

Efficacy Outcomes

The radical cure rate at 28 days (no recrudescence of infection) was highest with quinine monotherapy (7 days), and lowest with the artemisinin + doxycycline regimen, as shown in the following table. One of 59 (1.7%) quinine-treated patients had early clinical failure (no improvement within 48 hours); while no patients in the other treatment groups had initial clinical failure. A significantly higher number of patients had late recrudescence in the artemisinin + doxycycline group than in the other treatment groups. Additionally, 3 patients had an initial R3 parasitological response to treatment in the artemisinin + doxycycline group. Mean fever and parasite clearance times were longer with quinine monotherapy than with both artemisinin-based combination therapies.

Table 3. Clinical and Parasitological Response (adapted from author's table 2)

Outcome Parameter	Quinine N=59	Artemisinin + quinine N=45	Artemisinin + doxycycline N=53
28 day Cure rate (ITT)	36/59 (61%)	23/45 (51%)	13/53 (24%)
28 day Cure rate (evaluatable)	36/44 (82%)	23/32 (72%)	13/42 (31%)
Clinical Failure (early)	1	0	0
Clinical Failure (late)	0	0	3*
Recrudescence (early)	2	2	4
Recrudescence (late)	5	7	22
Total recrudescence (evaluatable)	7/43 (16%)	9/32 (28%)	26/39 (67%)
Mean Fever clearance time ± SD (range) (hours)	41 ± 23 (0-112)	34 ± 19 (0-80)	31 ± 23 (0-120)
Mean Parasite clearance time ± SD (range) (hours)	66 ± 24 (24-128)	43 ± 14 (16-42)	41 ± 19 (16-136)

*These 3 patients with late clinical failure had an R3 parasitological response
 SD= standard deviation

Medical Officer Comments: Treatment with 7 days quinine monotherapy resulted in higher cure rates at 28 days than treatment with artemisinin plus 3 days quinine or 3 days doxycycline. The RIII failures in the artemisinin+doxycycline group suggest high level parasite resistance. Because artemisinins are rapidly acting antimalarial agents,

the shorter fever and parasite clearance times observed with artemisinin-based therapy are not unexpected.

Efficacy Conclusions

1. The highest 28-day cure rates were observed with quinine monotherapy, followed by quinine+artemisinin. The lowest 28-day cure rates (highest rates of recrudescence) were observed with doxycycline+artemisinin.
2. The recrudescence rate of 16% with quinine monotherapy could actually reflect reinfection, because reinfection was not differentiated from relapse in this study.

Safety Data

A total of 35 patients had drug-related "symptoms" (adverse events), 18/59 (30.5%) in the quinine monotherapy group, 9/45 (20%) in the quinine+artemisinin group, and 8/53 (15.1%) in the quinine +doxycycline group. Adverse events are shown in the table below. Additional symptoms considered disease-related were loss of appetite, vomiting, and diarrhea. All "symptoms" were mild in severity, and none required discontinuation of therapy.

Table 4. Drug-Related Adverse events in Study

Adverse Event (AE)	Quinine N=59	Quinine +artemisinin N=45	Doxycycline+ artemisinin N=53
	n (%)	n (%)	n (%)
Any drug-related AE	18 (30.5)	9 (20)	8 (15.1)
Dizziness	9 (15.3)	4 (8.9)	4 (7.5)
Tinnitus	13 (22.0)	5 (11.1)	1 (1.9)
Impaired hearing	6 (10.2)	4 (8.9)	0
Excess salivation	2 (3.4)	0	0
Dry mouth	4 (6.8)	1 (2.2)	1 (1.9)
Hemoglobinuria	0	0	1 (1.9)
Skin rash	0	1 (2.2)	0

Medical Officer Comments: Not unexpectedly because of the longer duration of treatment, the quinine monotherapy group had the highest incidence of drug-related adverse events. Tinnitus and impaired hearing were observed more frequently in patients who received one of the two quinine-containing regimens.

Study 10: Metzger W, Mordmuller B, Graninger W, Bienzle U, and Kremsner PG. High Efficacy of short-term quinine antibiotic combinations for treating adult malaria patients in an area in which malaria is hyperendemic. *Antimicrob. Agents Chemother.* 1995; 39:245-246.

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

Study Location and Dates: Gabon; July, 1993-February, 1994

Study Objectives: to evaluate efficacy of 3-dose quinine regimen alone or in combination with clindamycin or doxycycline for treatment of *P. falciparum* malaria

Study Endpoints:

Primary endpoint was not stated in the publication.

1. Cure
2. Low-grade resistance

Treatment Groups:

1. Quinine
2. Quinine + clindamycin
3. Quinine + doxycycline

Inclusion/Exclusion Criteria:

- Outpatients with proven *P. falciparum* malaria mono-infection
- Asexual parasite count of > 200/ μ l
- Follow-up for 24 hours after parasite clearance
- No antimalarial therapy within 7 days prior to study entry (confirmed by urine tests for chloroquine and sulfonamides)
- Age > 15 years old
- Non-pregnant
- Informed consent

Drug Products: not described in publication

Dosage Regimens:

1. Quinine 12 mg/kg every 12 hours for 3 doses
2. Quinine 12 mg/kg every 12 hours for 3 doses plus clindamycin 5 mg/kg every 12 hours for 6 doses
3. Quinine 12 mg/kg every 12 hours for 3 doses plus doxycycline 2 mg/kg every 12 hours for 6 doses

Concomitant Therapy: not reported in publication

Assessments:

- Clinical signs and symptoms were recorded every 12 hours until patient symptom-free for 24 hours. Patients were observed for vomiting for 1 hour after medications were administered.
- Thick blood smears were prepared every 12 hours until negative for parasites for 24 hours, then on days 14, 21, and 28 post-treatment.

Determination of Efficacy:

- Cure was defined as follows: thick blood smear became negative after treatment and remained negative until day 28 of follow-up.
- Low-grade resistance was defined as disappearance of parasite within 7 days, followed by recrudescence on day 14, 21, or 28.

Safety Evaluation: Methods for monitoring adverse events were not specifically reported.

Statistical Methods:

Statistical analysis was performed with the Mann-Whitney and Kruskal-Wallis tests. Proportional data were tested by the chi-square method.

Study Results

Baseline Patient Demographics and Clinical Characteristics

Patient characteristics were generally similar for each of the treatment groups as shown in the table below. All patients were considered semi-immune because of multiple episodes of malaria in childhood.

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

Characteristic	Quinine N=40	Quinine + clindamycin N=40	Quinine + doxycycline N=40
Median age (year) (range)	32 (15-70)	35 (15-71)	28 (16-70)
Gender (M/F)	21/16	15/21	21/14
Geometric mean Parasite count/ μ l (range)	5,515 (450-68,000)	10,642 (200-115,000)	7,807 (1,000-140,000)

N= number of patients enrolled (ITT population)

Medical Officer Comments: Although not discussed by the authors, more females than males were randomized to the quinine+clindamycin regimen, which differs from the other 2 treatment groups in this study; and differs from gender distribution in most of the other studies submitted for this NDA. The method of randomization was not described. Additionally, the level of baseline parasitemia appeared to be lower in the quinine monotherapy than in combination therapy groups.

Patient Disposition

A total of 120 patients were randomized, and 108 completed the 28-day follow-up for the study. Three patients were lost to follow-up in the quinine monotherapy group, 4 in the quinine+clindamycin group and 5 from the quinine+doxycycline group.

Efficacy Outcomes

Radical cure at 28 days was highest in both quinine combination therapy groups compared to the quinine monotherapy group. Treatment failure was due to late recrudescence (days 14, 21 or 28) in all cases. However, recrudescence was not distinguished from reinfection in this study.

Table 2. Efficacy of Quinine Mono- and Combination Therapy

Outcome	Quinine N=40	Quinine + clindamycin N=40	Quinine + doxycycline N=40
28-day cure rate (ITT)	14/40 (35%)	33/40 (82%)	32/40 (80%)
28-day cure rate (evaluable)	14/37 (38%)	33/36 (92%)	32/35 (91%)
Recrudescence (late)*	23/37 (62%)	3/36 (8%)	3/35 (9%)
Recrudescence (early)*	0	0	0

* Considered low-level resistance according to definition described the section above, "Determination of Efficacy"

Medical Officer Comments: The cure rate with 3 doses of quinine (12 mg/kg per dose) was considerably lower than that observed in other studies with quinine monotherapy using lower doses (usually 10 mg/kg every 8 hours) for 7 days. The half life of quinine is such that every 12 hour dosing may not be appropriate. Alternatively, the low 28 day cure rates could be attributed to the short duration of quinine monotherapy. However, cure rates with both quinine combination regimens in this study were similar to those described in other studies in which more conventional quinine dosing was used.

Safety Data

The authors reported that all treatment regimens were well-tolerated, and there was no significant difference in adverse events between the 3 treatment groups. Overall, 25% patients had dizziness, and 42% had mild gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea). Those symptoms attributed to study drug were not differentiated from those which could be attributed to malaria.

Study 11: Segal HE, Chinvanthananond P, Laixuthai B, Phintuyothin P, Pearlman EJ, Nakhorn A, and Castaneda BF. Preliminary Study of WR 33063 in the treatment of falciparum malaria in northeast Thailand. Am. J. Trop. Med. 1974; 23:560-564.

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

Study Location and Dates: Northeastern Thailand; 1972

Study Objectives: To compare the efficacy and toxicity of WR33063, a phenanthrenemethanol derivative and quinine sulfate in treatment of *P. falciparum* malaria in adult Thai males

Study Endpoints:

Parasite clearance time
Fever clearance time
Cure rate and recrudescence up to day 28 post-treatment

Treatment Groups:

1. WR 33063 (an investigational antimalarial agent not further described in this study)
2. Quinine

Inclusion/Exclusion Criteria:

Thai males ≥ 15 years old with symptomatic falciparum malaria
Asexual parasitemia between 1,000 and 100,000 parasites/ μ l
No use of antimalarial medication within 4 days prior to study
No cerebral or renal complications

Drug Products:

WR 33063 was supplied as 200 mg capsules
Quinine was supplied as quinine sulfate, NF, 540 mg base (2 enteric-coated tablets)

Dosage Regimens:

1. WR 33063 600 mg every 8 hours for 6 days
2. Quinine sulfate 540 mg base every 8 hours for 6 days

Concomitant Therapy: not reported in this publication

Scheduled Assessments:

Patients were admitted to a research ward of the hospital for 6 days
Signs and symptoms were recorded daily
Oral temperatures were taken every 6 hours
Quantitative parasite counts were obtained twice daily during hospitalization, then on days 14, 21, and 28 post-treatment
Blood tests for leukocyte count, hematocrit, bilirubin, alkaline phosphatase, creatinine, and serum malaria-specific antibodies were obtained on admission, days 3, 6, and 28.
Urine specimens for qualitative protein tests were obtained on admission, days 3, 6, and 28.

Determination of Efficacy:

Clearance of asexual parasitemia (presumably by day 6, but not specifically stated)
Recrudescence on follow-up (by day 28)

Safety Evaluation: Methods for monitoring adverse events were not described, except to note that signs and symptoms were recorded daily during hospitalization.

Study Results

Baseline Patient Demographics and Clinical Characteristics

Patients were similar with regards to age, but mean parasite counts were somewhat higher in the WR 33063 treatment group.

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

Characteristic	Quinine N=26	WR 33063 N=25
Median age (years) (range)	23.0 (15-53)	23.5 (15-53)
Geometric mean parasite count (range)/ μ l	13,500 (1,240-91,880)	20,400 (3,840-87,814)

Patient Disposition

Twenty two of 25 (88%) patients treated with WR 33063 completed the 28-day follow-up; while 21 of 26 (81%) quinine-treated patients completed follow-up.

Efficacy Outcomes

Parasitemia was cleared initially in 24/25 (96%) patients who received WR33063, and in 25/26 (96%) patients who received quinine. Additionally, 1 patient in the quinine treatment group had recrudescence by day 28 of follow-up. These data are combined as "treatment failures" in the table below. Mean fever and parasite clearance times were similar for both treatment groups.

Table 2. Clinical and Parasitological Responses (adapted from author's tables 2 and 7)

Outcome	Quinine N=26	WR 33063 N=25
Cure rate (ITT)	21/26 (80.7%)	23/25 (92%)
Cure rate (evaluable)	21/22 (95%)	23/25 (92%)
Treatment failures	1/26**	2/25*
Lost-to-follow up	4	0
Mean Parasite Clearance Time (hours) (range)	65.1 (21-103)	66.3 (21-113)
Mean Fever Clearance time (hours) (range)	59.7 (12-126)	58.5 (16-112)

*Of the two patients treated with WR 33063 who were not cured, one had a possible RIII response to treatment, the other was parasitemic on day 28, and presumably had recrudescence rather than reinfection.

**The one quinine-treated patient who was not cured had "rare" parasitemia by day 4, from 91,000/ μ l on admission. Subsequent treatment with sulfadoxine-pyrimethamine did not clear the parasitemia, and the patient was lost to follow-up.

Medical Officer Comments: Cure rates were high for quinine and comparator. This is an older study, and presumably rates of resistance to chloroquinine, mefloquine, and quinine were low in Thailand during the study period (1972), and may not be applicable today.

Safety Data

Adverse Events

The authors listed “symptomatic complaints” by patient-days, as shown in the table below. No attempt was made to identify drug- versus disease-related events.

Table 3. Symptomatic Complaints in Study Patients (from author’s table 3)

Complaint	WR33063 N=25	Quinine N=26
Headache	18	16
Fever	4	8
Dizziness	5	3
Weakness	0	7
Tinnitus	5	30
Insomnia	4	3
Blurred vision	1	4
Chest pain	1	4
Anorexia	4	7
Nausea, vomiting	4	3
Abdominal pain	6	9
Diarrhea	4	4
Constipation	2	2
Myalgia	5	1
Persistent hiccups	0	1

n= number of patient days

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10.1.2 Review of Individual Studies which evaluate Quinine Combination Therapy for Treatment of Uncomplicated *P. falciparum* Malaria

In this section, 11 studies evaluating quinine combination therapy are reviewed. The applicant identified 16 randomized, controlled studies which evaluated various quinine combinations. Six of these were reviewed in section 10.1.1 because quinine monotherapy arms were also included in those studies. Additionally, a recent randomized, controlled study comparing a quinine-clindamycin combination therapy in children (Ramharter, et al., 2005) was identified in the literature, and another pediatric study provided by the applicant (Kremsner, et al., 1994), are also included in this review.

Study 1: Duarte EC, Fontes CJF, Gyorkos TW, and Abrahamowicz M. Randomized controlled trial of artesunate plus tetracycline versus standard treatment (quinine plus tetracycline) for uncomplicated *Plasmodium falciparum* malaria in Brazil. Am. J. Trop. Med. Hyg. 1996; 54:197-202.

Study Design: Randomized, triple-blind, active controlled study

Study Objectives: To evaluate effectiveness and incidence of adverse events of artesunate plus tetracycline (both 7 days) compared with quinine (3 days) plus tetracycline (7 days) in treatment of uncomplicated falciparum malaria in Brazil

Study Location and Dates: Brazilian Amazon, January, 1992-October, 1993

Patient Population: age > 14 years

Inclusion Criteria:

- Confirmed uncomplicated falciparum malaria
- Age > 14
- No previous malaria treatment related to current episode
- Non-pregnant women (lactation not assessed)

Exclusion Criteria:

Mixed infection

Treatment Groups:

1. QT: quinine+ tetracycline
2. AT: artesunate + tetracycline

Drug Products:

The authors noted that all drugs were obtained from Brazilian Ministry of Health; and that artesunate was originally manufactured in the People's Republic of China (Guilin

Pharmaceutical Works, Guangxi, China). No further details were provided regarding drug products.

Dosage Regimens:

QT: oral quinine 1g q12h for 3 days + oral tetracycline 500 mg q8h for 7 days

AT: oral artesunate 100 mg first dose, then 50 mg in 12h and continued q12h for another 6 days + oral tetracycline 500 mg q6h for 7 days

Medical Officer Comments: The authors did not specify whether the quinine was dosed by the salt or base. This quinine dosing regimen would not be considered standard (10mg salt/kg q8h).

Concomitant Therapy:

Both treatment groups received a single dose of primaquine (45 mg base) as a gametocide on the seventh day of treatment.

Medical Officer Comments: Primaquine has little or no activity against the erythrocytic stage of P. falciparum, but does have gametocidal activity and its use may reduce malaria transmission. Because both treatment groups received primaquine, any effect on treatment efficacy should be similar for each group.

Study Procedures:

- Clinical examination and assessment of signs and symptoms on visit day 0, 2,4,7,14, and 28
- Thick blood smear for parasitemia at baseline and all follow-up visits
- WBC, hematocrit (packed cell volume), BUN and creatinine, AST and ALT at baseline and all follow-up visits

Study Endpoints:

(Primary endpoint not specifically stated)

1. Cure rates (defined as WHO criteria for parasitological cure, S or RI, RII, or RIII)
2. Parasite clearance at 48 hours after start of therapy

Follow-up Period: 28 days

Study Results

Patient Demographics and Clinical Characteristics

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

Characteristic	AT N=88	QT N=88
Gender (M/F)	72/16	73/15
Mean age ± SD (range)	32.3 ± 11.5 (15-57)	30.9 ± 11.8 (14-70)
Mean number of parasites/µl (range)	6,670 (204-85,082)	5,174 (175-170,285)
Hematocrit %(mean ± SD)	35.6 ± 5.7	36.8 ± 5.9
WBC/µl (mean ± SD)	6,121 ± 3,656	5,760 ± 2,226

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

BUN mg/dL (mean ± SD)	39.1 ± 15.1	36.3 ± 15.3
Creatinine mg/dL (mean ± SD)	1.1 ± 0.3	1.2 ± 0.3

AT= artesunate + tetracycline; QT= quinine + tetracycline; SD= standard deviation

Medical Officer Comments: Patients appeared reasonably well-matched between treatment groups for the parameters shown.

Patient Disposition

Table 2. Patient Disposition

	AT N=88	QT N=88
Completed study (28 days)	72 (81.8)	69 (78.4)
Excluded prior to treatment Due to vomiting	2	3
Lost to follow-up before end of treatment	1	3
Lost to follow-up before end of study	13	13

Medical Officer Comments: Reasons for patient loss to follow-up were not provided. Total study completion was similar for each treatment group. Study completion was lower in this study than in many of the other studies submitted for this NDA, possibly because this was an outpatient study.

Efficacy Outcomes

Parasite clearance at 48 hours was significantly higher in the AT group (98.5%) than the QT group (47.6%). No data was presented, however, regarding resolution of clinical signs and symptoms, including fever.

Medical Officer Comments: More rapid parasite clearance would be expected with artesunate in comparison to quinine.

The following table shows parasitological responses at the 28-day follow-up visit. Notably, no RIII failures were observed with either treatment group.

Table 3. Parasiological Cure at day 28 (adapted from author's table 3)

Treatment Response	AT N=88	QT N=88
Cure (S)- ITT population	70/88 (80%)	68/88 (77%)
Cure (S)- evaluable population*	70/72 (97.2%)	68/69 (98.6)
Treatment Failure:		
RI	2	1
RII	0	0
RIII	0	0

N= number of patients in ITT population

* Number of evaluable patients = number who completed 28 days of study (data not presented by authors)

Medical Officer Comments: The parasitological response rates were relatively low in the ITT population for both treatment groups because of the high drop-out rates; while the response rates were > 95% for both in the evaluable population, because of low recrudescence rates.

Efficacy Conclusions:

Based on parasitological response at 28 days, the combination of quinine (3 days) plus tetracycline (7 days) was comparable in efficacy to that of the artesunate-tetracycline regimen used for comparison in this study in this geographic area in the early 1990's. There have been a few reports of quinine resistance or reduced susceptibility in this geographical area more recently, but in general, these results should be applicable to this population today.

Safety Data

The following table shows the incidence of adverse events reported in this study. The authors observed that 43/86 (50%) patients in the AT group, and 70/85 (82.3%) patients in the QT group reported at least one adverse event. Relative risk for any adverse event in the QT treatment arm was 1.65 relative to the AT treatment arm. All of the adverse events listed were more common in the QT than AT treatment group. The most common adverse events in patients who received QT were dizziness, tinnitus, and abdominal pain.

Table. 4 Incidence of Adverse Events (author's Table 2)

Comparative incidence of side effects observed in patients given artesunate plus tetracycline (AT) or quinine plus tetracycline (QT)

Side effect	Treatment groups*		Relative risk (95% CI) [†] QT/AT
	AT	QT	
Dizziness	7/85 (8.2)	28/82 (34.1)	4.15 (1.92-8.96) [‡]
Abdominal pain	14/85 (16.5)	20/84 (23.8)	1.44 (0.78-2.67)
Nausea	7/86 (8.1)	15/82 (18.3)	2.25 (0.97-5.23)
Weakness	7/85 (8.2)	14/82 (17.1)	2.07 (0.81-6.72)
Tinnitus [§]	0/85 (0.0)	20/82 (24.4)	20.73 (2.85-150.96) [‡]
Anorexia	4/85 (4.7)	14/82 (17.1)	3.63 (1.25-10.57) [¶]
Vomiting	6/86 (7.0)	10/84 (11.9)	1.71 (0.65-4.49)
Myalgia	6/85 (7.1)	10/83 (12.0)	1.71 (0.65-4.48)
Sweating	3/85 (3.5)	12/82 (14.6)	4.15 (1.21-14.16) [¶]
Headache	4/85 (4.7)	9/82 (11.0)	2.33 (0.75-7.28)
Bitter taste	5/85 (5.9)	8/82 (9.8)	1.66 (0.57-4.86)
Diarrhea	2/85 (2.3)	7/82 (8.5)	3.63 (0.78-16.96)
One or more side effect	43/86 (50.0)	70/85 (82.3)	1.65 (1.30-2.08) [‡]

* Values are the number of affirmative responses/number responding (%). Denominators differ due to missing information.

[†] Taylor series 95% confidence interval (CI) for relative risks (Greenland and Robins²⁰).

[‡] P < 0.001, by chi-square test.

[§] Approximate relative risk (cell containing zero was replaced by one).

[¶] 0.05 > P > 0.01, by chi-square test.

Laboratory values obtained during or post-treatment were not discussed in this publication.

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Medical Officer Comments: *The common adverse events, dizziness, tinnitus, abdominal pain, which could all be symptoms of cinchonism, were frequent in this study despite the short course of quinine (3days). This study used a different dosing regimen than "standard" quinine regimen of 10 mg/kg q8h. Thus, it is possible that serum levels of quinine were higher post-dose in this than in other studies, and quinine toxicity may be related to serum levels.*

Study 2: Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, and Masngammueng R. Compliance with artesunate and quinine plus tetracycline treatment of uncomplicated malaria in Thailand. Bull. WHO 1998; 76: 59-66.

Study Design: Randomized, active-controlled trial

Study Objectives: To compare compliance with standard regimen (7 days quinine plus tetracycline) to 5 days of oral artesunate for treatment of uncomplicated falciparum malaria in Thailand; and to determine reasons for compliance or non-compliance with treatment

Study Location and Dates: Thailand (near Thai-Cambodian border), October, 1994 to August, 1995

Study Population: patients aged 15-60 years with uncomplicated *P. falciparum* malaria

Inclusion Criteria:

Confirmed falciparum malaria

Exclusion Criteria:

Pregnant women

Severe or complicated malaria

History of renal and/or hepatic disease

Allergy to artesunate, quinine or tetracycline

Treatment Groups:

Artesunate monotherapy

Quinine + tetracycline

Drug Products:

Quinine: 300 mg tablets

Tetracycline: 250 mg tablets

Artesunate: 50 mg tablets

Further information on drug products was not provided in the publication.

Dosage Regimens:

1. Oral artesunate 300 mg on day 0 in clinic, then 100 mg daily at home on days 1-4

2. Oral quinine 600 mg + oral tetracycline 500 mg in clinic on day 0, then quinine 600 mg tid + tetracycline 500 mg bid at home on days 1-6.

Concomitant Therapy:

None reported

Study Procedures:

Patients were followed up on day 5 (artesunate group) or day 7 (quinine+ tetracycline group) to assess compliance

Peripheral blood smear was performed on day 5 (artesunate group) or day 7 (quinine+ tetracycline group) to assess curative effective

Study Endpoints:

Compliance: adherence to protocol, or not missing a single dose of prescribed treatment, as reported by interview, or absence of residual pills on follow-up visit

Curative effectiveness: Results of peripheral blood smear (positive or negative) at 5 days in the artesunate group, and at 7 days in the quinine + tetracycline group

Medical Officer Comments: This definition of cure is different from that used in most of the other studies reviewed for this NDA, so the results will be difficult to compare with other studies.

Duration of Follow-up: Patients who received artesunate were followed for 5 days, and those who received quinine+ tetracycline were followed for 7 days.

Medical Officer Comments: Because these patients were not followed for 28 days, as in most of the other studies, adequate clinical and parasitological cure cannot be determined for comparison.

Study Results:

Patient Demographic and Clinical Characteristics

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

Characteristic	Quinine + tetracycline N=60	Artesunate N=77
Mean age \pm SD	31.9 \pm 11.5	30.8 \pm 9.4
Gender (M/F)	59/1	61/16

SD= standard deviation

Medical Officer Comments: Significantly more males than females were enrolled in the quinine + tetracycline treatment arm than in the artesunate treatment arm of the study. Additionally, baseline level of parasitemia was not provided in this publication.

Patient Disposition

A total of 114/137 (83.2%) enrolled subjects returned for follow-up within the first. Although there was no statistically significant difference between treatment groups, 11.7% patients in the

quinine+tetracycline group, and 20.8% of those in the artesunate group were lost to follow-up, respectively.

Compliance with Antimalarial Drug Regimen

Compliance with therapy among patients who were not lost to follow-up was 98.4% in the artesunate group, and 71.7% in the quinine + tetracycline group. If patients lost to follow-up were considered non-compliant, 77.9% patients in the artesunate group, and 63.3% patients in the quinine + tetracycline group were compliant with treatment. The most common reason for non-compliance was adverse reactions, reported in 6/16 patients interviewed who received quinine + tetracycline.

Efficacy Outcomes

Table 2. Comparison of Cure Rates* for Artesunate and Quinine + Tetracycline Groups

Cure Rates*	Quinine + tetracycline N=60	Artesunate N=77
ITT Population	41/60 (68.3)	61/77 (79.2)
Evaluable Population**	41/53 (77.4)	61/61 (100)

* 5-day cure rate for artesunate group; and 7 day cure rate for quinine + tetracycline group

** Patients who completed study within 1 week

Efficacy Conclusions:

1. The 5-day cure rate for patients treated with artesunate was 79-100%; while the 7 day cure rate for the quinine + tetracycline regimen was 68-77% in this study.
2. Recrudescence rates and 28-day cure rates were not determined.

Safety Data

The authors reported that the rate of adverse events was 49% among patients who received artesunate, and 80% among those who received quinine + tetracycline. The specific adverse reactions reported were headache, vomiting, dizziness, diarrhea, drowsiness, tinnitus, and body ache. Incidence of these reactions by treatment group was not reported.

Adverse events that resulted in non-compliance in the quinine combination therapy group were tinnitus, vomiting, severe diarrhea, and "could not tolerate".

Study 3: Salcedo JMV, Camargo LMA, Braga, MFV, de Maria PS, and de Oliveira Macedo V. Evaluation of the efficacy of artesunate associated with tetracycline in the therapy of falciparum malaria. Brazil Soc. Trop. Med. J. 1997; 30:215-222 {English translation}

Study Design: Randomized, active-controlled trial

Study Objectives: To compare the efficacy of artesunate with quinine and mefloquine in therapy of non-severe falciparum malaria in Porto Velho, Rondonia, Brazil

Study Location and Dates: Brazil, dates not provided

Study Population: patients seeking care at CEMETRON (Tropical Medicine Center of Rondonia) with non-severe malaria

Inclusion Criteria:

Parasitological diagnosis of falciparum malaria
Residence in Porto Velho
Clinical condition of non-severe malaria

Exclusion Criteria:

Pregnant women
Use of antimalarial drugs in previous 15 days

Treatment Groups:

Group 1: artesunate (oral) + tetracycline (oral)
Group 2: artesunate (intravenous, IV) + tetracycline (oral)
Group 3 mefloquine (oral)
Group 4: quinine (IV) + tetracycline (oral)
Group 5: quinine (oral) + tetracycline (oral)

Drug Products:

Not described in publication

Dosage Regimens:

Quinine (IV): 10 mg/kg q8h for 3 days
Quinine (oral): 10 mg/kg q8h for 3 days
Artesunate (IV): 1.5 mg/kg at 0, 4, 24, and 48 hours
Artesunate (oral): 100 mg initial dose, then 50 mg q12h for 5 days
Tetracycline (oral): 500 mg q8h for 7 days
Mefloquine (oral): single dose 15 mg/kg (maximum dose 1000 mg)

Concomitant Medications:

Not described in publication

Study Procedures:

Clinical history on admission
Clinical follow-up daily during admission, then on day 7, 14, 21, and 28 post-treatment initiation
Vital signs (oral temperature): every 6 hours
Blood tests: hemogram, transaminases, bilirubin, urea, creatinine, and glucose on admission, and on days 3 and 7
Parasite count: every 12 hours during admission, the on same day as clinical follow-up

Medical Officer Comments: Although not specifically stated, it would appear that all patients were hospitalized for some unspecified time period.

Study Endpoints:

Primary endpoint was not specifically stated; and definitions for the following endpoints were not provided:

Time of fever resolution

Parasite clearance time

Percentage cure

Medical Officer Comments: Presumable the cure rates reflect the 28 day follow-up for recurrence of parasitemia or symptoms of malaria.

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

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

Characteristic	AT (PO) N=8	AT (IV) N=8	M (PO) N=12	QT (IV) N=6	QT (PO) N=8
Mean age ± SD (range)	28 ± 9.8 (15-43)	38 ± 8.7 (8-64)	32 ± 12.1 (12-54)	29 ± 14.6 (10-53)	37 ± 10.3 (22-57)
Gender (M/F)	7/1	5/3	10/2	6/0	7/1

AT (PO)= oral artesunate + tetracycline; AT (IV)= IV artesunate + oral tetracycline; M (PO)= oral mefloquine; QT (IV)= IV quinine + oral tetracycline; QT (PO) = oral quinine + tetracycline
SD= standard deviation

Medical Officer Comments: As in most of the other studies, more males than females were enrolled. The authors also presented initial parasitemia; however, the units presented were not clear in the English translation provided by the applicant, and are not presented here. Of note, average parasitemia was lowest in the group which received IV quinine plus tetracycline.

Patient Disposition

In all study groups, 26/42 (61.9%) completed 28 days of follow-up. Study completion by treatment group was not reported, and reasons for withdrawal or loss to follow-up were not provided.

Efficacy Outcomes

The authors pooled treatment groups by medication regardless of mode of administration, to determine 28-day cure rates in the evaluable population (e.g. quinine (IV) + tetracycline and quinine (oral) + tetracycline groups were pooled). For the 26 patients who completed the study, cure rates were 88%, 85.7%, and 81.8% for the pooled artesunate, mefloquine, and quinine treatment groups, respectively. The authors also reported that 1 patient from each group had an RI failure, and one patient in the quinine group was classified as an RIII failure (RI and RIII not

specifically defined in this publication, but as defined by the WHO, refer to initial clearance, followed by recrudescence by day 28 for RI, and no significant reduction in parasitemia by 48 hours for RIII).

Medical Officer Comments: Because cure rates were not presented separately for oral and IV therapy, these data are not directly applicable to this NDA for oral quinine sulfate.

Efficacy Conclusions:

For pooled treatment groups, in evaluable patients, 28-day cure rates were 88%, 85.7%, and 81.8% for regimens containing artesunate + tetracycline, mefloquine + tetracycline, and quinine + tetracycline, respectively.

Safety Data

Methods for collecting and reporting adverse event data were not described. Adverse events, as reported in this study are shown in the following table. The authors also noted that all patients complained of headache (cephalea), and that it was impossible to difference between symptoms of the infection and adverse drug reactions. All adverse events were mild, and self-limited. Additionally, no significant difference was observed in mean pre-and post- treatment laboratory values in any of the pooled treatment groups.

Table 2. Adverse Events Reported in Study by Pooled (IV and oral) Treatment Groups

Adverse Event	Artesunate + tetracycline	Mefloquine	Quinine + tetracycline
	%*	%*	%*
Diarrhea	12.5%	25%	12.5%
Abdominal pain	12.5%	16.6	37.5%
Nausea	12.5%	NR	NR

*Population (ITT or evaluable) was not specified

NR= not reported

Medical Officer Comments: The overall incidence of adverse events was not reported. Additionally, because adverse event profiles may differ depending on the route of drug administration, the validity of these data are uncertain because treatment groups were combined.

Study 4: De Alencar, FE, Cerutti C, Durlacher RR, Boulos M, Alves FP, Milhous W, and Pang LW. Atovaquone and proguanil for the treatment of malaria in Brazil. J. Infect. Dis. 1996; 175:1544-1547.

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

Study Objectives: To evaluate efficacy of atovaquone plus proguanil for treatment of uncomplicated *P. falciparum* malaria in comparison with the standard regimen of quinine plus tetracycline, in Brazil.

Study Location and Dates: Peixoto de Azevedo in the southern Brazilian Amazon, April, 1995 to January, 1996

Study Population: Adult males, aged 18-65 year with confirmed falciparum malaria (semi-immune population)

Inclusion Criteria:

Males aged 18-65 years

Confirmed *P. falciparum* malaria with parasite count of 1000-100,000/ μ L

Exclusion Criteria:

Grossly abnormal baseline laboratory results

Refusal to stay hospitalized for 28 days

Intolerance or missing doses of study medication

Treatment Groups:

Atovaquone plus proguanil

Quinine plus tetracycline

Drug Products:

All drugs were prepared by Wellcome Diagnostics (Research Triangle Park, NC). Further details were not provided in publication.

Dosage Regimens:

Atovaquone 1g plus proguanil 400 mg daily for 3 days

Quinine 600 mg tid plus tetracycline 250 mg qid for 7 days

Concomitant Medications:

If patients developed *P. vivax* malaria during hospitalization, 450 mg chloroquine was administered, followed by "complete treatment" at discharge.

Patients with resistant *P. falciparum* were treated with a single dose mefloquine, 1g.

Study Procedures:

- Patients were admitted to research ward of hospital for 28 days.
- Baseline laboratory data: CBC and differential count, serum creatinine, urea, liver enzymes, bilirubin, albumin, glucose, urinalysis, and blood smear for parasite count, and parasite culture
- On-treatment evaluation: physical examination daily for first week, then weekly. Blood smears for parasites were obtained every 6 hours until 3 consecutive slides were negative, then on days 7, 14, 21, and 28. CBC and serum chemistries were obtained on days 3, 7, 14, and 28.
- Signs and symptoms were reported with a standardized questionnaire at each examination, and until resolution.

Study Endpoints:

- Primary endpoint was not stated.
- Cure rates
- Level of Resistance: Defined by WHO criteria (RI= clearance of parasitemia by day 7, but recurrence on or before day 28; RII= parasite count < 25% of the initial count at 48hours, and parasitemia on day 7; RIII= parasite count \geq 25% initial parasite count 48 hours after initiation of therapy.
- Parasite clearance time (PCT)
- Fever clearance time (FCT)

Duration of Follow-up: 28 days

Study Results

Patient Demographics and Clinical Characteristics

There was no significant difference between treatment groups for patient age or initial parasite count. There was no significant difference in baseline laboratory data between treatment groups except for somewhat higher mean AST and ALT in the quinine+tetracycline group. The mean AST was 20.2 ± 1.1 for the atovaquone-proguanil group and 24.2 ± 2.9 for the quinine-tetracycline group; while the mean ALT was 17.4 ± 1.1 for the atovaquone-proguanil group and 24.4 ± 3.5 for the quinine-tetracycline group.

Medical Officer Comments: The difference in mean AST and ALT at baseline is probably not clinically significant.

Patient Disposition

A total of 175 patients were randomized, but the number randomized to each treatment group was not provided. A total of 77 patients in each treatment group were considered evaluable. Twenty one patients were withdrawn from the study. The reasons for study withdrawal are listed below, although treatment group was not specified:

- Left the ward before day 28 (6)
- Failed to take study drug for 24 hours (1)
- Treated with complete course of chloroquine and primaquine (9)
- Mistaken diagnosis of *P. falciparum* malaria (2)
- Mixed *P. falciparum* and *P. vivax* infection (1)
- Concomitant cutaneous leishmaniasis (1)
- Hemolytic syndrome (1)

Medical Officer Comments: The nature of the hemolytic syndrome was not discussed, not is it clear whether this event occurred during treatment.

Efficacy Outcomes

Both regimens were effective in this population for treatment of uncomplicated *P. falciparum* malaria, as shown in the table below. One patient in the atovaquone-proguanil group had recrudescence (on day 21). Mean fever and parasite clearance times were shorter in the atovaquone-proguanil group than in the quinine-tetracycline group.

Table 1. Reported Efficacy Outcomes

Outcome	Atovaquone + proguanil N=77	Quinine + tetracycline N=77
Cure* (Evaluable population)	76 (99%)	77 (100)
RI	1	0
Mean PCT (hours) ± SD	56.1 ± 14.1	64.5 ± 23.1
Mean FCT (hours) ± SD	18.8 ± 17.7	28.5 ± 19.8

N= evaluable patients; SD= standard deviation

*Cure= presumably 28 day cure rate, although not specifically defined in publicaion

Efficacy Conclusions:

In this population of semi-immune adults in Brazil, both treatment regimens were highly effective (> 95%) in the treatment of uncomplicated falciparum malaria.

Safety Data

The incidence of adverse events was 48/77 (62.3%) in the atovaquone-proguanil group, and 69/77 (89.6%) in patients treated with quinine-tetracycline. Adverse events are shown in the table below. The most common adverse events were tinnitus, dizziness, abdominal pain, and nausea. Those events which occurred more frequently in patients who received quinine-tetracycline than the comparator were tinnitus, dizziness, nausea, and anorexia.

Table 2. Adverse Events Reported in Study (author's Table 1)

Table 1. Number of patients receiving atovaquone plus proguanil (n = 77) or quinine plus tetracycline (n = 77) who had adverse side effects.

Symptom	Atovaquone + proguanil	Quinine + tetracycline	P*
Tinnitus	3	55	<.01
Dizziness	10	39	<.01
Abdominal Pain	20	18	.71
Nausea	12	22	.05
Weakness	9	15	.08
Headache	17	9	.08
Diarrhea	5	9	.26
Anorexia	5	13	.04
Pruritus	6	4	.51
Vomiting	4	5	.73
Without any side effect (%)	29 (37.6)	8 (10.4)	—

* By χ^2 analysis.

Medical Officer Comments: No deaths or serious adverse events were reported in this study. The adverse events which occurred more often in the quinine-tetracycline group fit

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the known profile of quinine toxicity. It is notable that adverse events were reported only for evaluable patients, and not for the ITT population, although the authors did not report any patient withdrawal due to adverse events.

Study 5: Bunnag D, Karbwang J, Na-Bangchang, Thanavibul A, Chittamas Su, and Harinasuta T. Quinine-tetracycline for multidrug-resistant falciparum malaria. Southeast Asian J. Trop. Med. Pub. Health 1996; 27:15-18.

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

Study Objectives: To compare efficacy and toxicity of 5- or 7-day regimen of quinine combined with 7-day course of tetracycline

Study Location and Dates: Bangkok, Thailand, 1990-1992

Study Population: adult males, aged 16-54 years

Inclusion/Exclusion Criteria:

Acute uncomplicated malaria with asexual parasitemia < 5%
No history of liver or kidney disease
Hospitalized patients
Weight 40-81 kg
Written informed consent

Treatment Groups:

Group A: Quinine 5 days plus tetracycline 7 days (Q5T7)
Group B: Quinine 7 days plus tetracycline 7 days (Q7T7)

Drug Products:

Information not provided in publication

Dosage Regimens:

Q5T7: quinine 600 mg tid for 5 days plus tetracycline 250 mg qid for 7 days
Q7T7: quinine 600 mg tid for 7 days plus tetracycline 250 mg qid for 7 days

Concomitant Medications: none reported in publication

Study Endpoints:

Primary Endpoint was not identified.
Parasite clearance time
Fever clearance time
Cure rate
Occurrence of adverse events

Study Procedures:

Parasite count was performed every 6 hours until negative, then daily for 28 days
 Onset and resolution of adverse reactions were recorded, as well as severity
Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

Table 1. Patient Characteristics at baseline (from author's Table 1)

Characteristic	Q5T7 N=48	Q7T7 42
Median age (range) (years)	24 (17-40)	25 (16-54)
Median Parasitemia (count/ μ L) (range)	23,424 (159-292,432)	24,542 (630-343,800)

Medical Officer Comments: Patients appeared fairly well matched by age, except for a wider age range in the Q7T7 group. The baseline level of parasitemia was similar for both groups.

Patient Disposition

Two patients in each group did not complete the 28-day follow-up period. Reasons for adverse events were not provided, except that no patient withdrew from the study due to adverse events. A total of 86 patients were considered evaluable.

Efficacy Outcomes

Table 2. Efficacy Outcomes (adapted from author's Table 2)

	Q5T7 N=48	Q7T7 N=42
Median FCT (hours) (range)	75 (4-136)	75 (12-132)
Median PCT (hours) (range)	88 (45-159)	90 (45-135)
Cure Rate n(%) (28-day) (ITT)	40/48 (83)	40/42 (95)
Cure Rate n (%) (28 day) (Evaluable population)	40/46 (87)	40/40 (100)
RI response	6	0

Medical Officer Comments: The longer course of quinine (7 days) in combination with tetracycline was better than the shorter course (5 days quinine) for cure of falciparum malaria despite very similar fever and parasite clearance times.

Efficacy Conclusions:

The combination of quinine (7 days) plus tetracycline (7 days) resulted in higher cure rates than quinine (5 days) plus tetracycline (7 days).

Safety Data

The incidence of adverse events was similar in both treatment groups. The most common events were tinnitus, nausea, vomiting, dizziness, loss of appetite, and tinnitus. These data were not provided individually by treatment group.

Study 6: Vaninjanonta S, Chantra A, Phophak N, Chindanond D, Clemens R, and Pukrittayakamee S. Therapeutic effects of chloroquine in combination with quinine in uncomplicated falciparum malaria. *Ann. Trop. Med. Parasitol.* 1996; 90:269-275.

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

Study Objectives: To determine whether the addition of chloroquine to quinine had any antimalarial or antipyretic effects on chloroquine-resistant falciparum malaria

Study Location and Dates: Bangkok, Thailand, 1993-1994

Patient Population: males with uncomplicated falciparum malaria

Inclusion Criteria:

Hospitalized males with uncomplicated falciparum malaria
Written informed consent

Exclusion Criteria:

Severe falciparum malaria
Receipt of antimalarial drugs in previous 24 hours or positive urine test for sulfonamides or 4-aminoquinolines

Treatment Groups:

Quinine plus tetracycline
Quinine plus chloroquine

Drug Products: no information provided in publication

Dosage Regimen:

Quinine plus tetracycline: 10 mg salt/kg tid for 7 days plus 4 mg/kg qid for 7 days
Quinine+ chloroquine: quinine 10 mg salt/kg tid for 7 days plus chloroquine 5 mg base/kg at 0, 6, 30, and 54 hours

Concomitant Medications:

Oral paracetamol(0.5-1.0g q4h was given for fever (temperature > 38°C.)

Medical Officer Comments: Receipt of paracetamol (acetaminophen) could alter fever clearance times.

Study Endpoints:

Primary endpoint was not specifically stated.

Recrudescence rates were analyzed in patients who remained in Bangkok (either hospitalized or at home, i.e. outside of malarious area) for at least 2 months post-treatment

Parasite clearance time (PCT)

Fever clearance time (FCT)

Medical officer Comments: Cure rates in this study were calculated by the medical officer and Statistical review from recrudescence rates which were determined from a 2 month, rather than 28 day follow-up, as in most other studies.

Study Procedures:

All patients were hospitalized for 1-2 months

Baseline: clinical assessment, confirmation of diagnosis, baseline hematology and biochemistry, and electrocardiogram

On-Treatment Assessments:

Electrocardiogram at 48 hours after starting treatment

Weekly hematology and biochemistry

Vital signs every 4 hours until resolution of fever, then every 6-12 hours

Blood smears for parasite counts every 12 hour until clearance, then daily for 28 days

Medical Officer Comments: This is one of the few studies who evaluated ECGs during treatment.

Duration of Follow up: 2 months

Study Results

Patient Demographic and Clinical Characteristics

Table 1. Baseline Patient Characteristics

Characteristic	Quinine + Tetracycline N=25	Quinine + Chloroquine N=25
Mean age ± SD	27 ± 9	23 ± 7
Mean Parasite count/μL	19,498	18,197
Mean hematocrit (%)± SD	33.8 ± 7.7	33.2 ± 6.9
Mean serum bilirubin (mg/dL) ± SD	1.4 ± 1.2	1.6 ± 0.9
Mean serum creatinine (mg/dL)± SD	1.1 ± 0.2	1.1 ± 0.3
Mean AST (mg/dL) ± SD	40.9 ± 26.3	45.5 ± 22.8

SD= standard deviation

Medical Officer Comments: Patients appeared to be fairly closely matched for age, baseline parasitemia, and laboratory values between treatment groups.

Patient Disposition

Eighteen of 25 (72%) patients in each treatment group completed 2 months follow-up in the study. Reasons for loss to follow-up were not provided.

Efficacy Outcomes

Table 2. Treatment Outcomes

Outcome	Quinine + Tetracycline N=25	Quinine + Chloroquine N=25
Cure Rate (ITT Population)	17/25 (68%)	11/25 (44%)
Cure Rate (Evaluable population)	17/18 (94%)	11/18 (61%)
Recrudescence rate	1/18 (6%)	7/18 (39%)
PCT (hours) ± SD	83 ± 21	80 ± 25
FCT (hours)	42 ± 27	51 ± 33

PCT= parasite clearance time; FCT = fever clearance time

Medical Officer Comments: Cure rates were determined by subtracting number of patients with recrudescence from the number of patients evaluated. In the ITT analysis, patients lost to follow-up were considered treatment failures. Cure rates may have been somewhat lower in this study for the ITT population than in other because of the longer follow-up period in this case. Addition of chloroquine to quinine had no positive effects on PCT or FCT in comparison to quinine-tetracycline.

Efficacy Conclusions:

1. Cure rates were higher in patients who received the combination of quinine plus tetracycline than those treated with quinine plus chloroquine.

Medical Officer Comments: Because of high levels of chloroquine resistance in this area, treatment with quinine plus chloroquine would not be expected to have efficacy any greater than quinine monotherapy, which was not used in this study.

Safety Data

No serious adverse events were reported in this study. The authors also state that there was no evidence of cardiotoxicity or iatrogenic hypotension. Cinchonism was common in both groups, but was always reversible. Adverse events by treatment group were not reported. There were no significant laboratory changes reported in either treatment group.

Median QTc prolongation in the quinine-chloroquine group at 48 hours post-initial dose, was 11% (range -17% to +21%), and 7% (range -5% to +24%) in the quinine-tetracycline group.

Medical Officer Comments: Although not clearly defined, the values for QTc prolongation shown above probably refer to the median difference in QTc from baseline to 48 hours post-initial dose. A 25 % change in QTc (upper end of range for both groups) could be clinically significant.

Study 7: Looareesuwan S, Vanijanonta S, Viravan C, Wilairatana P, Charoenlarp P, Lasserre R, canfield C, Kyle DE, and Webster HK. Randomized trial of mefloquine-tetracycline and quinine-tetracycline for acute uncomplicated falciparum malaria. Acta Tropica 1994; 57:47-53

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

Study Objectives: To evaluate the efficacy of mefloquine plus tetracycline with the standard regimen of quinine plus tetracycline for treatment of uncomplicated falciparum malaria

Study Location and Dates: Bangkok, Thailand, June to November, 1991

Study Population: patients hospitalized for uncomplicated malaria

Inclusion Criteria:

Parasite counts 100-400,000/ μ L
Aged 16-60 years old
Weight 45-60 kg
Informed consent
Agreed to remain hospitalized for 28 days

Exclusion Criteria:

Pregnancy
Severe malaria
Receipt of antimalarial drugs within preceding week

Treatment Groups:

MT: Mefloquine + tetracycline
QT: Quinine + tetracycline

Drug Products:

Mefloquine (Lariam®, Roche)
Tetracycline hydrochloride (Government Pharmaceutical Organization, GPO)
Quinine sulphate (GPO)

Dosage Regimens:

MT: mefloquine 750 mg (oral) first dose, then 500 mg (oral) 6 hours later, plus tetracycline 250 mg (oral) q6h for 7 days
QT: quinine sulfate 600 mg salt (oral) q8h with tetracycline 250 mg (oral) q6h for 7 days

Study Endpoints:

Primary endpoint not described in publication

Cure rate at 28 days (defined as absence of recrudescence during 28 day follow-up)

Parasite clearance time (PCT) was defined as time from start of treatment until first time the blood smears were negative.

Fever clearance time (FCT) was defined as time from start of treatment until oral temperature fell to 37.5°C, and remained therefore 48 hours.

Study Procedures:

All patients were hospitalized for 28 days.

Vital signs every 4 hours

Signs and symptoms daily for first 7 days, then weekly

Laboratory tests: CBC, platelet count, erythrocyte sedimentation rate, electrolytes, total and direct bilirubin, alkaline phosphatase, blood urea, creatinine, albumin, globulin, AST, ALT performed at baseline, then on days 7, 14, 21, and 28

Blood smears for parasites were performed every 6 hours until negative, then daily

Blood samples were also obtained on admission and at time of recrudescence to assess parasite growth and *in vitro* drug susceptibility.

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

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

Characteristic	MT N=52	QT N=50
Age range (years)	16-51	17-67
Gender (M/F)	36/16	39/11
Parasite count/ μ L (range)	267-183,300	200-367,770

Medical Officer Comments: Patients were fairly closely matched for these parameters.

Patient Disposition

Of 102 patients randomized, a total of 93 patients, 47/52 randomized to the MT group, and 46/50 to the QT group completed the 28-day follow-up period. Reasons for loss to follow-up were not provided in the publication.

Efficacy Outcomes

Cure rates were similar for both treatment groups. There were no patients that had RIII recrudescence (high level resistance). Parasite isolates obtained from the 3 patients with recrudescence showed an increased IC50 for mefloquine and quinine in comparison to the admission isolate in 2 of 3 cases.

Table 2. Outcomes for Patients in Study (from author's Table 2)

Outcome Measure	MT N=52	QT N=50
Cure rate (28 days) (ITT Population)	44/52 (85%)	45/50 (90%)
Cure rate (28 days) (Evaluable population)	44/47 (94%)	45/46 (98%)
Number of patients with recrudescence (RI response)	3	1
Mean FCT (hours) (range)	47.8 (4-128)	61.8 (4-156)
Mean PCT (hours) (range)	64 (26-127)	73.9 (23-128)

Efficacy Conclusions:

1. Cure rates were similar for the mefloquine-tetracycline and the quinine-tetracycline regimen in this population in the early 1990's in Thailand.
2. Clearance of parasitemia and fever was more rapid in the mefloquine-tetracycline treatment group.

Medical Officer Comments: The authors note that the cure rates for mefloquine-tetracycline were higher than observed for mefloquine alone in earlier studies in this geographical region, cited in the publication. Apparently addition of tetracycline to mefloquine results in higher mefloquine concentrations in the plasma which may be required to prevent recrudescence, as the IC50's increased in 2/3 isolates with recrudescence. Alternatively, there may an additive or synergistic effect of mefloquine with tetracycline. Similar conjectures can be made about the quinine-tetracycline combination, although the isolate from the single patient with recrudescence was not further evaluated.

Safety Data

The authors reported symptoms after the start of treatment, but acknowledged the difficulty in distinguishing disease-related and drug-related reactions. These data are shown in the table below. The authors also noted that 6 patients, 4 in the MT group, and 2 in the QT group had normal transaminases on admission, but increased levels (103-154 IU) 2-3 weeks after starting treatment. These values returned to normal in 3-6 weeks.

Table 3. Adverse Events ("Symptom") reported in Study

Symptom	MT N=52	QT N=50
Headache	67%	82%
Dizziness	71%	70%
Cinchonism	12%	94%
Nausea	48%	52%
Vomiting	13%	28%

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

Abdominal pain	8%	12%
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Medical Officer Comments: Assuming these symptoms are adverse events, those more frequent in the quinine-tetracycline group were headache, cinchonism, nausea, vomiting, and abdominal pain.

Study 8: Karbwang J, Na-Bangchang K, Thanavibul A, Bunnag D, Chongsuphajaisiddhi T, and Harinasuta T. Comparison of oral artesunate and quinine plus tetracycline in acute uncomplicated falciparum malaria. Bull. World Health Org. 1994; 72:233-238.

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

Study Objectives: To assess the efficacy of artesunate in patients with multidrug-resistant falciparum compared with that of the second-line drug treatment, quinine-tetracycline

Study Location and Dates: Bangkok, Thailand; study dates not provided

Study Population: adult males

Inclusion Criteria:

Male patients aged 15-35 years with acute, uncomplicated falciparum malaria
Written informed consent

Exclusion Criteria:

Parasitemia > 5%
Severe malaria
History of liver or kidney disease
Receipt of antimalarial drugs for this illness

Treatment Groups:

1. Artesunate
2. Quinine sulfate + tetracycline

Drug Products:

Information not provided in publication

Dosage Regimens:

1. Artesunate 200 mg (oral) initial dose, then 100 mg 12 hours later, then 100 mg daily for 4 days
2. Quinine sulfate 600 mg (oral) q8h + tetracycline 250 mg (oral) q6h for 7 days

Concomitant Medications:

Patients who had *P. vivax* malaria during follow-up were given chloroquine 150 mg (suppressive therapy), then definitive treatment on discharge.

Study Endpoints:

Primary endpoint not specifically stated in publication

Parasite clearance time (PCT)

Fever clearance time (FCT)

Rate of treatment failure (RI, RII, and RIII):

- RI was defined as disappearance of parasitemia, but reappearance within 28 days
- RII was defined as decrease of parasitemia, but parasites never disappeared from peripheral blood
- RIII was defined as no marked decrease or even increase in parasitemia within 48 hours
- S was defined as cure, with no reappearance of parasite within 28 days

Occurrence of adverse events

Study Procedures:

All patients were hospitalized.

Blood smears were performed at baseline, and then every 6 hours until parasites were undetectable, then twice daily until day 28.

CBC, biochemistry (renal and hepatic laboratory tests) were performed on admission, on days 2, 4, 7, then weekly through day 28.

ECGs were obtained daily in the artesunate group through day 7, then weekly

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

Baseline characteristics are shown in the following table. In addition, there was no significant difference in mean laboratory values for hematocrit, WBC, bilirubin, alkaline phosphatase, AST, ALT, creatinine, BUN, or albumin.

Table 1. Baseline Patient Characteristics

Characteristic	Artesunate N=31	Quinine+tetracycline N=33
Mean age (range)	25 (15-35)	23 (17-35)
Geometric mean parasitemia (per μL) (range)	50,206 (504-292,560)	35,188 (351-175,010)

Medical Officer Comments: Treatment groups were similar with regards to age and baseline parasitemia.

Patient Disposition

In the artesunate treatment group, 30/31 (%) patients completed the 28 days of follow-up; while in the quinine+tetracycline group, 30/33 patients completed the study. Reasons for loss-to follow-up were not provided, but it was noted that the patients that left the study did not have parasitemia.

Efficacy Outcomes

Fever and parasite clearance time were more rapid in the artesunate treatment group than in the quinine-tetracycline group; while 28 day cure rates were similar, as shown in the following table.

Table 2. Therapeutic Outcomes (adapted from author's Table 2)

Outcome measures	Artesunate N=31	Quinine + tetracycline N=33
28 day cure rate (ITT population)	29/31 (93%)	30/33 (91%)
28 day cure rate (evaluable population)	29/30 (96.7%)	30/30 (100%)
Mean PCT (hours) (range)	36.5 (24-52)	73.2 (36-135)
Mean FCT (hours) (range)	31.3 (4-67)	55.4 (4-104)

Medical Officer Comments: *In this study, the rate of recrudescence in the artesunate treatment group was lower in comparison to other studies which used lower total doses of artesunate. In the evaluable population, the efficacy of the quinine-tetracycline combination was 100% in these hospitalized patients. Lower cure rates might be expected in outpatients or in those not enrolled in a clinical study, due to lower rates of compliance with quinine due to adverse events.*

Safety Data

Drug-related adverse events, defined as signs or symptoms which first occurred after drug administration, or increased from baseline, were reported in this study, as shown in the following table. Tinnitus was significantly more common in the quinine-tetracycline group than in the artesunate group.

Table 3. Incidence of Drug-Related Adverse Events in Study (adapted from author's Table 3)

Drug-Related Adverse Event	Artesunate N=31 n (%)	Quinine + tetracycline N=33 n (%)
Nausea	14 (45)	20 (60)
Dizziness	16 (52)	16 (48)
Vomiting	8 (26)	30 (91)
Tinnitus	0	29 (88)
Convulsions	1 (3)	0
Bradycardia	7 (23)	NE

NE= not evaluated

Medical Officer Comments: *The authors note that the incidence of nausea, and dizziness were not significantly different in the two groups; while the incidence of vomiting and tinnitus were significantly higher in the quinine+tetracycline group than in the comparator group. ECGs were not performed in the quinine-tetracycline group, so the*

incidence of cardiac arrhythmia or QTc prolongation could not be determined for that regimen.

Study 9: Kremsner PG, Zotter GM, Feldmeier H, Graninger W, Rocha RM, Wiedermann G. A comparative trial of three regimens for treating uncomplicated falciparum malaria in Acre, Brazil. *J. Infect. Dis.* 1988; 158:1368-1371.

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

Study Objectives: To evaluate short course regimens of quinine plus sulfadoxine-pyrimethamine and quinine plus clindamycin to amodiaquine, the drug officially recommended by public health authorities in Brazil at the time.

Study Location and Dates: Rio Branco, Acre, Brazil, January to July 1987

Study Population: patients attending the outpatient clinic in Rio Branco, with confirmed *P. falciparum* malaria

Inclusion Criteria:

Patients \geq 14 years of age

No antimalarial treatment within preceding 7 days

Patients able to stay under observation for 48 hours after clearance of parasites from blood

Patients able to stay in Rio Branco municipality (non-malarious area)

Exclusion Criteria:

Severe clinical illness requiring hospitalization

Chronic diarrhea

Pregnancy

Treatment Groups

1. Group A: Amodiaquine

2. Group QSP: quinine + sulfadoxine-pyrimethamine

3. Group QC: quinine + clindamycin

Drug Products: information not provided in publication

Dosage Regimen:

Group A: amodiaquine 25 mg base/kg given in 3 doses (10 mg/kg initially, then 7.5 mg/kg at 24 and 48 hours)

Group QSP: quinine sulfate 15 mg/kg q12h for total of 6 doses, plus sulfadoxine-pyrimethamine (500/25 mg) two tablets initially, then one tablet 24 hours later

Group QC: quinine sulfate 15 mg/kg q12h for total of 6 doses, plus clindamycin 10 mg/kg q12h for total of 6 doses

Concomitant Medications: none reported

Study Endpoints:

- Cure (thick blood smear became negative by day 7 and remained negative on day 14 and 28 of follow-up)
- Grade I resistance (RI): disappearance of parasites from peripheral blood within first week, followed by recrudescence at day 7, 14, 21, or 28
- Grade II resistance (RII): persistence of asexual parasitemia until day 7, and a reduction in parasitemia to < 25% initial value during first 48 hours of treatment
- Grade III resistance (RIII): reduction of parasitemia to < 75% during initial 48 hours, and persistence until day 7; or reduction of parasitemia to < 75% during initial 48 hours, accompanied by clinical deterioration on days 2 and 3
- Parasite clearance time

Study Procedures:

- Clinical observations (assessment of signs and symptoms and measurement of axillary temperature) daily until symptoms were absent and patient was afebrile for 48 hours
- Thick and thin blood smears were performed daily for 7 days or until smears were parasite-negative for 48 hours, then on days 14 and 28

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

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

Characteristic	Amodiaquine N=25	QSP N=30	QC N=40
Age range (years) n (%)			
15-25	11 (44)	13 (43)	22 (55)
26-40	6 (24)	12 (40)	11 (28)
>40	8 (32)	5 (17)	7 (17)
Gender (MF)	20/5	22/7	32/8
Parasite count/ μ L (range)	5360 (500-68,000)	3630 (500-58,500)	6989 (500-56,200)

N= number of evaluable patients

Medical Officer Comments: The low enrollment in the amodiaquine group was reportedly due to a high failure rate and early closure of the treatment arm. Patient characteristics for all enrolled patients were not provided. Overall, the groups were fairly well-matched by gender and baseline parasite count; however, patients in the quinine-clindamycin group were younger than in the other treatment groups.

Patient Disposition

A total of 95/115 patients enrolled in the study were monitored for 28 days. Patients lost to follow-up included 4 in the amodiaquine group, 10 in the QSP group, and 6 in the QC group. Reasons for loss to follow-up were not provided in the publication.

Efficacy Outcomes

Cure rates at 28 days were considerably better for the QC group than the QSP or amodiaquine groups, as shown in the following table.

Table 2. Therapeutic Responses (adapted from author's Table 2)

Outcome measure	Amodiaquine	QSP	QC
28 day cure rate (ITT population)	1/29 (3%)	9/40 (22%)	36 /46 (78%)
28 day cure rate (evaluable population)	1/25 (4%)	9/30 (30%)	36/40 (90%)
RI resistance	6	19	4
RII resistance	7	2	0
RIII resistance	11	0	0
Mean PCT (hours)	82.7	78.2	86.4

Medical Officer Comments: High failure rates were noted with the amodiaquine and quinine+sulfadoxine-pyrimethamine regimens due to resistance or recrudescence after initial clearance. The authors noted that 6/11 amodiaquine-treated patients with RIII resistance had to be treated with quinine before day 7 of follow-up due to clinical deterioration. The short course quinine+clindamycin regimen (3 days) was reasonably efficacious in the evaluable population in this geographic region, although 10% patients failed due to recrudescence.

Efficacy Conclusions:

1. Amodiaquine and Quinine+sulfadoxine-pyrimethamine were unsatisfactory regimens for treatment of uncomplicated *P. falciparum* malaria in this study.
2. Quinine+clindamycin administered as 6 total doses for each drug was reasonably effective for treatment of falciparum malaria in this setting.

Safety Data

Table 3. Adverse Events Reported on day 2 of Study

Adverse Event	A N=29	QSP N=40	QC N=46
Dizziness	0	(70%)	(59%)
Tinnitus	0	(63%)	(46%)
Diarrhea	(7%)	(20%)	(35%)*
Rash	0	1 ()	0

*Two patients with diarrhea in the QC group had for *C. difficile* toxin-positive stools

Medical Officer Comments: Adverse events reported on day 2, particularly dizziness and tinnitus, were more frequent in patients who received quinine-containing regimens.

Study 10: De Souza JM, Sheth UK, De Oliveira RMG, Roulet H, and De Souza SD. An open, randomized, phase III clinical trial of mefloquine and of quinine plus sulfadoxine-pyrimethamine in the treatment of symptomatic falciparum malaria in Brazil. Bull. World Health Org. 1985; 63:603-609.

Study Design: randomized, open-label, active-controlled trial

Study Objectives: To compare tolerance and clinical and parasitological response to mefloquine and to a combination of quinine and Fansidar in adult males with symptomatic malaria.

Study Location and Dates: Belem, Brazil; study dates not provided in publication

Patient Population: males between the ages of 18 and 55 years from the endemic areas of Paragominas with symptomatic falciparum malaria

Inclusion Criteria:

Males ages 18-55 years old
Symptomatic falciparum malaria
Informed consent

Exclusion Criteria: none reported in publication

Treatment Groups:

1. Mefloquine
2. Quinine plus Fansidar

Drug Products: information not provided

Dosage Regimens:

1. Mefloquine 1000 mg base as single dose
2. Quinine 600 mg base orally, followed 4 hours later by 3 tablets of Fansidar on day 0, then quinine 600 mg q8h for the next 2 days

Concomitant Medications:

Patients with recrudescence or treatment failure were given 1000 mg mefloquine base as a single oral dose.

Patients received analgesics as needed.

Study Endpoints:

Primary endpoint was not stated in publication.

Parasitological Response (S, RI, RII, RIII)
Parasite Clearance Time (PCT)
Fever Clearance Time (FCT)

Study Procedures:

All patients were hospitalized
Baseline physical examination, laboratories, chest X-ray and electrocardiogram (ECG)
Physical examination was repeated on days 0-7, and weekly from day 7 to 42.
Vital signs were recorded daily on days 0-7, then on days 10, 14, 28, 35, and 42
Hematological studies were obtained on day 2, 4, 7, 10, 14, 28, and 42.
Biochemical studies were obtained on days 1, 4, 7, 14, 28, and 42.
ECGs were performed on days 1, 4, 7, 28, and 42.
Urinalysis was done daily for first week, then on days 14, 28 and 42.
Blood smears for malaria parasites were obtained daily on days 0 to 42.
In vitro drug susceptibility tests for *P. falciparum* were performed on day 0, and as needed.
Plasma samples were collected for estimation of drug levels on day 7, and additionally, in cases of recrudescence, vomiting, or serious adverse reactions.

Duration of Follow-up: 42 days

Study Results

Patient Demographic and Clinical Characteristics

Mean age was not provided for the treatment groups; mean parasite count at baseline was similar for both groups, 19,580/ μ L for the mefloquine group, and 19,626/ μ L for the quinine+sulfadoxine-pyrimethamine group.

Patient Disposition

A total of 49/50 randomized patients in the mefloquine group, and 50/50 patients in the quinine+sulfadoxine-pyrimethamine group completed the study.

Treatment Outcome

Table 1. Treatment Response (from author's Table 2)

Outcome Measure	Mefloquine N=50	Quinine+sulfadoxine- pyrimethamine N=50
Cure rate* (ITT population)	49/50 (98%)	46/50 (92%)
Cure rate* (Evaluable population)	49/49 (100)	46/50 (92%)
RI	0	4
RII	0	0
RIII	0	0

*Although not specifically stated, presumably the cure rate refers to 28 days, and all recrudescence occurred by day 21.

Efficacy Conclusions:

1. In this geographic location, a 3 day course of quinine + sulfadoxine-pyrimethamine resulted in cure of falciparum malaria in 92% patients. Since this study was published in 1985, presumably the study was performed in the early 1980's prior to the high incidence of Fansidar® resistance present today.

Safety Data

The authors note that the most common adverse events were nausea, vomiting, abdominal pain, loose stools, and dizziness. Nausea and vomiting were more common in the quinine+sulfadoxine-pyrimethamine group; while abdominal pain and diarrhea were more frequent in patients who received mefloquine. These results were not quantified in the publication. Tinnitus and partial hearing loss were reported only in patients who received quinine + sulfadoxine-pyrimethamine, with a reported incidence of 34%, and 8%, respectively. These reactions, however, were considered mild, and transient.

Study 11: Ramharter M, Oyakhiroma S, Klouwenberg PK, Adegnika AA, Agnandji ST, Missinou MA, Matsiegui P-B, Mordmuller B, Borrmann S, Kun JF, Lell B, Krishna S, Graninger W, Issifou S, and Kremsner PG. Clin. Infect. Dis. 2005; 40:1777-1784.

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

Study Objectives: To compare the efficacy and tolerability of artesunate + clindamycin to that of quinine + clindamycin for treatment of uncomplicated *P. falciparum* malaria in Gabonese children

Study Location and Dates: Lambarene, Gabon, December 2003 to May 2004

Study Population: Children who presented at outpatient department of Hospital

Inclusion Criteria:

Age 3-12 years

Microscopically confirmed *P. falciparum* mono-infection, with signs and symptoms of uncomplicated malaria

Parasitemia 1000 to 100,000 parasites

Body weight of 10-70 kg

Ability to tolerate oral therapy

Written informed consent of parents or legal representative

Exclusion Criteria:

Severe malaria

Current antibiotic treatment or antimalarial use within preceding 7 days

Hematocrit < 23%

WBC > 15 x 10⁹ cells/L

Presence of other severe underlying disease

Treatment Groups:

Artesunate-Clindamycin
Quinine-Clindamycin

Drug Products:

Artesunate 50 mg tablets (Arsumax, Sanofi-Synthelabo)
Quinine sulphate 300 mg tablets (Pharmamed)
Clindamycin 75 and 150 mg capsules (Dalacin, Pfizer)

Doseage Regimens:

1. Artesunate 2 mg/kg + clindamycin 7 mg/kg q12h for total of 6 doses
2. Quinine sulfate 15 mg/kg + clindamycin 7 mg/kg q12h for total of 6 doses
If vomiting occurred within 30 minutes after drug intake, the same dose was readministered. If vomiting occurred within 30 minutes after readministration of the dose, patients were withdrawn from the study, and given "rescue treatment".

Comcomitant Medications: none reported in publication

Study Endpoints:

Primary: End Point: Cure Rate, defined as proportion of patients who did not have reappearance of asexual parasitemia during 28-day follow-up after initial clearance of parasites, corrected by PCR genotyping

Response to Treatment, based on WHO guidelines, was classified as:

- Adequate
- Early treatment failure (occurring days 1 to 3)
- Late treatment failure (occurring days 4-28)

The secondary endpoint was rate of adverse events in the 2 treatment groups.

Study Procedures:

Baseline evaluation: vital signs, CBC, and thick blood smear for malaria

Follow-up evaluations: patients were followed-up twice daily for 3 days, or until resolution of clinical signs and symptoms and 2 consecutive negative blood smears. Follow-up visits were done on days 7, 14, and 28, with vital signs, thick blood smear performed at each visit.

CBC was repeated on days 2 and 28.

Dried capillary blood spots were obtained at baseline, and if patient had recrudescence of parasitemia to perform PCR-based genotyping for merozoite surface antigen.

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

Patients were fairly closely matched for age, and parasitemia. More females than males were enrolled in the artesunate-clindamycin group; while the opposite proportion of males and females were enrolled in the quinine-clindamycin group.

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

Characteristic	Artesunate-Clindamycin N=50	Quinine-Clindamycin N=50
Mean age (years) ± SD	7.1 ± 2.6	7.7 ± 3.3
Male/Female	23/27	30/20
Mean Weight (kg)	22.3 ± 8.0	24.0 ± 10.2
Median Parasitemia (counts per µL) (range)	12,000 (1100-96,000)	19,750 (1200-96,000)

SD= standard deviation

Patient Disposition

A total of 4/50 randomized patients in the artesunate-clindamycin group were excluded, and 2/50 randomized patients in the quinine-clindamycin group were excluded. In the artesunate-clindamycin group, reasons for exclusion were antimalarial self-treatment in 3 patients, and treatment visit missed in 1 patient. In the quinine-clindamycin group, 1 patient had vomiting of readministered study drugs, and 1 patient was withdrawn due to tinnitus.

Treatment Outcome

No significant difference was observed between 28-day cure rates for the two treatment regimens.

Table 2. Response to Treatment (from author's Table 2)

Outcome measurement	Artesunate-clindamycin	Quinine-clindamycin
Cure rate* (ITT population)	40/50 (80%)	45/50 (90%)
Cure rate* (evaluable population)	40/46 (87%)	45/48 (94%)
Mean Parasite clearance time (hours) (range)	29.3 (26.4-32.1)	46.0 (41.0-51.0)
Mean Fever clearance time (hours) (range)	21..2 (16.3-26.1)	30.2 (23.6-36.8)

*PCR-corrected cure rates. In the artesunate-clindamycin group, parasitemia reappeared in 10 patients by day 28, 4 of these were considered reinfections by PCR, so 6 patients had recrudescence. In the quinine-clindamycin group, 10 patients had reappearance of parasitemia by day 28. Of these, 5 were considered reinfections, and 5 were considered recrudescence by PCR genotyping.

Efficacy Conclusion:

1. Cure rates at 28 days were similar for the two treatment groups.

2. The shortened course of quinine in combination with clindamycin was similar in efficacy to that of quinine monotherapy or other quinine combinations used in other studies in this geographical region.

Safety Data

No difference was noted in the overall incidence of adverse events between the two treatment groups. Adverse events are shown in the table below. Those considered at least possibly drug-related were diarrhea in 1 patient in the artesunate-clindamycin group, and diarrhea and tinnitus in 2 patients in the quinine-clindamycin group.

Table 3. Adverse Events in Study (adapted from author's table 3)

Adverse Event	Artesunate-Clindamycin N=50	Quinine-Clindamycin N=50
	n (%)	n (%)
Loose stool	9 (28)	12 (24)
Increased stool frequency	20 (40)	18 (36)
Diarrhea	1 (2)	1 (2)
Abdominal pain	11 (22)	12 (24)
Headache	4 (8)	2 (4)
Common-cold like symptoms	13 (26)	8 (16)
Vomiting	5 (10)	6 (12)
Skin rash or eruption	4 (8)	2 (4)
Other	11 (22)	13 (26)

Medical Officer Comments: The incidence of specific adverse events was similar between treatment groups.

Study 12: Kremsner PG, Winkler S, Brandts C, Neifer S, Bienzle U, and Graninger W. Clindamycin in combination with chloroquine or quinine is an effective therapy for uncomplicated Plasmodium falciparum malaria in children from Gabon. J. Infect. Dis. 1994; 169:467-470.

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

Study Objectives: To compare treatment with 3-day regimens of chloroquine, quinine, chloroquine plus clindamycin, and quinine plus clindamycin in the treatment of acute uncomplicated *P. falciparum* malaria in children from Gabon.

Study Location and Dates: Gabon, April to September, 1992

Study Population: children attending outpatient clinic of Albert Schweitzer Hospital who fulfilled study criteria.

Inclusion Criteria:

Children, ages 4-15 years old
Parasitologically proven *P. falciparum* mono-infection
Asexual parasitemia of 200-200,000 per μL
Observation for 48 hours after parasite clearance
No antimalarial therapy within preceding 7 days

Exclusion Criteria:

Severe or complicated malaria

Treatment Groups:

Group C: chloroquine
Group CCl: chloroquine plus clindamycin
Group Q: quinine
Group QCl: quinine plus clindamycin

Drug Products: no information provided

Dosage Regimens:

1. Group C: chloroquine 25 mg base/kg in 3 doses (10 mg/kg on admission, 10 mg/kg 24 hours later, then 5 mg/kg 48 hours after first dose)
2. Group CCl: Chloroquine as in group C, plus clindamycin 5 mg base/kg q12h for total of 6 doses
3. Group Q: Quinine 12 mg base/kg q12h for 6 doses
4. Group QCl: Quinine as in group Q plus clindamycin 5 mg base/kg q12h for 6 doses

Concomitant Medications: none reported

Study Endpoints:

Cure: Blood smear negative by day 7 and parasite-free on days 14, 21, and 28 of follow-up

Resistance Grades:

RI: disappearance of parasites within first 7 days, followed by relapse on days 14, 21, or 28

RII: persistence of parasites until day 7, then reduction of parasitemia to < 25% initial value after 48 hours of treatment

RIII: parasitemia > 25% initial value after 48 hours of treatment and persistence of parasitemia until day 7; or parasitemia of > 25% initial value after 48 hours of treatment, accompanied by clinical deterioration on days 2 and 3

Study Procedures:

Clinical signs and symptoms: every 12 hours, until symptom-free for 48 hours

Temperature: every 12 hours during treatment or until patient afebrile for 48 hours

Thick blood smears for parasite counts: every 24 hours for 7 days or until smears were parasite-negative for 48 hours

Duration of Follow-up: 28 days

Study Results

Patient Demographic and Clinical Characteristics

Treatment groups were fairly closed matched for age. However, proportionately fewer female patients were enrolled in treatment groups Q and QCl. Additionally, mean parasitemia although in the same general range for each of the groups, was highest in the two quinine-containing regimens.

Table 1. Baseline Patient Characteristics

Characteristic	Chloroquine N=32	Chloroquine + clindamycin N=33	Quinine N=31	Quinine+ clindamycin N=34
Median age (years)	10	10	10	9
Gender (M/F)	18/14	18/15	22/9	21/13
Geometric mean parasitemia (count/ μ L) (range)	4986 (200-104,000)	8170 (380-200,000)	11,966 (240-200,000)	12,545 (220-160,000)

N= number of evaluable patients

Medical Officer Comments: the method of randomization was not provided, so it is not clear why there were fewer female patients in the quinine treatment regimens. The differences in mean parasitemia are likely not clinically significant.

Patient Disposition

A total of 144 patients were enrolled in the study, and 130 were monitored for the full 28 days. Fourteen patients (10%) were lost to follow-up, as shown in the table below. Reasons for loss to follow-up were not provided.

Table 2. Patient Disposition in this Study

Patient Disposition	Chloroquine (N)	Chloroquine plus clindamycin (N)	Quinine (N)	Quinine plus clindamycin (N)
Number of patients enrolled (intent-to-treat population)	32	37	36	39
Number of evaluable patients	32	33	31	34
Number of patients lost to follow-up	0	4	5	5

Efficacy Data

Cure rates were higher in treatment arms of combination regimens rather than in chloroquine or quinine alone. No RII or RIII resistance was observed in the quinine-containing regimens. All treatment failures were retreated with quinine 12 mg base /kg twice daily for 7 days and no recrudescence was reported.

Table 3. Parasitological Response to Treatment (from Table 2 of Kremsner, et al., 1994)

Outcome measure	Chloroquine N=32	Chloroquine + clindamycin N=33	Quinine N=31	Quinine+ clindamycin N=34
Cure rate (28 day) in evaluable population	3/32 (9)	23/33 (70)	10/31 (32)	30/34 (88)
Cure rate (28 day) in intent to treat population	3/32 (9)	23/37 (62)	10/36 (28)	30/39 (77)
RI resistance	14/32 (44)	10/33 (30)	21/31 (68)	4/34 (12)
RII resistance	10/32 (31)	0	0	0
RII resistance	5/32 (16)	0	0	0

N= number of evaluable patients

Medical Officer Comments: This study showed high failure rates with chloroquine and with short-course monotherapy with quinine. Cure rates were improved with addition of clindamycin to either quinine or chloroquine; however, cure rates were still under 90% for quinine plus clindamycin. It should be noted that non-standard quinine dosing was used in this study (12 mg quinine base/kg twice daily rather than 8 mg quinine base/kg 3 times daily).

Safety Data

The authors noted that all adverse events in this study were rare and transient. Adverse events reported in this study are summarized in the following table. It is not clear whether the intent-to-treat or evaluable population was used for determination of incidence for these data.

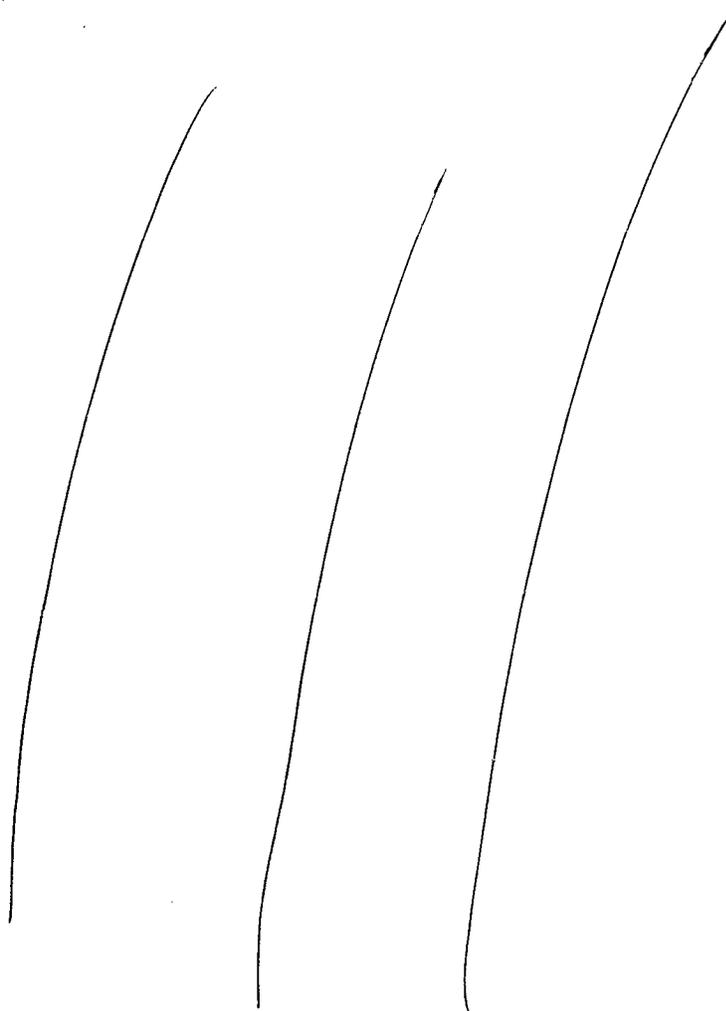
Table 4. Adverse Events reported in Study

Adverse Event	Chloroquine (%)	Chloroquine plus clindamycin (%)	Quinine (%)	Quinine plus clindamycin (%)
Dizziness	6	12	29	3
Nausea	6	0	6	0
Diarrhea	0	6	0	6
Abdominal pain	3	18	13	15
Pruritus	13	15	0	3

Medical Officer Comments: It is not clear why dizziness occurred in 29% patients who received quinine, but only 3% of those who received quinine plus clindamycin, since the quinine dosing regimen was the same. There is no known drug interaction between quinine and clindamycin. Diarrhea was reported only in patients who received clindamycin, and pruritus was more frequent in patients who received chloroquine alone or in combination with clindamycin.

10.2 Line-by-Line Labeling Review

TABLE 10.2.1. Line-by-Line Labeling Review



22 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

from the US, used quinine to treat cramps (leg, muscle, and foot) and experienced a serious outcome. There were more females than males reporting adverse events with the use of quinine, and there were more reports in the 51-60 age-group than in any other age-group. Approximately 14% of all the reports indicated a fatality; of these, slightly less than half (43%) were overdose cases (either intentional or accidental) where almost all used two or more drugs.

DSPIDP also requested that we provide an overview of AERS cases reporting a serious outcome up to the same cut off date of March 31, 2005. This search included all reports considered serious by regulatory definition¹. After removal of duplicate reports, we identified 537 unique serious outcome cases. Similar to the global overview, we found that the majority of cases are from the US (82%; 432/537); that there are slightly more female than male users (292 versus 219); and that there were more reports in the 51-60 age group than in any other age group.

To address a specific request for indication and causality association in the serious outcome reports, we randomly selected a majority of reports for hands-on review. We examined 400 unique reports to determine indication or use. We found that the majority of patients used quinine for cramps² (56%) and the other two most frequent indications were malaria (4%) and malignant melanoma (3%). Eleven percent of these reports stated accidental or intentional overdose and another 19% did not list an indication or use. We reviewed 313 cases to determine an association between the use of quinine and one or more of the stated adverse events. The majority of the reports showed a positive association, as determined by temporal association, positive dechallenge or determination by the reporter.

In addition, DSPIDP requested that we provide AERS data on specific adverse events. The results derived from hands on review of unduplicated reports are listed below under the specific events or categories. A detailed summary of these cases is located under the Results- specific events of interest section.

Table 1 – AERS search results on specific events of interest	
Event of Interest	Number of AERS Cases
Fatalities	81
Teratogenic events	1
Cardiac Events	63
Torsade de pointes	11
Chest Pain	7

¹ Cases are considered to have a serious outcome when one or more of the following outcomes are checked in the MedWatch form: death, hospitalization, life-threatening, disability, congenital anomaly, required intervention and other.

² However, if additional reports of related symptoms (i.e., leg spasms, pain, ache; muscle pain and spasm; and restless leg syndrome) the total increases to 247 cases (62%).

Palpitations	5
Arrhythmia	6
Tachycardia	5
Worsening CHF	4
Ventricular tachycardia	3
Syncope	4
Heart arrest, abnormal EKG, atrial fibrillation	2 each
Bradycardia	1
Thrombocytopenia	173
HUS/TTP	25
Agranulocytosis	5
Renal Failure	49
Nephritis	2
Hypersensitivity/skin reactions	101
Ophthalmologic events	29
Hearing Disorders	28
Glucose Metabolism	7
Hypotension	19

Data from AERS regarding these unique reports showed that among the fatalities, approximately half of the reports were associated with cases of intentional or accidental overdose, where for most quinine was one of several drugs ingested. Specific cause of death was identified in 58 reports as multiple-drug overdose (36), thrombocytopenia (6), cardiac arrest (4), anemia (2), pulmonary embolism (2), multiple myeloma (2), and one each of atherosclerotic heart disease, multiple organ failure, aspergillus infection, pneumonia, respiratory failure and suicide by hanging. AERS information also showed that in the one report listing teratogenic effects quinine was one of several drugs ingested during the pregnancy, and that in almost all of the cardiac cases (including the fatalities) there was multiple drug use, co-morbidities or provided limited information. About 18% of the renal failure cases reported a fatality, two of which were in patients receiving IV quinine for protozoal infections, and one additional case resulted in a renal transplant.

AERS reports also indicated that many patients experienced thrombocytopenia, where approximately one third required a transfusion or intervention to correct the platelet decrease, and hypersensitivity reactions, where rash was reported most frequently. However, three fatalities were associated with angioedema (2) and ARDS/overdose following quinine use. Permanent/on-going vision and hearing events were reported after quinine use, some in a setting of multiple drug overdose, and were described as loss of vision (1), pale and ischemic retina (1), permanent changes to the retinal and optic nerves (1) and abnormal vision with papilloedema and retinal hemorrhage (1), failure to recover normal hearing ability (11), tinnitus (4), hearing loss without tinnitus (9). There were few reports in AERS of altered glucose metabolism, but three indicated severe hypoglycemia after quinine use. None of the hypotension cases indicated IV administration. Note that

almost all of these events (ex. arrhythmias, tinnitus, rash, hypotension) are known to occur subsequent to quinine use.

In summary, as expected, our search of AERS produced more reports listing quinine as suspect drug than the figures provided by the sponsor, most likely due to our extended search period and probably to the use of more index terms for identifying quinine. We identified reports where patients experienced cardiac events, including Torsade de pointes (TdP), severe hematological events, serious hypoglycemia, and permanent visual and auditory disturbances. The cases in the AERS database did not allow us to determine if serious hypotensive effects were associated with intravenous quinine use although this event has been reported in the literature. Despite finding confounders in several cases, we recommend based on this review that the labeling mentions that these serious events (cardiac rhythm alterations, thrombocytopenia, hypersensitivity reactions, permanent visual and hearing disturbances, and hypoglycemia), including fatalities, have been reported in patients using quinine orally.

INTRODUCTION

Mutual Pharmaceutical Company, Inc. (the sponsor), submitted an electronic application on December 13, 2004, for quinine sulfate to treat uncomplicated *Plasmodium falciparum malaria*. The sponsor provided postmarketing data from FDA's Spontaneous Reporting System and AERS, as well as from WHO in support of their application. The NDA summary provided by the sponsor was obtained from published line listings, and covered reports submitted between 1969 through June 2003. The sponsor's submission does not indicate that further analysis or manual review of the postmarketing FDA cases was done. To obtain more current information and more in-depth analysis of the FDA postmarketing reports, DSPIDP requested that DDRE review the available quinine reports in AERS³ up to March 31, 2005. In addition, DSPIDP requested analysis on selected adverse events identified in the executive summary and elsewhere in this document.

METHODS

AERS was searched for cases listing quinine as suspect drug up to the cut-off date of March 31, 2005. For the four types of searches outlined below the search product code used was "Quinine Gish 5/4/05". AERS search criteria is in parenthesis.

Search 1: a global search for all reports regardless of outcome, to provide an overview of quinine safety profile. (All reports listing quinine as suspect drug; data retrieved from line listings; non-manual review)

Search 2: a stratified search from the total figure of AERS reports, for those indicating a serious outcome (by regulatory definition), to provide a better understanding of events associated with a serious outcome. (All reports were retrieved using the advanced miscellaneous criteria and selecting each of the individual seven serious outcomes listed (i.e., congenital anomaly, death,

³ Current AERS data contains reports originally submitted to the FDA's Spontaneous Reporting System from 1969 through October 1997, as well as reports submitted to AERS since October 1997.

disability, hospitalization, life-threatening, other, required intervention); data retrieved from line listing; removal of duplicates from line listings; non-manual review)

Search 3: a manual review of randomly selected cases from the serious outcome group to determine indication and probable association. (Serious outcome cases as retrieved in b), random selection of cases from this group, manual review; criteria for possible association included one or more of the following: positive dechallenge, temporal association, a statement of possible or probable association with quinine use by the reporter)

Search 4: a manual review of cases reporting the following specific events of interest, regardless of outcome:

- Fatalities (Advanced miscellaneous criteria selection and death as an outcome)
- Teratogenic events (MedDRA System Organ Class (SOC) Congenital, familial and genetic disorders)
- Cardiac events (SOC Cardiac disorders) Hypotension (High Level Group Term (HLGT) Decreased and non-specific blood pressure disorders and shock Thrombocytopenia (HLGT Platelet Disorders)
- Agranulocytosis (HLGT White Blood Cell Disorders)
- HUS/TTP (search under 5 Preferred Terms⁴ (PTs) associated with HUS/TTP)
- Renal failure (two searches: a) 19 individual PTs associated with renal failure⁵ and b) Nephritis (High Level Term (HLT) Nephritis NEC and HLT Glomerulonephritis and nephrotic syndrome) Skin and hypersensitivity reactions (two searches: a) 42 individual PTs⁶ and b) ODS standardized search “ODS serious skin reaction” code group)
- Ophthalmologic events (SOC Vision disorders)
- Loss of hearing (SOC Ear and labyrinth disorders)
- Glucose metabolism (HLGT Glucose Metabolism Disorders (incl Diabetes Mellitus))

RESULTS

Search #1: Global overview from line listings (n=642, all outcomes, includes duplicates, non-manual review):

The AERS Search #1 for all reports listing quinine as suspect drug revealed there are 642 cases in the database. This line listing, which includes duplicates, was reviewed electronically to provide the general characteristics outlined in the table below.

Table 2 – Overall Characteristics of AERS quinine reports up to March 31, 2005		
[n=642]		
# of reports	642	
Country (n=631)	US	523

⁴ The 5 PT terms used to capture HUS/TTP cases are listed on Appendix Two

⁵ The 19 PT terms used to capture renal event cases are listed on Appendix Two

⁶ The 42 PT terms used to capture hypersensitivity/skin reaction cases are listed on Appendix Two

**Table 2 – Overall Characteristics of AERS quinine reports up to March 31, 2005
 [n=642]**

	Foreign	108
Gender	Females	341
	Males	254
	Unknown	47
Age in years (n=532)	Average	56
	Median	59
	Range	20 months to 101 years
Outcome (n=576)	Death	91
	Hospitalization	314
	Life threatening	23
	Congenital anomaly	1
	Other serious outcomes*	147
More frequent indications (frequency > 15) (n=213)	Cramps	97
	Overdose	55
	Malignant melanoma	19
	Malaria	17
Dosage form (n=436)	Oral	428
	IV	8 (all protozoal infections)

* includes the remaining regulatory serious outcomes of disability, required intervention, and other

There were more reports in the 51-60 age group than for any other group of those reports where age was stated (22%; 119/532), and there were approximately 2% of reports in pediatric patients 0-16 years (12/532),

• Age stratification: (111 not stated)	0-20	(23)	51-60	(119)
	21-30	(26)	61-70	(105)
	31-40	(45)	71-80	(94)
	41-50	(87)	≥81	(33)

Approximately 14% of all reports were fatalities and approximately one third of the fatalities were associated with intentional or accidental overdose⁷. The majority of the overdose cases (82%; 28/34) listed 3 or more drugs as suspect drug.

Approximately 33% listed an indication or use; of these, almost half (46%; 97/212) listed use as cramps (i.e., leg, foot and muscle cramps); an additional one-fourth (26%; 55/212) were associated with an overdose, either intentional or accidental, where most of the patients took two or more drugs at the same time (82%; 45/55); Other indications mentioned at least twice were pain (8), restless leg syndrome (4), ill-defined disorder (4), and arthritis (2).

The few reports listing IV administration (n=8) indicated quinine was used as prophylaxis or treatment of malaria in 6 and in the treatment of babesiosis in 2; half of the reports listed hospitalization and half listed fatalities; two of the fatalities were associated with aspergillosis (probably duplicate reports), a third with babesiosis, and a fourth with suicide by hanging.

Search#2: Serious outcome reports (by regulatory definition) (n=537, unduplicated reports, from line listings, non-manual review)

⁷ This category of overdose cases includes cases coded with one or more of the following MedDRA Preferred Terms: Overdose, Accidental Overdose, Intentional Overdose, Inentional Misuse, Suicide, Completed Suicide, Multiple Drug Overdose and Cinchonism.

AERS was searched for serious outcome reports using the regulatory criteria for serious outcome. Electronic removal of duplicates of the 574 reports yielded 534 unique reports with a serious outcome. Three cases were added that had been incorrectly coded as non-serious. Thus, the final tally is 537 unique cases.

Table 3 - Characteristics of AERS serous outcome quinine reports up to March 31, 2005 [n=537]	
# of reports	537
Country (n=527)	US 432 Foreign 95
Gender (n=511)	Females 292 Males 219
Age (n=462)	Average 56 years Range 20 months to 101 years
Outcome (n=537)	Death 80 Hospitalization 293 Life threatening 21 Congenital anomaly 1 Other serious outcomes* 181
More frequent indications (> 13) (n=332, from manual inspection)	Cramps 228 Overdose 47 Malignant melanoma 14 Malaria 15
IV Dosing (n=8)	IV 8 (all protozoal infections)

* includes the remaining regulatory serious outcomes of disability, required intervention, and other

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Search#3: Random selection from the unduplicated serious outcome cases to determine indication and probable association

A majority of cases from the serious outcome reports previously identified were selected at random for hands on review to determine indication and possible association of quinine use to the reported events.

# of cases manually reviewed	400		
Indications	Cramps ¹	225	56%
	Overdose ²	44	11%
	Malaria	15	4%
	Malignant melanoma	11	3%
	Not stated	76	19%

¹ Includes cases reporting cramps not otherwise identified, leg cramps and muscle cramps

² Includes fatal, non-fatal, accidental and intentional overdose

Regarding indication, we found that the majority of patients used quinine for cramps⁸ and the other two most frequent indications were malaria and malignant melanoma. An additional 11% of the reports (stated accidental or intentional overdose

# of cases manually reviewed	313	100%
# of cases with a probable association ¹	174	56%
# of cases with a negative association ²	103	33%
# of cases where determination was not possible	36	11%

¹ Includes reports listing a positive dechallenge, a temporal association, or a positive or probable association statement by reporter

² Includes reports listing several drugs as suspect drugs or indicating a drug interaction; reports lacking a temporal association; and reports where reporters attributed events to other drugs, underlying illnesses or determined that there was no association with quinine.

Regarding a possible association, we found that the majority of the reports showed a probable association, as determined by temporal association, positive dechallenge or determination by the reporter

In an additional 33% we determined that there was a negative association between quinine use and the adverse events reviewed because 1) the reporters attributed the event to all of the drugs used by the patient, suspected a drug interaction between quinine and another drug, or specifically discounted an association between quinine use and the adverse event; 2) a temporal association could not be determined or there was a closer temporal association with the use of another drug; and 3) the event was more closely associated with an underlying disease or co-morbidity ;

In the remaining 11% there was insufficient information to make a determination.

⁸ However, if additional reports of related symptoms (i.e., leg spasms, pain, ache; muscle pain and spasm; and restless leg syndrome) the total increases to 247 cases (62%).

d) Specific events of interest: For specific events, summaries of the cases and additional pertinent case information are listed in Appendix One.

Fatalities

Ten of the fatal outcome cases were duplicates; thus the information in Table 6 pertains to the 81 unique fatal outcome reports.

Table 6- Characteristics of the AERS cases listing a fatal outcome in quinine users through March 31, 2005

Total number of reports	81
Gender (n=77)	Females 42 Males 35
Country (n=81)	US 63 Foreign 18
Age in years (n=74)	Average 49 Range 2-85
Indication or use (n=69)	Overdose ¹ 36 Cramps 19 Malignant melanoma 10 Protozoal infection 3 Joint symptoms 1
# of cases reporting events associated with selected SOCs ²	Hematologic events 23 Neuro-psychiatric events 18 Cardiac disorders 16 Respiratory events 15 Renal events 10 Hepatobiliary events 7 Skin and hypersensitivity events 5
Identified cause of death (n=43)	Overdose 32 Thrombocytopenia 3 Organ failure 2 Arteriosclerotic heart disease 1 Anemia 1 Fungal infection 1 Respiratory arrest 1 Pulmonary embolus 1 Suicide by hanging 1

¹ Includes reports coded as overdose, accidental or intentional, as well as cinchonism, drug level increased, misuse and intentional misuse.

² One case may report events in more than one SOC; thus one case may be included in more than one category.

This search indicated that there were more fatalities reported in females and in US patients. Indication or use was reported in the majority of the reports with intentional or accidental overdose listed the most. Specific cause of death was identified in almost ¾ of the reports with multiple-drug overdose being the most frequently reported.

Teratogenic events (n=1)

We retrieved one report from France that listed cerebellar hypoplasia in a premature male (32-weeks) whose mother had ingested five medications during the pregnancy. The physician does not attribute the outcome to any of the ingested medications. There was no information regarding indication or duration of therapy for any of the medications

Cardiac events (n=63)

A search in AERS under the SOC Cardiac Disorders identified 133 cardiac events in association with quinine use as of 3/31/2005. Hands-on review of these reports enabled us to exclude 64 reports because of multiple reasons including: 46 reports most closely associated with non-cardiac events (includes cases of hypersensitivity reactions, skin reactions, pulmonary reactions, thrombocytopenia, dyspnea, urticaria etc.) or with cinchonism (ringing in the ears, dizziness, blurring of vision and sometimes complete blindness, rashes, fever, and low BP); 10 reports where the events appear to be unrelated to quinine use; 2 where the events are associated with quinidine use instead of quinine; and 6 duplicate reports. Thus a total of 69 unduplicated cases of cardiac events were reviewed. Further review of the 69 case indicated that an additional 6 cases were duplicates as shown in the table below.

The types of cardiac events reported were (one report may contain more than one adverse event term):

Adverse Event	Number of Counts	Unique cases
Torsades de pointes	13 ¹	11
Overdosage/Poisonings ²	11	11
Chest pain	7	7
Palpitations	6 ¹	5
Arrhythmia	6	6
Tachycardia	5	5
CHF, worsening	5 ¹	4
Ventricular tachycardia	4 ¹	3
Syncope	4	4
Heart arrest	2	2
Abnormal EKGs	2	2
Atrial fibrillation	2	2
Bradycardia	2 ¹	1
Total	69	63

1=Includes duplicates/follow-up reports

2=Cardiac events included arrhythmia, myocardial infarction (heart attack), shock, and cardiac (heart) arrest.

A report may contain more than one adverse event term but was included in only one of the above categories.

We retrieved 63 unique reports indicating a cardiac event following the use of quinine, where almost all indicated a serious event (12 deaths, 36 hospitalization, 11 other serious events by regulatory definition). The majority of the patients were adults (average age 59), females (n=34), from the US, and where stated, used quinine for cramps. The type of cardiac events reported were: Torsades de Pointes (11), chest pain (7), palpitations (5), arrhythmia (6), tachycardia (5), worsening congestive heart failure (4), ventricular tachycardia (3), syncope (4), two each of heart arrest, abnormal EKG and atrial fibrillation, and one report of bradycardia. An additional 11 cases were associated with overdose. From the limited information provided in the cases, we were able to determine a positive association between cardiac event and quinine use in 5 cases.

The characteristics of the cardiac cases of interest are presented below. Summaries of the cases and additional pertinent case information are listed in Appendix One.

Torsades de pointes (n=11)

Table 7 – Characteristics of quinine AERS cases listing Torsade de pointes	
Total number of reports	11
Gender (n=11)	Males 3 Females 8
Country (n=10)	US 8 Foreign 2 Not stated 1
Age in years	Median 75 Range 41-93 Not stated 1
Outcome	Death 1 Serious 10
Indication or use	Leg muscle cramps 7 Not stated 4

Most of the patients who experienced Torsades were female adults, from the US who used quinine for leg or muscle cramps. The reported fatality occurred in an elderly female (83 years) who had multiple pre-existing cardiac illnesses and who was also using other medications in addition to quinine at the time of her death. Two additional cases indicated patients were also using astemizole. Two other elderly patients experienced Torsades shortly after quinine ingestion. One patient who was an 83-year old female experienced Torsade after one dose. She had a past medical history of chronic atrial fibrillation and was using furosemide concomitantly. The second patient, a 72-year male who experienced Torsades after taking quinine for about a week had pre-existing medical conditions (including hemodialysis-treated renal insufficiency, hypertension and diabetes) and was taking digoxin concomitantly. In six additional patients the occurrence of Torsades was confounded by multiple drug use (one patient who used 20 medications) and serious underlying conditions (5 patients). Overall these 11 cases of Torsades appear to be confounded by other drugs or pre-existing medical conditions.

Syncope (n=4)

Table 8 – Characteristics of quinine AERS cases listing syncope (n=4)	
Total number of reports	4
Gender	Males 2 Females 1 Not stated 1
Country (n=4)	US 3 F 1
Age in years (n=2)	Median 58 Range 56-60 Not stated 2
Outcome (n=3)	Hospitalization 3 Not stated 1
Indication or use (n=1)	Leg cramps 1 Not stated 3

The majority of patients who experienced syncope was from the US and required hospitalization. None of the reports listed duration of use prior to the event, and only one listed indication which was listed as leg cramps. None of these were compelling cases of quinine-associated syncope because of limited information and other confounding drugs or medical conditions.

Arrhythmia (n=6)

Total number of reports	6
Gender	Males 1 Females 4 Not stated 1
Country	US 3 Foreign 3
Age in years	Median 58 Range 16-78
Outcome	Hospitalization 5 Other 1
Indication or use	Leg cramps 1 Restless leg syndrome 1 Not stated 4
Causality assessment (n=)	Positive Negative

Arrhythmia was reported mostly in adult female patients who experienced a serious outcome but no fatalities. In three reports that listed duration of use, arrhythmia occurred within two weeks of use. Five of the cases appear to be confounded due to overdose in three and underlying cardiac illness in two. The sixth case was that of a 59-year old patient who was on atorvastatin for over nine months and experience arrhythmia 11 days after introduction of quinine for leg cramps. This is the only case that may be possibly associated with quinine intake but we don't have all the information.

Ventricular Tachycardia (n=3)

Total number of reports	3
Gender	Males 1 Females 2
Country	US 2 Foreign 1
Age in years	Median 78 Range 50-80
Outcome	Serious 3
Indication or use	Leg cramps 2 Restless leg syndrome 1

Few reports listed ventricular tachycardia as the adverse event. In these three cases patients were adults who used quinine for leg cramps and restless leg syndrome. It should be noted that all three cases are confounded by use of drugs associated with arrhythmia (ibutilide and cisapride) and multiple drug intake in the setting of accidental overdose.

Tachycardia (n=5)

Total number of reports	5
Gender	Males 3 Females 2
Country	US 4 Foreign 1
Age in years	Median 51 Range 34-72
Outcome	Death 1 Hospitalization 2 Other 2
Indication or use	Leg spasms/cramps 2 Malaria 1 Multiple myeloma 1 Not stated 1

Most of the adult patients reporting tachycardia were from the US and ingested quinine for both approved and off-label use. The one fatality in a young adult female (34 years of age) was listed as cardiac arrest. This patient had previously experienced positive rechallenge with quinine and was diagnosed with SLE when she was 17 years old. She was also on dialysis. In one instance towards the end of dialysis, 4 hours after quinine intake this patient experienced multiple symptoms including tachycardia. Two patients experienced tachycardia shortly (20 minutes in one case and after first dose in the other) after quinine ingestion. In the first case quinine was mentioned as the only drug that was ingested and in the second case, patient was taking multiple drugs concomitantly. In two other cases patients were on multiple concomitant medications due to multiple myeloma therapy and malaria. One case, where the patient was only using quinine, may be possibly associated with quinine intake.

Chest Pain (n=7)

Total number of reports	7
Gender	Males 2 Females 5
Country	US 5 Foreign 2
Age in years	Median 73 Range 60-78
Outcome	Death 1 Hospitalization 4 Other 2 5
Indication or use	Leg cramps 5 Not stated 2
Causality assessment (n=0)	Not applicable

There were seven unique cases of chest pain in association with quinine use. Five of these cases originated from within the US and two were foreign cases. This event occurred more frequently in adult females. All patients experienced a serious outcome, including one death in a 65-year old female who had pre-existing medical conditions including CHF, and angina. Indication or use was leg cramps in 5 of the cases that stated indication in the reports. In two cases, chest pain was experienced shortly (15 minutes and 10 hours) after quinine intake. However all the cases

appeared to be confounded by the concomitant intake of multiple drugs or pre-existing medical conditions.

Poisoning/Overdosage cases (n=11)

Table 13 – Characteristics of quinine AERS cases listing a cardiac event in association with overdose/poisoning (n=11)	
Total number of reports	11
Gender	Males 8
	Females 3
Country	US 7
	Foreign 4
Age in years	Median 26
	Range 2-86
Outcome	Death 7
	Hospitalization 3
	Other 1
Indication or use	Suicide/intentional overdose 7
	Overdose/accidental overdose 4
	(includes 3 listing leg pain/pain)

Overdose/poisoning was listed in more males than females, and in more US than foreign patients. The majority of patients died (7/11). In at least six cases suicide appeared to be the motive and half of them died. Two of the three cases of apparently accidental overdose also died. In two cases quinine appeared to be the only drug used. IN the first a case, a 2-year old patient was hospitalized 2.5 hours following quinine overdosage/poisoning, experienced visual damage, arrhythmia and died. In the second case, a 17-year old patient ingested multiple quinine pills, complained of hearing loss and dizziness, was brought to ER, became hypotensive and had a fatal cardiac arrest. One may interpret a possible association between quinine and the cardiac events in these two cases. Overall, cardiac events included arrhythmia, myocardial infarction, shock and heart arrest.

Palpitations (n=5)

Table 14 – Characteristics of quinine AERS cases listing palpitations (n=5)	
Total number of reports	5
Gender	Females 5
Country	US 4
	Foreign 1
Age in years	Median 64
	Range 60-89
Outcome	Life-threatening 1
	Hospitalization 1
	Other 3

Indication or use	Leg cramps/pain	3
	Arthritis	1
	Not stated	1

All the patients who reported palpitations were adult females. There were no fatalities in this group. Duration of therapy was stated in three reports and ranged from 2 to 14 days (median 9 days). However, most cases seemed to be confounded by multiple medications and/or medical conditions.

Worsening of congestive heart failure (n=4)

There were 4 unduplicated cases of “worsening CHF”. Three of the cases were from the US and one was foreign. Age ranged from 55-81 years (median 68). There were three males and one female. Hospitalization was mentioned as a serious outcome in three cases and death in one. The 70-year old male who died was on multiple medications and experienced lactic acidosis, cardiac failure and coma. This case does not appear to be associated with quinine intake. Duration of use was mentioned in two reports and was 1.5 hours in one and 8 days in the other. Both of these events occurred in the setting of pre-existing cardiac conditions and it may not be possible to associate the event with quinine. The fourth case was also confounded by multiple medications and pre-existing medical conditions.

Atrial fibrillation

There were two cases of atrial fibrillation and both were from the U.S. A 60-year old male experienced atrial fibrillation in the setting of multiple myeloma. It is not clear if quinine was administered as part of some protocol or separately or not at all. The second case occurred in a 65 year old female who had a pacemaker implanted and was on 15 or so other concomitant drugs. This case is confounded by preexisting cardiac condition and concomitant use of multiple drugs. Both cases appear to undergo hospitalization.

Heart Arrest

There was one U.S. and one foreign case of heart arrest. In both cases, heart arrest was preceded by myocardial infarction. One case occurred in a 68 years old male who was diagnosed with multiple myeloma and was on some protocol which included quinine. The second case occurred in a 71 year old male where quinine was used as an antimalarial. This patient experienced heart arrest in association with an unknown surgery and was on multiple medications. The outcome of the first case was death and hospitalization in the second case. From the limited information provided it is difficult to associate quinine with the adverse event.

Abnormal EKGs

There were two U.S. cases of abnormal EKGs (AV-block, and T-wave abnormality) in elderly females (75 and 88 years old). Hospitalization and required intervention was stated as the serious outcomes. One patient took quinine for night cramps and indication or use was not stated

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

in the other. Both these cases were confounded by multiple medications and preexisting cardiac conditions.

Bradycardia

There was one U.S. case of bradycardia in a 53 years old male in the setting of multiple myeloma. Per the reporting physician, quinine may have played a role in this adverse event or that the patient may have a sick sinus syndrome. Outcome was reported to be life threatening.

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Hematological events: thrombocytopenia, HUS/TTP, and agranulocytosis, leucopenia

Thrombocytopenia (n=173)

The search under the HLGT Platelet disorders revealed 185 cases listing thrombocytopenia as an adverse event. Twelve of these reports were duplicates, thus reducing the number of unique thrombocytopenia cases for review to 173.

Table 15- Characteristics of the AERS thrombocytopenia cases through March 31, 2005 (n=173)		
Total number of reports	173	
Gender (n=171)	Male	59
	Females	112
Country (n=173)	US	157
	Foreign	16
Age in years (n=157)	Average	56
	Median	55
	Range	20 months to 101 years
Outcome (n=164)	Death	15
	Hospitalization	129
	Life-threatening	6
	Disability	1
	Required intervention	2
	Other	11
Indication or use (n=139)	Cramps, leg/muscle	123
	Pain/pain in extremities	8
	Spasms, leg, muscle, night	3
	Malaria	2
	Joint symptoms	2
	Restless leg syndrome	1
	Required intervention (n=55)	Blood/platelet transfusion
	Plasma exchange	12
	Plasmapheresis	2
	Fresh frozen plasma	1
Causality association (n=173)	Positive	77
	Negative	96
Types of hemolytic events reported	Thrombocytopenia	
	Idiopathic thrombocytopenia purpura	
	Thrombotic thrombocytopenia purpura	
	Haemolytic uremic syndrome	
	Anemia	
	Agranulocytosis	
	Leukopenia	

There were 173 unique cases reporting thrombocytopenia, where the majority of patients were adult females from the US used quinine for leg or muscle cramps and experienced hospitalization or death (129 hospitalization, 15 death). Approximately one third of the patients required a transfusion or intervention to correct the platelet decrease. (From the information provided in the cases, we were able to determine that there was a probable association between the use of quinine and the adverse events in 77 cases.

HUS/TTP (n= 25)

Our search criteria yielded 184 cases coded under one or more of the PTs specified previously. Manual inspection indicated that 25 of the 184 cases were coded as HUS/TTP (n=4) or listed a diagnosis of HUS, TTP or both in the text of the report (n=21). Thus the information on these 25 unique cases is presented in the table below.

Total number of reports	25	
Gender (n=25)	Males	5
	Females	20
Country (n=25)	US	all
Age in years (n=24)	Average	55
	Range	21-75
Outcome (n=25)	Hospitalization	25
Indication or use (n=25)	Leg cramps	24
	Leg and muscle cramps	1
Probable association (n=24)	Positive	23
	Negative	1

Agranulocytosis (n=5)/leucopenia (n=15):

Our search criteria using the HLGT White Blood Cell Disorders yielded 33 cases. Electronic review of the cases allowed us to exclude 13 from further review (three were duplicates, nine reported increases in white blood cells, and one provided an alternate unconfirmed diagnosis of Felty's syndrome in a rheumatoid arthritis patient). Of the remaining 20 cases, 5 reported agranulocytosis and an additional 15 reported leucopenia. Because the Division's question pertained to agranulocytosis, these were the only cases in this group reviewed manually. The table below containing the characteristics for the leucopenia cases was derived from electronic review. No further discussion is provided in this document for the leucopenia reports.

Total number of reports	5	
Gender (n=5)	Males	3
	Females	2
Country (n=5)	US	all
Age in years (n=5)	Average	57
	Range	43-85
Outcome (n=5)	Hospitalization	4
	Death	1
Indication or use (n=3)	Leg cramps	1
	Muscle cramps/spasms	2
Causality assessment (n=4)	Positive	2
	Negative	2

One case reported a fatality where the agranulocytosis was most closely associated with the use of ceftriaxone. Two reporters stated that the agranulocytosis was due to quinine use; determination of association in the remaining three cases was not possible due to concomitant drug use, co-morbidities, or lack of information. Note that only one of the five reports also listed thrombocytopenia.

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

Table 18 - Characteristics of AERS cases listing leucopenia in quinine users through March 31, 2005

Total number of reports	15
Gender (n=15)	Males 6 Females 9
Country (n=15)	US all
Age in years (n=14)	Average 5 Range 32-84
Outcome (n=14)	Death 2 Hospitalization 9 Other 3
Indication or use (n=2)	Malignant melanoma in both
Causality assessment	Not applicable

Renal Events: Renal Failure (49)/Nephritis (2)

Adverse events in the Renal and Urinary Disorders System Organ Class (SOC) were named in 16% (101/642) of quinine reports in the AERS database. About 16% (16/101) of these renal adverse event reports had a fatal outcome (based on raw counts, may include duplicates).

Table 19 - Preferred terms (PT) listed under SOC Renal and Urinary Disorders

PT	# of reports	PT	# of reports
Renal Failure	29	Albuminuria	1
Renal Failure Acute	21	Azotaemia	1
Haematuria	13	Chromaturia	1
Renal Impairment	9	Hydronephrosis	1
Anuria	4	Nephrogenic Diabetes Insipidus	1
Urine Abnormality	4	Nocturia	1
Dysuria	2	Polyuria	1
Kidney Small	2	Renal Cyst	1
Nephritis	2	Renal Failure Chronic	1
Oliguria	2	Urinary Incontinence	1
Renal Atrophy	2	Urinary Retention	1

We focused only on the unique reports listing renal failure (49) and nephritis (2).

Table 20 - Characteristics of the AERS cases listing Renal Failure in quinine users through March 31, 2005 (n=49)

Total number of reports	49
Gender (n=49)	Males 19 Females 30
Country (n=47)	US 38 Foreign 9
Age in years (n=)	Average 56 Range 18-84
Outcome (n=47)	Death 9 Hospitalization 36 Disability 2 Other 1
Indication or use (n=12)	Leg cramps 6 Protozoal infection 2 Malignant melanoma 2 Leg pain 1 Intentional overdose 1
Probable association (n=9)	Positive 5 Could not be determined 4
Types of renal failure reported (n=49)	Renal failure 26

Table 20 - Characteristics of the AERS cases listing Renal Failure in quinine users through March 31, 2005 (n=49)

	Acute renal failure	22
	Chronic renal failure	1

In 5 cases with an indication of leg cramps there is a possible relation with the use of quinine and the development of renal failure.

Table 21 - Characteristics of the AERS cases listing Nephritis in quinine users through March 31, 2005 (n=2)

Total number of reports	2	
Gender (n=2)	Male	1
	Female	1
Country (n=2)	US	all
Age in years (n=2)	Average	69
		65, 73
Outcome (n=2)	Hospitalized	1
	Other	1
Indication or use (n=1)	Leg cramps	
Probable association (n=2)	Positive	2

Both cases of nephritis were in elderly US patients (each over 60 year of age). In one (65-year old male) nephritis was reported in association with a hypersensitivity reaction to quinine, and in the other (73-year old female) with hemolytic anemia and thrombocytopenia. Quinine was intermittently used for leg cramps for over three years by one of the patients. The second did not reveal indication or use; however in this case there was a probable association between events and quinine use.

Hypersensitivity/skin reactions (n=101):

Our search for skin/hypersensitivity cases under the PT terms listed in the Methods section retrieved 111 adverse event reports or 17% of the quinine reports in the AERS database. These figures are raw counts, and may include duplicates. Six cases had a fatal outcome with 3 of the 6 unrelated to quinine administration.

Table 22 - Preferred Terms (PT) listed in the skin/hypersensitivity reactions cases

PT	# of reports	PT	# of reports
Dermatitis	26	Skin Necrosis	2
Pruritis	18	Stevens-Johnson Syndrome	2
Hypersensitivity	13	Tongue Oedema	2
Urticaria	9	Acute Pulmonary Oedema	1
Rash	7	Anaphylactic Reaction	1
Angioneurotic Oedema	6	Blister	1
Erythema	6	Blood Blister	1
Face Oedema	6	Dermatitis Atopic	1
Acute Respiratory Distress Syndrome	4	Exanthem	1
Asthma	4	Oral Mucosal Blistering	1
Dermatitis Bullous	4	Pemphigoid	1
Erythema Multiforme	4	Pruritis Generalised	1
Rash Maculo-Papular	4	Rash Erythematous	1
Vasculitis	4	Rash Morbilliform	1
Drug Hypersensitivity	3	Rash Papular	1
Photosensitivity Reaction	3	Rash Pruritic	1

Table 22 - Preferred Terms (PT) listed in the skin/hypersensitivity reactions cases			
Anaphylactoid Reaction	2	Stridor	1
Dermatitis Exfoliative	2	Swelling Face	1
Drug Eruption	2	Tongue Blistering	1
Leukocytoclastic Vasculitis	2	Wheezing	1
Rash Generalized	2		

After removal of duplicates (8) and exclusion of reports where the patients received quinidine instead of quinine (n=2), we reviewed 101 adverse events reports indicating a hypersensitivity/skin reaction associated with quinine use. Within this group, 13 were also captured under ODS Serious Skin Reaction group.

Table 23- Characteristics of the AERS skin/hypersensitivity reaction quinine cases through March 31, 2005 (n=101)	
Total number of reports	101
Gender (n=95)	Males 49
	Females 46
Country (n=101)	US 79
	Foreign 22
Age in years (n=91)	Average 59
	Median 61
	Range 5-84
Outcome (n=75)	Death 6
	Hospitalization 49
	Life-threatening 1
	Disability 2
	Required intervention 3
	Other 14
Indication or use (n=79)	Cramps (leg, muscle, foot) 68
	Malaria 6
	Babesiosis 2
	Pain 1
	Restless leg syndrome 1
	Arrhythmia 1
Probable association (n=19)	Positive 7
	Negative 12
Types of events reported (n=101)	Erythema multiforme 4
	Blisters 4
	Stevens-Johnson Syndrome 2
	Erythema 1
	Overdose 1
	Penphigoid 1
	Rash 60
	Non-skin hypersensitivity 28*

* Some of the events in this group are dyspnea/bronchospasms, angioedema, hypotension/syncope, anaphylaxis, and acute pulmonary edema

AERS contained 101 unique cases describing a hypersensitivity or skin reaction in quinine users. There were six fatalities; three of the fatalities were associated with quinine use; two were more closely associated with underlying protozoal disease and one was unrelated to a hypersensitivity reaction. Approximately half of the hospitalizations were associated with severe rash/skin reactions. The most frequent non-skin hypersensitivity events were associated with respiratory events (shortness of breath/bronchospasms (10), angioedema (6), acute pulmonary edema (4) and ARDS (4)). A positive association between use and the adverse events was found in seven of 19 reports reviewed.

Ophthalmologic events (n=28)

Approximately 5% of all the quinine reports in AERS mentioned an ophthalmologic event. The PT terms associated with eye disorders that were mentioned in this group are listed below.

PT	# of reports	PT	# of reports
Visual disturbance	8	Miosis	1
Blindness	6	Optic Neuritis	1
Vision Blurred	4	Papilloedema	1
Amblyopia	2	Pupillary disorder	1
Eye Disorder	2	Retinal Haemorrhage	1
Retinal Disorder	2	Retinal Oedema	1
Eye Hemorrhage	1	Swollen Tear Duct	1
Eyelid Ptosis	1	Visual Acuity Reduced	1
Glaucoma	1	Visual Field Defect	1

Of the 31 cases included in the SOC Eye Disorders, three were duplicates. Thus we reviewed 28 unique cases, which listed an ophthalmologic event. The characteristics of the 28 cases are listed below.

Total number of reports	28
Gender (n=27)	Males 13 Females 14
Country (n=28)	US 20 Foreign 8
Age in years (n=25)	Average 48 Median 51 Range 2-80
Outcome (n=25)	Death 4 Hospitalization 14 Disability 2 Other 5
Indication or use (n=19)	Leg cramps 4 Overdose 11 Malaria prophylaxis 1 Multiple melanoma 1 Medication error 2
Causality assessment (n=13)	Positive 7 Negative 6
Types of events reported	Blindness 7 Visual disturbances 6 Double vision/blurred vision 4 Worsening vision 1 Abnormal vision 1 Visual field defect 1 Miosis 1 Not vision related* 5

* One each of the following events: droopy eye, eye trouble, eyelid ptosis, swollen tears duct and retinal hemorrhage.

Four patients experienced permanent/on going events described as permanent loss of vision (1), pale and ischemic retina (1), permanent changes to the retinal and optic nerves (1) and abnormal vision with papilloedema and retinal hemorrhage (1). In three of the four patients events were

associated with overdose. There was a probable association between quinine use and the adverse events in six cases.

Hearing disorders (n=28)

Thirty cases indicating a hearing disorder were retrieved using the Ear and Labyrinth Disorders (SOC). These represent approximately 5% of all the quinine AERS reports. The PT terms associated with hearing disorders and tinnitus, which were mentioned in this group, are listed below.

PT	# of reports	PT	# of reports
Deafness	19	Hearing impaired	1
Tinnitus	19	Hypoacusis	1

Of the 30 cases included in the SOC Ear and Labyrinth Disorders, two were duplicates. Thus we reviewed 28 unique cases, which listed a hearing disorder. The characteristics of the 28 cases are listed below. Please note that an event was considered permanent if it met the following criteria: a) report does not indicate that event stopped, patient recovered, symptoms improved, nor checked for positive dechallenge; and/or b) symptoms improved but some disability remains; and/or c) disability or negative dechallenge slots were checked in the absence of a) and b).

Total number of reports	28
Gender (n=24)	Males 13 Females 11
Country (n=28)	US 26 Foreign 2
Age in years (n=21)	Average 54 Range 17-86
Outcome (n=20)	Death 2 Hospitalization 10 Disability 2 Required intervention 1 Other 5
Indication or use (n=22)	Leg cramps 12 Malaria 2 Multiple myeloma 2 Medication error 2 OD/Suicide attempt 4
Association (n=24)	Positive 23 Negative 1
Types of events (n=28)	Deaf/hearing loss with tinnitus 11 Deaf/hearing loss, no tinnitus 9 Tinnitus 8

These events were clinically severe as determined by outcome (two fatalities, 10 hospitalization and two disability) and failure to recover normal hearing ability (11). Permanent events were described as tinnitus (4), and hearing loss with or without tinnitus (9). Half of the patients experience the adverse event within two weeks of initiating quinine therapy. The most frequent indication or use was leg/muscle cramps, although there were four cases of overdose/suicide attempt. The majority of cases (meet our criteria for positive association between event and quinine use).

Glucose Metabolism

Seven cases indicating glucose metabolism alterations were retrieved using the HLGT MedDRA term Glucose Metabolism Disorders (incl Diabetes Mellitus). This represents approximately 1% of all the AERS quinine reports. The PT terms associated with glucose metabolism disorders mentioned in this group of cases are listed below.

Table 28 - Preferred terms (PT) listed under HLGT Glucose Metabolism Disorders (incl Diabetes Mellitus)

PT	# of reports	PT	# of reports
Diabetes Mellitus	4	Hypoglycemia	3

All of the seven cases were reviewed, as there were no duplicates or cases requiring further exclusion. The characteristics of the cases are listed below.

Table 29 - Characteristics of the AERS cases indicating glucose metabolism disorders in quinine users through March 31, 2005 (n=7)

Total number of reports	7
Gender (n=7)	Males 3 Females 4
Country (n=7)	US 6 Foreign 1
Age in years (n=6)	Average 58 Median 63 Range 32-72
Outcome (n=7)	Death 2 Hospitalization 2 Required intervention 1 Other 2
Indication or use (n=5)	Cramps 4 Restless leg syndrome 1
Causality assessment (n=4)	Positive 3 Negative 1
Types of events reported	Diabetes mellitus 4 Hypoglycemia 3

DM was in women who had risk factors (obesity-2) or were diagnosed with DM prior to the use of quinine (2). Hypoglycemia was reported in 2 females and 1 male who all had renal disease. Fatalities were associated with hypoglycemia in two renal patients. Hospitalizations were associated with hypoglycemia in one patient and with thrombocytopenia in the other. In three cases (all hypoglycemia) the reporters considered there was a probable association with the use of quinine (two indicated a possible drug interaction).

Hypotension

Adverse events in the Decreased and Nonspecific Blood Pressure Disorders and Shock HLGT were named in approximately 7% (44/642) of quinine reports in the AERS database. PT terms mentioned in these cases possibly associated with hypotension are listed below.

Table 30 - Preferred terms (PT) listed under the HLGT Nonspecific Blood Pressure Disorders and Shock cases

PT	# of reports	PT	# of reports
Hypotension	22	Circulatory Collapse	1
Syncope	15	Fall	1

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

Table 30 - Preferred terms (PT) listed under the HLGT Nonspecific Blood Pressure Disorders and Shock cases

Dizziness	3	Lethargy	1
Orthostatic Hypotension	3	Loss of Consciousness	1
Shock	3	Pulse Absent	1
Blood Pressure Decreased	2	Septic Shock	1
Anaphylactic Reaction	1		

Of the 44 cases we excluded 25 for further review for numerous reasons. Cases were not reviewed if the patient was poly-medicated (3 or more products) at the time of the hypotensive/syncopal or anaphylactoid episode (12), which made it difficult to isolate the effects of quinine. Cases were also excluded if the report was more closely associated with another drug or disease (5), procedure (2), or if the report did not list hypotension/syncope as an adverse event (1). Finally, we also excluded duplicates (4), and an additional report where the sender was an attorney and the event was not verified by a health professional or patient. The characteristics of the 19 reports listing a hypotensive/syncopal episode that were reviewed are listed below.

Table 31 - Characteristics of the AERS cases indicating hypotension in quinine users through March 31, 2005

Total number of reports	19	
Gender (n=18)	Males	5
	Females	13
Country (n=19)	US 19	
Age in years (n=14)	Average	53
	Median	56
	Range	17-67
Outcome (n=16)	Death	3
	Hospitalization	10
	Other	3
Indication or use (n=3)	Leg/muscle cramps	13
	Overdose	2
	Muscle relaxant/pain relief	1
Causality assessment (n=19)	Positive	17
	Negative/not applicable	2

None of the 19 unique reports listing hypotension/syncopal episode as adverse events mentioned IV administration. The majority were clinically severe as indicated by the outcome (3 fatalities and 7 hospitalizations). In most the adverse event took place shortly after administration. Two of the fatalities were associated with overdose of quinine or quinine and another drug, and the third fatality was associated with thrombocytopenia that developed after ingestion of three doses over a 60-hour period. Eight patients reported events took place within 24 hours after ingestion of quinine, and another two after 3-4 doses within one week. According to our criteria, we found a positive association between drug use and the adverse event in 17 of the 19 reports.

DISCUSSION

Data obtained from line listings (crude, unreviewed counts) indicate that between 1969 and March 31, 2005, AERS contained 642 reports listing quinine as a suspect drug. This represents an additional 194 reports that are not included in the sponsor's submission. This increment is due to the extended search time frame of an additional 21 months. It may also be due to the inclusion of a greater number of identifiers for quinine (i.e., active ingredient, trade name, and verbatim terms) in our internal search. For instance, a comparison of the sponsor's FDA

postmarketing figures (total=448) with our in-house search using the same time frame as that identified by the sponsor yielded an additional 97 reports (total= 545). The figures for individual outcomes were also greater in our in-house search; we uncovered a total of 65 deaths, 284 hospitalization, 69 life-threatening, 21 disability, and 70 required intervention (sponsor's figures were lower by at least 20% in each category).

Our non-manual, electronic review of all the AERS reports listing quinine as a suspect drug provided a global characterization of these reports. It should be noted that this information is derived from line listings that provide crude counts that may contain duplicate reports, and that some of these figures were further modified upon manual review of individual reports in specific areas of interest. Despite the limitations associated with spontaneous reporting and the incompleteness of many of the reports, the results support that there was little use of quinine to treat protozoal infections and that the majority of users experienced events that were clinically severe, as determined by the number of reports listing fatalities and hospitalizations. The data also indicate that quinine-associated adverse events occurred more frequently in older females (50 years of age and older) where the most frequently listed indication was cramps or pain in the legs; however, without drug utilization data it is difficult to determine if this trend is true. It should also be noted that almost all of the AERS data for quinine associated adverse event reports is derived from US reports (83% of the total), so that a true worldwide safety profile of this drug can't be accurately determined from the AERS data.

In the subset of serious outcome⁹ cases, we identified 537 unduplicated reports. Similar to the findings for all quinine reports, we found that the majority of cases are from the US (80%; 432/537); that there are more female than male users (292 vs. 219); that there were more reports in the 51-60 age group than in any other age group and that the most frequently mentioned use was treatment of leg cramps. This stratification of the data showed that the percentage of deaths increased by one percent. This slight increase is most likely due to the removal of the non-serious outcome reports from the total.

Our manual review of 400 reports selected at random to determine indication or use corroborated the results of the electronic review. Similar to the crude results obtained for all the AERS quinine-associated cases, the two most frequently mentioned indications or use were cramps¹⁰ (56%) and overdose 11%, with a considerable lesser proportion of malaria (4%) and malignant melanoma (3%) mentions. Unlike the electronic review, we were able to determine with greater accuracy the proportion of reports (19%) where the indication or use could not be determined. This shows that for most parameters electronic reviews providing crude counts can illustrate the general safety profile of a drug. However, when greater precision is desired or for issues when the information is included in the text, manual review, albeit time consuming, is still the more accurate method.

⁹ Cases are considered to have a serious outcome when one or more of the following outcomes are checked in the MedWatch form: death, hospitalization, life-threatening, disability, congenital anomaly, required intervention and other.

¹⁰ However, if additional reports of related symptoms (i.e., leg spasms, pain, ache; muscle pain and spasm; and restless leg syndrome) the total increases to 247 cases (62%).

A second parameter of interest to the division was the attribution of causality between the adverse events and the use of quinine. To answer this question we selected at random approximately half of the quinine reports in the AERS database for manual inspection, and formulated specific attribution criteria. We determined that there was a positive association between quinine use and the adverse events when one or more of these conditions were met: a) in addition to listing quinine as a suspect drug, the reporters specifically attributed the events to the use of quinine; b) positive dechallenge; c) the same or similar events occurring in the patient after each administration of quinine; and d) a strong temporal association between quinine use and event. We found that the majority (56%) of the 313 randomly selected cases showed a positive association as determined by our criteria.

This hands-on inspection also showed that 11% did not include sufficient information to make any determination and that 33% fitted our criteria for a negative association. These criteria were a) the reporters attributed the event to all of the drugs used by the patient, suspected a drug interaction between quinine and another drug, or specifically discounted an association between quinine use and the adverse event; b) temporal association could not be determined or there was a closer temporal association with the use of another drug; and c) the event was more closely associated with an underlying disease or co-morbidity. To determine if the less elaborate and quicker electronic review would provide sufficient information to answer this question accurately, we also reviewed 386 randomly selected cases in this fashion, utilizing only dechallenge information which is a parameter that is captured electronically. Our results (41% positive association, 10 % negative association and 49% no information) show that unlike the global safety profile characteristics, electronic review of crude reports does not correlate closely to the results obtained from manual review.

The Division also requested that reports in AERS be reviewed for specific events of interest. Cases for each section were reviewed manually by several members of DDRE staff¹¹. Each event of interest will be discussed individually.

Fatalities:

The 81 fatalities follow the pattern outlined in the global characteristics for the AERS quinine reports, which are greater number of US cases, greater number of female patients, wide range in age of users, and little use in protozoal infections. In this group, we find that overdose, cramps and malignant melanoma were the three most frequent indications in decreasing order. Because almost all of the overdose cases lack quinine dosing or plasma levels, indicate polypharmacy (two to 17 drugs ingested concomitantly), and have a broad age distribution (13 to 70 years) we can't determine if the adverse events in these cases are dose dependent or specific to a particular age group.

the nationality of the reports is skewed towards domestic cases.

¹¹ S. R. Ahmad, MD, reviewed cardiac events; A. Rothstein, Pharm.D. reviewed renal events; P. Gish, R. Ph. Reviewed hypersensitivity/skin reactions; E. R. Farinas, R.Ph, M.G.A., reviewed all remaining events

Although a specific cause of death was identified in 75% of the case, it is worth noting that one report may show events spanning several organ/class categories. The specific cause of death was listed as multiple-drug overdose (36), thrombocytopenia (6), cardiac arrest (4), anemia (2), pulmonary embolism (2), multiple myeloma (2), and one each of atherosclerotic heart disease, multiple organ failure, aspergillus infection, pneumonia, respiratory failure and suicide by hanging. However, the type of events associated with these fatalities was more diverse. In addition to overdose and intentional misuse (36), hematologic events, mainly thrombocytopenia, were mentioned most often (23). Neuro-psychiatric events, such as coma, suicide, and convulsion were described in 18 cases. Cardiac disorders, including cardiac arrest and cardiac failure, were listed in 16, where one listed Torsade de Pointes. Respiratory events, such as ARDS, apnea and respiratory arrest, were described in 15 cases. Renal events, including renal failure, anuria and oliguria, were mentioned in 10 and hepatobiliary disorders, such as hepatic failure and jaundice, were listed in seven. Skin/hypersensitivity events, including rash and edema, were mentioned in five cases. Events in other systems were mentioned in less than five case (ex. Gastrointestinal events were listed in three cases).

Teratogenicity/congenital abnormalities:

At this time the AERS database contains only one report of congenital abnormality in an infant whose mother used quinine during the pregnancy. The details of the case, which include polypharmacy during the pregnancy, and the scarcity of similar reports in AERS, do not allow for proper assessment of the role of quinine into the teratogenic effects of quinine. However, it should be noted that quinine can cross the placenta and that in high doses quinine can cause fetal injury¹³.

Cardiac events:

Although it appeared from the global overview of AERS that 21% of the cases reported a cardiac event, our manual search showed that in reality the majority of the reported cardiac events was more closely associated with other conditions. Of the 63 reports where there was a closer association between a cardiac event and the use of quinine, the majority reported alterations in cardiac rhythm, which is not unexpected as this is a well known adverse event with quinine use. We noted also that in the majority of the patients in this group other factors, such as concomitant drugs including those known to cause rhythm alterations, or pre-existing illnesses, may have a contributory role. Because almost all of the cases had a serious outcome, including several fatalities not associated with multiple drug overdoses, clinicians should be aware that serious and even fatal cardiac events may occur following quinine administration.

Hematologic events (thrombocytopenia):

In this area, the Division requested that we concentrate our efforts in cases reporting platelet disorders and agranulocytosis. The 173 thrombocytopenia cases follow closely the characteristics for all of the quinine AERS reports. However, this group differs from the global population of quinine reports in that the majority of patients used quinine for leg cramps (123/173), and the percentage of fatalities is smaller (9%; 15/173). Half of the

¹³ Apo-Quinine Core Data Sheet, **Pharmacokinetics and Warnings and Precautions** sections; APOTEX NZ LTD, Auckland, New Zealand; June 1999

fatalities identified the cause of death, which was listed as thrombocytopenia, pulmonary embolus, cardiac arrest, anemia, intra-ventricular hemorrhage and secondary to drug-induced thrombocytopenia. Unique to the thrombocytopenia cases is our analysis to determine if additional intervention was needed to correct the platelet disorder. We were able to determine that in approximately one third (33%; 57/173) an intervention took place as follows: blood or platelet transfusion (41), plasma exchange (12), plasmapheresis (3), and administration of fresh frozen plasma (1). A comparison of the US and foreign cases showed that there were almost 10 times more US cases than foreign (159 US, 16 foreign), that US patients were younger (US average age 56, foreign average age 66), and that almost half of the foreign reports listed a fatality (44%; 7/16), whereas a small fatalities represented a small portion of proportion of the US cases (6%; 9/150). From the information provided in the cases, we were able to determine a probable association between thrombocytopenia and the use of quinine in 77 of the reports, including nine of the 15 deaths.

(HUS/TTP) (n=25)

Twenty five unduplicated cases listed a diagnosis of HUS, TTP or both. All the patients in this group were adults from the US with a median age of 58, who used quinine for leg cramps and required hospitalization. The majority (68%; 17/25) required an intervention (ex. plasmapheresis, platelet transfusion, plasma exchange, and blood transfusion) to normalize the hematologic parameters. In addition, the majority of the patients were females (80%; 20/25). Approximately half (48%; 12/25) of the patients had used quinine prior to the reported adverse events. Causal association with the reported events was positive for almost all of the cases (92%; 23/25). Note that 22 reported thrombocytopenia, and 11 reported renal failure.

Agranulocytosis:

Few adult patients experienced agranulocytosis as indicated by the AERS cases. Even when one case was more closely associated with the administration of another drug, these cases are still clinically severe as indicated by the outcome. As with the other events of interest, most patients used quinine off-label to treat leg or muscle cramps. Two reporters stated that the agranulocytosis was due to quinine use; determination of causal association in the remaining three cases is difficult due to concomitant drug use or illness, or lack of information

Renal events: Renal failure (49)/nephritis (2)

Although in several of the AERS reports listing renal failure there were other drugs or illnesses that may have contributed to the development of adverse events, AERS cases show that renal failure and nephritis can occur in patients following quinine therapy for a benign condition. For five of the six cases with indication of leg cramps, the event of renal failure was possibly related to quinine use based on the reported temporal relationship and positive dechallenge information. In all of the nine fatal reports, however, the occurrence of renal failure is possibly confounded by the use of multiple drugs and co-morbidities at the time of the event. Two of the nine fatalities were in association with IV quinine; but in either case the route of administration was not significant as deaths in both patients was

associated with underlying infections. One of the nephritis cases suggest that adverse events (i.e., nephritis, thrombocytopenia, hemolytic anemia and myalgia) may develop after intermittent use of quinine.

Hypersensitivity/skin reactions (n=28)

Approximately 16% of the AERS quinine cases described a hypersensitivity or skin reaction in quinine users, where in about a third (30) of the events were clinically severe manifestations of rash/skin conditions that included three fatalities associated with quinine use. In addition, quinine use in this group of patients was associated with severe systemic hypersensitivity reactions, such as bronchospasms and angioedema. These events are not considered unusual as cutaneous reactions, anaphylactoid shock, wheezing and asthmatic symptoms have been observed with quinine therapy¹⁴.

Ophthalmologic events (n=29)

A small percentage of the total number of AERS quinine reports (5%) indicated that patients had experienced an ophthalmologic adverse event subsequent to quinine use. Visual disturbances, including blindness, are known to occur with long term therapy and overdose. It was not unexpected then to find that in slightly more than half of the cases in this group the reported visual disturbance was associated with an overdose, where four listed a permanent condition. The reported permanent blindness and retinal effects could be the result of direct quinine toxicity to the retina¹⁵. It should be kept in mind, though, that visual disturbances can occur even with small doses in some individuals¹⁶.

Hearing disorders (28):

It was not surprising to find reports of hearing loss or tinnitus, even in small numbers (4% of the total number of AERS quinine reports) as these are well known possible adverse events of quinine therapy. It was interesting to find that in approximately one third of the cases (11 of 28) a permanent hearing disorder was reported, where in most (8/11) quinine was used to treat leg/muscle cramps. Even when six of these permanent disability reports may be confounded due to previous conditions or concomitant drugs, it is worrisome to find that a permanent disabling condition results from therapy for a benign illness such as leg/muscle cramps.

Glucose metabolism disorders (7):

Despite the small number of reports in this category, it appears that quinine played a role only in the development of hypoglycemia. The DM cases are confounded by patients with risk factors for DM and pre-quinine therapy DM. The AERS cases indicate that severe quinine-induced hypoglycemia can also occur in populations outside those most sensitive to this effect (i.e., pregnant women, children or patients with severe cases of malaria).

¹⁴ Clinical Pharmacology on Line, 2005; quinine monograph; <http://cpip.gsm.com/>

¹⁵ Drugs and Drugs of Abuse, Chapter 78, Quinine section

¹⁶ Apo-Quinine Core Data Sheet, Adverse Reactions section; APOTEX NZ LTD, Auckland, New Zealand; June 1999

Hypotension (19):

The AERS reports do not allow us to determine if hypotension/syncopal episodes follow the IV administration of quinine given that all AERS reports in this category list an oral product. Severe hypotension has been reported in the literature, following IV quinine administration¹⁷. The AERS reports indicate that clinically severe episodes of hypotension or syncope can occur after short term therapy with oral quinine.

SUMMARY/CONCLUSION:

As expected, our search in AERS identified more reports listing quinine as suspect drug than the figures provided by the sponsor, most likely due to our extended search period and probably to the use of more index terms for identifying quinine. Also as expected, our search identified reports where patients experienced cardiac events, including torsades, severe hematological events, serious hypoglycemia, and permanent visual and auditory disturbances as these are known adverse events associated with quinine use. The cases in the AERS database did not allow us to determine if serious hypotensive effects were associated with intravenous quinine use although this event has been reported in the literature. Despite finding confounders in several cases, we recommend based on this review that the labeling mentions that these serious events (cardiac rhythm alterations, thrombocytopenia, hypersensitivity reactions, permanent visual and hearing disturbances, and hypoglycemia), including fatalities, have been reported in patients using quinine orally.

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Concur:

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Acknowledgment to Paula Gish, R. Ph., and Adrienne Rothstein, Pharm.D., for their contributions to the hypersensitivity and renal sections, respectively.

CC: NDA 21-799
HFD-590 Singer/Navarro/Miller

10.2.1.1.1HFD-430 Avigan / Truffa / Farinas / Nguyen

¹⁷ Jacqz-Aigrain E, Bennisr S, Desplanques L, Peralma A., Beaufils F. Severe poisoning risk linked to intravenous administration of quinine. Arch Pediatr. 1994 Jan; 1(1): 14-9.

Appendix One

Fatalities/Summary of cases:

- a) the majority of patients were females, from the US, and slightly younger than the average age for all the reports (49 years in the fatalities versus 56 in the global overview),
- b) the youngest patient in this group is a 2-year old male from Great Britain who experienced arrhythmia and visual disturbances with oral quinine. The oldest fatality was in an 85-year old US male who used quinine for leg cramps and developed agranulocytosis. In this case the adverse event was more temporally associated with the use of ceftriaxone¹⁸,
- c) US patients were slightly younger in age (average 49) than the foreign patients (average age 51),
- d) more than two thirds (85%; 69/81) of the fatalities list the indication or use for quinine; in approximately half of the reports listing indication or use (36/69) the patients used quinine in an overdose experience; nine patients used oral quinine for malignant melanoma, where quinine was used in a vincristine-adriamycin early SWOG protocol; 20 listed relief of leg/muscle cramps and joint symptoms (29%; 20/69), and four indicated protozoal infection in four (three malaria and one babesiosis),
- e) in the overdose fatalities (12 intentional overdose, six accidental and no determination was made in the remaining half), very few list the amount of quinine ingested or the dosage form used (plasma levels listed in three case are each over 10 mcg/ml, average 18.9 mcg/ml); most (34/36) used two or more drugs concomitantly (range is two to 17 drugs); of the concomitant drugs used, opiates are mentioned more frequently, with oxycodone having the most mentions (n=17); almost all of the overdose reports are from the US (32/36) and most (24) are cited in annual published summaries of fatalities from Medical Examiner/ poison centers summaries listing cases where individuals used oxycodone,
- f) the majority of cases (58) list more than one adverse event, where in many cases events correspond to different SOC; the types of events mentioned more often (five times or greater) were:
- overdose and intentional misuse (36),
 - hematologic events, mainly thrombocytopenia (23),
 - neuro-psychiatric events, such as coma, suicide, and convulsion (18),
 - cardiac disorders, including cardiac arrest and cardiac failure(16); none of the fatalities listed Torsades or QT prolongation,
 - respiratory events, such as ARDS, apnea and respiratory arrest (15)
 - renal events, including renal failure, anuria and oliguria (10)
 - hepatobiliary disorders, such as hepatic failure and jaundice (7)
 - skin/hypersensitivity events, including rash and edema (5), were mentioned in five cases.
- g) a specific cause of death was identified in almost ¾ of the reports (72%;58/81); the cause of death was identified as multiple-drug overdose (36), thrombocytopenia (6), cardiac arrest (4), anemia (2), pulmonary embolism (2), multiple myeloma (2), and one each of atherosclerotic heart disease, multiple organ failure, aspergillus infection, pneumonia, respiratory failure and suicide by hanging.

¹⁸ Agranulocytosis is listed in the ceftriaxone labeling under the **ADVERSE REACTIONS** section.

Teratogenic events/ Summary of cases:

There was only one report in this category.

- a) cerebellar hypoplasia was diagnosed in a 32-week male French infant, whose mother took 5 drugs during pregnancy for an undetermined amount of time (i.e, Advil, sodium ferredetate, hexaquine, tenormin and Epoetin Alfa),
- b) this infant was diagnosed with an unidentified congenital neurologic disorder, and
- c) the physician in this case does not attribute adverse events to any of the medications nor provide an alternate cause for the events.

Cardiac events/Summary of cases:

Torsades de Pointes (n=11):

- a) the majority of cases were from the U.S, and in females users, (US 8, foreign 2; females 8, males 3)
- b) almost all the cases listed the patient's age; the median age was 75 years, which is much older than that of the total quinine AERS reports (median 59 years); the range was 41-93 years
- c) all the cases listed a serious outcome (life-threatening; hospitalization; required intervention), and included one death,
- d) the majority listed indication for use; this was described as leg/muscle crampse) positive association between quinine use and the development of Torsades de Pointes was found in two reports.

Additional case information:

- Death occurred in an 83-year old female. Concomitant medications included erythromycin and dopamine. This report mentioned pre-existing medical conditions (congestive heart failure, left bundle branch block, paroxysmal supraventricular tachycardia, acute renal failure, etc.) as possible 'contributing' factors for torsades.
- Two of the cases involved concomitant administration of astemizole, an allergy drug ; removed from the market because of its potential to be associated with torsades. In the first case, the patient developed torsades after the first dose of quinine, and in the second case after the third dose. In the first case, patient was on astemizole for one year and for one month in the second case.
- One case, an 83-year old female with a significant history of chronic atrial fibrillation was admitted to CCU with prolonged QT interval which progressed to torsades apparently after first dose of quinine.
- One 72-year old male, who was on dialysis, experienced torsades following quinine intake for a few days to a week.
- The youngest patient, a 41-year old female, was reported to be a drug abuser and on 20 medications. The dose, duration, and indication was not specified.
- Four patients experienced torsades in the setting of potentially serious pre-existing medical conditions including congestive heart failure, hypertension, and chronic renal failure; atrial fibrillation; coronary heart disease; and renal insufficiency.

Syncope (n=4):

- a) the majority of reports were from the US (3), and most syncope cases were in males (2 males, 1 female),
- b) half of the reports indicated the age of the patient, where the median age was 58 years,
- c) three cases indicate the outcome, listed as hospitalization; there were no fatalities in this group,
- d) duration of therapy was not mentioned in any of the reports,
- e) diagnosis or indication was mentioned in only one report as leg cramps,
- f) drug use-event association was possible in two cases; both were considered to have a negative association because in one, the 60-year old male patient had a history of coronary artery disease and heavy alcohol use, and in the other, a 56-year old female who had syncope in the setting of QT prolongation, was using more than 20 drugs at the time of the event, and had a history of smoking and chronic alcoholism.

Arrhythmia (n=6):

- a) half of the reports were foreign, and most reports involved female users,
- b) all the cases listed the patient's age, where the median age was 58 years,
- c) there were no fatalities associated with arrhythmia,
- d) two reports listed the indication for use, described as leg cramps in one and as restless leg syndrome in the other; however, there were three reports of overdose,
- e) a negative association was found in four cases due to medical history in one patient, and overdose in the other three (see below),
- f) duration of use was known in 3 cases and was reported as 3 days in one case; 11 days in the second, and 12-14 days in the third.

Additional case information:

- A 65-year old female was on a pacemaker, and the antiarrhythmic drug dofetilide for atrial fibrillation
- Three cases were overdose reports with additional cinchonism and irreversible visual damage in two, and with loss of hearing in the third.

Ventricular tachycardia (n=3):

- a) there were two US and one foreign report; and involved two females and one male ,
- b) all the patients were 50 years or older, with a median age of 78,
- c) all the cases indicated a serious outcome, but there were no fatalities,
- d) indication was listed in all reports, as leg cramps in two and restless leg syndrome in the third,
- d) none of the cases showed a positive association between drug use and adverse event

Additional case information:

- One case involved possible interaction between the antiarrhythmic drug ibutilide (Corvert) indicated for atrial fibrillation and quinine. The event occurred after the second IV dose of ibutilide (which is labeled for Ventricular tachycardia).
- One case involved concomitant administration of cisapride, a drug removed from the market because of its association with torsades. This patient had chronic renal failure and was on dialysis. Duration of quinine use was not mentioned.