TH, Hung LN, Eggelte TA, Anh TK, and Kager PA. 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.

Study Design: Randomized, open-label, active-controlled study

Study Location and Dates: Vietnam; 1993 – (end of study date not provided)

Study Objectives: To compare a 7 day course of quinine with single dose artemisinin plus either quinine or doxycycline for 3 days.

Study Endpoints:

Primary endpoint was not stated in the publication.

Fever clearance time

Parasite clearance time

Clinical response

Parasitological response

Treatment Groups:

1. Quinine monotherapy for 7 days
2. Quinine (3 days) plus artemisinin (single dose)
3. Doxycycline (3 days) plus artemisinin (single dose)

Inclusion Criteria:

- Uncomplicated falciparum malaria
- Parasite density 1000-100,000/ μ l

- Age between 8 and 65 years old

Exclusion Criteria:

- Pregnancy or lactation
- Mixed infections
- Inability to take oral medication
- Allergy to one of study medications
- Quinine use in previous 12 hours, artemisinin use in previous 24 hours, or mefloquine, tetracycline, or doxycycline within previous 7 days

Drug Products:

- Quinine was supplied as quinine sulfate 250 mg tablets (Pharmaceutical Factory no. 24, Hanoi, Vietnam)
- Artemisinin was supplied as 250 mg capsules (ACE Chemie, Maarssen, The Netherlands)
- Doxycycline was supplied as 100 mg Vibramycin ® capsules (Pfizer BV, Rotterdam, The Netherlands)

Dosage Regimen:

- Quinine 10 mg/kg 3 times daily for 7 days
- AQ: single dose artemisinin 20 mg/kg, followed in 6 hours by quinine 10 mg/kg 3 times daily for 3 days
- AD: single dose artemisinin 20 mg/kg, followed in 6 hours by doxycycline 4 mg/kg for 3 days

Concomitant Therapy: not reported in this publication

Baseline Assessments:

All patients were admitted to the hospital

Vital signs, physical examination

Blood tests: hemoglobin, hematocrit, WBC with differential count, glucose, AST, ALT, creatinine, and BUN

Urine tests: albumin, glucose, and sediment

Blood smears for malaria

On-Treatment Assessments:

- Vital signs every 8 hours until at least 3 normal temperature readings were obtained
- Blood smears for malaria every 8 hours until 3 negative smears were obtained, then on days 7, 14, 21, and 28 post-treatment
- Treatment day 3: blood tests for hemoglobin, hematocrit, WBC with differential count, glucose, AST, ALT, creatinine, and BUN

Determination of Efficacy:

- Fever clearance time was defined as time from initiation of treatment to first of 3 consecutive normal ($\leq 37^\circ$) axillary temperature readings.

- Parasite clearance time was defined as time from initiation of treatment to first of 3 consecutive negative blood smears.
- Clinical failure was defined as no improvement necessitating additional treatment within the first 48 hours of treatment (early failure) or after 48 hours of treatment (late failure).
- Parasitological response was defined as:
 - Radical cure: parasite clearance by day 7 without recrudescence up to day 28
 - R1: initial disappearance of parasites with recrudescence before day 14 (early R1) or from day 14 to 28 (late R1)
 - R2: initial decrease of parasite count to < 25% of initial value, followed by resurgence without clearance by day 7
 - R3: no response, or small decrease (>25%) of initial value, assessed at 48 hours after initiation of therapy

Safety Evaluation:

Symptoms were considered drug-related if they occurred after the initiation of therapy, or increased in intensity, if present prior to first dose, or persisted 2 or more days after defervescence and parasite clearance. Symptoms were recorded daily during hospitalization.

Statistical Methods: Data was evaluated by Analysis of variance and chi-square tests. Cumulative fever and parasite clearance times, and recrudescence rates were analyzed by Kaplan Meier curves and Cox' regression analysis. No interim analysis was planned, however, analysis was performed once 161 patients were enrolled due to differences noted in treatment regimen.

Medical Officer Comments: According to the companion publication, DeVries, et al., (2000), the quinine+doxycycline treatment arm of this study was terminated early due to a high rate of failure, and study continued with a different treatment arm (quinine-5 days + artesimisin) although this is not discussed in this publication. Results shown in this publication are results of the interim analysis of the De Vries, et al. (2000) study.

Study Results

Baseline Patient Demographics and Clinical Characteristics

There were no significant differences between treatment groups for age, gender, or initial parasitemia, as shown in the table below.

Table 1. Baseline Patient Characteristics (adapted from author's Table 1)

Characteristic	Quinine N=59	Artemisinin + quinine N=45	Artemisinin + doxycycline N=53
Mean age (years) ± SD (range)	25 ± 12 (14-66)	27 ± 13 (12-64)	26 ± 13 (9-63)
Gender (M/F)	47/12	34/11	47/6
Baseline parasitemia (mean count/μl) ± SD (range)	29,636 ± 39720 (1058-190,133)	21,321 ± 21,877 (1060-111,294)	46,088 ± 91,523 (1152-461,386)

Medical Officer Comments: Although reportedly not statistically significant the mean parasite count at baseline was higher in the artemisinin+doxycycline treatment group than in the other 2 groups. Whether this is due to a single outlier, or more than one outlier, is not clear. Higher levels of parasitemia could affect treatment outcomes.

Patient Disposition

Similar rates of study completion were reported for all 3 treatment groups.

Table 2 . Patient Disposition (adapted from author's table 2)

Disposition	Quinine N=59	Artemisinin + quinine N=45	Artemisinin + doxycycline N=53
Early dropout (not evaluable)	4	0	2
Lost to follow-up before day 7	2	3	1
Lost to follow-up between day 7 and 28	9	10	8
Completed study (28 day follow-up) (evaluable patients)	44 (74.5%)	32 (71.1)	42 (79.2)