CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-799

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**21-799 (N-000)**
Submission Date:	**13 October 2004; 27 January 2005: 28 March 2005; 29 April 2005; 7 June 2005**
Drug Product:	**Quinine Sulfate Capsules, 324 mg**
Trade Name:	**N/A**
Sponsor:	**URL Mutual Pharmaceutical Company**
Submission Type:	**Original NDA Submission**
OCPB Reviewer:	**Gerlie Gieser, Ph.D.**
Team Leader:	**Philip M. Colangelo, Pharm.D., Ph.D.**

Table of Contents

I. Executive Summary

A. Recommendations

The applicant's NDA submission for Quinine sulfate capsules (324 mg) consisted of study reports for a relative bioavailability and food-effect study and a dose-proportionality study, as well as literature regarding the pharmacokinetics of quinine.

The pharmacokinetics of quinine in malaria patients is different from that in healthy subjects. Because the clearance and the Vd of quinine are reduced in direct proportionality to the severity of malaria infection, the total plasma quinine concentrations tend to be higher (by about 1.4-fold to 2-fold) in patients with acute malaria as compared to healthy subjects. However, it appears that these higher total quinine concentrations are better tolerated by malaria patients than by healthy subjects mainly because of the one-half to one-third lower free (unbound) fraction of

quinine in malaria patients and also because the total plasma quinine concentrations usually decrease as the patient approaches the recovery phase, without a significant change in the fraction of unbound or free quinine.

The therapeutic plasma concentration range of quinine in patients with uncomplicated *P. falciparum* malaria, when given in combination with other antimicrobials (tetracycline, doxycycline, or clindamycin) is not well established. Some clinicians consider a target total plasma quinine concentration range of 8 – 20 mcg/mL for optimal clinical effectiveness of quinine monotherapy although ≥10 mcg/mL concentrations in malaria patients may be associated with ototoxicity albeit, largely reversible.

At least in the case of oral tetracycline, the combination with oral quinine sulfate results in approximately a 2-fold increase in plasma quinine concentrations in patients with uncomplicated *P. falciparum* malaria. Based on WinNonLin® simulation, it is likely to achieve in patients with uncomplicated malaria, steady state quinine concentrations of approximately 9 - 16 mcg/mL by Day 3 with quinine monotherapy or approximately 18 – 32 mcg/mL in quinine plus tetracycline combination therapy.

The origin of the infection (e.g., Southeast Asia or Africa) or the susceptibility of the *P. falciparum* parasite is considered in determining the duration of malaria therapy. The current treatment guidelines of the Centers for Disease Control (CDC) recommend the combination of oral quinine sulfate 650mg q8h with oral tetracycline, doxycycline, or clindamycin in order to prevent the development of parasite resistance. All these three ancillary antibiotics were shown to possess (slow acting) antimalarial activity *in vitro* which probably helps minimize or prevent recrudescence infection by offsetting the decline in total quinine concentrations towards the recovery or convalescence phase of malaria.

The standardized high-fat meal did not alter the oral bioavailability of quinine in healthy subjects who received the sponsor's quinine sulfate 324mg capsules. However, it may be advisable to take the quinine sulfate capsules with food in order to minimize the gastrointestinal irritation effects of the drug. Antacids containing aluminum and magnesium may delay or decrease absorption of quinine (a weak base).

Quinine is moderately bound to plasma protein primarily to α1-acid glycoprotein (AAG). In healthy subjects, free or unbound quinine is about 15 to 20%. In malaria patients, the percentage of the free quinine is reduced (5.5 to 7.5%) *In vitro* studies suggest that drugs that are highly protein bound (e.g., warfarin) do not have a significant effect on the plasma protein binding of quinine.

The biotransformation of quinine to its major metabolite, 3-hydroxyquinine is catalyzed mainly by CYP3A4 and to a minor extent, by CYP2C19. The systemic exposure to quinine was shown to increase by concomitant use of potent CYP3A4 inhibitors (e.g., ketoconazole, troleandamycin) and was decreased by potent CYP3A4 inducers (e.g., rifampin). Thus, the concurrent use of quinine with potent inhibitors and inducers of CYP3A4 should be avoided. If the combination of such drugs with quinine cannot be avoided, quinine dosage should be adjusted accordingly.

Quinine is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. Quinine was shown to inhibit the metabolism of drugs that are substrates of CYP3A4 (e.g., carbamazepine, phenobarbital). Careful monitoring for adverse effects of these drugs, as well as whenever practical, frequent monitoring of drug concentrations should be done when these drugs are used concurrently with quinine. Furthermore, quinine has the potential to prolong the QT interval. Thus, co-administration of quinine with drugs that are CYP3A4 substrates and that also prolong the QT interval (e.g., astemizole, cisapride, terfenadine, pimozide, halofantrine, disopyramide, dofetilide) should be avoided. In addition, when mefloquine is concurrently administered with quinine, there may be an increased risk of QT prolongation and seizures as a consequence of reduced

mefloquine metabolism. Quinine was shown to inhibit the metabolism of CYP2D6 substrates (e.g., desipramine, debrisoquine, dextromethorphan) *in vivo*, especially in rapid CYP2D6 metabolizers but not as potently as compared to its diastereomer, quinidine. Thus, caution should be taken when concomitantly administering quinine with CYP2D6 substrates, especially if the drug is also capable of prolonging the QT interval (e.g., flecainide). There is available, albeit limited evidence from *in vitro* metabolism studies regarding the potential inhibitory activity of quinine for other CYP450 enzymes, i.e., CYP1A, CYP2A6, CYP2C8 and CYP2C9.

Quinine may increase or decrease the effects of warfarin and oral anticoagulants. During concurrent therapy with quinine in patients receiving oral anticoagulant therapy with warfarin, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored and the warfarin dosage adjusted accordingly.

Quinine had also been shown to increase the steady state AUC of digoxin by 35% by decreasing its biliary excretion without affecting its renal clearance. When quinine is co-administered with digoxin, frequent monitoring of digoxin concentrations should be done.

The urinary excretion of quinine (a weak base) is two-fold faster in acidic urine than in basic urine. Urinary alkalinifying agents (e.g., acetazolamide, sodium bicarbonate) may increase plasma quinine concentrations. In cases of quinine overdosage, the use of multiple-dose activated charcoal (50 grams every 4 hours) is recommended. Forced acid diuresis, hemodialysis, plasma exchange transfusion, and charcoal column hemoperfusion do not appear to be effective in treating quinine overdosage.

Based on the published medical literature, age (young adults versus elderly and pediatrics), gender, race (Caucasian versus Thais and Africans), body weight (lean versus obese), concurrent diabetes, pregnancy, and smoking do not appear to alter quinine pharmacokinetics substantially in malaria patients to warrant dosage adjustment in relevant special populations. On the other hand, dosage reduction and dosing interval prolongation should be considered in uncomplicated malaria patients with concurrent chronic severe renal failure. Although dosage reduction is not needed in patients with mild to moderate hepatic impairment, these patients should be monitored closely for adverse reactions associated with quinine.

This NDA submission for quinine sulfate in the treatment of uncomplicated malaria is acceptable. The sponsor should address the labeling recommendations in Part III of this review.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology studies conducted by the sponsor of quinine sulfate 324 mg capsules in healthy volunteers include: (1) R03-085: a relative bioavailability and food-effect study, and (2) R04-0376: a dose-proportionality study that compared the 324mg dose to the 648 mg dose.

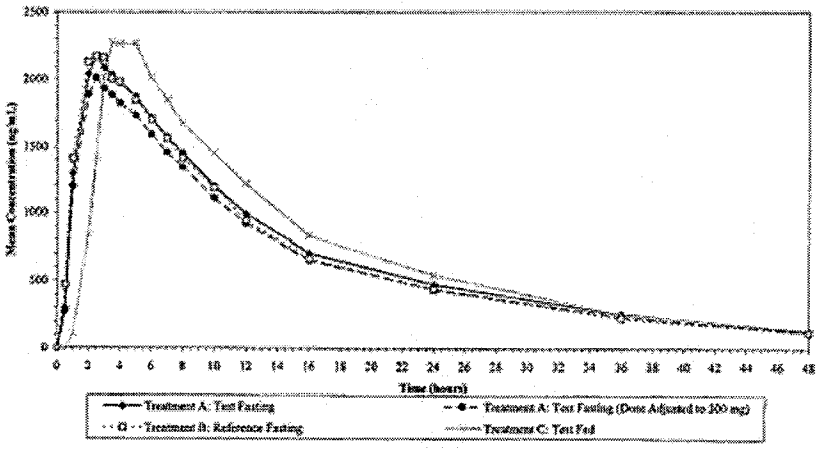
<u>Pharmacokinetics of Quinine in Healthy Volunteers</u>

Based on the findings of these randomized, crossover, single-dose studies, it was concluded that under fasted conditions, the dose-normalized Cmax and AUC_{0-24} of quinine from the sponsor's quinine sulfate 324 mg capsules were similar to that from the reference GPO-Thailand 300mg tablets (Figure 1), a product that was used in several published controlled studies involving quinine sulfate in the treatment of malaria. Additionally, a high-fat meal prolonged the quinine Tmax but did not significantly alter the Cmax and the AUC_{0-24} of quinine from the applicant's 324mg quinine sulfate capsule (Figure 1). Furthermore, at 648mg (2 capsules) the dose-normalized Cmax of quinine was about 25% lower than expected from that at the 324mg dose whereas the dose-normalized AUC_{0-24} from the higher dose was only 11% lower than expected from that at the lower dose (Figure 2).

QT Prolongation in Healthy Volunteers

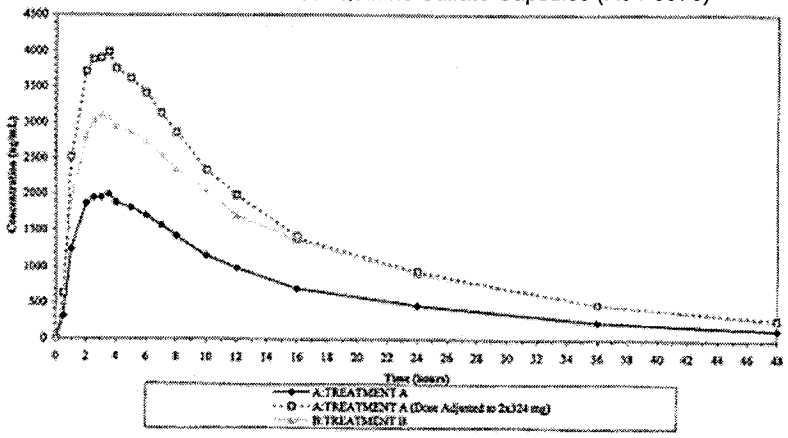
In the healthy subjects who were included in the two clinical pharmacology studies, single doses of 324mg and 648mg quinine sulfate resulted in an average maximum QTc change from baseline (ΔQTc) of 10 ± 19 msec and 12 ± 18 msec, respectively. A temporal relationship was seen between the total plasma quinine concentration and the ΔQTc, i.e., the greatest increase in mean ΔQTc occurred at around the mean Tmax (2- 4 hours). However, a weak correlation was observed between the time-matched individual plasma quinine concentrations and the ΔQTc (Figure 3). In general, females appeared to have a greater propensity for QT prolongation than males, however, this gender effect was probably confounded by the higher mean age and the lower mean bodyweight of the females in these studies. None of the subjects who received the sponsor's quinine sulfate capsule at the 324mg and 648mg dose under fasted or fed conditions had a ΔQTc of >60msec nor a QTc interval >500msec. In the food-effect study, the standardized high-fat meal prolonged the mean time to maximum QTc change from baseline but did not affect the magnitude of the mean ΔQTc following a single dose of the 324mg quinine sulfate capsule.

FIGURE 1
Mean Plasma Quinine Concentrations Following Single Doses of
Three Quinine Sulfate Treatments[a] in Healthy Volunteers (R03-085)



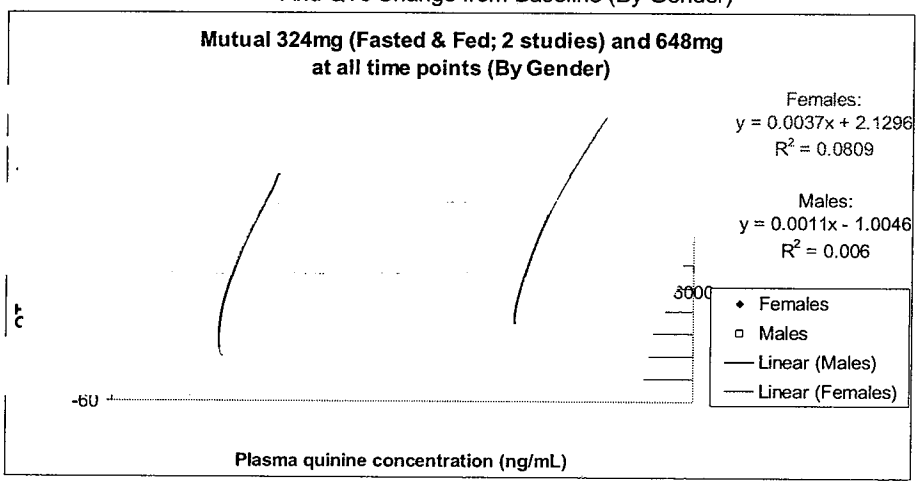
[a] Test: Mutual 324mg Quinine sulfate capsule
Reference: GPO-Thailand 300mg tablet

FIGURE 2
Mean Plasma Quinine Concentrations Following Single 324mg and 648mg Doses
of the Mutual Quinine Sulfate Capsules (R04-0376)



[a] Treatment A: 324mg
Treatment B: 2 x 324mg

FIGURE 3
Linear Correlation between Individual Plasma Quinine Concentrations
And QTc Change from Baseline (By Gender)



The following is a summary of important clinical pharmacology findings as they relate to intrinsic and extrinsic factors and is based largely upon the review of the published literature submitted with this NDA for the Mutual Quinine Sulfate 324mg capsules.

Pharmacokinetics of Quinine in Patients with Uncomplicated P. falciparum Malaria: Adults versus children; Acute versus convalescence stage

The pharmacokinetics of quinine in children (1.5 to 12 years old) with uncomplicated *P. falciparum* malaria is similar to that seen in adults (Table 1). in line with the recommendations of the CDC even though the elimination half-life of quinine in healthy children appear to be substantially shorter as compared to adults. As observed in adults, quinine exposure in children who are healthy is relatively lower than in those with uncomplicated malaria. Moreover, the disposition of quinine changes depending on the stage of the parasitic infection, i.e., total plasma quinine concentrations are significantly lower during convalescence than during the acute phase which is mainly due to the increased renal and total clearance of quinine in convalescence than during acute illness but the percentage of the free or unbound quinine appears to be comparable between these two stages of infection.

Therapeutic Quinine Concentration in Uncomplicated P. falciparum Malaria

In patients (N=22) with uncomplicated *P. falciparum* malaria who received oral quinine sulfate at 10 mg/kg q8h, those who did not experience recrudescence (N=16) had total plasma quinine pre-dose concentrations that were above 7.0 mcg/mL over the 7-day quinine monotherapy period.

Pharmacokinetics of Quinine in Elderly Patients

Following a single oral dose of 600mg quinine sulfate, the AUC of free quinine in otherwise healthy elderly subjects (65 – 78 years) was about 21% higher as compared to that in younger subjects (20 – 35 years). Because the renal clearances were similar between age groups, the significantly higher % unchanged quinine in the urine of the elderly subjects could probably be related to a slight decrease in hepatic function. Dosage adjustment in elderly patients is not warranted.

TABLE 1
Cross-study comparison of Mean ± SD Quinine Pharmacokinetic Parameters Following a First 10 mg/kg Quinine Sulfate Oral Dose in Patients with Acute Uncomplicated P. falciparum Malaria: Pediatrics versus Adults

PHARMACOKINETIC PARAMETER	CHILDREN[a] (n = 15)	ADULTS[b] (N = 15)
Tmax (h)	4.0	5.9 ± 4.7 (3.5 – 8.4)
Cmax (mcg/mL)	7.5 ± 1.14[c] (5.7– 7.3)	8.4 (7.3 – 9.4)
Half-life (h)	12.05 ± 1.44	16 ± 7[d]
Total CL(L/h/kg)	0.06 ± 0.007	0.09 ± 0.05
Vd (L/kg)	0.87 ± 0.12	0.78 ± 0.42
Free (unbound) quinine fraction (%)		5.3 ± 2.5

[a] serum concentrations; Sabchareon et al., 1982
[b] Supanarond et al., 1991
[c] equivalent to 22.5 ± 3.43 nmol/mL
[d] White et al., 1982

Pharmacokinetics in Various Ethnic Groups: Caucasians versus Thais
Following a single oral 600mg dose of quinine sulfate, the mean quinine Cmax, Tmax, AUC, apparent oral clearance, elimination half-life, and % dose excreted as unchanged quinine in the urine were similar between healthy Thais and Caucasians. Likewise, the fraction of free quinine reported for both racial groups were similar (15% versus 17%).

Pharmacokinetics in Males versus Females
In healthy subjects who received a single oral 648mg dose of the sponsor's capsule, it appears that females achieved a 20% higher mean quinine Cmax, a 30% higher mean AUC_{0-24}, and a longer mean elimination half-life (13.9 h versus 11.8 h) as compared to males. However, it was revealed that the female group had a higher mean age (39 versus 28 years) and a lower mean bodyweight (152 versus 174 lbs) than the male group. A review of the literature did not reveal a notable difference in quinine pharmacokinetics between male and female malaria patients. Thus, dosage adjustment based on gender does not appear to be necessary.

Pharmacokinetics of Quinine in Pregnant Females
In pregnant females with severe (cerebral) malaria, the mean total clearance of quinine was increased by 33% as compared to non-pregnant females with severe malaria. In uncomplicated malaria, there appears to be no difference in the AAG concentrations and the fraction of free quinine between pregnant and non-pregnant females (7.2% versus 7.5%). Overall, the observed difference in total quinine clearance is not substantial enough to warrant dosage adjustment in pregnant females with uncomplicated malaria.

Pharmacokinetics of Quinine in Patients with Hepatic Impairment
Following a single oral dose of 600mg quinine sulfate in otherwise healthy subjects with moderate hepatic impairment (Child-Pugh B), the mean AUC of total quinine and the mean Vd increased by 55% and by 51%, respectively, without a significant change in mean Cmax. The elimination half-life of quinine was prolonged in those with hepatic impairment (23.4 hours) as compared to healthy subjects (9.7 hours). Thus, for patients with concurrent mild to moderate chronic liver failure, reduction of quinine dosage is not warranted but close monitoring for signs and symptoms of quinine toxicity should be done.

Pharmacokinetics of Quinine in Patients with Renal Impairment
Following a single oral 600mg dose of quinine sulfate in otherwise healthy subjects with chronic renal failure not on dialysis (mean serum creatinine = 9.6 mg/dL), the median total quinine Cmax and AUC increased by 80% and 195%, respectively, as compared to those with normal renal function (mean serum creatinine = 1 mg/dL). However, because there was a parallel decrease in

the fraction of free quinine the resulting increase in the Cmax and AUC of free quinine was only by 33% and by 128% in those with renal impairment. The elimination half-life was prolonged in subjects with renal disease. (26 hours versus 9.7 hours). Thus, in acute uncomplicated malaria patients with concurrent chronic severe renal failure, the following modified dosing regimen is recommended: one loading dose of 648 mg followed 12 hours later by maintenance doses of 324 mg every 12 hours . In another study involving severe malaria patients who developed acute renal failure (ARF), the daily median plasma quinine Cmin were 10-30% higher than in malaria patients without ARF. Dosage reduction in severe malaria patients with ARF is not needed.

Pharmacokinetics in Subjects on Hemodialysis or Hemofiltration
Negligible to minimal amounts of circulating quinine in the blood are removed by hemodialysis and hemofiltration. In subjects with chronic renal failure (CRF) on hemodialysis, only about 6.5% of quinine is removed in 1 hour. Plasma quinine does not change during or shortly after hemofiltration in subjects with CRF.

Pharmacokinetics of Quinine When Given with Activated Charcoal: Treatment of Overdosage
In seven healthy fasted adult volunteers who received a single oral 600mg dose of quinine sulfate, multiple-dose activated charcoal (50 grams administered 4 hours after quinine dosing followed by 3 further doses over the next 12 hours) significantly lowered the quinine elimination half-life from 8.23 ± 0.57 to 4.55 ± 0.15 hours and the clearance was significantly increased by 56% (from 11.8 ± 1.23 L/h to 18.4 ± 2.8 L/h). Likewise, in five symptomatic patients with acute quinine poisoning, the mean elimination half-life was 8.1 ± 1.1 hours after each had been administered activated charcoal 50 grams every 4 hours as compared to the half-life (~26 hours) in poisoned patients treated supportively.

Drug Interactions
Quinine is metabolized mainly into 3-hydroxyquinine by CYP3A4 and to a minor extent by CYP2C19. A literature review revealed that quinine may interact significantly *in vivo* with drugs that are substrates and modulators of CYP3A4 and CYP2D6 (Table 2 and Table 3). *In vitro* metabolism findings suggest that based on the [I/]Ki approach, there is a likely to possible inhibition effect of quinine on the metabolism of drugs that are substrates of not only CYP3A4 and CYP2D6 but also CYP1A, CYP2A6, CYP2C8, and CYP2C9 but the evidence for the last 4 enzymes is rather limited at this time (Table 5).

Unlike quinidine, quinine does not alter the renal clearance of digoxin but like other basic drugs (e.g., verapamil, quinidine), quinine was shown to decrease the biliary excretion of unchanged digoxin. When quinine is co-administered with digoxin, frequent monitoring of digoxin concentrations is needed.

Pharmacokinetics of Quinine in Smoking
Cigarette smoking is a potent inducer of CYP1A2, which does not seem to play a major role in quinine metabolism based on the results of *in vitro* metabolism studies. In healthy subjects, smoking has been shown to increase quinine clearance by an average of 77% in healthy males who smoked > 10 cigarettes a day for at least 5 years. However, in malaria patients who received the full 7-day course of quinine therapy, cigarette smoking produced only a 25% decrease in median quinine AUC and a 16.5% decrease in median Cmax. Additionally, smoking did not appear to influence the therapeutic outcome in those patients who were smokers.

Pharmacokinetics of Quinine: Lean versus Obese Subjects
Quinine is a lipophilic drug (octanol/water = 1.94 at pH 7.4). Following a single oral 600mg dose of quinine sulfate, obese healthy subjects (n = 9) exhibited a 13% lower mean quinine AUC and a 20% lower mean Cmax as compared to age-matched lean subjects (n =8). There was a negative correlation between individual bodyweight and quinine Cmax. However, these changes would not warrant an increase in the quinine dosage.

Pharmacokinetics of Quinine in Subjects with Concurrent Diabetes

Following a single oral 600mg dose of quinine sulfate, the pharmacokinetic parameters of quinine were comparable between diabetics (n =12) and nondiabetics (n = 10).

TABLE 2

In Vivo Drug Interactions Resulting in Alteration in Quinine Pharmacokinetics

OVERALL EFFECT	QUININE DOSE, INTERVAL AND ROUTE	PRECIPITANT	PRECIPITANT DOSE AND INTERVAL	PERCENT CHANGE AUC/CL	REFERENCE and COMMENTS
In Vivo Induction > 20% Effect	10 mg/kg (7 days) t.i.d.	Rifampin (mainly CYP3A4 inducer)	15 mg/kg/day (7 days)	AUC: 75.4 (Decrease)	Pukrittayakamee et al.,2003
	600 mg single dose alone or after rifampin treatment		600 mg/day (2 weeks)	AUC: 83.3 (Decrease) CL: 521.4 (Increase)	Wanwimolruk et al., 1995
In Vivo Inhibition > 20% Effect	500mg single dose Oral	Ketoconazole (CYP3A4 inhibitor)	100 mg (3.5 days) at 12 and 1 hours before quinine intake, and every 12 h after, up to 72 h	AUC: 44.7 (Increase) CL: 31.2 (Decrease)	Mirghani et al., 1999
	600mg single dose	Troleandomycin (CYP2D6 inhibitor)	500 mg (2 days) first dose given 2 hours before quinine administration, then tid until the end of 48 hour period	AUC: 87.3 (Increase) CL:45.9 (Decrease)	Wanwimolruk et al., 2002

TABLE 3

In Vivo Drug Interactions Resulting in Alteration in Drug Pharmacokinetics/Pharmacodynamics By Quinine

OVERALL EFFECT	DRUG	DRUG DOSE AND INTERVAL	QUININE DOSE, INTERVAL AND ROUTE	PERCENT CHANGE AUC/CL	COMMENTS/REFERENCE
In Vivo Inhibition > 20% Effect	Astemizole (CYP3A4 substrate)	10 mg daily for the past 10 months	260mg single dose	Not Determined	Case report of Torsade de Pointes (TdP) after a single dose of quinine while taking Hismanal® (Martin et al., 1997)
		10 mg/day for 1 month	dose for Tx of nocturnal leg cramps, 3 days		Case report of TdP after the 3rd day of quinine Tx; astemizole levels on day after last quinine dose was 0.74 ng/mL (equivalent to the reported Cmax in healthy volunteers who received the same dose).
	Desipramine (CYP2D6 substrate)	Single oral doses of 25mg DMI	750 mg quinine/day for 2 days pretreatment		In rapid hydroxylators, quinine decreased the excretion of 2-hydroxydesipramine by 54% compared to control. In slow hydroxylators, no significant changes in

					excretion pattern was observed (Steiner et al., 1988)
	Digoxin	1mg single dose as an infusion over 10 min, alone or with quinine	200mg IV (9 days) tid, 4 days before and after the second digoxin administration	CL: 25.5 (Decrease)	Wandell et al., 1980
		0.5 to 0.75 mg/day, alone or with quinine	750mg/day	35% decrease in steady state biliary excretion; no effect on CLrenal of digoxin	Hedman et al., 1990
	Flecainide (CYP2D6 substrate)	150mg single infusion over 30 minutes	500mg three doses, administered before flecainide administration and 12 hours and 24 hours after	AUC: 20.9 (Increase) CL: 16.5 (Decrease)	Quinine administration did not change the apparent Vd or the CLrenal of flecainide. The PR interval in the ECG was slightly more prolonged with the combination than with flecainide alone (Munafo et al., 1980)

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Gerlie Gieser, Ph.D.
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Division of Pharmaceutical Evaluation 3

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

III. Question Based Review

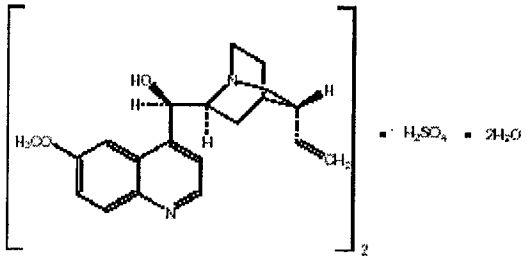
A. General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Not applicable.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The chemical structure of quinine sulfate dihydrate, a weakly basic drug, is shown in Figure 4 below.



The physical and chemical attributes of quinine sulfate are as follows:

Appearance: White, crystalline powder
Molecular formula: $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$
Relative molecular mass: 782.96

Each soft gelatin capsule contains the active ingredient, 324mg of quinine sulfate dihydrate (equivalent to — ,ng free quinine base) and standard capsule excipients (talc, corn starch, magnesium stearate). The expiration dating period for this product is 24 months. Batch BB 102 0105 was used as the bioequivalence study batch. These capsules were manufactured at a scale of

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of antiplasmodial activity of quinine sulfate is not completely understood but is proposed to be via inhibition of the *Plasmodium* heme polymerase, required to convert heme to non-toxic malaria pigment hemozoin. The primary activity *in vitro* and *in vivo* is against the blood schizont form of the *Plasmodia* species; it is not gametocidal and has little effect on the sporozoite or pre-erythrocytic forms.

The proposed therapeutic indication is for the treatment of uncomplicated malaria due to chloroquine-resistant *Plasmodium falciparum*.

4. What are the proposed dosage(s) and route(s) of administration?

For the treatment of malaria, the proposed usual adult oral dose is 648 mg (two capsules) three times daily for 7 days,

Combination antimicrobial therapy is preferred over quinine monotherapy in order to minimize the development of *P. falciparum* resistance, i.e., by additive/synergistic antimalarial activity of the drugs and/or by a pharmacokinetic interaction that leads to increased plasma quinine concentrations (e.g., by tetracycline). For the treatment of chloroquine-resistant uncomplicated *P. falciparum* malaria, the Centers for Disease Control (CDC) recommends for nonpregnant adults, oral quinine sulfate 650mg every 8 hours for 3 days (or 7 days if infection was acquired from Southeast Asia) in combination with tetracycline (250mg qid x 7days) or doxycycline 100mg tid x 7 days, or clindamycin (20mg base/kg/day po divided tid x 7 days). For children 8 years and older, the recommended dose is 10mg/kg quinine sulfate plus tetracycline (25 mg/kg/day po divided qid x 7days) or doxycyline (4mg/kg/day po divided bid x 7days). For children < 8 years old, oral quinine sulfate plus clindamycin (20mg base/kg/day po divided tid x 7 days) is recommended.

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Because quinine sulfate has been used for more than a century in the treatment of malaria infections, the sponsor of this NDA for quinine sulfate was not required to conduct Phase III clinical trials to support claims pertaining to efficacy and safety in the treatment of malaria. However, a single-dose, crossover study in healthy volunteers was conducted to evaluate the oral bioavailability of the sponsor's capsule (324mg, when given fasted or with a high-fat meal) relative to a reference quinine sulfate dosage form (GPO-Thailand 300mg tablet; fasted) that had previously been shown to be efficacious in the treatment of uncomplicated *P. falciparum* malaria based on the medical literature. In addition, in light of a known potential for quinine to prolong QT intervals, ECG monitoring was accomplished in this study, as well as in the single-dose proportionality, crossover study to compare in healthy volunteers the PK and safety of the 648mg dose (for treatment of malaria) and the 324mg dose (commonly used off-label for prophylaxis of nocturnal leg cramps).

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Total plasma quinine concentrations and QT prolongation effect were measured in both of the clinical pharmacology studies conducted. In published clinical trials reviewed with the primary PK data submitted with this NDA, the common efficacy endpoints were cure rates, parasite clearance times, fever clearance times, and recrudescence infection (RI) rates; the safety endpoints included those related to cardiotoxicity, ototoxicity, and common adverse events (e.g., nausea, vomiting, tinnitus).

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, refer to II. F, Analytical Section.

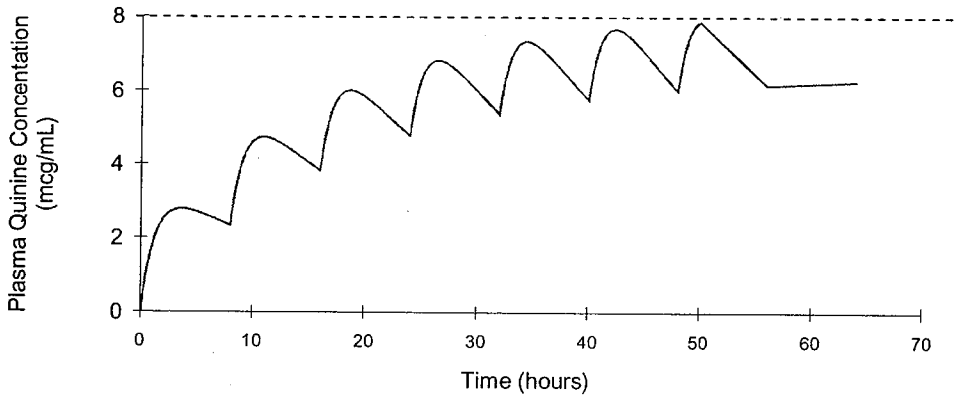
4. Exposure-response

a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Clinical trials involving malaria patients were not conducted for the purpose of this NDA application; the submission was reviewed for efficacy claims based on information in the medical literature. Based on a review paper published by White (1996), the therapeutic concentration range of quinine in malaria patients is probably 8 to 20 mcg/mL (as total plasma quinine) or 0.8 to 2 mcg/mL (as unbound or free quinine). Based on WinNonlin® simulation of single-dose quinine PK data obtained in healthy subjects, this "target" total plasma quinine concentration (~ 8 mcg/mL) could be reached as a peak concentration in healthy subjects with 648mg every 8 hours within 3 days of therapy as shown in Figure 5 below. Depending on severity of malaria, higher than these steady state plasma quinine concentrations may be achieved in the clinical realm because of a reduction in plasma quinine clearance in malaria patients particularly during the acute phase (estimated range: 9 - 16 mcg/mL), and with concomitant administration of tetracycline which has the potential to increase systemic quinine levels (estimated range: 18 – 32 mcg/mL). Towards the recovery or convalescence phase of the infection, total plasma quinine concentrations decline gradually as the clearance of quinine increases but the percentage of the unbound (free) quinine may not significantly change

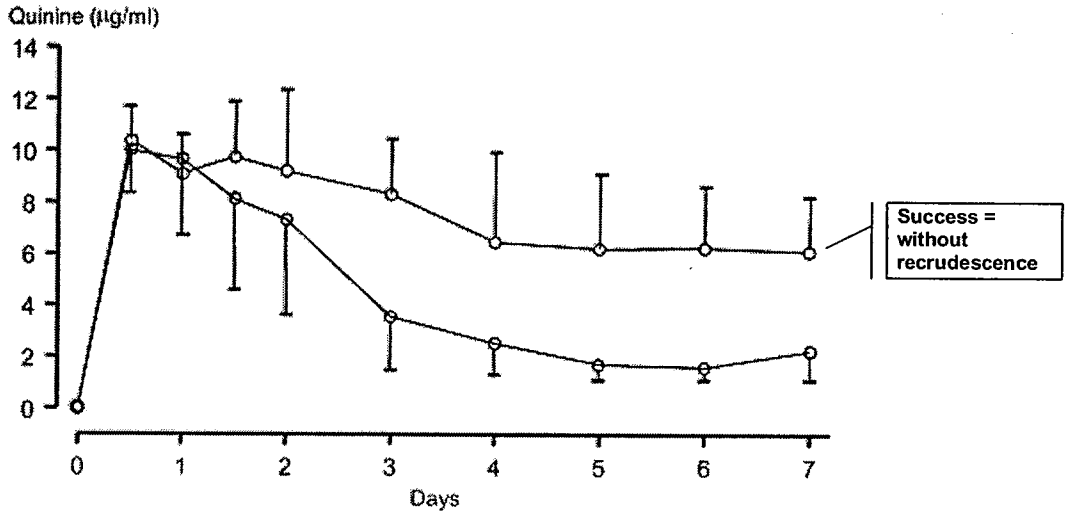
Based on medical evidence, a longer duration, i.e., 7 days of therapy appears to be more efficacious when quinine is used alone.

FIGURE 5
WinNonLin® Simulation of Total Plasma Quinine Concentrations in Healthy Volunteers Following 648mg Quinine Sulfate Every 8 Hours for Three Days of Quinine Monotherapy



For malaria infection acquired in Southeast Asia where *P. falciparum* resistance is a concern, the CDC recommends a longer, i.e, 7-day duration of quinine therapy in combination with tetracycline, doxycycline, or clindamycin. Based on the findings of Pukrittayakamee et al (2003), uncomplicated malaria patients who were able to maintain total quinine pre-dose concentrations exceeding 7.0 mcg/mL throughout the 7-day quinine monotherapy (or quinine + rifampin) period did not experience recrudescence infections (Figure 6).

FIGURE 6
Median and 90% CI concentrations of quinine in the plasma of patients with *P. falciparum* malaria with (upper line graph) and without (lower line graph) subsequent recrudescences



b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

In studies involving healthy subjects who received the sponsor's quinine sulfate capsules at 324mg and 648mg doses, there was no apparent relationship between quinine sulfate dose and average maximum QTc change from baseline. Overall, there was only a weak correlation between the total (bound + unbound) plasma quinine concentration and the maximum QTc change from baseline. However, a temporal relationship was observed between the mean plasma quinine Cmax and the mean maximum QTc effect, i.e., the average maximum QTc change from baseline occurred around the plasma Tmax (2 to 4 hours post-dose).

As shown in Figure 9, there was a weak linear correlation between total plasma quinine concentration and maximum QTc change from baseline in healthy volunteers who received single doses of 324mg and 648mg of the Mutual Quinine Sulfate tablets (under fasted and fed conditions) in two crossover studies. As seen from the slopes of the overlapping regressed lines, there is no perceptible difference between the two quinine sulfate doses; the average (± SD) maximum change from baseline at around the quinine Tmax were 10 ± 19 msec and 12 ± 18 msec following a single dose of 324mg and 648mg quinine sulfate, respectively. None of the healthy subjects in the pooled studies experienced a QTc change of > 60 msec nor did any show a QTc interval of > 500 msec.

Figure 7A shows the linear correlation between plasma quinine concentration and the matched QTc change from baseline. It appears from the figure that the slope of the regressed line representing the female subjects was slightly higher than that for the male subjects.

As shown in Figure 8, the magnitude of the QT-effect (as maximum QTc change from baseline or area under the QTc change curve (AUQTcC) was consistently greater with the 648 mg dose than the 324 mg dose, although the increase in QT prolongation parameters at the 648 mg dose did not appear to be commensurate with the increases in Cmax and AUC at the same dose.

FIGURE 7
Linear Correlation Between Plasma Quinine Concentration and Maximum QTc Change from Baseline

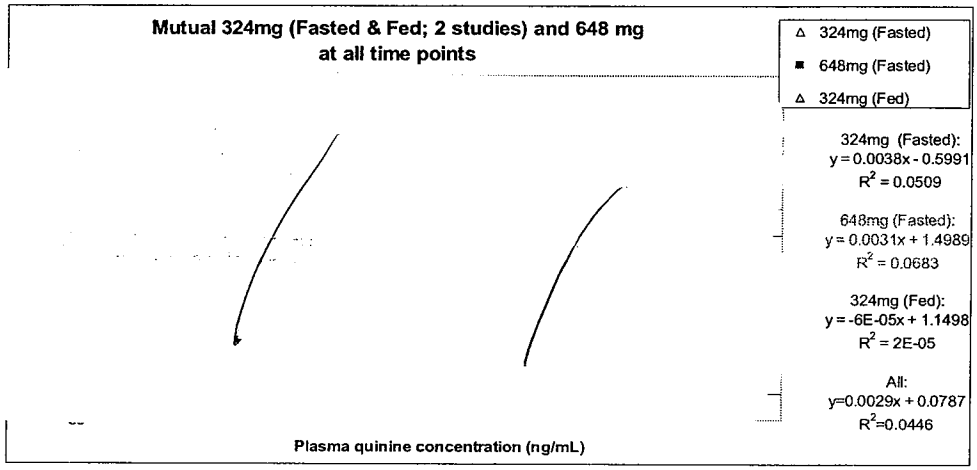


FIGURE 7A
Linear Correlation Between Plasma Quinine Concentration and Maximum QTc Change from Baseline (By Gender)

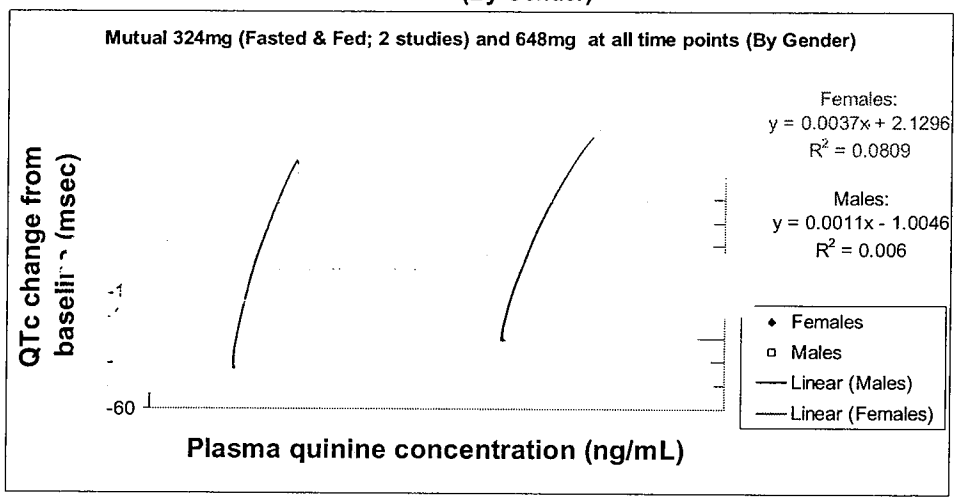
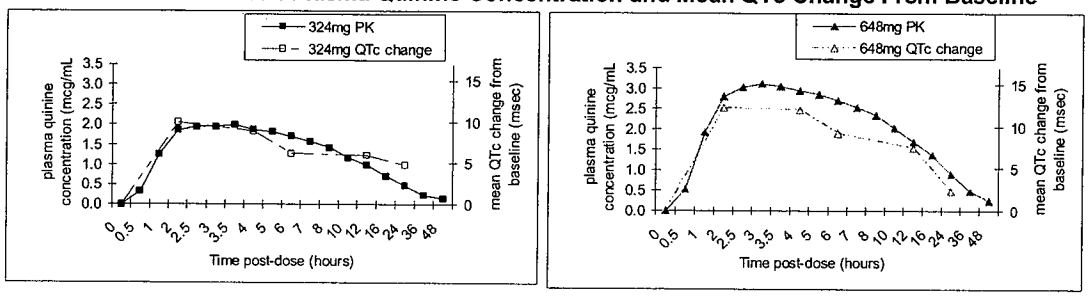


FIGURE 8
Time Course of Mean Plasma Quinine Concentration and Mean QTc Change From Baseline



c) Does this drug prolong the QT or QTc interval?

Yes, as shown in healthy volunteers (refer to 4b above). The magnitude of the QT and other safety effects of quinine in acute malaria patients may be approximately equivalent or slightly lower than that seen in healthy volunteers.

In view of the difference in quinine pharmacokinetics between healthy subjects and malaria patients, the ability to extrapolate the QT prolongation effect observed in healthy volunteers to patients was evaluated. Indeed, it is recognized that malaria patients tend to tolerate higher total plasma concentrations of quinine better than do healthy subjects. Based on a comparison of quinine exposures and AAG concentrations between Caucasians who are healthy and those with uncomplicated malaria, the known % free (unbound) quinine in healthy Caucasians, as well as the assumption that the rate of adverse effects of quinine is directly related to the free (unbound) drug concentration, it is possible that the QT-prolongation potential of quinine is about 2-fold greater in healthy volunteers than in patients with uncomplicated malaria; Table 4 presents a summary of the algorithm used to arrive at this conclusion.

TABLE 4
Algorithm for Estimating Relative Potential of Quinine To Induce Pharmacodynamic Effects in Caucasians: Healthy subjects versus Patients with *P. falciparum* Malaria [a]

	Healthy Subjects (N=12)	Patients with Uncomplicated Malaria (N=10)
Total Quinine Cmax after a single dose of Quinine dihydrocholoride 600mg (mcg/mL)	4.0[b]	6.0
Alpha-1 acid glycoprotein concentration (g/L)	0.58 ± 0.24	1.83 ± 0.36
Free (Unbound) Quinine Fraction	0.148[c]	-
Estimated free (unbound) quinine Cmax after a single dose of Quinine dihydrocholoride 600mg (mcg/mL)[d]	0.6	0.3

[a] data from Tange et al (1997) unless otherwise specified
[b] normalized from a 300mg dose
[c] Wanwimolruk et al, 1992 ; (N=10)
[d] Free (unbound) Quinine Cmax = Total Quinine Cmax * free fraction

d) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosage regimen for the treatment of uncomplicated malaria is 648 mg quinine sulfate (2 capsules) three times daily for 7 days, , the CDC Guidelines for the use of quinine sulfate in the treatment of uncomplicated malaria in adult patients, as summarized in Table 3 below.

TABLE 5

Centers for Disease Control (CDC) Guidelines for the Treatment of Malaria in the United States

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose Pediatric dose should NEVER exceed adult dose
Uncomplicated malaria/ *P. falciparum* or Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale:* see *P. vivax* and *P ovale* (below) re. treatment with primaquine	**Chloroquine-resistant or unknown resistance** (All malarious regions except those specified as chloroquine-sensitive listed in the box above. Middle Eastern countries with chloroquineresistant *P. falciparum* include Iran, Oman, Saudi Arabia, and Yemen. Of note, infections acquired in the Newly Independent States of the former Soviet Union and Korea to date have been uniformly caused by *P. vivax* and should therefore be treated as chloroquine-sensitive infections.)	**Quinine sulfate[1] plus one of the following: Doxycycline, Tetracycline, or Clindamycin** **Quinine sulfate:** 542 mg base (=650 mg salt) po tid x 3 to 7 days **Doxycycline:** 100 mg po bid x 7 days **Tetracycline:** 250 mg po qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days	**Quinine sulfate[1] plus one of the following: Doxycycline[2], Tetracycline[2] or Clindamycin** **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 to 7 days **Doxycycline:** 4 mg/kg/day po divided bid x 7 days **Tetracycline:** 25 mg/kg/day po divided qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days
Uncomplicated malaria/ *P. vivax*	**Chloroquine-resistant** (Papua New Guinea and Indonesia)	**Quinine sulfate[1] plus either Doxycycline or Tetracycline plus Primaquine phosphate[3]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above	**Quinine sulfate[1] plus either Doxycycline[2]or Tetracycline[2] plus Primaquine phosphate[3]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above
Uncomplicated malaria: alternatives for pregnant women[4,5,6,7]	**Chloroquine resistant *P. falciparum*[4,5,6]** (see uncomplicated malaria sections above for regions with known chloroquine resistant *P. falciparum*)	**Quinine sulfate[1] plus Clindamycin** **Quinine sulfate:** Treatment as above **Clindamycin:** Treatment as above	**Not applicable**
	Chloroquine-resistant *P. vivax*[4,5,6,7] (see uncomplicated malaria sections above for regions with chloroquine-resistant *P. vivax*)	**Quinine sulfate** **Quinine sulfate:** 650 mg salt po tid x 7 days	**Not applicable**

[1] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired in Africa and South America, quinine treatment should continue for 3 days.

[2] Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, quinine (given alone for 7 days or given in combination with clindamycin) and atovaquone-proguanil are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax,* quinine (given alone for 7 days) or mefloquine are recommended treatment options. If none of these treatment options are available or are not being tolerated and if the treatment benefits outweigh the risks, doxycycline or tetracycline may be given to children less than 8 years old.

[3] Primaquine is used to eradicate any hypnozoite forms that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in persons with G6PD deficiency, patients must be screened for G6PD deficiency prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for

8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

[4] For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[5] Because there are no adequate, well-controlled studies of atovaquone and/or proguanil hydrochloride in pregnant women, atovaquone-proguanil is generally not recommended for use in pregnant women. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks. There are no data on the efficacy of atovaquone-proguanil in the treatment of chloroquine resistant *P. vivax* infections.

[6] Because of a possible association with mefloquine treatment during pregnancy and an increase in stillbirths, mefloquine is generally not recommended for treatment in pregnant women. However, mefloquine may be used if it is the only treatment option available and if the potential benefit is judged to outweigh the potential risks.

[7] For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Medical literature provides the PK-efficacy basis for the currently recommended quinine sulfate dosage and duration for the treatment of malaria. For example, Earle and colleagues (1948) compared the therapeutic effects of various quinine sulfate dosages at 4 to 6-hour intervals that maintained stable plasma concentrations over a therapy duration from 4 to 8 days in subjects with experimentally induced malaria. Table 6 below summarizes the relationship between dose/duration/plasma concentration and the antimalarial effect obtained by these investigators. Based on these findings, it appears that an average plasma quinine concentration of at least 5.6 mcg/mL was desirable; based on WinNonlin® simulation, this plasma concentration may be achieved as a peak concentration in healthy subjects after the first day of therapy with 648 mg of quinine sulfate (Figure 5 above). In patients with uncomplicated malaria, about 2-fold higher plasma quinine concentrations are achieved by Day 1 of quinine monotherapy (See Figure 6 and Figure 11).

TABLE 6
Comparison of various dosage regimens of quinine sulfate in the treatment of P. falciparum malaria

MEAN DAILY DOSE AND DURATION	NUMBER OF SUBJECTS INOCULATED WITH *P. FALCIPARUM*	AVERAGE PLASMA CONCENTRATION (MCG/ML)	THERAPEUTIC OUTCOME
100mg to 1.5 grams for 4 days	15	2.1 to 10.4	Temporary therapeutic effect
300mg to 2.1 g for 6 days	13	2.9 to 8.7	Plasma concentrations of ≥ 5.6 mcg/mL produced permanent disappearance of parasites and fever
720 mg for 8 days	6		Cure in all but one patient

Furthermore, based on the sponsor's review of randomized and non-randomized efficacy trials, 7 days of quinine therapy resulted in parasitological cure in at least 80% of patients at 28 days of follow-up, regardless of the country in which the study was performed. In the randomized studies, quinine was most commonly administered as 10 mg quinine sulfate per kg three times daily for 7 days to treat uncomplicated *P. falciparum* malaria. The drug was well tolerated with tinnitus and GI intolerance (nausea, vomiting, abdominal pain, diarrhea) being the most common adverse events.

When given with other antimalarial agents (clindamycin, tetracycline, doxycycline, sulfadoxine/pyrimethamine, primaquine, or artemisinin), quinine showed an equal or greater efficacy as compared to when given as monotherapy; some combination therapies even allowed for a shorter therapy course without loss of efficacy. In 6 of 16 randomized (one blinded, others

open-label) studies, the AE profiles reported in combination studies was similar to those seen in monotherapy.

5. What are the PK characteristics of the drug and its major metabolite?
a) What are the single dose and multiple dose PK parameters?

The mean ± SD pharmacokinetic parameter values of quinine following a single 648 mg dose of the sponsor's quinine sulfate (equivalent to 2 capsules) is provided in Table 7 below. The elimination half-life of quinine obtained in the sponsor's single-dose PK study involving healthy volunteers is consistent with mean values reported in the literature (7.0 to 13.5 hours). In published studies, the reported volume of distribution for quinine ranged from 1.43 to 3.78 L/kg in healthy adults. The literature does not provide the corresponding pharmacokinetic parameters for quinine sulfate when given in multiple doses to healthy subjects, presumably because of the drug's greater toxicity potential in non-malaria subjects.

TABLE 7
Mean ± SD Quinine Pharmacokinetic Parameters in Healthy Volunteers
Following a Single Dose of 648 mg (Study R04-0376)

PHARMACOKINETIC PARAMETER (Range)	SINGLE DOSE (648 mg)	MULTIPLE DOSE
Tmax (h)	2.80 ± 0.82 (1.00-4.00)	N/A
Cmax (mcg/mL)	3.24 ± 0.69 (2.10 – 4.80)	N/A
AUC_{0-t} (mcg*h/mL)	56.20 ± 15.68 (36.47 – 91.00)	N/A
t½ (h)	12.78 ± 3.03 (8.24 – 19.02)	N/A
AUC_{inf} (mcg*h/mL)	61.57 ± 19.29 (38.34 – 109.24)	N/A

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of quinine differ between healthy subjects and malaria patients. In malaria, the percentage of free or unbound quinine is 50% to 66% lower, thereby leading to lower clearance rates and lower volume of distribution (Vd) as compared to healthy subjects. Together, these PK changes result in higher total plasma quinine concentrations during the acute phase as compared with the convalescent phase.

c) What are the characteristics of drug absorption?

Following a single oral dose of quinine to healthy adults, plasma levels are detectable within 0.5 hours. Peak plasma concentrations are attained in an average of 2.4 to 4.4 hours. In healthy subjects, the absolute bioavailability of quinine is approximately 76% to 88% (Paintaud *et al.*, 1993; Salako *et al.*, 1992).

In vitro, quinine is a substrate and inhibitor of the organic cation transporter (OCT) that is found in intestinal and other tissues.

Based on a comparison of *in vitro* dissolution profiles of the Mutual Quinine Sulfate 324mg capsules in various media, the magnitude of quinine solubility occurs in the following rank order:

d) What are the characteristics of drug distribution?

Quinine is moderately protein bound (about 69 to 92% in healthy volunteers), primarily to the acute phase protein, α1-acid glycoprotein (AAG). It also binds to albumin (approximately 35% *in*

vitro in human serum albumin, Wanwimolruk and Denton, 1992). The extent of protein binding and the fraction of free (unbound) quinine are determined mainly by the AAG concentrations in the plasma which is about 3-fold higher in *P. falciparum* malaria patients than in healthy subjects (1.83 ± 0.36 g/L versus 0.58 ± 0.24 g/L; Tange et al., 1997).

The alpha1-acid glycoprotein (AAG) fraction in the plasma appears to be higher in malaria patients than in healthy subjects (Table 8; Wanwimolruk and Denton, 1992); plasma protein binding was reported to range from 78 to 95% in patients with malaria. Both the AAG and the albumin fractions in the plasma of healthy Caucasians were comparable to that in healthy Thais. The extent of plasma protein binding in patients varies depending on severity of malaria, which is reportedly higher in severe/cerebral malaria compared to uncomplicated malaria (Table 8; Silamut et al., 1991). In acute malaria, the clearance of quinine from systemic circulation is lower than in the convalescent phase but the percentage of free or unbound quinine does not change as shown in Table 9 below.

TABLE 8
Plasma Protein Binding Data in Various Populations

Source of Plasma	Unbound (Free) Quinine (%)	Albumin (g/L)	AAG (g/L)	Total Protein (g/L)
Wanwimolruk and Denton, 1992				
Pooled Blood Bank Plasma (N=6)	20.7 ± 1.3	39	0.75	63
Healthy Caucasians (N=10)	14.8 ± 6.7 (7.9-31.0)	43.8 ± 4.2	0.86 ± 0.16*	72 ± 6
Healthy Thai Subjects (N=15)	17.0 ± 5.3 (9.2-29.5)	40.2 ± 3.3	0.6 ± 0.19	68 ± 5
Thai Patients[1] (N=20)	10.9 ± 4.0** (5.5-22.1)	36.5 ± 4.0†	1.23 ± 0.48*	66 ± 7
Silamut *et al.*, 1991				
Healthy Thai Men (N=16)	–	–	0.76 ± 0.20	–
Healthy Thai Women (N=20)	–	–	0.66 ± 0.16	–
Healthy Pregnant Thai Patients (N=21)	–	–	0.38 ± 0.11††	–
Thai Patients with Cerebral Malaria (N=25)	5.5 ± 2.4‡‡	–	1.93 ± 0.53‡	–
Thai Patients with Uncomplicated Malaria (N=36)	7.2 ± 1.9‡‡	–	1.55 ± 0.58‡	–
Pregnant Thai Patients with Uncomplicated Malaria (N=20)	7.5 ± 2.6	–	1.40 ± 0.75	–

AAG=α_1-acid glycoprotein
[1]16 patients with uncomplicated *P. falciparum* malaria and 4 patients with cerebral *P. falciparum* malaria
*P < 0.05 as compared with healthy Thai subjects
**P < 0.001, compared to healthy Thai subjects
†P < 0.05, compared to healthy subjects
††P < 0.01, compared to healthy, nonpregnant Thai men and women
‡ P = 0.008, compared to patients with uncomplicated *P. falciparum* malaria
‡‡ P = 0.03, compared to those with uncomplicated malaria

TABLE 9
Mean Plasma Clearance and Protein Binding Parameter Values in Sixteen Patients During Acute Malaria (n=16) and During Convalescence (n=12)

Phase of Malaria	Mean ± Standard Deviation		
	Quinine Clearance (L/kg·h)		Free Quinine (%)
	Total	Free	
Acute	0.084 ± 0.035	0.77 ± 0.41	9.5 ± 4.5
Convalescent	0.20 ± 0.12	2.33 ± 1.00	9.3 ± 2.1
P Value[1]	0.001	< 0.001	NS

NS=the difference was not statistically significant (P > 0.05)
[1] Mann-Whitney U-test
From: Pukrittayakamee *et al.*,1997

The volume of distribution (Vd) of quinine decreases in proportion to the severity of malaria and consequently total plasma levels are higher in malaria patients than in healthy subjects. However, despite these higher total plasma quinine concentrations, there is usually a less than proportional increase in free (unbound) quinine concentrations because of the 50% to 66% lower free quinine fraction in malaria patients as compared to that in healthy subjects.

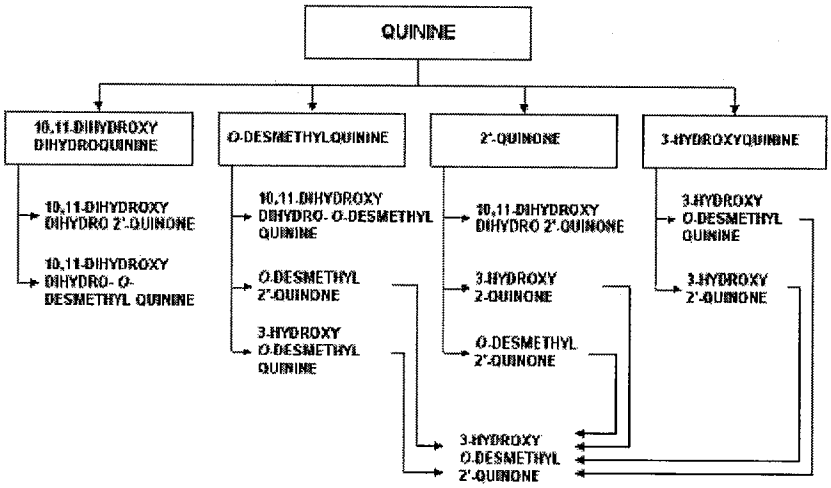
e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not conducted specifically for the sponsor's quinine sulfate product. According to medical literature, about 80% of the orally administered quinine dose is eliminated by hepatic oxidative metabolism; the remainder is eliminated as unchanged drug by the kidney (Tracy and Webster, 1996: White et al, 1982).

f) What are the characteristics of drug metabolism?

The formation of the major metabolite (3-hydroxyquinine) is catalyzed mainly by CP3A4 and to a minor extent by CYP2C19, as shown both *in vitro* and *in vivo*; this metabolite is believed to possess 12% of the antimalarial activity of the parent drug (Nontprasert et al., 1996). The percentage of the dose excreted as 3-hydroxyquinine is only 14% suggesting that further metabolism to minor metabolites and/or biliary excretion take place. The metabolites that appear in the urine after oral dosing are shown in Figure 9 (Bannon et al., 1998).

FIGURE 9
Proposed Metabolic Pathway for Quinine



g) What are the characteristics of drug excretion?

The elimination half-life of quinine is about 12 hours in healthy subjects; this is prolonged in elderly patients (~18 hours) and in adult malaria patients (~17 hours). The estimated plasma clearance in healthy subjects following single oral doses varies from 0.08 to 0.47 L/h/kg (median 0.176 L/h/kg) and is reduced in patients with malaria, 0.09 L/h/kg.

About 23% of quinine is excreted into urine as unchanged drug and about 16% as glucuronide conjugate. Urinary recovery of quinine and four of its known metabolites following hydrolysis with β-glucuronidase are summarized in Table 10 (Mirghani et al., 2003). The remaining quinine that was unaccounted for is probably eliminated in the bile and/or feces.

Renal excretion of quinine, a weak base, is twice as rapid when urine is acidic than when it is alkaline (Goodman and Gilman, 2001).

Extracorporeal elimination: The effect of multiple-dose activated charcoal on quinine elimination was studied following a therapeutic (600mg) dose of quinine bisulfate to 7 adult fasted volunteers (Lockey and Bateman, 1989). Activated charcoal 50 g was administered 4 hours after quinine dosing and 3 further doses were given over the next 12 hours. Activated charcoal significantly lowered the quinine elimination half-life from 8.23 ± 0.57 to 4.55 ± 0.15 hours and the clearance was significantly increased by 56% (from 11.8 ± 1.23 L/h to 18.4 ± 2.8 L/h). In 5 symptomatic patients with acute quinine poisoning, the mean elimination half-life was 8.1 ± 1.1 hours after each had been administered activated charcoal 50 g every 4 hours (Prescott et al, 1989). The half-life was approximately 26 hours in poisoned patients treated supportively (Bateman et al., 1985).

TABLE 10
Percentage of Quinine and Its Metabolites Excreted in Urine within 48 Hours Following a Single Oral 500-mg Dose of Quinine Hydrochloride in Healthy Subjects

Substance Measured	Percent Excreted in 48 Hours Mean ± S. D.	
	Free	Total
Quinine	13 ± 4	23 ± 7
3-hydroxyquinine	15 ± 6	18 ± 8
2'-quininone	6 ± 3	9 ± 5
(10S)-11-dihydroxydihydroquinine	3 ± 2	4 ± 2
(10R)-11- dihydroxydihydroquinine	2 ± 1	3 ± 2
Total	39 ± 11	56 ± 16

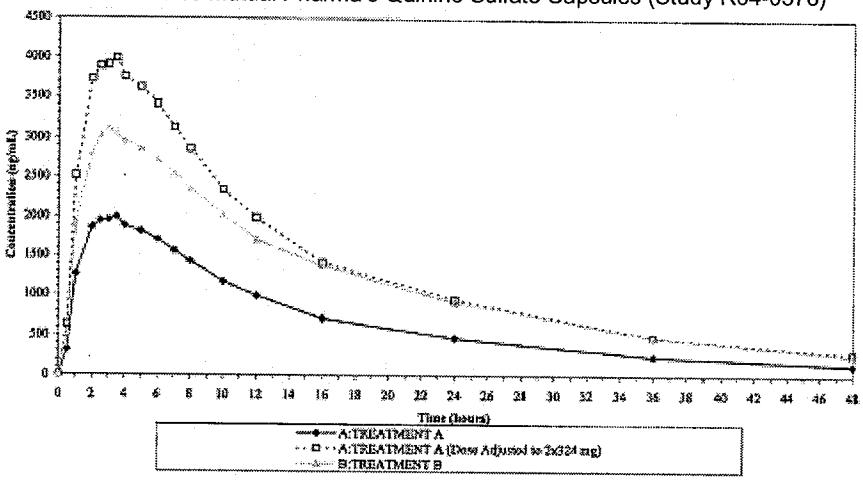
h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose-proportionality study conducted by the sponsor compared the pharmacokinetics of quinine at two quinine sulfate doses, 324mg and 648 mg. At the higher dose, the plasma quinine AUC was 12% lower than expected and the Cmax was 25% lower than expected as compared to those obtained following the 324mg dose. Figure 10 provides a comparison of plasma quinine concentration-time profiles of the two test doses. This finding of less than dose-proportional exposure increases (particularly Cmax) at higher quinine doses appears to be consistent with that obtained previously by other groups as seen in Table 11. Based on this table, it appears that the Vd of quinine increases with increasing doses. However, quinine exhibits linear, dose-related pharmacokinetics in terms of AUC.

TABLE 11
Mean ± SD Pharmacokinetic Parameter Values Following Administration of Single Oral Doses of Quinine in Healthy Subjects (R-04-0376 and Published Literature)

Reference	No. of Subjects (M/F)	Dose (mg base)	Tmax (h)	Cmax (h)	AUCinf (mcg*h/mL)	T½ (h)	CL (L/h/kg)	Vd (L/kg)
Study R04-0376	25 (11/12)	268	2.76 ± 0.91	2.12 ± 0.52	35.20 ± 12.68	12.69 ± 4.91	-	-
		535	2.80 ± 0.82	3.24 ± 0.69	61.57 ± 19.30	12.78 ± 3.03	-	-
Babalola et al., 1997	7 (7/0)	250	2.67 ± 1.48	1.73 ± 0.65	28.05 ± 13.83	10.06 ± 4.28	0.20 ± 0.17	2.46 ± 1.46
		500	2.36 ± 1.58	2.39 ± 1.08	52.15 ± 37.75	12.34 ± 1.61	0.21 ± 0.09	3.36 ± 1.00
		750	4.40 ± 2.15	3.18 ± 1.84	62.97 ± 51.04	9.03 ± 2.82	0.27 ± 0.11	3.32 ± 1.65
		1000	2.90 ± 1.56	6.09 ± 4.11	110.79 ± 85.14	13.36 ± 7.04	0.25 ± 0.18	3.78 ± 2.59
Sowumni et al., 1996	7 (7/0)	250	2.4 ± 1.5	1.6 ± 0.6	18.5 ± 7.7	9.0 ± 3.2	0.29 ± 0.19	2.1 ± 1.3
		500	2.8 ±1.4	2.7 ± 0.5	30.2 ± 3.5	11.4 ± 2.7	0.28 ± 0.04	2.5 ± 1.4
		1000	3.2 ± 1.2	4.97 ± 3.1	92.4 ± 43.3	12.7 ± 3.9	0.22 ± 0.16	3.1 ± 2.8

FIGURE 10
Mean concentration-Time Profiles of Quinine Following Administration of One and Two Mutual Pharma's Quinine Sulfate Capsules (Study R04-0376)



Treatment A: 324mg
Treatment B: 648mg

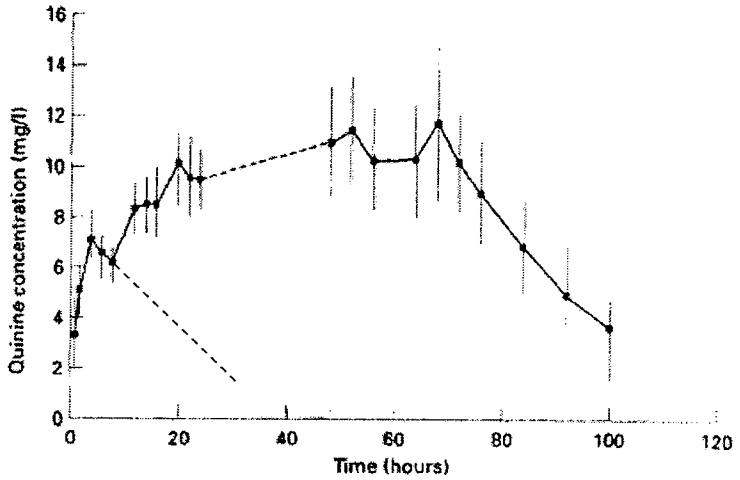
i) How do the PK parameters change with time following chronic dosing?

The mean ± SD pharmacokinetic parameters of quinine sulfate in healthy subjects following a single 648 mg dose of the sponsor's Mutual Quinine Sulfate Capsules is shown in Table 7 above. Simulation using WinNonlin® predicts that with a dosing regimen of 648mg every 8 hours, steady state may be achieved in healthy volunteers on Day 3 of dosing (Figure 5 above).

Based on the pharmacokinetics of quinine following multiple dosing with 600mg quinine dihydrochloride IV given as a 4-hour infusion every 8 hours for 3 days to malaria patients (Figure 11; Claessen et al., 1998), it is possible to achieve quinine plasma steady state concentrations by Day 3 of multiple IV infusion dosing in Caucasian patients with *P. falciparum* malaria acquired in Africa. Similarly, it can be surmised from a comparison of the quinine PK profiles after the first dose and after the last dose of quinine dihydrochloride 4-hour infusion that the elimination rate

constant of quinine from the first dose is similar to that after the last dose on the 3rd day of therapy suggesting similar pharmacokinetics of quinine between single and chronic dosing in malaria patients. However, the clearance of quinine significantly and gradually drops from approximately Day 4 towards Day 7 of quinine monotherapy as the patient recovers (See Figure 6). Note: The Tmax after IV infusion in this study (4 hours) is similar to the Tmax after oral dosing with 648 mg quinine sulfate in Study R04-0376 (3 hours).

FIGURE 11
Plasma quinine concentrations (mean ± SD) in 10 malaria patients who received 9 fixed doses of 600 mg quinine diHCL intravenously over 4h at 8-hour intervals



From: Claessen et al., 1998. Quinine pharmacokinetics: ototoxic and cardiotoxic effects in healthy Caucasian subjects and in patients with falciparum malaria. Tropical Medicine and International Health, 3(6): 482-489.
---------- (extrapolated elimination line for the first IV infusion)

j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In the two clinical pharmacology studies conducted by the sponsor, the intersubject % CV for plasma quinine Cmax and AUC were <40%.

C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age (Elderly)
Compared to young subjects, the mean oral clearance of quinine is significantly decreased and the mean elimination half-life is significantly increased in the elderly (Wanwimolruk *et al.*, 1991a). Table 12 below compares the PK parameters of quinine in young versus elderly healthy subjects who received a single 600mg dose of quinine sulfate. In elderly subjects, the mean AUC of total quinine was about 38% higher and the mean AUC of free quinine was about 21% higher as compared to healthy young subjects. According to the authors of this publication, the higher percentage of unchanged quinine in the urine of elderly subjects suggests reduced hepatic clearance of quinine in old age.

TABLE 12
Pharmacokinetic Parameter Values of Quinine Following a Single Oral 600-mg (Quinine Sulfate) Dose in Young and Elderly Healthy Adults

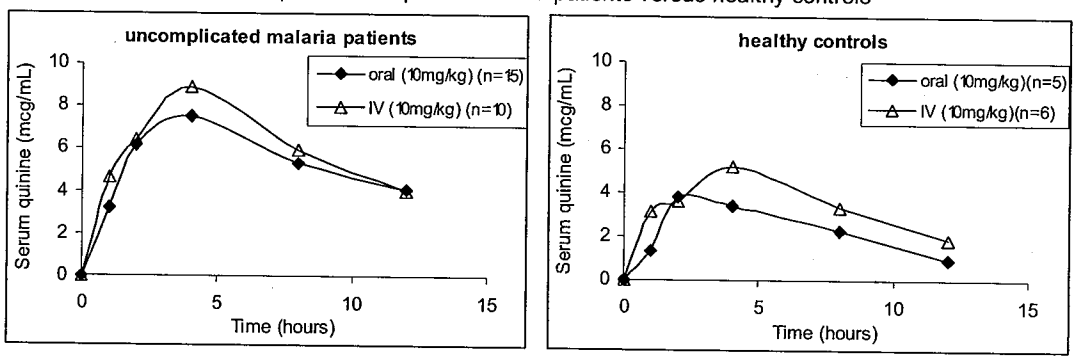
Parameter (units)	Young (N=12; Ages 20 – 35 Years)	Elderly (N=8; Ages 65 – 78 Years)
C_{max} (µg/mL)	5.6 ± 1.2	5.0 ± 1.3
T_{max} (h)	2.5 ± 0.7	2.3 ± 1.2
$T_{1/2}$ (h)	10.5 ± 1.6	18.4 ± 5.7*
AUC (µg·h/mL)	87 ± 23	120 ± 30*
% Unbound	12.4 ± 1.9	10.9 ± 2.7
% Unchanged in urine	11.2 ± 2.5	16.6 ± 3.7*
CL/F (L/h/kg)	0.084 ± 0.02	0.062 ± 0.01*
CL_0 (L/h/kg)	0.0097	0.0123

*P < 0.05

Age (Pediatrics)
Although the mean elimination half-life of quinine in healthy children was reported to be shorter (3 to 7 hours), the pharmacokinetics of quinine in children with malaria are comparable to that in adults with malaria.

The serum quinine concentrations were compared in 51 children with uncomplicated malaria and 22 healthy pediatric controls. In those children (n = 15 patients, 5 controls; 1.5 to 12 years old) who received quinine 10 mg salt/kg orally (as crushed tablet), the Tmax was observed at 4 hours post-dose and in those who received the same dose via a 4-hour infusion. The mean Cmax for the two schedules were not significantly different, ranging from 5.7 – 7.3 mcg/mL. As seen in adults: (1) the serum concentrations in malaria patients were significantly higher as compared to the healthy control, (Figure 12), (2) the total clearance of quinine in patients were approximately 1 mL/min/kg (=0.06 L/h/kg) , which was significantly less than in controls (1.43 L/kg), (3) the total apparent Vd of quinine was reduced (0.8 L/kg in patients versus 1.43 L/kg in healthy children). The elimination half-times were 9-11 hours in patients and 3-7 hours in healthy controls. No side effects were observed at the 10mg/kg dose.

FIGURE 12
Mean serum quinine concentration-time profiles of children who received oral and intravenous 10mg/kg doses of quinine sulfate or quinine dihydrochloride:
uncomplicated falciparum malaria patients versus healthy controls



Comparison with Adults with malaria
The plasma elimination half-life of quinine was reportedly shorter in healthy children (3 to 7 hours) but in malaria patients (9 to 11 hours) is not substantially shorter compared to that observed in adults with malaria (~16 hours; White et al., 1982). Likewise, following a single standard adult oral dose of quinine sulfate (10 mg/kg salt), the Tmax, Cmax, total clearance, and Vd in children (1.5 to 12 years old) with uncomplicated malaria were comparable to those reported in adult malaria patients (Table 13).

TABLE 13
Cross-study comparison of Mean ± SD Quinine Pharmacokinetic Parameters Following a First 10 mg/kg Quinine Sulfate Oral Dose in Patients with Uncomplicated Malaria: Pediatrics versus Adults

PHARMACOKINETIC PARAMETER	CHILDREN[a] (n = 15)	ADULTS[b] (N = 15)
Tmax (h)	4.0	5.9 ± 4.7 (3.5 – 8.4)
Cmax (mcg/mL)	7.5 ± 1.14[c] (5.7– 7.3)	8.4 (7.3 – 9.4)
Half-life (h)	12.05 ± 1.44	16 ± 7[d]
Total CL(L/h/kg)	0.06 ± 0.007	0.09
Vd (L/kg)	0.87 ± 0.12	0.78
Free (unbound) quinine fraction (%)		5.3 ± 2.5

[a] serum concentrations; Sabchareon et al., 1982
[b] Supanarond et al., 1991
[c] equivalent to 22.5 ± 3.43 nmol/mL
[d] White et al., 1982

Gender
In the dose-proportionality study conducted by the sponsor (R-040376), it was observed that at the 648mg dose, healthy females had slightly higher mean quinine plasma Cmax (by 19%), AUC_{inf}, (by 35%) and a slightly longer mean elimination half-life (by 2.1 hours) compared to healthy males. However, it was also noted that females in this study had a higher mean age and a lower mean body weight compared to male subjects.

Table 14 provides a comparison of the two gender groups based on quinine PK parameters following the 324mg quinine sulfate dose, combining the data from the dose-proportionality study and the relative bioavailability study. As seen in this table, healthy females demonstrated a slightly higher Cmax and AUC (by 15% each parameter) than healthy males. Apparent oral clearance values when adjusted for body weight were similar between genders.

TABLE 14
Comparison of Quinine Pharmacokinetic Parameter Values in Healthy Men and Women Following a Single 324-mg Oral Dose in a Mutual Pharma's-Sponsored Studies (Data From Study RA3-085 and Study R04-0376)

Parameter (units)	Mean ± Std. Dev.	
	Men (N = 24)	Women (N = 25)
Mean weight (kg)	81.65 ± 9.69	58.33 ± 5.78
C_{max} (µg/mL)	2.0 ± 0.005	2.3 ± 0.010
T_{max} (h)	2.58 ± 0.75	2.64 ± 0.80
$AUC_{0-\infty}$ (µg·h/mL)	33.2 ± 0.132	38.45 ± 0.209
$T_{1/2}$ (h)	12.5 ± 3.77	13.7 ± 5.10
Weight-Adjusted Parameter		
CL/F (L/h/kg)	0.1194 ± 0.000	0.1444 ± 0.000

Race
The quinine pharmacokinetics of Caucasians do not seem to differ significantly from those of Thais. In a study that compared healthy Thais and Caucasians who were given a single oral 600mg dose of quinine sulfate, the mean quinine Cmax, Tmax, AUC, apparent oral clearance, elimination half-life, and % dose excreted as unchanged quinine in the urine were similar between the two racial groups (Viriyayudhakorn *et al.*, 1996).

Table 15 presents a cross-study comparison of quinine PK parameters of various ethnic groups. It appears from the data in this table that Africans (Nigerians) have generally lower mean quinine AUC compared to Caucasians and non-smoking healthy Thai subjects. However, this relatively lower quinine exposure in Africans does not seem to adversely affect the efficacy of quinine in this ethnic group. In fact, a meta-analysis study that evaluated the efficacy and safety of quinine in six African countries showed a high efficacy rate (>90%) with a fever clearance time of < 2 days and a parasite clearance time of 2.5 days to 1 week (Mengesha and Makonnen, 1999).

TABLE 15
Comparison of Quinine Pharmacokinetic Parameter Values in Healthy Caucasians, Africans, and Asians (Various Publications)

	Caucasians	Africans (Nigeria)			Healthy Thai Volunteers				
Reference	1	2	3	4	5	6	1	7	8
N (M / F)	10 (10 / 0)	7 (7 / 0)	11 (11/0)	10 (10/0)	8 (8 / 0)	7 (7 / 0)	9 (9 / 0)	10 (10/0)	6 (6/0)
Mean Age (yrs) (range)	-- (20 – 35)	-- (21 – 29)	21 (16 – 24)	-- (21 – 30)	29 (19 – 41)	-- (24 – 47)	-- (25 – 35)	30 (25 – 35)	-- (29 – 43)
Mean Weight (kg) (range)	80 ± 10	-- (55 – 73)	61.8 ± 4.6	56.2 ± 8.5	57 ± 5	-- (50 – 65)	57 ± 5	57 (48 – 65)	59 (53 – 67)
Smokers?	No	No	No	No	No	--	No	No	Yes
Dose (mg Base)	500	500	500	500	500	500	500	500	497
C_{max} (µg/mL)	5.6 ± 1.4	2.7 ± 0.5	2.9 ± 0.5	3.8 ± 2.7	5.0 ± 0.3	3.3 (2.47 – 6.6)	5.1 ± 0.5	5.0 ± 0.8	4.3 ± 0.9
T_{max} (h)	2.5 ± 0.5	2.8 ± 1.4	3.3 ± 0.8	2.1 ± 0.57	2.4 ± 0.9	2.0 (1.0 – 2.5)	3.6 ± 2.5	3.4 ± 2.5	1.5 ± 0.7
$AUC_{0-\infty}$ (µg·h/mL)	87 ± 25	30.2 ± 3.5	54.9 ± 19.2	45.4 ± 23.0	98 ± 33	53.2 (40.1 – 98.2)	99 ± 31	93 ± 35	53.9 ± 16.9
$T_{1/2}$ (h)	10.7 ± 1.6	11.4 ± 2.7	11.7 ± 2.9	11.5 ± 2.7	12.5 ± 3.1	12.5 (7.9 – 18.3)	12.4 ± 3.0	12.0 ± 3.1	7.6 ± 1.3
Cl (L/h/kg)	0.08 ± 0.02	0.28 ± 0.04	0.15 ± 0.04	0.24 ± 0.12	0.33 ± 0.08	0.47 (0.22 – 62)	0.096 ± 0.023	0.11 ± 0.04	0.182 ± 0.063
V_d (L/kg)	--	2.5 ± 1.4	2.5 ± 0.7	--	--	7.1 (4.9 – 11.4)	--	--	--

1 = Viriyavadhakorn *et al.*, 1996 (Thailand)
2 = Sowunmi *et al.*, 1996
3 = Sowunmi, 1996
4 = Salako *et al.*, 1992
5 = Viriyayudhakorn *et al.*, 2000
6 = Na-Bangchang, *et al.*, 1999
7 = Wanwimolruk *et al.*, 1993
8 = Wanwimolruk *et al.*, 1986

Weight

Quinine is a lipophilic drug (octanol:water = 1.97 at pH 7.4); it is logical to expect lower systemic quinine concentrations in obese subjects which is probably due to increased distribution into excess adipose tissue. In a study of young, lean and obese age-matched Thai male volunteers given a single 600-mg dose of quinine sulfate, the mean plasma Cmax and mean AUC were lower and weight-adjusted clearance lower in obese subjects (Viriyayudhakorn *et al.*, 2000). There was a negative correlation between body weight and Cmax ($r = -0.701$, $p<0.005$) when data from the two bodyweight groups were combined. Table 16 compares the quinine PK parameters of the lean and obese subjects.

TABLE 16
Pharmacokinetic Parameter Values in Lean and Obese Healthy Thai Men Following a Single Oral 600-mg Dose of Quinine Sulfate

Parameter (units)	Lean (N=8)	Obese (≥ 125% IBW) (N=9)
C_{max} (μg/mL)	5.0 ± 0.3	4.0 ± 0.8*
T_{max} (h)	2.4 ± 0.9	2.1 ± 0.8
$T_{1/2}$ (h)	12.5 ± 3.1	11.9 ± 3.2
AUC (μg·h/mL)	98 ± 33	85 ± 18
CL/F (L/h)	5.5 ± 1.4	6.0 ± 1.2
CL/F (L/h/kg TBW)	0.096 ± 0.023	0.064 ± 0.016*
CL/F (L/h/kg IBW)	0.091 ± 0.024	0.091 ± 0.018

CL/F=oral clearance; IBW=ideal body weight; TBW=total body weight
* $P < 0.05$

Disease

Malaria: Uncomplicated versus Severe; Acute versus Convalescence

In malaria, the increased fraction of the free quinine in the plasma results in reduced systemic clearance and reduced volume of distribution, in proportion to the severity of the disease. Additionally and for similar reasons, the total plasma quinine concentrations are higher in the acute phase than in the convalescence (recovery) phase of malaria. Table 17 compares the PK parameters of quinine in patients with cerebral malaria to those with uncomplicated malaria following administration of quinine dihydrochloride IV infusion over 2 or 4h at a dose of 10 mg/kg (equivalent to 8.3 mg/kg base) at 8-hour intervals; Table 18 compares the quinine pharmacokinetics between the acute and convalescent phases of these patients with uncomplicated malaria (White et al.,1982). Although the mean serum creatinine was significantly higher in those with cerebral malaria than those with uncomplicated malaria (2.57 versus 1.05 mg/dL), the mean renal clearance of quinine in these patients were very similar.

TABLE 17
Quinine Pharmacokinetics in Acute Malaria: Uncomplicated Malaria versus Severe Malaria

	Cerebral Malaria			Uncomplicated Malaria			Significance (p value)
	Number of Patients	Mean	Standard Deviation	Number of Patients	Mean	Standard Deviation	
Total clearance (ml/min/kg)	18	0.92	0.42	11	1.35	0.60	0.031
Vd (liter/kg)	18	1.18	0.37	11	1.67	0.34	0.0013
Elimination t/2 (hours)	25	18.2	9.7	13	18.0	7.0	N.S.
Renal clearance (ml/min/kg)	15	0.21	0.16	11	0.21	0.08	N.S.
Renal / Total clearance	15	0.20	0.16	11	0.21	0.12	N.S.

Vd = total apparent volume of distribution; N.S. = not significant at 5 percent level. Seven patients with cerebral malaria and two patients with uncomplicated malaria had baseline plasma samples that revealed quinine, indicating pretreatment. These patients are excluded from the calculations of Vd and total clearance. Accurate urine volumes were not obtained from 10 patients.

TABLE 18
Quinine Pharmacokinetics in Uncomplicated P. falciparum Malaria: Acute versus Recovery Phase

	Number of Patients	Acute		Convalescent		Significance (p value)
		Mean	Standard Deviation	Mean	Standard Deviation	
Total clearance (ml/min/kg)	8	1.28	0.63	3.09	1.18	0.0002
Vd (liter/kg)	8	1.62	0.36	2.74	0.47	0.0002
Elimination 1/2 (hours)	9	17.0	7.0	11.1	4.1	0.006
Renal clearance (ml/min/kg)	9	0.20	0.06	0.53	0.20	0.0004
Renal / Total clearance	8	0.21	0.13	0.22	0.16	N.S.

N.S. = not significant.

Diabetes

The pharmacokinetic parameters of quinine were comparable in diabetics and non-diabetics, as shown by the findings of a study that evaluated the pharmacokinetics of quinine from a single oral dose of quinine sulphate 600 mg in 12 elderly non-insulin dependent diabetics and 10 elderly non-diabetic controls (Table 19;Dyer *et al.*, 1994) However, the administration of quinine produced a mean reduction in serum glucose of 1 mmol/L from 3 to 5 hours post-dose in both groups without affecting serum insulin concentrations.

TABLE 19
Mean ± SD Pharmacokinetic Parameters of Quinine in 10 Non-diabetic and 12 Diabetic Subjects[a]

	Non-diabetics	*Diabetics*	*95% CI on difference*
Volume of distribution (V/F) l kg^{-1}	1.70 ± 0.56	1.70 ± 0.63	0.56, −0.56
Absorption lag-time (t_{lag}) h	1.0 ± 0.5	1.2 ± 0.6	0.3, −0.7
Absorption half-time ($t_{1/2,abs}$) h	0.6 ± 0.2	0.7 ± 0.6	0.3, −0.5
Maximum concentration (C_{max}) mg l^{-1}	3.4 ± 0.8	3.7 ± 0.8	0.5, −1.1
Elimination half-time ($t_{1/2,z}$) h	19.9 ± 6.3	20.0 ± 7.5	6.4, −6.6
Systemic clearance (CL/F) ml kg^{-1} min^{-1}	1.07 ± 0.42	1.14 ±-0.58	0.41, −0.55
Serum unbound drug (%)	19 (10–39)	16 (9–24)	11, −3

[a]Median and (range) are shown for percentage unbound drug

Genetic Polymorphism

No information available.

Pregnancy

It appears from literature data that pregnancy results in a more rapid quinine elimination, as well as in a lower Vd of quinine in patients with severe malaria but the difference in the clearance between pregnant and non-pregnant patients is not substantial to warrant dosage adjustment i.e, dosage increase in pregnant patients. In female patients with uncomplicated malaria, it appears

that pregnancy does not affect the plasma AAG concentration and thus, the fraction of free quinine.

Following a 10mg or 20mg per kg loading dose of quinine dihydrochloride infused over 4 hours, pregnant females with severe malaria demonstrated a more rapid elimination as judged from the shorter elimination half-life and the 33% higher total clearance and a 20% smaller mean total Vd Table 20; Philips et al., 1986) compared to non-pregnant females with severe (cerebral) malaria (White et al., 1982). The smaller Vd in pregnant women with severe malaria could be attributed to alterations in plasma protein and tissue binding associated with severe plasmodial infection and pregnancy itself.

In the women who delivered infants during the course of quinine therapy, the placental cord plasma quinine concentrations were from 1.0 to 4.6 mcg/mL which correlated significantly with maternal plasma quinine concentrations ($r = 0.78$, $p<0.05$). The mean placental cord to maternal plasma ratio was 0.32 ± 0.14.

Table 8 above compares the alpha1-acid glycoprotein (AAG) concentrations in the plasma of pregnant and non-pregnant Thai subjects and malaria patients (Silamut et al., 1991). As seen from this table, the plasma AAG concentration is significantly lower in pregnant healthy females than non-pregnant healthy females (0.38 versus 0.66 g/L; $p<0.001$), confirming that pregnancy itself contributes to the decrease in free fraction of quinine. As observed in the general population, the AAG was higher in pregnant patients with uncomplicated malaria than in pregnant healthy females (1.40 versus 0.38 g/L). However, both the AAG concentrations and the % free quinine in pregnant and non-pregnant Thai patients with uncomplicated malaria were comparable. Thus, indicates that both the total and the free quinine concentrations are at best 30% lower in pregnant patients than in nonpregnant patients with uncomplicated malaria. Therefore, no dosage adjustment (increase) is necessary in patients who are pregnant.

TABLE 20
Mean ± SD Pharmacokinetic Parameter Values of Quinine in Pregnant and Non-Pregnant Women With Malaria

	Patient Group	Number of Patients	T½ (h)	Vd (L/kg)	CL (L/h/kg)
1	Non-pregnant females with uncomplicated malaria	13	16.0 ± 7.0	1.67 ± 0.34	1.35 ± 0.60
2	Non-pregnant females with severe (cerebral) malaria	25	18.2 ± 9.7	1.18 ± 0.37	0.92 ± 0.42
3	Pregnant females with severe malaria	10	11.3 ± 4.3	0.96 ± 0.27	1.22 ± 0.77
	P value (1 versus 3)		<0.02	<0.001	NS
	P value (1 versus 2)		NS	<0.002	<0.05

Lactation

Weakly basic drugs like quinine tend to concentrate in acid milk. Based on the findings of Philipps, et al. (1986), the mean quinine concentrations of quinine in breast milk is about 31% (11-53%) of the existing maternal plasma quinine concentrations. The estimated total dose of quinine excreted in breast milk will usually be less than 2-3 mg/day. The authors concluded that hypersensitivity reactions such as thrombocytopenia could be triggered by such doses. Other toxic effects as a consequence of the immature metabolic capacity of the neonate liver may also be possible. Based on these findings, it may be advisable to avoid breastfeeding in female malaria patients who are on quinine therapy. However, it is noted that the American Academy of Pediatrics (AAP) considers quinine therapy compatible with breastfeeding.

Organ Dysfunction

Hepatic Impairment

In hepatic disease, the pharmacokinetics of quinine are altered as a consequence of reduced metabolic enzyme activity and reduced synthesis of plasma binding proteins theoretically leading to higher total quinine concentrations and higher free (unbound) quinine concentrations. In Thai subjects with moderate hepatic impairment (Child-Pugh B), following a single oral dose of 600mg quinine sulfate, the absorption of quinine was prolonged, the elimination half-life was increased, the volume of distribution was higher but there was no difference in weight-adjusted clearance (Table 21; Auprayoon et al., 1995). In moderate hepatic impairment, the increase in AUC was by 55% and in Vd was 51%, without a significant increase in mean Cmax. Therefore for patients with concurrent mild to moderate chronic hepatic impairment, reduction of quinine dosage is not warranted but close monitoring for signs and symptoms of quinine toxicity should be performed. However, if quinine AUC exposure similar to that achieved in healthy subjects is desired, prolongation of the oral quinine sulfate dosing interval from 8 hours to 12 hours may be considered.

TABLE 21
Median (Range) Quinine Pharmacokinetic Parameter Values in Non-Malaria Patients with Chronic Liver Disease

	Healthy Volunteers (N=6)	Chronic Liver Disease (N=9)
C_{max} (µg/mL)	3.45 (2.25 – 3.91)	3.74 (1.22 – 4.47)
T_{max} (h)	1.6 (0.8 – 2)	2 (1 – 5)*
AUC (µg·h/mL)	1.03 (0.7 – 1.4)	1.6 (0.48 – 2.3)
MRT (h)	11.3 (14.1 – 24.1)	25.9 (11.2 – 29.5)
CL/F (L/h/kg)	0.17 (0.098 – 0.24)	0.14 (0.073 – 0.46)
V_d/F (L/kg)	2.78 (1.49 – 3.38)	4.21 (2.33 – 15.87)*
$T_{1/2}$ (h)	9.7 (7.8 – 17.2)	23.4 (17.4 – 41.7)*
% Free Quinine (at 4 hrs)	–	17 (8.4 – 17.8)

* $p<0.05$

Similar results were seen in subjects with Hepatitis B. The mean quinine AUC was about 47% higher and the elimination half-life was longer in subjects with hepatitis than those without hepatic disease, after a single 2-hour IV infusion of 10mg/kg quinine. Table 22 compares the quinine PK parameters between healthy subjects and those with acute or convalescent hepatitis.

TABLE 22
Median (Range) Pharmacokinetic Parameter Values in Thai Males with Hepatitis B Compared with Healthy Subjects Following a Single 10-mg/kg Intravenous Dose of Quinine

Parameter (units)	Healthy Subjects (N=6)	Hepatitis Patients (N=6)	
		Acute	Recovery
C_{max} (µg/mL)	3.2 (2.1 – 3.8)	3.5 (2.1 – 5.3)	3.4 (2.8 – 4.5)
T_{max} (h)	1.0	1.1 (1.0 – 1.2)	1.1 (1.0 – 1.2)
AUC (µg·h/mL)	47.6 (36 – 72)	70.2 (49 – 115)*	69.1 (56 – 85)*
CL (L/h/kg)	0.23 (0.078 – 0.28)	0.174 (0.1 – 0.24)*	0.14 (0.06 – 0.2)
$T_{1/2}$ (h)	10 (9 – 14)	17 (11 – 26)*	15 (11 – 19)*
% unbound quinine at 2 hours	10.3 (7.6 – 15.0)	10.1 (7.4 – 14.0)	9.8 (8.1 – 11.3)

* $P < 0.05$ when compared to healthy subjects

Renal Impairment

In patients with impaired renal function, the total quinine clearance is reduced thereby leading to higher total plasma quinine concentrations. Minimal amounts of circulating free quinine are removed by hemodialysis and hemofiltration.

Following a single oral 600mg dose of quinine sulfate, the mean total quinine clearance was decreased, the mean half-life increased, and accumulation was evident in 6 subjects with **chronic renal failure not on dialysis** (mean serum creatinine = 9.6 mg/dL) compared to those

for 6 healthy control subjects (Table 23; Rimchala et al., 1996). Although the median quinine Cmax and AUC increased by 80% and 195%, respectively in subjects with chronic renal failure (CRF) compared to healthy controls, there was an observed parallel decrease in the free quinine fraction thereby resulting in an increase in Cmax and AUC of free quinine in CRF patients by only 33% and 120%, respectively as compared to the healthy controls.

Table 24 provides a comparison of the quinine PK parameters between healthy volunteers and patients on chronic hemodialysis following a single dose of quinine sulfate 300mg (Roy *et al.*, 2002). Both the mean AUC and the mean Cmax of total quinine increased by 75% in 8 subjects with **chronic renal failure on hemodialysis** (mean serum creatinine = 7.04 mg/dL) as compared to 8 healthy control subjects (mean serum creatinine = 0.94 mg/dL; Roy et al., 2002). However, because of the significant increase in serum AAG in the subjects with chronic renal failure (1.52 g/L versus 0.63 g/L in healthy subjects), the Cmax and the AUC of free quinine was lower in those with CRF (only 66% of the controls). The mean AUC of 3-hydroxyquinine and 10,11-dihydroxydihydroquinine also increased by 250%, and 84%, respectively in subjects with CRF. The mean clearance by the dialysis apparatus after 1 hour was 6.4%

WinNonLin® was used to simulate plasma quinine concentrations in acute malaria patients during the first 3 days of quinine therapy. The effect of severe renal failure as observed by Rimchala et al., 1996 was then superimposed on the disease PK model to generate PK parameters that were used subsequently to simulate concentrations in patients with acute uncomplicated malaria and concurrent severe chronic renal failure. Based on simulation, the use of the regular dose (648mg) as a loading dose, followed by maintenance doses of 324mg every 12 hours is the dosing regimen that brings immediate and sustained therapeutic quinine concentrations ranging from 8 to 20 mcg/mL (Figure 13). Thus, when treating acute uncomplicated malaria patients with chronic renal failure (serum creatinine ≥10 mg/dL), a loading dose of 648mg followed by maintenance doses of 324mg every 12 hours is recommended.

TABLE 23
Median (Range) Pharmacokinetic Parameter Values of Quinine Following a Single Oral 600-mg (Quinine Sulfate) Dose in Patients with Chronic Renal Failure versus Healthy Controls

Parameter (unit)	Healthy Volunteers (N=6)	Chronic Renal Failure (N=6)
C_{max} (µg/mL)	3.45 (2.25 – 3.91)	6.17* (3.76 – 10.2)
T_{max} (h)	1.6 (0.8 – 2)	4.5* (1 – 6)
$AUC_{0-\infty}$ (µg·h/mL)	61.8 (41.8 – 81.1)	181.5* (51.6 – 718)
$T_{1/2}$ (h)	9.7 (7.8 – 17.2)	26* (12.5 – 62.2)
CL/F (L/hr·kg)	0.170 (0.116 – 0.239)	0.056* (0.014 – 0.082)
% Free Quinine (at 4 hours)	9.8 (8.7 – 13.5)	7.3 (3.4 – 12.1)

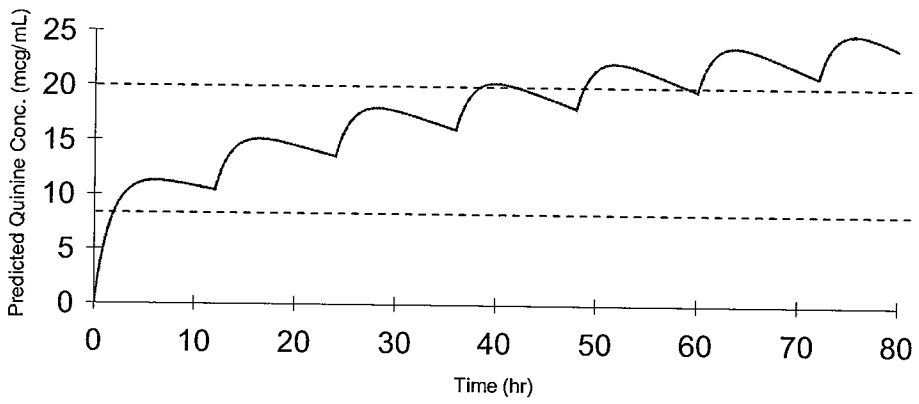
* P<0.05

TABLE 24
Pharmacokinetic Parameter Values of Quinine in Chronic Hemodialysis Patients Following a Single Oral 250-mg (Base) Dose

Parameter (unit)	Healthy Volunteers (N=8)	Patients on Hemodialysis (N=8)	P Value
C_{max} (µg/mL)	2.60 ± 0.99	4.56 ± 1.58	0.004
T_{max} (h)	1.6 ± 0.7	1.9 ± 0.4	NS
V_d (L/kg)	1.43 ± 0.78	0.95 ± 0.29	NS
$T_{1/2}$ (h)	7.02 ± 1.72	8.26 ± 2.10	NS
CL/F (L/h/kg)	0.08 ± 0.04	0.15 ± 0.09	NS
Free quinine	0.063 ± 0.014	0.024 ± 0.015	0.001
CL/F free quinine (L/h/kg)	2.47 ± 1.44	4.07 ± 1.92	0.033

NS=the difference was not statistically significant (P > 0.05)
[1] Mann-Whitney

FIGURE 13
WinNonLin® simulation of plasma quinine concentrations in patients with acute malaria and concurrent severe chronic renal failure



Acute renal failure (ARF) is a common and serious manifestation of **severe** *P. falciparum* malaria occurring in about 50% of patients with cerebral malaria. In 5 severe malaria patients with acute oliguric renal impairment (2 patients required peritoneal dialysis) and were given quinine dihydrochloride at a 20mg/kg loading dose followed by 10mg/kg over 2 hours q8h, the total clearance of quinine was lower (Table 25; Newton et al., 1999) compared to the healthy subject controls but comparable to that obtained in patients with chronic renal failure with mean serum creatinine of 10 mg/dL in Tables 23 and 24 above.

In 1 of 3 cerebral malaria patients with ARF being treated with hemofiltration, a 50% reduction in the dosage of quinine dihydrochloride to 15 mg/kg/day resulted in plasma quinine concentrations closer to the lower limit of the therapeutic range of 5-15 mcg/mL. In the three subjects, plasma quinine did not change during or shortly after hemofiltration and quinine concentrations in the hemofiltrate were below the limit of assay sensitivity (25 ng/mL; Franke et al., 1987).

In a larger study involving 32 severe falciparum malaria patients with ARF who were treated with quinine dihydrochloride at a standard regimen consisting of a loading dose of 20mg/kg followed by a maintenance dose of 10mg/kg, had median trough concentrations that were approximately 10-30% higher in ARF patients than in non-ARF patients during acute infection. There were no significant changes in plasma quinine concentrations in patients with ARF during hemodialysis (Sukontason et al., 1996). Thus, it does not appear that dosage reduction is necessary in severe malaria patients who develop acute renal failure. It was noted that the World Health Organization recommends for severe malaria patients with persistent acute renal failure that dosage reduction by 1/3 to ½ be considered after 48 hours of therapy. Accumulation of quinine is less likely to occur if there is clinical improvement and associated increases in Vd and systemic clearance as the patient moves towards the recovery phase.

TABLE 25
Median (Range) Pharmacokinetic Parameter Values in Malaria Patients with Severe Renal Failure Following Intravenous Dose of Quinine Dihydrochloride

Parameter (unit)	Severe Renal Failure (N=5)
Dose	20 mg/kg loading dose, 10 mg/kg over 2 hrs Q 8 hours
Age (years)	25 (18 – 60)
Sex (M/F)	3/2
Weight (kg)	48 (47.0 – 53.5)
Serum Creatinine (μmol/L)	415 (167 – 769)
C_{ss} (μg/mL)	14
CL (L/h·kg)	0.050
$AUC_{0-\infty}$ (μg·h/mL)	2678

Css=concentration at steady state

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied, (e.g., healthy volunteers vs. patients vs. specific populations) what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

a) Elderly

Elderly subjects (65-78 years old) have a 38% higher mean AUC of total quinine and approximately 20% higher mean AUC of free quinine than young subjects (20 -35 years old). Thus, adjustment of quinine dosage does not seem necessary in elderly patients.

b) pediatric patients

The plasma elimination half-life of quinine in healthy children is shorter (3 - 7 hours) but in malaria patients (9 to 11 hours; Sabcahareon et al., 1982) is not substantially shorter than in adult patients with uncomplicated malaria (~17 hours). Likewise, the mean quinine total clearance, Vd, Cmax and Tmax in these pediatric patients were comparable to those reported for adult patients. Furthermore, there were no adverse events observed in these children who received the adult dosage of 10 mg/kg quinine salt (Sabcahareon et al., 1982).

The CDC recommends that the quinine dose in children be adjusted by patient weight (10 mg/kg salt q8h x 3 to 7 days) and that the pediatric dose should NEVER exceed the recommended adult dose (650 mg salt). For children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine (given alone for a full 7 days regardless of where the infection was acquired or given in combination with clindamycin) as shown in Table 26.

For comparison, the following table summarizes the quinine sulfate dosage recommendations for pediatric patients with uncomplicated malaria as seen in foreign labeling.

TABLE 26
Pediatric Dosage Recommendations in Foreign Labeling

COUNTRY	Brand Name	PEDIATRIC DOSAGE RECOMMENDATION
Thailand	GPO	25 mg/kg every 8 hours [sic] for 3-7 days
Taiwan	Sulgin	25 mg/kg/day divided into 4 doses a day for 3 – 7 days
France	Lafran	8 mg/kg (base) every 8 hours for 5-7 days
New Zealand	Q200 & Q300	8.3 mg/kg every 8 hours for at least 3 days (with tetracycline, clindamycin or pyrimethamine) Adolescents: same as adult dose *Note: Elimination half-life prolonged and Vd decreased.*
Germany	Limptar-N	-

Sweden	Kinin NM Pharma	10 mg/kg 3x daily for 7 days
Australia	Quinate, Biquinate	10 mg/kg every 8 hours for 7 days
Netherlands		Children > 6 years old: 10 mg/kg every 8 hours for 7 days after the patient is fever free (to be taken after a meal)

c) gender

None.

d) race

There does not appear to be clinically significant differences in the PK of quinine among Caucasians, Thais and Africans.

The CDC recommends that the 3-day course of quinine combination therapy be extended to 7 days for malaria acquired from Southeast Asia.

e) renal impairment

Otherwise healthy subjects with severe chronic renal failure (mean serum creatinine =9.6 mg/dL) have about a 3-fold higher mean AUC of total quinine than those with normal renal function (mean serum creatinine = 1 mg/dL; Rimchala et al., 1996). Thus, in uncomplicated *P. falciparum* malaria patients with severe renal impairment, the following modified dosage regimen is recommended: one loading dose of 648mg quinine sulfate followed 12 hours later by maintenance doses of 324mg every 12 hours.

f) hepatic impairment

Subjects with hepatic impairment of moderate severity (Child-Pugh B) showed a 55% higher AUC of free quinine and a 51% higher Vd than those with normal hepatic function (Aprayoon et al., 1995). Thus, in uncomplicated *P. falciparum* malaria patients with mild to moderate hepatic impairment, dosage reduction is not warranted but close monitoring for signs and symptoms of quinine toxicity should be done; prolongation of dosage interval from 8 hours to 12 hours may also be considered.

g) what pharmacogenetics information is there in the application and is it important or not

None.

h) What pregnancy and lactation use information is there in the application?

Quinine sulfate is

In pregnant females with severe malaria, the mean total clearance of quinine was increased by approximately 33% compared to non-pregnant patients with severe malaria. However, there appears to be no significant difference in the plasma AAG concentrations and thus, the % free quinine between pregnant and non-pregnant females with malaria. Therefore, whenever indicated, quinine sulfate dosage adjustment (i.e, dosage increase) is not needed in pregnancy. The CDC recommends that the standard dose and duration of quinine sulfate (with clindamycin but not tetracycline or doxycycline) be used as an option for the treatment of uncomplicated malaria in pregnant females.

In 8 women who delivered infants during the course of quinine therapy for malaria, the placental cord plasma quinine concentrations were from 1.0 to 4.6 mcg/mL which correlated significantly with maternal plasma quinine concentrations ($r = 0.78$, $p<0.05$). The mean placental cord to maternal plasma ratio was 0.32 ± 0.14.

The total dose of quinine excreted in breast milk will usually be less than 2 - 3 mg/day. The mean quinine concentration in breast milk is approximately 30% of the corresponding maternal plasma quinine concentration. Reportedly, hypersensitivity reactions such as thrombocytopenia could be triggered by such doses. Other toxic effects as a consequence of the immature metabolic capacity of the neonate liver may also be possible. The health care provider should apprise the mother of the potential risks of quinine therapy to the breastfed infant.

i) Other human factors that are important to understanding the drug's efficacy and safety

None.

D. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Drugs and Herbal Products
See Section D.3.

Diet
-Grapefruit juice:
In a crossover study, the administration of a single 600mg dose of quinine sulfate with grapefruit juice (full-strength or half-strength) did not significantly alter the PK parameters of quinine as compared to when quinine was given with orange juice (Table 27; Ho et al., 1999). Orange juice components are known inhibitors of P-glycoprotein and OATP transporters but not CYP3A4 (Takanaga et al., 2000). It is generally believed that grapefruit juice inhibits the CYP3A4 in the gut.

TABLE 27
Mean (± S.D.) Pharmacokinetic Parameter Values of Quinine
after Oral Single Dose of 600 mg Quinine Sulfate in 10 Healthy Volunteers

Parameter (Unit)	Treatment Period			95% CI of mean difference	
	Orange Juice (Control)	Grapefruit Juice		Grapefruit Juice	
		Full Strength	Half Strength	Full Strength vs. Control	Half Strength vs. Control
C_{max} (μg/mL)	3.1 ± 1.0	3.0 ± 0.6	2.6 ± 0.6	-0.91 – 0.69	-1.31 – 0.29
T_{max} (h)	2.3 ± 0.8	2.5 ± 0.8	2.2 ± 0.8	-0.39 – 0.89	-0.84 – 0.64
$T_{1/2}$ (h)	8.7 ± 2.7	8.2 ± 3.4	7.5 ± 2.2	-2.59 – 1.65	-2.81 – 1.44
$AUC_{0-\infty}$ (μg·h/mL)	52 ± 24	50 ± 20	40 ± 20	-17.4 – 13.4	-27.3 – 3.5
CL/F (L/h·kg)	0.238 ± 0.2	0.171 ± 0.07	0.219 ± 0.09	-0.06 – 0.09	-0.012 – 0.14
CL_R (L/h·kg)	0.009 ± 0.0042	0.014 ± 0.006	0.017 ± 0.007*	-0.01 – 0.002	-0.014 – -0.001
Dose excreted as quinine (%)	6.1 ± 3.2	6.3 ± 2.8	7.7 ± 3.2	-2.2 – 2.6	-0.8 – 3.9

CL/F=oral clearance; CL_R=renal clearance
*P = 0.02 compared with control

-Dietary Salt Intake
The pharmacokinetic parameters (AUC_{inf}, Tmax, and Cmax) of quinine when a single 600mg dose of quinine sulfate was administered with low-salt and high-salt diets were similar to those obtained in previous studies when quinine sulfate was given alone (Table 28;Newton *et al.*, 2001).

TABLE 28
Median (Range) Pharmacokinetic Variables for Oral Quinine After Low-Salt and High-Salt Diets (n=7)

Variable	High-salt diet	Low-salt diet	P
Dose, mg quinine base/kg body weight[a]	6.7 (5.5–8.3)	6.8 (5.6–8.2)	0.3
Urinary sodium excretion, mmol/24 h	195 (132–466)	118 (35–189)	0.043
t_{lag}, h	0.47 (0.38–0.89)	0.45 (0.22–0.88)	0.6
C_{max}, mg/L	6.4 (4.1–7.4)	5.3 (4.8–6.7)	0.3
t_{max}, h	2.0 (1.5–4.0)	3.0 (1.0–4.0)	0.5
$k01$/h	1.75 (0.72–3.86)	1.71 (0.92–4.65)	0.5
$k10$/h	0.081(0.068–0.160)	0.069 (0.047–0.908)	0.028
$t_{1/2}$, h	8.5 (4.3–10.2)	10.0 (7.6–14.8)	0.043
V_d/f, l/kg	1.03 (0.77–1.12)	1.15 (0.70–1.58)	0.1
CL/f, l/kg/h[b]	0.072 (0.048–0.150)	0.060 (0.042–0.113)	0.2
$AUC_{0-\infty}$, mg h/L	91.4 (54.9–116.6)	108.9 (63.1–165.0)	0.1
AIC	7.5 (–0.24–28.0)	3.7 (–5.18 to 22.6)	0.3

[a]To convert quinine free base to quinine sulphate salt, divide by 0.826
[b]To convert clearance (CL) in l/kg/h to ml/kg/min, divide by 0.06

Smoking

Cigarette smoking is a potent inducer of CYP1A2, which does not appear to play a major role in quinine metabolism based on *in vitro* metabolism studies. In healthy subjects, smoking has been shown to increase quinine clearance by an average of 77% in healthy males who smoked > 10 cigarettes a day for at least 5 years (Table 29; Wanwimolruk *et al.*, 1993). However, it appears that acute malaria abrogates the quinine PK-altering effects of smoking, i.e., the reduced Vd and clearance of quinine in malaria outweighs any metabolic induction effect of smoking. Thus, in uncomplicated malaria patients who received the full 7-day course of quinine therapy, cigarette smoking produced only a 25% decrease in median quinine AUC and a 16.5% decrease in median Cmax; smoking also did not have a significant effect on therapeutic response (Table 30; Pukrittayakamee et al., 2002). Thus, there is no need to increase quinine dosage in malaria patients who are heavy smokers.

Alcohol

No information available.

TABLE 29
Pharmacokinetic Parameter Values Following of a Single Oral 600-mg Dose of Quinine Sulfate in Smoking and Nonsmoking Healthy Subjects

Parameter	Smokers (N=10)	Non-Smokers (N=10)	P Value
C_{max} (µg/mL)	4.1 ± 1.2	5.0 ± 0.8	NS
T_{max} (h)	2.7 ± 0.6	3.4 ± 2.5	NS
$T_{1/2}$ (h)	7.5 ± 1.4*	12.0 ± 3.1	0.001
$AUC_{0-\infty}$ (µg·h/mL)	52 ± 19*	93 ± 35	0.006
% unbound	12.0 ± 2.7	10.3 ± 2.6	NS
CL/F (L/hr·kg)	0.189 ± 0.075*	0.107 ± 0.045	0.008

TABLE 30
Median (Range) Pharmacokinetic Parameters of Quinine and 3-Hydroxyquinine (3OH-Q) in Patients with Uncomplicated P. falciparum Malaria Treated with a 7-Day Course of Oral Quinine

Parameters	Non-smokers ($n=12$)	Smokers ($n=10$)	Total ($n=22$)
AUC_{0-7} quinine (μg/ml/day)	67.0 (33.1–89.8)	51.3 (39.5–83.5)	40.2 (33.1–89.8)
AUC_{0-7} quinine (μg/kg/ml/day)	1.4 (0.5–1.9)	0.9 (0.7–1.8)	0.8 (0.5–1.9)
t_{max} quinine (days)	1.5 (0.5–5.0)	1.5 (0.5–4.0)	1.5 (0.5–5.0)
C_{max} quinine (μg/ml)	12.7 (6.2–17.1)	10.6 (9.0–15.5)	8.9 (6.2–17.1)
AUC_{0-7} 3OH-Q (μg/ml/day)	6.2 (4.0–8.3)	4.8 (2.8–10.7)	2.8 (2.8–10.7)
AUC_{0-7} 3OH-Q (μg/kg/ml/day)	0.02 (0.01–0.04)	0.02 (0.01–0.04)	0.02 (0.01–0.04)
t_{max} 3OH-Q (days)	4.5 (1.5–7.0)	3.5 (1.0–7.0)	1.5 (1.0–7.0)
C_{max} 3OH-Q (μg/ml)	1.2 (0.8–1.5)	1.0 (0.6–2.1)	0.7 (0.6–2.1)
AUC quinine/AUC 3OH-Q	9.5 (4.9–22.6)	12.1 (4.5–15.6)	10.0 (4.5–22.6)
C_{max} quinine/C_{max} 3OH-Q	10.1 (5.0–19.6)	10.7 (4.5 –15.6)	11.2 (4.5–19.6)

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

3. Drug-Drug Interactions

a) Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, *in vitro* as well as *in vivo* evidence indicates the involvement of CYP3A4 in quinine-drug interactions. For example, the potent CYP3A4 inducer, rifampin substantially decreased plasma quinine concentrations *in vivo* whereas some drugs like ketoconazole, and troleandomycin have been shown to inhibit the metabolism of quinine *in vivo*.

Furthermore, based on *in vitro* findings, interactions with drugs that are highly bound to plasma proteins (as listed in Table 31) via a mechanism involving the displacement of quinine from protein binding is unlikely (Wanwimolruk et al., 1992).

TABLE 31
Effects of Drugs on the Binding of Quinine 3 μg/mL to Human Plasma Proteins *In Vitro*

Drugs	Concentration Added (μg/mL)	Unbound Quinine (% of control value)
Antimalarial Drugs		
Chloroquine	0.2	99.9%
Mefloquine	0.5	90.7%
Primiquine	0.2	89.2%
Proguanil	0.5	89.0%
Pyrimethamine	0.4	92.8%
Basic Drugs		
Diazepam	2	95.5%
Indapamide	0.25	90.6%
Lidocaine	5	100.7%
Propranolol	1	96.9%
Acidic Drugs		
Warfarin	2	101.5%
Salicylic acid	300	103.1%
Phenytoin	20	92.8%
Naproxen	40	104.9%
Ketoprofen	5	101.7%
Diclofenac	2	89.9%

b) Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Quinine is metabolized mainly by CYP3A4 and to a minor extent by CYP2C19 (Zhao et al., 1996). It is not known whether quinine metabolism is influenced by genetics but clinically significant inter-ethnic differences in quinine pharmacokinetics are not evident from literature data (Caucasians versus Thais versus Africans). Furthermore, the elimination half-life and the oral clearance of quinine after a single dose of quinine sulfate (600mg) were not significantly different between PMs and EMs of debrisoquine, suggesting that the oxidative biotransformation of quinine is not carried out largely by CYP2D6 (Wanwimolruk and Chalcroft, 1991). On the other hand, quinidine, the diastereomer of quinine is a potent selective inhibitor of debrisoquine metabolism in subjects with a PM genotype (Ayesh et al., 1991).

c) Is the drug an inhibitor and/or an inducer of CYP enzymes?

A search of the University of Washington Drug Interaction Database reveals literature reports of *in vitro* inhibition of CYP1A, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 by quinine (Table 32). Based on the [I]/Ki approach, the inhibitory potential of quinine against these CYP450 enzymes is possible to likely.

TABLE 32
Enzymes Inhibited by Quinine In Vitro

Enzyme	Object	Object Metabolite	System	Inhibition Results
CYP3A4	Etoposide	3-desmethyletoposide	Microsomes HL	IC_{50}: 90 uM
	Halofantrine	N-desbutylhalofantrine	Microsomes HL	Ki: 49 ± 16 uM
	Midazolam	1-hydroxymidazolam	Microsomes HL	IC_{50}: 250 uM
CYP2A6	Coumarin	7-hydroxycoumarin	Microsomes (recombinant)	IC_{50}: 160 uM
CYP2C9	Naproxen	O-desmethylnaproxen	Microsomes (recombinant)	IC_{50}: 96 uM
	Naproxen	O-desmethylnaproxen	Microsomes HL	IC_{50}: 481 uM
CYP2C8	Torsemide	tolyl methylhydroxytorsemide	Microsomes (recombinant)	Percent Inhibition: 80 %
	Torsemide	tolyl methylhydroxytorsemide	Microsomes (recombinant)	Percent Inhibition: 90 %
CYP2D6	3-(2-(N,N-diethyl-N-methylamino)-ethyl)-7-methoxy-4-methylcoumarin	3-(2-(N,N-diethyl-N-methylamino)-ethyl)-7-hydroxy-4-methylcoumarin	Microsomes HL	IC_{50}: 4 ± 1 uM
	bufuralol	1-hydroxybufuralol	Microsomes HL	IC_{50}: 15 ± 3 uM
	4-methoxyamphetamine (PMA)	4-hydroxyamphetamine	Microsomes HL	IC_{50}: 30 uM
	bufuralol	1-hydroxybufuralol	Microsomes HL	IC_{50}: 30 ± 3.7 uM
	dextromethorphan	dextrorphan	Microsomes (recombinant)	IC_{50}: 20.0 uM
	dihydrocodeine	dihydromorphine	Microsomes HL	Ki: 3.63 ± 0.54 uM
	debrisoquine	4-hydroxydebrisoquine	Microsomes (recombinant)	IC_{50}: 3.75 ± 2.07 uM
	bufuralol	1-hydroxybufuralol	Microsomes HL	Ki: 15.51 uM

			(pooled)	
	dextromethorphan	dextrorphan	Microsomes (recombinant)	Ki: 1.8 - 2.8 uM Binding: Total
	paroxetine	formate	Microsomes HL	IC_{50}: 500 uM
	dextromethorphan	dextrorphan	Microsomes (recombinant)	IC_{50}: 4 uM
	dextromethorphan	dextrorphan	Microsomes (recombinant)	IC_{50}: 8 uM
	metoprolol	O-desmethylmetoprolol	Microsomes (recombinant)	IC_{50}: 4 uM
CYP1A	debrisoquine	4-hydroxydebrisoquine	Microsomes (recombinant)	IC_{50}: 3.31 ± 0.14 uM
	riluzole	N-hydroxyriluzole	Microsomes HL	IC_{50}: 444 ± 62 uM
	riluzole	N-hydroxyriluzole	Microsomes HL	Percent Inhibition: 63%
Not Available	mefloquine	carboxymefloquine	Microsomes HL	Ki: 28.5 uM

d) Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Although its diastereomer, quinidine is possibly a substrate of P-glycoprotein (Kaukonen et al., 1997), there are currently no literature reports suggesting that quinine is also a substrate of this efflux transporter.

e) Are there other metabolic/transporter pathways that may be important?

Quinine is used in *in vitro* studies as an inhibitor of organic cation transporters (OCT); the IC_{50} is about 5 μM as quinine base.

f) Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Based on the guidelines of the Centers for Disease Control (CDC), the treatment of uncomplicated malaria with oral quinine sulfate should be used in combination with one of three other antimicrobials, namely doxycycline, tetracycline, and clindamycin for 3 to 7 days. Combination therapy has been demonstrated to result in improved cure rates as compared with quinine monotherapy.

In a study conducted to determine the mechanism of drug interaction, it was shown in *P. falciparum* patients who received the full course of drug therapy that quinine plasma concentrations were consistently and about 2-fold higher when quinine was given with tetracycline than with quinine alone. The increase in quinine concentrations was explained to be possibly due to tetracycline's impairment of quinine hepatic metabolism (Karbwang et al., 1991). Although *in vitro* studies have shown that in addition to tetracycline, doxycyline is a potent inhibitor of quinine conversion to 3-hydroxyquinine (Zhao and Ishizaki, 1997), *in vivo* studies have failed to show that intravenous doxycycline increases plasma quinine concentrations.

g) What other co-medications are likely to be administered to the target patient population?

Other antimalarials, antibiotics (e.g., tetracycline, doxycycline, clindamycin), antifungals, analgesics/antipyretics, anti-emetics, anti-arrhythmics (e.g., digoxin)

h) Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

TABLE 33
In Vivo Drug Interactions Resulting in Alteration in Quinine Pharmacokinetics

OVERALL EFFECT	QUININE DOSE, INTERVAL AND ROUTE	PRECIPITANT	PRECIPITANT DOSE AND INTERVAL	PERCENT CHANGE AUC/CL	REFERENCE
In Vivo Induction > 20% Effect	10 mg/kg (7 days) t.i.d.	rifampin	15 mg/kg/day (7 days)	AUC: 75.4 (Decrease)	Pukrittayakamee et al.,2003
	600 mg single dose alone or after rifampin treatment	rifampin	600 mg/day (2 weeks)	AUC: 83.3 (Decrease) CL: 521.4 (Increase)	Wanwimolruk et al., 1995
In Vivo Inhibition > 20% Effect	500mg single dose Oral	ketoconazole	100 mg (3.5 days) at 12 and 1 hours before quinine intake, and every 12 h after, up to 72 h	AUC: 44.7 (Increase) CL: 31.2 (Decrease)	Mirghani et al., 1999
	600mg single dose	troleandomycin	500 mg (2 days) first dose given 2 hours before quinine administration, then tid until the end of 48 hour period	AUC: 87.3 (Increase) CL:45.9 (Decrease)	Wanwimolruk et al., 2002

TABLE 34
In Vivo Drug Interactions Resulting in Alteration in Drug Pharmacokinetics/Pharmacodynamics By Quinine

OVERALL EFFECT	OBJECT	OBJECT DOSE AND INTERVAL	QUININE DOSE, INTERVAL AND ROUTE	PERCENT CHANGE AUC/CL	COMMENTS/REFERENCE
In Vivo Inhibition > 20% Effect	astemizole	10 mg daily for the past 10 months	260mg single dose	Not Determined	Case report of Torsade de Pointes (TdP) after a single dose of quinine while taking Hismanal® (Martin et al., 1997)
		10 mg/day for 1 month	dose for Tx of nocturnal leg cramps, 3 days		Case report of TdP after the dose of quinine Tx; astemizole levels on the day after last quinine dose was 0.73 ng/mL (equivalent to the reported Cmax in healthy volunteers who received the same dose).
	desipramine	Single oral doses of 25mg DMI	750 mg quinine/day for 2 days pretreatment		In rapid hydroxylators, quinine decreased the excretion of 2-hydroxydesipramine by 54% compared to control. In slow hydroxylators, no significant changes in

					excretion pattern was observed (Steiner et al., 1988)
	digoxin	1mg single dose as an infusion over 10 min, alone or with quinine	200mg IV (9 days) tid, 4 days before and after the second digoxin administration	CL: 25.5 (Decrease)	Wandell et al., 1980
		0.5 to 0.75 mg/day, alone or with quinine	750mg/day	35% decrease in steady state biliary excretion; no effect on CLrenal of digoxin	Hedman et al., 1990

A. Based on the literature, the following drugs may produce significant interactions with quinine:

1. Drugs that alter quinine pharmacokinetics

Antacids
Both magnesium hydroxide and aluminum hydroxide decreased gastrointestinal absorption of quinine in rats, the former by raising the pH sufficiently to cause quinine precipitation and the latter primarily by retarding gastric emptying (Hurwitz, 1971). Antacids containing aluminum decrease or delay the absorption of quinine (Prod Info, Quinamm®, 1994).

Cimetidine (CYP3A4 inhibitor)
In healthy volunteers who were given a single oral 600mg dose of quinine sulfate after pretreatment with cimetidine (200mg three times daily and 400mg at bedtime for 7 days) or ranitidine (150mg twice daily for 7 days), the apparent oral clearance of quinine decreased and the mean elimination half-life increased significantly when given with cimetidine but not with ranitidine. Compared to untreated controls, the mean AUC of quinine increased by 20% with ranitidine and by 42% with cimetidine ($p<0.05$) without a significant change in Cmax. Table 35 provides the statistical comparison of the quinine PK parameters with and without cimetidine or ranitidine (Wanwimolruk et al., 1986)

TABLE 35
Mean ± SD Quinine Pharmacokinetic Parameter Values after 7-Day Pretreatment with Cimetidine and with Ranitidine versus Untreated Controls

Parameter (unit)	Quinine Values			ANOVA
	Control	After Cimetidine	After Ranitidine	
C_{max} (μg/mL)	4.3 ± 0.9	4.4 ± 1.0	4.5 ± 1.4	NS
T_{max} (h)	1.5 ± 0.7	1.6 ± 0.4	1.6 ± 0.8	NS
$T_{1/2}$ (h)	7.6 ± 1.3	11.3 ± 3.7*	8.6 ± 2.5	P < 0.005
$AUC_{0-\infty}$ (μg·h/mL)	53.9 ± 16.9	76.8 ± 32.3*	64.9 ± 28.5	P < 0.05
CL/F (L/h·kg)	0.182 ± 0.063	0.133 ± 0.055*	0.168 ± 0.093	P < 0.05

NS=not a statistical difference, Newman-Keuls test
*Comparison with control value is statistically significantly different, Newman-Keuls test

Clindamycin (CYP3A4 substrate, weak to moderate CYP3A4 inhibitor)
The addition of clindamycin to standard quinine treatment substantially improved and shortened the chemotherapy of African children with severe malaria (Kremsner et al., 1995), as well as in studies involving adult and pediatric patients with uncomplicated *P. falciparum* malaria (Kremsner et al., 1994, 1988). In a clinical trial, the addition of clindamycin (5 mg/kg q12h x 3 days) resulted in an improved cure rate (92% versus 38%) and a lower recrudescence rate (on day 21, 8%

versus 39%) over a shortened treatment period (Metzger et al., 1995). In addition, there appeared to be no significant difference in adverse event profiles between the quinine monotherapy and the quinine + clindamycin therapy group after 3 doses of quinine; all reported side effects were mild and self-limiting (disappeared after 1 to 2 days).

Clindamycin was shown to inhibit CYP3A4 activity *in vitro* by 26% at a test concentration of 100 µM whereas after a single oral 600mg dose of clindamycin, the plasma Cmax achieved is about 7 µM (Wynalda et al., 2003). There is currently no literature evidence to support the possibility that clindamycin increases quinine plasma concentrations *in vivo* or that any such pharmacokinetic alterations are clinically relevant with regard to increased quinine toxicity.

Ketoconazole (potent CYP3A4 inhibitor)
In a crossover study, 9 healthy Caucasian subjects who received a single oral dose of quinine hydrochloride (500 mg), on three different occasions: (A) alone, (B) concomitantly with ketoconazole (100 mg twice daily for 3 days) and (C) concomitantly with fluvoxamine (25 mg twice daily for 2 days). Co-administration with ketoconazole (CYP3A4 inhibitor) significantly increased quinine AUC by 45%, decreased the mean apparent oral clearance of quinine significantly by 31% (from 8.7 to 6.0 L/h), whereas coadministration with fluvoxamine (which inhibits CYP1A2 and to some extent CYP2C19) had no significant effect on the mean apparent oral clearance of quinine. Coadministration with ketoconazole also decreased the mean area under the plasma concentration versus time curve (AUC) of 3-hydroxyquinine significantly by 31% whereas coadministration with fluvoxamine increased 3-hydroxyquinine AUC significantly by 11% (Mirghani et al., 1999).

Rifampin (potent CYP3A4 inducer)
In healthy volunteers (N=9) who received a single oral 600mg dose of quinine sulfate after 2 weeks of pretreatment with rifampin 600mg/day, there was a 83% decrease in mean quinine AUC, a 52% decrease in mean Cmax and a 78% decrease in the mean fraction of unchanged quinine excreted into the urine as compared to when given quinine alone. Table 36 compares the pharmacokinetic parameters of quinine with and without rifampin pretreatment (Wanwimolruk et al., 1995).

TABLE 36
Mean ± S.D. Pharmacokinetic Parameter Values of Quinine With and Without Rifampin Pretreatment

Parameter (unit)	Quinine Alone	Rifampin Pretreatment	95% CI of Difference (Rifampin vs. Quinine)
C_{max} (µg/mL)	4.6 ± 1.0 (2.9 – 6.4)	2.2 ± 1.1** (1.3 – 4.6)	-2.4 (-3.5 – -1.4)
T_{max} (h)	2.5 (1.5 – 10)	2.5 (0.7 – 4)	--
$AUC_{0-\infty}$ (µg·h/mL)	66 ± 20 (32 – 105)	11 ± 4** (5 – 19)	-55 (-69 – -41)
$AUC_{0-\infty}$ Unbound (µg·h/mL)	9.8 ± 3.5 (3.8 – 16.9)	1.6 ± 0.8** (0.6 - 3.2)	-8.2 (-10.7 – -5.7)
$T_{1/2}$ (h)	11.1 ± 3.0 (6.6 – 16.3)	5.5 ± 3.0** (2.1 – 10.8)	-5.6 (-8.6 – -2.6)
Cl/F (L/kg·h)	0.14 ± 0.05 (0.08 – 0.25)	0.87 ± 0.35** (0.62 – 1.6)	0.73 (0.48 – 0.98)
% Unbound	14.8 ± 1.2 (12.6 – 16.3)	13.8 ± 2.7 (11.0 – 17.5)	-1.0 (-3.1 – 1.1)
Cl_u/F (L/kg·h)	1.00 ± 0.45 (0.51 – 2.10)	6.87 ± 3.64* (2.7 – 14.5)	5.9 (3.3 – 8.5)
% Unchanged in Urine	7.9 ± 6.5 (2.0 – 22.2)	1.7 ± 1.8* (0.5 – 6.3)	-6.2 (-11 – -1.5)
Cl_R (L/kg·h)	0.011 ± 0.009 (0.003 – 0.029)	0.014 ± 0.017 (0.002 – 0.055)	0.003 (-0.018 – 0.007)

* P < 0.05
** P < 0.005

In patients with uncomplicated *P. falciparum* malaria who received quinine sulfate 10 mg/kg concomitantly with rifampin 15 mg/kg/day for 7 days (N=29), the median AUC of quinine between

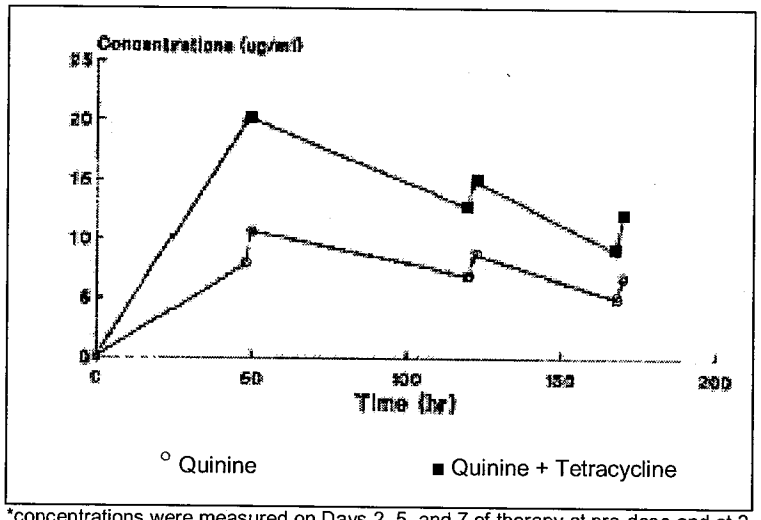
Days 3 and 7 of therapy was 75% lower as compared to those who received quinine monotherapy. Patients treated with both quinine and rifampin had significantly higher concentrations of 3-hydroxyquinine in the first two treatment days as compared to those in the group who received quinine alone. Additionally, although the mean parasite clearance time was shorter in the rifampin + quinine treated patients, the mean recrudescence rate was 5-fold higher during combination therapy than that during quinine monotherapy (Pukrittayakameee et al., 2003). Co-administration of rifampin and quinine should be avoided.

Tetracyclines (tetracycline, doxycycline)
The combination of quinine with tetracycline or doxycycline has resulted in an improvement of cure rates (≥90%) in the treatment of *P. falciparum* malaria (Metzger et al., 1995; Bunnag and Harinasuta, 1986; Colwell and Hickman, 1973).

In vitro drug interaction studies have demonstrated the ability of tetracycline and doxycycline to inhibit the metabolism of quinine in human liver microsomes (Zhao and Ishizaki, 1999, 1997a, 1997b). Doxycycline showed relatively potent inhibition of quinine 3-hydroxylation with a mean IC_{50} value of 17 microM, followed by tetracycline, with mean IC_{50} values of 29 microM. Tetracycline (500mg p.o. q12h x 7 days) was shown to increase the AUC0-τ and Cmax of halofantrine (a CYP3A4 substrate) by 99% and 150%, respectively (Basi et al., 2004)

In 8 patients with acute uncomplicated malaria who were treated with oral quinine sulfate (600mg q8 hours for 7 days) in combination with oral tetracycline (250mg q6 hours for 7 days), the plasma quinine concentrations were about 2-fold higher than in 8 patients who received quinine monotherapy (Figure 14; Karbwang et al, 1999). The trough plasma quinine concentrations were above the MIC (10 mcg/mL) throughout the 7-day treatment period in the combination therapy group but not in those in the quinine monotherapy group. Recrudescence rates were higher in the monotherapy group than in the combination therapy group (25% versus 0%). This paper did not report about the adverse event profile of the combination therapy although in a later study, the same group showed that a 5-day regimen of the oral quinine + tetracycline combination produced a slightly higher but comparable cure rate (100% versus 91%) and a significantly higher incidence of adverse effects (e.g., tinnitus, vomiting) as compared to artesunate (Karbwang et al., 1994).

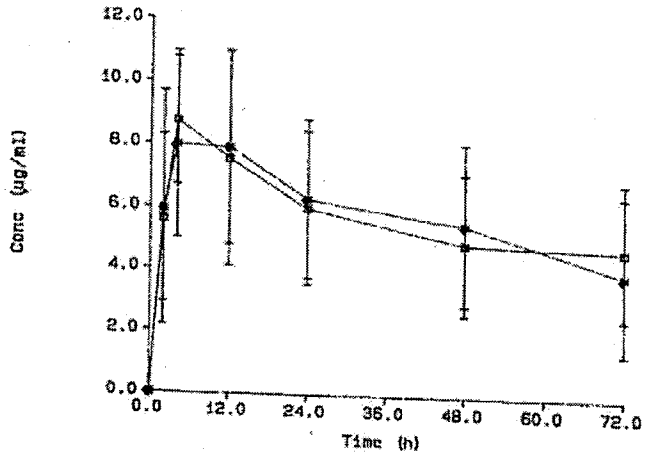
Figure 14
Mean Plasma Quinine Concentrations* in Patients with *P. falciparum* Malaria Following 7-day therapy with Quinine sulfate 600mg q8h alone or with Tetracycline 250mg q6h



*concentrations were measured on Days 2, 5, and 7 of therapy at pre-dose and at 2 hours post-dose

In a case report, it was suspected that oral doxycycline (100mg q12h or 250mg q6h based on the figure) resulted in substantially higher than expected plasma quinine concentrations in a male *P. falciparum* malaria patient who received quinine hydrochloride 600mg intravenously q8 hours. On the second day of combination therapy with IV quinine and oral doxycycline, due to severe nausea and tinnitus, the dose of quinine in this patient was reduced to 300mg q6h (Karbwang et al., 1994). However, in the given scenario, it would be difficult to conclude that the high quinine concentration measured on Day 4 of therapy was due to a drug interaction with doxycycline given that a third antimalarial (mefloquine 500mg intitially followed by 250mg q24h) was introduced on Day 2 in order to offset the 50% reduction in quinine hydrochloride dosage. Furthermore, this conclusion was not corroborated by a later drug interaction study with intravenous doses of quinine and doxycycline. No pharmacokinetic interaction was seen in patients with acute *P. falciparum* malaria during a 3-day regimen of IV quinine dihydrochloride (20mg/kg infused over 4 hours, followed by 15 mg/kg over 20h, then by 25 mg/kg/day for the next 2 days) alone in n = 13 patients or in combination with IV doxycycline (200mg over 1 minute q24h) in the same number of patients (Figure 15; Couet et al., 1991). In a clinical trial that compared the efficacy and safety of quinine monotherapy (12 mg/kg p.o. x 3 doses) to quinine-doxycycline combination therapy (quinine plus oral doxycycline 2 mg/kg q12h x 6 doses), the addition of doxycycline resulted in improved cure rate (91% versus 38%) and lower recrudescence rate (on day 21, 9% versus 39%) over a shortened treatment period (Metzger et al., 1995).

FIGURE 15
Mean (SD) Plasma Concentrations of Quinine in Patients Treated By Quinine Alone (□) or By Quinine plus Doxycycline (♦)



Troleandomycin (potent CYP3A4 inhibitor?)
In a crossover study, 10 healthy adult volunteers received either a single oral dose of quinine sulfate (600 mg) alone, or quinine sulfate (600 mg) plus the CYP3A4 inhibitor troleandomycin (TAO; 500 mg every 8 h). Compared with control, TAO treatment significantly increased the mean AUC of quinine by 87%, and decreased the mean time-averaged erythromycin breath test (ERMBT) result by 77% (95% CI, 68, 85%), the mean apparent oral clearance of quinine (CL/F) by 45% (95% CI, 39, 52%), and the mean apparent formation clearance of 3-hydroxyquinine (CL3-OH) by 81% (95% CI, 76, 87%).

Urinary alkalinizers (acetazolamide, sodium bicarbonate)
(No literature provided)
Acetazolamide may increase plasma levels of quinine because of increased urine alkalinity (Prod Info Quinamm®, 1994). The half-life and duration of quinine may be increased by sodium bicarbonate due to urinary alkalinization (Olin, 1990).

2. Drugs affected by quinine

Amantadine
In healthy subjects (27 to 72 years old) who received a single oral 3mg/kg dose of amantadine hydrochloride with or without a single dose of 200mg quinine sulfate, quinine appeared to decrease the renal clearance of amantadine by about 30%, moreso in males than in females (Gaudry et al., 1993). Like quinine, amantadine is an organic cation at physiologic pH; quinine might have competed with amantadine for transporters involved in renal tubular secretion.

Astemizole
There were two case reports of torsade de pointes (TdP) when quinine sulfate at doses typical for the treatment of nocturnal leg cramps were taken by subjects who were receiving astemizole 10mg/day chronically along with other drugs. In one of these cases, astemizole concentrations were measured. On the day after the third (last) quinine dose, the plasma astemizole concentration was approximately equivalent to the Cmax after a single astemizole dose, suggesting that quinine boosted astemizole systemic concentrations. Quinine (at doses of 450mg and larger) increases plasma astemizole concentrations (March 25, 1996 Dear Healthcare Professional Letter, Janssen).

Similar cases of TdP were reported for combined use of astemizole (a CYP3A4 substrate) and other CYP3A4 inhibitors namely ketoconazole (Tsai et al, 1997) and erythromycin (Hsieh et al., 1996). A drug interaction study involving another CYP3A4 inhibitor (itraconazole) demonstrated that itraconazole could lead to a 82% increase in astemizole AUC within 24-hours from administration of the astemizole dose (Lefebvre et al., 1997).

Carbamazepine
A single 600mg oral dose of quinine sulfate was shown to increase plasma Cmax, and AUC_{0-24} of single doses of carbamazepine (200mg p.o.) and phenobarbitone (120mg p.o.) but not phenytoin (200mg p.o.) in eight healthy subjects (Amabeoku et al., 1993). The mean increases in AUC of carbamazepine, phenobarbital, and phenytoin were 104%, 81% and 4%, respectively; the mean Cmax increases were 56%, 53%, and 4%, respectively. Mean urinary recoveries of the three anticonvulsants over 24 hours were also profoundly increased by quinine. The pharmacokinetic parameters of the anticonvulsants are summarized in Table 37. Possible mechanisms of drug interaction are inhibition of metabolism and/or inhibition of renal tubular secretion of the affected anticonvulsants by quinine.

TABLE 37
Mean ± SEM Pharmacokinetic Parameter Values of Carbamazepine, Phenobarbitone, and Phenytoin With or Without a Single Dose of Quinine Sulfate 600mg

Pt. Group	Plasma Concentrations N=6 Mean ± SEM		
	C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	Urinary Recovery (mg/24 hrs)
Carbamazepine	3.45 ± 0.32	69.22 ± 4.09	0.14 ± 0.02
Carbamazepine + quinine	5.43 ± 0.18*	141.34 ± 5.24*	0.23 ± 0.018*
Phenobarbitone	7.61 ± 0.64	204.09 ± 8.71	0.39 ± 0.05
Phenobarbitone + quinine	11.68 ± 0.78*	368.72 ± 11.17*	0.73 ± 0.11*
Phenytoin	7.40 ± 1.12	211.37 ± 10.48	0.18 ± 0.03
Phenytoin + quinine	7.71 ± 1.07	219.93 ± 16.17	0.35 ± 0.018*

P < 0.05, Student's t test

Desipramine, Debrisoquine, Dextromethorphan, Flecainide and other CYP2D6 substrates
In human liver microsomes, quinine 100 µM inhibited the activity of debrisoquine 4-hydrolase (CYP2D6) by >95% (Kobayashi et al., 1989), suggesting a possible interaction between quinine and CYP2D6 substrates *in vivo*.

After treatment with 750mg quinine/day for 2 days, excretion of 2-hydroxydesipramine in rapid CYP2D6 metabolizers was 54% lower as compared to control, whereas there was no effect on CYP2D6 poor metabolizers (Steiner et al., 1987). It appears that the CYP2D6-inhibitory activity of quinine is dose dependent because lower quinine doses did not produce clinically significant alterations in the metabolism of CYP2D6 substrates. Quinine (200 to 400mg) did not alter the metabolic ratios of debrisoquine (CYP2C19 probe) in six subjects (Ayesh et al., 1991) and 300mg quinine sulfate did not alter the renal excretion of methoxyphenamine (60.3mg) and its metabolites in either rapid or poor metabolizers (Muralidharan et al., 1991). Likewise, quinine (80mg) in the form of tonic water was not shown to alter the metabolic ratios of dextromethorphan (30mg) in 11 healthy subjects (Donovan et al., 2003).

Quinine was shown to interfere with the metabolism of flecainide (a CYP2D6 substrate) in humans, resulting in a prolonged PR interval when the two drugs were given together (Munafo et al, 1990). Quinine administration did not change the apparent Vd or the renal clearance of flecainide, but it significantly reduced its systemic clearance by 16% (9.1 vs 7.6 ml.kg-1.min-1), thus increasing the elimination half-life (9.6 vs 11.5 h). The total clearance of the dealkylated metabolite and the dealkylated lactam metabolite decreased without a significant change in renal clearance of these metabolites.

Except for desipramine, fleicanide, and debrisoquine, formal *in vivo* drug interaction studies have not been conducted between quinine and the following drugs that are known CYP2D6 substrates. Of the drugs listed in Table 38 below, quinine was shown to inhibit the *in vitro* metabolism of debrisoquine, dextromethorphan, metoprolol, and paroxetine. Thus, the potential for drug interaction *in vivo* between these drugs and quinine cannot be excluded presently.

TABLE 38
Substrates of Cytochrome P450 CYP2D6

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

Source: Spina et al., 2003 Table 1

Digoxin

In 4 healthy subjects, there was a 33% increase in steady state AUC of digoxin and a 35% reduction in the steady-state biliary clearance of digoxin (0.5 to 0.75 mg/day) during treatment with quinine (750mg/day) as compared to when digoxin was given alone. Quinine did not alter the steady-state renal clearance of digoxin (Hedman et al., 1990). In a similar study involving 7 healthy subjects, a lower dose of quinine (250mg/day) was shown to increase mean steady-state plasma digoxin concentration by only 25%, also without affecting its renal clearance (Table 39; Pedersen et al., 1985). Another study involving 6 subjects found similar results and concluded that quinine reduced the biliary excretion of digoxin (1mg IV) because there were no observed changes in the renal clearance and the Vd of digoxin despite a 25% decrease in the total clearance of digoxin (Wandell et al., 1980). Thus, if quinine is to be given to patients on digoxin, there should be close monitoring of plasma digoxin and reductions in digoxin dose as needed.

TABLE 39
Mean Steady-State (± S.D.) Pharmacokinetic Variables of Digoxin in Healthy Subjects with or without Quinine 250mg/day 0r 750mg/day

Digoxin Parameter (units)	Treatment (N=7)		
	Digoxin[1] (Control)	+ Quinine 250 mg/day	+ Quinine 750 mg/day
Plasma concentration (ng/mL)	0.64 ± 0.12	0.80 ± 0.18*	0.85 ± 0.12**
Renal clearance (L/hr)	10.89 ± 1.46	10.45 ± 1.59†	10.24 ± 2.06†
Amount recovered in urine over 24 hours (mg/24 hours)	0.154 ± 0.019	0.181 ± 0.022††	0.204 ± 0.037†

1Steady state conditions: Initially, 1 mg and then 0.1875 mg every 12 hours for 2 weeks (oral)
*P < 0.05, compared with control
**P < 0.02, compared with control
†The difference was not statistically significant compared to control
††P < 0.01, compared with control

Halofantrine (CYP3A4 substrate)
Halofantrine, an antimalarial drug that prolongs QT interval is metabolized mainly into N-debutyl-halofantrine by CYP3A4. Severe cardiotoxicity has been reported to be correlated with high plasma concentrations of halofantrine but not with its metabolite N-debutylhalofantrine.

In a system of human liver microsomes, quinine at 10μM, 100μM and 500μM inhibited the metabolism of halofantrine (50μM) to N-debutylhalofantrine by 18%, 52%, and 100%, respectively. It was predicted that at peak quinine concentrations from a 25mg/kg/day oral dose of quinine, the percent inhibition of halofantrine metabolism will be about 49%.

Mefloquine (CYP3A4 substrate?)
The metabolism of mefloquine is likely mediated mainly by CYP3A4 because chronic 600mg oral rifampin administration was shown to reduce the AUC of single oral 500mg mefloquine by 68%, the Cmax by 19%, and the half-life by 63% while increasing the $AUC_{0-\infty}$ and the Cmax of the carboxylic acid metabolite by 30% and 47%, respectively. *In vitro*, quinine was shown to inhibit the formation of carboxymefloquine with IC_{50} and Ki of 122 and 28.5 microM, respectively; since the Cmax were very close to the Ki value, there is likely to be inhibition of mefloquine metabolism in patients receiving both drugs (Bangchang et al., 1992).

When quinine dihydrochloride (20mg/kg followed by 10mg/kg q8h infusion) was discontinued on Day 7 of concomitant therapy with mefloquine hydrochloride (250 – 500mg q 1h for up to total dose of 1000mg) in 19 patients with cerebral malaria, a marked rise in mefloquine plasma concentrations was observed (Figure 16, Chanthavanich, 1985). A later study conducted by the same group (Na-Bangchang et al., 1999) in 7 healthy volunteers who received a single oral 600mg dose of quinine sulfate or mefloquine 750mg alone or 24 hours before the quinine dose showed that when these two drugs were dosed 24 hours apart, the AUC of mefloquine increased by 22% as compared to when given alone (Table 40). Furthermore, the QTc interval was significantly prolonged in these subjects following the combination regimen (8% versus 4.5% of baseline). Overall, the findings of published studies indicate that quinine has the potential to alter mefloquine pharmacokinetics, as well as enhance its QTc prolonging effect even if the administration of quinine and mefloquine is separated by 24 hours. Furthermore, concomitant administration with mefloquine and quinine may also produce electrocardiographic abnormalities and may increase the risk of convulsions (Prod Info, Lariam®, 2002). Although some references and foreign labeling recommend spacing the mefloquine and quinine sulfate doses by 12 hours, no data had been submitted with the NDA that would allow the reviewer to verify or justify such dosing strategy for the two drugs.

FIGURE 16
Mean ± SE plasma mefloquine concentrations over a 9-day period in 19 patients with cerebral malaria

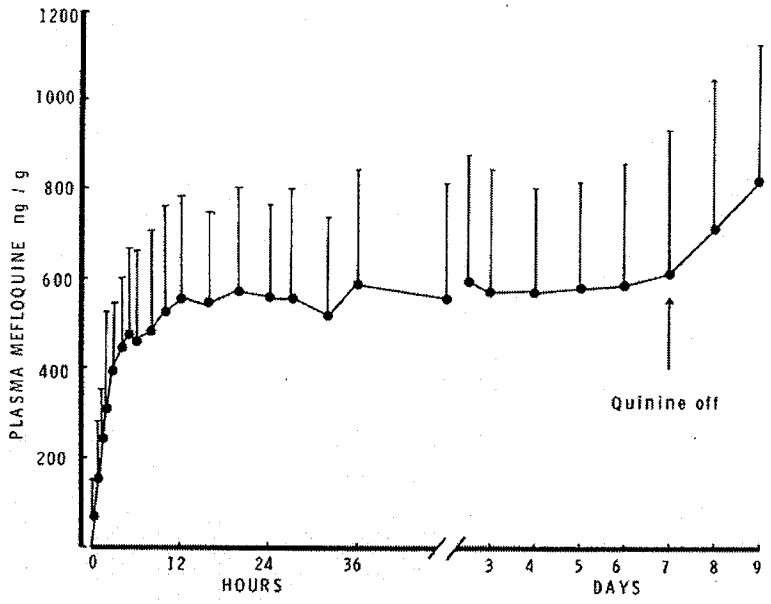


TABLE 40
Mean (Range) Pharmacokinetic Parameters of Quinine and Mefloquine after Oral Administration Alone and in Combination in 7 Healthy Adults

Parameter (units)	Quinine		Mefloquine	
	Alone	+ Mefloquine	Alone	+ Quinine
C_{max} (µg/mL)	3.32 (2.47 – 6.6)	3.27 (2.66 – 4.71)	1.09 (0.753 – 1.364)	1.072 (0.75 – 1.682)
T_{max} (h)	2 (1 – 2.5)	2 (1.5 – 3)	4 (4 – 6)	4 (4 – 6)
AUC (µg·h/mL)	53.2 (40.1 – 98.2)	55 (NP)	467 (285 – 583)	571 (235 – 609)
Cl (L/h·kg)	0.47 (0.22 – 0.62)	0.45 (0.31 – 0.51)	0.03 (0.02 – 0.05)	0.033 (0.02 – 0.04)
$t_{1/2}$	12.5 hours (7.9 – 18.3)	15.4 hours (8.2 – 19.7)	16.2 days (13.6 – 21.6)	17.3 days (14.8 – 23.6)
V_d (L/kg)	7.1 (4.9 – 11.4)	7.8 (5.7 – 10.4)	21 (11.8 – 25.8)	17.3 (14.8 – 23.6)

NP=not provided

Neuromuscular Blocking agents (pancuronium, succinylcholine, tubocurarine)
(No literature provided.)
Quinine has neuromuscular blocking activity (Bateman and Dyson, 1986). Concomitant use with neuromuscular blocking agents should be avoided. In a case report, a patient had pancuronium (6mg) during an operative procedure. Three hours post-operatively, the administration of quinine (1800mg daily) resulted in further neuromuscular blockade (Sher and Mathews, 1983). Likewise, quinine may enhance the neuromuscular blocking effects of succinylcholine (Product info, Anectine®, 1999), and tubocurarine (Prod info, Tubocurarine chloride, 1988).

Phenobarbitone (Phenobarbital)
See Carbamazepine.

Warfarin and Oral anticoagulants
In vitro, quinine was shown to inhibit the metabolism of coumarin to 7-hydroxycoumarin (by CYP2A6) with an IC_{50} of 160 µM suggesting potential for weak inhibitory activity at high quinine

doses; quinidine produced a less potent inhibitory activity with IC_{50} of 1.12 mM (Hirano and Mizutani, 2003).

By contrast, quinine and quinidine (50 μM) were shown to increase the CYP3A4-mediated metabolism of warfarin to 4'hydroxyl S-warfarin and 10-hydroxyl-R-warfarin by 130% to 400% in human liver microsomal systems and CYP3A4 recombinant systems (Ngui et al., 2001). Since cinchona alkaloids including quinine and warfarin are believed to depress the hepatic enzymes responsible for the synthesis of clotting factors, and there have been various case reports suggesting that quinine and quinidine potentiates the hypoprothrombinemic effect of warfarin, it remains a conundrum why quinidine had been reported to reduce (not increase) the anticoagulant effect of warfarin (Koch-Weser, 1968; Sylven and Anderson, 1983).

Thus, quinine may increase or decrease the effects of warfarin and oral anticoagulants. In patients receiving oral anticoagulant therapy with warfarin, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of treatment with quinine, and should be reassessed periodically during concurrent therapy. Adjustments of the warfarin dose may be necessary in order to maintain the desired level of anticoagulation.

B. Based on the literature, the following drugs and food products were not shown to significantly alter the pharmacokinetics of quinine:

Cholestyramine
In eight healthy Thai male volunteers who received quinine sulfate 600mg with or without 8 grams of cholestyramine resin, no significant difference in quinine pharmacokinetic parameters were seen (Table 41, Ridtitid et al., 1998).

TABLE 41
Mean ± SD Pharmacokinetic Parameter Values of Quinine in 8 Healthy Male Volunteers Following a Single 600 mg dose of Quinine Sulfate with and without Cholestyramine

Parameter (unit)	Quinine Alone (Control Phase)	Quinine and Cholestyramine
C_{max} (μg/mL)	5.7 ± 2.5	5.6 ± 2.5
T_{max} (h)	1.35 ± 0.4	1.02 ± 0.3
$AUC_{(0-\infty)}$ (μg·h/mL)	90.2 ± 43.4	80.3 ± 32.1
V_d (L/kg)	1.91 ± 0.6	1.94 ± 0.5
$T_{\frac{1}{2}}$ (h)	10.1 ± 1.2	9.5 ± 1.7
Cl_o (L/h/kg)	0.13 ± 0.05	0.15 ± 0.05

None of the parameter values were statistically significantly different (P >0.05)

Oral Contraceptives (Estrogen, Progestin)
The pharmacokinetics of quinine were not significantly different in healthy females using single-ingredient progestin or combination estrogen-containing oral contraceptives (n = 7) and who took a single oral 600mg dose of quinine sulfate, as compared to age-matched female cohorts (n = 7) who were given a single quinine sulfate 600mg dose (Table 42; Wanwimolruk et al., 1991b).

The effect of quinine on the pharmacokinetics of these oral contraceptives has not been reported.

TABLE 42
Quinine Pharmacokinetic Parameter Values Following a Single 600-mg Dose in Women Who Do and Do Not Use Oral Contraceptives

Parameter (unit)	Users of Oral Contraceptives N=7	Controls N=7
Age (years) (range)	28 ± 4 (24 – 34)	26 ± 5 (19 – 35)
Weight (kg)	49 ± 5	48 ± 5
C_{max} (µg/mL)	5.3 ± 1.0	5.6 ± 0.9
T_{max} (h)	1.4 ± 0.7	2.1 ± 0.9
AUC (µg·h/mL)	85.7 ± 24.4	88.3 ± 32.2
CL/F (L/h/kg)	0.133 ± 0.055	0.125 ± 0.025
$T_{1/2}$ (h)	12.5 ± 1.9	11.8 ± 2.7
% Unbound	22.7 ± 6.2	22.7 ± 6.2

Diazepam
The findings of an *in vitro* protein binding study suggests that diazepam has a low potential to displace quinine from plasma protein binding (See Table 31 in Section 3.a Drug-Drug Interactions).

Grapefruit juice
Quinine AUC and Cmax when a single oral 600mg dose of quinine sulfate was given with either full strength or half-strength grapefruit juice was comparable to that when quinine was given with orange juice (See Table 27 in Section D.1, Extrinsic Factors, Diet).

Isoniazid
A 1-week pre-treatment with isoniazid 300 mg/day given prior to a single 500 mg dose of quinine was included as an arm in the three-way crossover trial described earlier (Wanwimolruk *et al.*, 1995). Isoniazid did not significantly alter the pharmacokinetic parameters of quinine except the mean quinine half-life (Table 43).

TABLE 43
Mean (± S.D.) Quinine Pharmacokinetic Parameter Values in 9 Healthy Volunteers after a Single Dose of 600 mg Quinine Sulfate Alone or Following Isoniazid Pretreatment

Parameters (Unit)	Quinine Alone	Isoniazid Pretreatment	95% CI of Difference Isoniazid vs. Control
C_{max} (µg/mL)	4.6 ± 1.0 (2.9 – 6.4)	4.4 ± 1.6 (2.8 – 8.4)	-0.2 (-1.5 – 1.1)
T_{max} (h)	2.5[a] (1.5 – 10)	3.0[a] (2.0 – 6.0)	--
$T_{1/2}$ (h)	11.1 ± 3.0 (6.6 – 16.3)	14.2 ± 2.9* (9.5 – 19.0)	3.1 (0.15 – 6.1)
CL/F (L/h/kg)	0.14 ± 0.05 (0.08 – 0.25)	0.16 ± 0.04 (0.1 – 0.2)	0.02 (-0.03 – 0.07)
CL_U/F (L/h/kg))	1.00 ± 0.45 (0.51 – 2.10)	1.22 ± 0.34 (0.72 – 1.90)	0.22 (-0.18 – 0.6)
AUC (µg·h/mL)	66 ± 20 (32 – 105)	56 ± 13 (39 – 79)	-10 (-27 – 7)
AUC (unbound) (µg·h/mL)	9.8 ± 3.5 (3.8 – 16.9)	7.5 ± 2.1 (5 – 5.1)	-2.3 (-5.2 – 0.6)
% Unbound	14.8 ± 1.2 (12.6 – 16.3)	13.9 ± 2.1 (11.9 – 16.5)	-0.9 (-2.6 – 0.8)
% Dose excreted as unchanged quinine in the urine (0 – 48 h)	7.9 ± 6.5 (2.0 – 22.2)	5.4 ± 3.1 (1.6 – 10.0)	-2.5 (-7.6 – 2.5)
CL_R (L/h/kg)	0.011 ± 0.009 (0.003 – 0.029)	0.009 ± 0.006 (0.002 – 0.013)	-0.002 (-0.009 – 0.006)

CL/F=oral clearance; CL_U=unbound oral clearance; CL_R=renal clearance
[a]Median values are given (range).
*P <0.05 compared with control.

Phenytoin
See Carbamazepine.

Ranitidine
See Cimetidine.

i) Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Based on the CDC guidelines for the treatment of uncomplicated *P. falciparum* malaria, quinine should be co-administered with tetracycline or doxycycline or in the case of pregnant females and children > 8 years old, quinine should be used in combination with clindamycin in order to reduce recrudescence rates. These co-administered drugs complement quinine by their antibacterial and inherent (slow-acting) antimalarial activity as demonstrated *in vitro*, in addition to their potential (particularly tetracycyline) to increase plasma quinine concentrations.

The co-administration of quinine with other drugs that also prolong the QT interval (e.g., cisapride, astemizole) should be avoided.

j) Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None.

k) What issues related to dose, dosing regimens or administrationare unresolved, and represent significant omissions?

None.

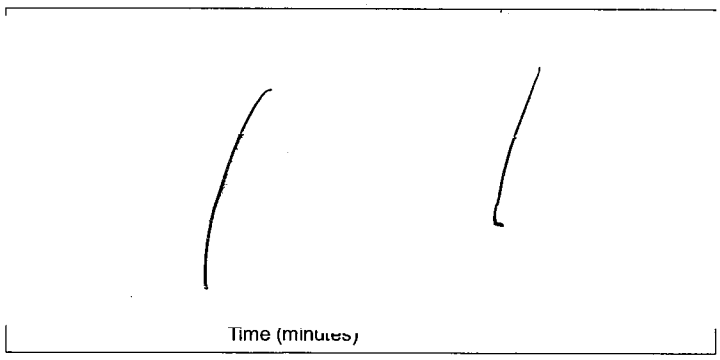
E. General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The absorption of quinine sulfate is approximately 76% to 88% in healthy subjects (Paintaud et al., 1993; Salako et al., 1992). The dissolution profiles of the Mutual quinine sulfate 324 mg capsule in various pH media is shown in Figure 17. Based on this figure, quinine sulfate is highly soluble in gastric pH ([illegible] in 30 minutes) but not in water and other media at higher pH conditions.

Based on the absorption and dissolution characteristics of quinine sulfate, it can be categorized as BCS Class II (poorly soluble, highly permeable) or Class IV (poorly soluble, poorly permeable).

FIGURE 17
Dissolution Profiles of Mutual Pharma's Quinine Sulfate 324 mg Capsule
(Lot No. NBB 102 0105) in Various Media



2. What is the relative bioavailability of the proposed to-be-marketed formulation to the formulation used in the pivotal clinical trial?

The relative bioavailability of the proposed commercial formulation was determined using GPO-Thailand 300mg Quinine Sulfate Tablets as a reference product. Based on various published studies, this reference product was proven effective in the treatment of uncomplicated *P. falciparum* malaria.

a) What data support or do not support a waiver of in vivo BE data?

A waiver of *in vivo* BE is not recommended because quinine sulfate dihydrate cannot be classified as a Class I drug under the Biopharmaceutics Classification Scheme (BCS).

b) What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

c) If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Based on the 90% C.I. findings of the food-effect study conducted by the sponsor, quinine Cmax and AUC when the sponsor's quinine 324mg was given with a high-fat meal were comparable to those when quinine was given under fasted conditions; the statistical comparison of the two treatments is provided in the Table 44A below. Furthermore, Table 44B provides a comparison of the AE rates for the two treatments. Thus, although the quinine Cmax was slightly higher when quinine was given with a high-fat meal, the AE rates for quinine/fed were not substantially different from quinine/fasted.

Thus, the lack of a food-effect indicates that the quinine sulfate tablets may be given without regard to meals. However, it is advisable to recommend taking the tablets with food as quinine has gastrointestinal irritation potential.

TABLE 44A
Statistical Comparison of Geometric Means of Quinine Pharmacokinetic Parameters Following A Single Doses of Mutual Quinine Sulfate, 325 mg under Fasted versus Fed Conditions

Statistical Analysis Summary
(LN-TRANSFORMED DATA)

Parameter	*Geometric Mean		90% Confidence Interval
	Treatment C (Fed): Quinine Sulfate Capsules USP, 324 mg	Treatment A (Fasting): Quinine Sulfate Capsules USP, 324 mg	
C_{max}	2438.84	2169.43	(104.74, 120.66)
AUC_{0-t}	32942.74	31590.14	(99.01, 109.84)
AUC_{inf}	35114.58	34599.61	(95.49, 107.86)

* Geometric means based on least squares means of ln-transformed values.

TABLE 44B
Comparison of Adverse Events Rates Following A Single Doses of Mutual Quinine Sulfate, 325 mg under Fasted versus Fed Conditions

TREATMENT	Number of Subjects With AE	Number of Reported AEs
Fasted	7	11
Fed	7	14

4. When would a fed BE study be appropriate and was one conducted?

Not applicable.

5. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed analytical method for release of commercial product is summarized below. The proposed release specification for *in vitro* dissolution testing of quinine sulfate capsules is: Not less than 75% (Q) of labeled amount of quinine sulfate dissolved in 45 minutes. Both the proposed method and the proposed release specification are in accordance with the current USP recommendations.

Apparatus: USP Apparatus 1 (Basket)
Medium: 0.1 N Hydrochloric Acid (900 mL)

Speed: 100 rpm increased to 200 rpm after 45 minutes
Temperature: 37 ± 0.5 °C
Sampling Times: 15, 30, 45, and 60 minutes
Assay Method: UV/Visible Spectrophotometer at

When the biobatch of the sponsor's quinine sulfate tablets (Lot No. BB 102 0105) was subjected to this proposed dissolution method of the labeled amount was dissolved in 15 minutes and the capsules were completely dissolved in

6. If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

7. If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

9. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

Not applicable.

G. *Analytical Section*

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Total (bound and unbound) quinine was measured in plasma samples using a validated LC/MS/MS method.

2. Which metabolites have been selected for analysis and why?

None of the known (microbiologically active or inactive) quinine metabolites in human plasma samples were quantified in the clinical pharmacokinetic studies. The major metabolite of quinine is 3-hydroxyquinine which possesses 12 to 25% of the antimalarial activity of the parent compound.

3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

In the two pharmacokinetic studies conducted by the sponsor, the total plasma quinine concentrations were determined, i.e., no special sample preparation and assay techniques were used to distinguish the protein-bound from the unbound/free quinine in plasma samples of healthy volunteers. It was not deemed necessary to measure free (unbound) quinine concentrations in the plasma samples of the healthy volunteers because the studies were conducted mainly to obtain comparative quinine pharmacokinetics of various formulations, various doses of the same formulation, or to determine the effect of food on quinine PK.

4. What bioanalytical methods are used to assess concentrations?

An LC/MS/MS procedure was developed and validated for the determination of quinine in human EDTA plasma. Plasma samples containing quinine and the internal standard [redacted] were [redacted] was injected into a HPLC system and quantitated using tandem mass spectrophotometer.

a) What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve was linear from 25 ng/mL to 5000 ng/mL, with a linear regression correlation coefficient of >0.990 (mean =0.9981). Based on the range of quinine concentrations obtained in the two clinical pharmacology studies conducted, this calibration curve was adequate to determine with certainty the quinine concentrations of blood samples obtained.

b) What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limit of quantification (LLOQ) for quinine in plasma was 25 ng/mL and upper limit of the calibration curve was 5000 ng/mL.

c) What is the accuracy, precision and selectivity at these limits?

The accuracy and precision of the assay were determined by spiking blank plasma with quinine ranging from 25 to 5000 ng/mL. Calibration standards at each spiking level were analyzed from a total of 12 or 26 analytical runs. The fitted concentrations were interpolated from the standard curve.

Accuracy. The accuracy ranged from -7.71% to 4.50%.
Precision. The precision of quinine calibration standards ranged from 2.05% to 5.88%.
Specificity. Aliquots of six lots of blank human plasma were processed individually and screened for peaks at [redacted] for quinine and [redacted] internal standard), respectively. No peaks were found, indicating that there is no interference from endogenous plasma constituents.

d) What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

The study samples were stored at the analytical services laboratory within the stability parameters demonstrated during method validation. These parameters include re-injection or on-system stability of extracted samples for 43 hours; refrigeration stability of extracted samples for 45.5 hours; bench-top or room-temperature stability of unextracted samples for 29 hours; freeze-thaw stability from zero through four cycles; long-term stability of unextracted samples at -20°C for 2.5 months; room temperature stability of stock solution for 19 hours; working standard solution stability at 2-8°C for 3 months.

e) What is the QC sample plan?

QC samples spiked with quinine at 75, 1500, and 3750 ng/mL levels were analyzed from a total of 12 or 26 analytical runs. The precision of quinine QC samples ranged from 3.89% to 6.11% for all samples. The accuracy ranged from -3.80% to 7.11%. The QC acceptance criterion for accuracy is <15% error.

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_____ Deliberative Process

B. Individual Study Reviews

1. Study RA3-085

Title: A Relative Bioavailability Study of Quinine Sulfate Capsules Under Fasting and Fed Conditions

Objectives:

1. To determine the single dose relative bioavailability of the applicant's Quinine Sulfate Capsules USP, 324 mg against the reference Quinine Sulfate Tablets (300 mg) manufactured by The Government Pharmaceutical Organization, Thailand

2. To evaluate the effect of food on the applicant's product in healthy adult volunteers

Study Design:
This was a randomized, single dose, three-way crossover study under fasting and fed conditions.

Study Population (Enrolled and Completed):
Twenty-seven (27) healthy subjects (12 males, 15 females) entered the study but 26 were evaluable for PK. One subject was disqualified due to a positive pregnancy screen. Two other subjects did not complete the study either because they did not return for the last sampling time point or because of personal reasons. The following table summarizes the demographic characteristics of the study population that was evaluable for PK and QT.

Subjects who had a QTc interval of >480 msec at the time of screening were excluded.

TABLE 45
Demographic Characteristics of Healthy Subjects in this Study

	All Subjects (n=27)	Males (n=12)	Females (n=15)
Age (years)	24.2 ± 8.9	23.3 ± 6.7	24.9 ± 10.5
Weight (lbs)	155.7 ± 30.3	184.8 ± 16.5	132.4 ± 13.5
Height (in)	66.9 ± 4.0	70.3 ± 2.5	64.3 ± 2.8

Dosing and Administration:
Volunteers received a single dose of the following three treatments, separated by a 7-day washout period.

Treatment A: Quinine sulfate, 324 mg capsules/Mutual Pharmaceuticals (fasted)
Treatment B: Quinine sulfate tablets, 300 mg/Government Pharmaceutical Organization, Thailand (fasted)
Treatment C: Quinine sulfate, 324 mg capsules/Mutual Pharmaceuticals (fed)

Pharmacokinetic Sampling and Assay:
Blood samples were collected in EDTA vacutainers at -1, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours post-dose. The blood samples were centrifuged and the plasma was stored at -20°C until shipment and subsequent analysis by HPLC-MS-MS.

Safety Evaluation:
The patients were monitored for adverse events.

Pharmacokinetic and Statistical Analysis:
- Cmax, AUC_{0-t}, AUC_{inf}, Tmax, kel, t½
- 90% confidence interval about the Geometric Mean of the Log-transformed Cmax, AUC_{0-t}, AUC_{inf} and the Least Squares Mean of the Non-Transformed Cmax, AUC_{0-t}, AUC_{inf}

RESULTS:
Pharmacokinetics:

FIGURE 18

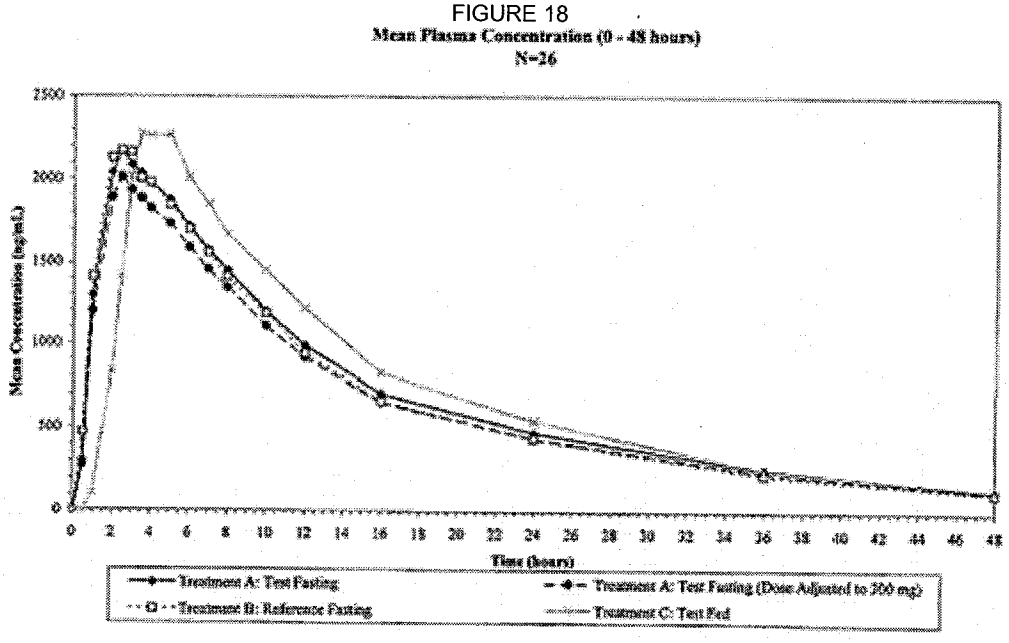

TABLE 46
Treatment A (Mutual Quinine Sulfate, 325 mg) versus
Treatment B (GPO Quinine Sulfate, 300 mg) Under Fasting Conditions

Statistical Analysis Summary
(LN-TRANSFORMED DATA)
Treatment A Dose Adjusted to 300 mg

Parameter	*Geometric Mean		90% Confidence Interval
	Treatment A (Fasting): Quinine Sulfate Capsules USP, 324 mg	Treatment B (Fasting): Quinine Sulphate 300 mg Tablets	
C_{max}	2008.74	2195.26	(85.25, 98.22)
AUC_{0-t}	29250.17	30214.93	(91.91, 101.97)
AUC_{inf}	32036.83	32512.15	(92.71, 104.73)

* Geometric means based on least squares means of ln-transformed values.

Statistical Analysis Summary
(NON-TRANSFORMED DATA)
Treatment A Dose Adjusted to 300 mg

Parameter	Least Squares Mean		90% Confidence Interval
	Treatment A (Fasting): Quinine Sulfate Capsules USP, 324 mg	Treatment B (Fasting): Quinine Sulphate 300 mg Tablets	
C_{max}	2084.29	2258.27	(84.21, 100.38)
AUC_{0-t}	30284.86	31584.60	(89.57, 102.2)
AUC_{inf}	33487.29	34342.02	(89.42, 105.6)

TABLE 47
Treatment A (Mutual Quinine Sulfate, 325 mg) Fasted versus
Treatment C (Mutual Quinine Sulfate, 325 mg) Fed

Statistical Analysis Summary
(LN-TRANSFORMED DATA)

Parameter	*Geometric Mean		90% Confidence Interval
	Treatment C (Fed): Quinine Sulfate Capsules USP, 324 mg	Treatment A (Fasting): Quinine Sulfate Capsules USP, 324 mg	
C_{max}	2438.84	2169.43	(104.74, 120.66)
AUC_{0-t}	32942.74	31590.14	(99.01, 109.84)
AUC_{inf}	35114.58	34599.61	(95.49, 107.86)

* Geometric means based on least squares means of ln-transformed values.

Statistical Analysis Summary
(NON-TRANSFORMED DATA)

Parameter	Least Squares Mean		90% Confidence Interval
	Treatment C (Fed): Quinine Sulfate Capsules USP, 324 mg	Treatment A (Fasting): Quinine Sulfate Capsules USP, 324 mg	
C_{max}	2535.89	2250.71	(104.45, 120.89)
AUC_{0-t}	34643.77	32705.79	(99.84, 112.01)
AUC_{inf}	37419.45	36164.03	(95.74, 111.21)

Safety:

Vital signs and Clinical Laboratory:

None of the reported changes in vital signs (heart rate, blood pressure) and clinical laboratory measurements were considered clinically significant. None of these changes were attributed to the test drug products.

Electrocardiogram:

An electrocardiogram was recorded at baseline and at 2, 4, 6, 12, and 24 hours after each dose administration. None of the observations were clinically significant (no subject had a QTc interval >450 msec, and no mean change from baseline was >7.1 msec). The mean values and change from baseline are shown in the table below.

Adverse Events:

Thirty-two adverse events were reported by 11 subjects over the course of the study. Headache and vomiting were the most common AEs reported. Twenty-one of these 32 AEs were judged by the investigator to have been probably/possibly related to the study medication. None of the adverse events were considered serious. The adverse events are summarized in Table 49 below:

TABLE 48

Mean QTc Measurements and Change from Baseline Over 24-hours Following a Single Oral Dose in Patients in Mutual-Sponsored Bioequivalence Study RA3-085

	Study RA3-085 QTc (msec)					
	Baseline	2 hr	4 hr	6 hr	12 hr	24 hr
Mutual Pharma's 324 mg Capsule (Fasting)						
Mean ± SD N=26	399 ± 18	402 ± 23	399 ± 20	400 ± 22	398 ± 20	399 ± 23
Change from Baseline	--	2.3	-0.5	1.0	-1.6	-0.3
GPIP's 300 mg Tablet (Fasting)						
Mean ± SD N=23	399 ± 15	406 ± 24	400 ± 24	400 ± 19	396 ± 17	394± 20
Change from Baseline	--	7.1	1.3	1.0	-3.0	-5.24
Mutual Pharma's 324 mg Capsule (Fed)						
Mean ± SD N=27	397 ± 18	397 ± 19	396 ± 25	402 ± 22	400 ± 19.6	400 ± 20
Change from Baseline	--	-0.0	-1.7	4.4	2.3	3.0

TABLE 49

Event No.	Subject No.	Event	Relationship to Study Drug	Study Drug
01	26	Dyspepsia (Heartburn)	2	C
02	05	Headache	1	B
03	07	Headache	1	C
04	07	Headache	1	A
05	07	Headache	1	B
06	10	Headache	4	C
07	13	Headache	1	A
08	17	Headache	1	C
09	17	Headache	1	A
10	18	Headache	1	B
11	18	Headache	1	C
12	05	Musculoskeletal Stiffness (Stiff Neck)	1	A
13	10	Nasal Congestion (Stuffy Nose)	4	A
14	02	Nausea	3	A
15	05	Nausea	1	B
16	18	Nausea	1	B
17	18	Nausea	1	C
18	02	Pharyngolaryngeal Pain (Sore Throat)	4	A
19	04	Pharyngolaryngeal Pain (Sore Throat)	3	A
20	10	Pharyngolaryngeal Pain (Sore Throat)	4	A
21	11	Pharyngolaryngeal Pain (Sore Throat)	4	C
22	04	Sinus Pain (Sinus Pressure)	4	A
23	07	Syncope (Fainted)	3	B
24	11	Unintended Pregnancy	4	C
25	13	Upper Respiratory Infection	4	A
26	01	Viral Syndrome	1	C
27	18	Vomiting (Vomited)	2	B
28	18	Vomiting (Vomited)	1	C
29	18	Vomiting (Vomited)	1	C
30	18	Vomiting (Vomited)	1	C
31	18	Vomiting (Vomited)	1	C
32	18	Vomiting (Vomited)	1	C

Legend: Relationship to Study Drug: 1 = Probable; 2 = Possible; 3 = Remote; 4 = Unrelated

Study Drug: A = Quinine Sulfate Capsules [Mutual Pharmaceutical Co., Inc.] - fasting
B = QUININE SULPHATE TABLETS [THE GOVERNMENT PHARMACEUTICAL ORGANIZATION] - fasting
C = Quinine Sulfate Capsules [Mutual Pharmaceutical Co., Inc.] - fed

Clarification: The general description in parenthesis is at the request of the FRACS IRB to avoid the occasional misleading terminology of MedDRA.

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Concomitant Medications:
Ibuprofen (200 mg to 1800mg daily) was the most commonly used OTC medication by 12 subjects in this study for the treatment of pain, as needed. The concurrent use of this medication was not considered to have compromised the outcome of the study.

Conclusions:

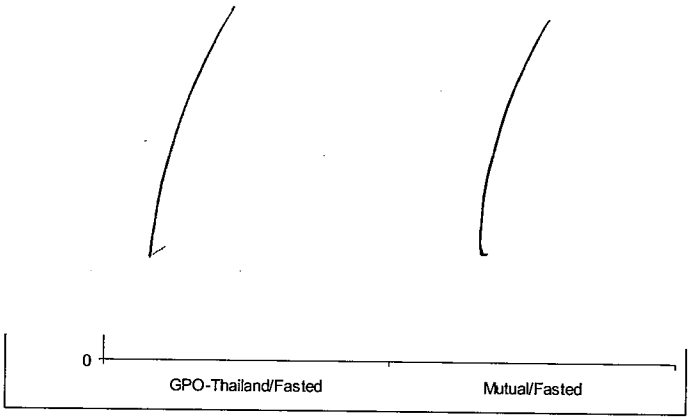
1. The applicant's Quinine sulfate capsule (325 mg) was bioequivalent to the reference Quinine sulfate tablets (300 mg) manufactured by G.P.O., Thailand.

2. Food (standard high-fat breakfast) did not significantly alter the AUC and Cmax of Quinine sulfate from the applicant's capsule.

REVIEWER'S COMMENTS:

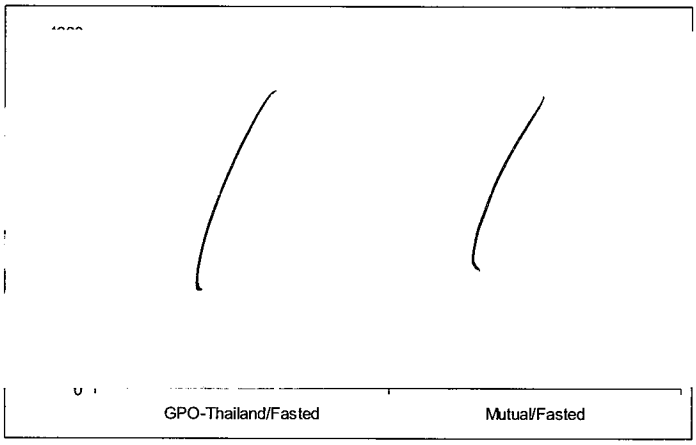
1. The mean values for quinine Cmax and AUC, as well as Tmax and t½ obtained for the various treatments in this single-dose PK study are comparable to that reported for oral quinine in the literature. Figures 17A and 17B compare the individual subject quinine AUC and Cmax values following GPO-Thailand 300mg tablet and Mutual Quinine sulfate 324mg tablet.

FIGURE 17A
Spaghetti Plot of Quinine $AUC_{(0-t)}$ values in Individual Patients:
Reference GPO-Thailand 300mg tablet versus Mutual Quinine sulfate 324mg tablet



***$AUC_{(0-t)}$ values were not dose-normalized.**
*** Both treatments were given under fasted conditions.**
***Red box markers represent the mean AUC values.**

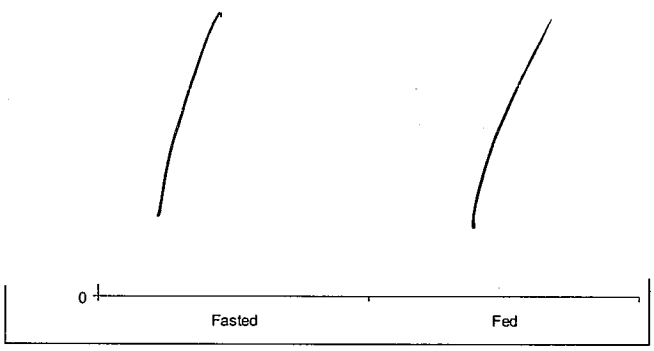
FIGURE 17B
Spaghetti Plot of Quinine Cmax values in Individual Patients:
Reference GPO-Thailand 300mg tablet versus Mutual Quinine sulfate 324mg tablet



***Cmax values were not dose-normalized.**
*** Both treatments were given under fasted conditions.**
***Red box markers represent the mean Cmax values.**

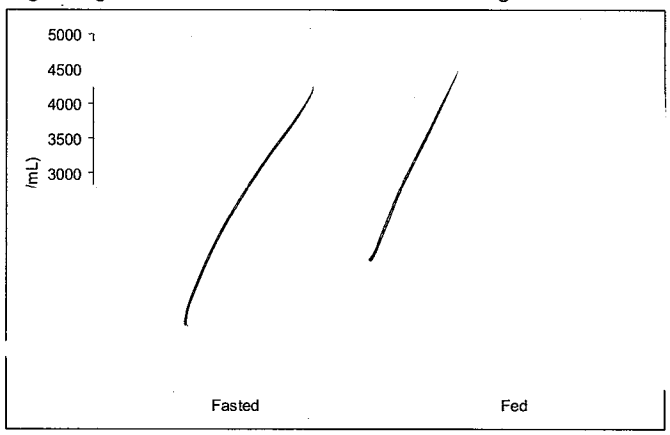
2. Figures 18A and 18B provide the individual subject quinine AUC and Cmax values following a single dose of Mutual Quinine sulfate 324mg tablet given under fasted versus under fed conditions.

FIGURE 18A
Spaghetti Plot of Quinine $AUC_{(0-t)}$ values in Individual Patients
after receiving a single dose of Mutual Quinine sulfate 324mg tablet: Fasted versus Fed



***$AUC_{(0-t)}$ values were not dose-normalized.**
*** Both treatments were given under fasted conditions.**
***Red box markers represent the mean AUC values.**

FIGURE 18B
Spaghetti Plot of Quinine Cmax values in Individual Patients
after receiving a single dose of Mutual Quinine sulfate 324mg tablet: Fasted versus Fed



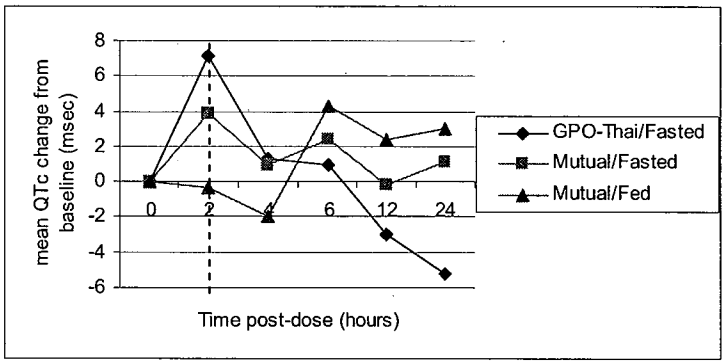
***Cmax values were not dose-normalized.**
*** Both treatments were given under fasted conditions.**
***Red box markers represent the mean Cmax values.**

3. Table 50 provides the mean QT prolongation parameters of the three treatments. Based on a comparison of the mean maximum change from baseline and the area under the QTc change curve (AUQTcC), the QT effects of the three treatments were similar.
4. Figure 19 shows the time course of Mean QTc change from baseline from the three treatments. Food prolonged the time to maximum QTc change from baseline but did not affect the magnitude of the mean max QTc change from baseline. When both Max QTc change and AUQTcC are considered, the three treatments appear to be produce comparable QTc prolongation effect.

TABLE 50
Comparison of the Mean ± SD QT Parameters of the Three Treatments

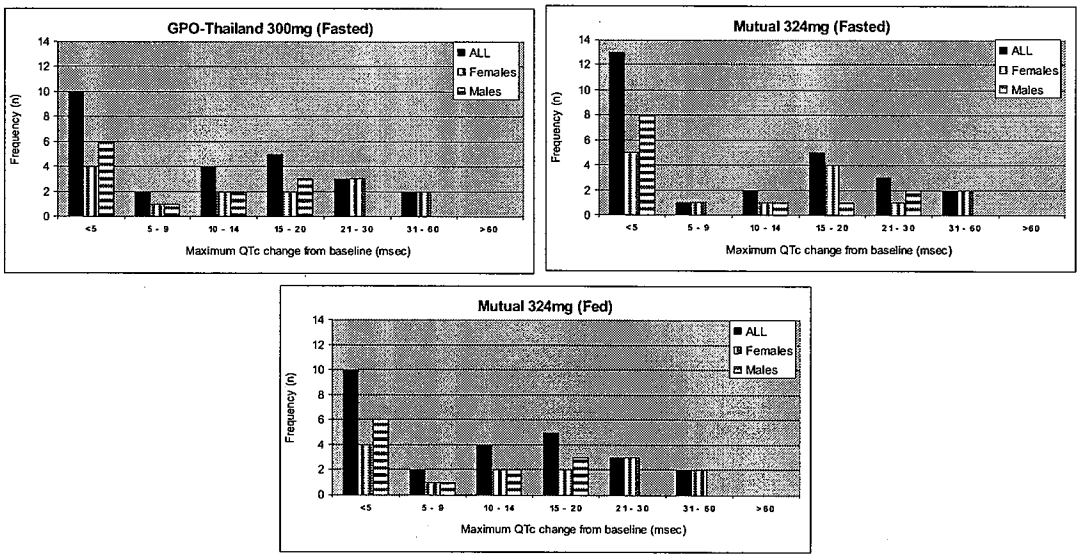
TREATMENT	N	Time to Max QTc change (h)	Maximum QTc change from baseline (msec)	AUQTcC (change from baseline) (msec*h)
GPO-Thai/Fasted	25	2.0	6.9 ± 20.7	-6.8 ± 183
Mutual/Fasted	26	2.0	3.9 ± 17.0	15.4 ± 196
Mutual/Fed	26	6.0	4.3 ± 13.1	30.7 ± 137

FIGURE 19
Time course of Mean QTc Change From Baseline from the Three Treatments



5. Figure 20 below provides the frequency distribution histograms of the maximum QTc change from baseline following the three treatments. Based on a comparison of the frequency distribution curves, the QT prolongation effect of the three quinine sulfate treatments appear to be comparable. All the three treatments had a mode corresponding to maximum QTc change from baseline of <5 msec. Furthermore, regardless of treatment, more females than males experienced a QTc change of >21 msec. However, none of the subjects in this crossover study experienced a maximum QTc change of >60 msec nor a QT interval >450 msec while on any of the three treatments.

FIGURE 20
Frequency Histograms for Maximum QTc Change from the Three Treatments



6. In the relative BA Study, Subject #7 s — experienced syncope in period 3 after treatment with the 300mg GPO reference tablet (fasted). The plasma concentration at the time of syncope (24h) was — ncg/mL which is higher than the mean for the study population at that time (0.435 mcg/mL). The maximum QTc change from baseline values for this subject were 13 msec and 16 msec at 2h and 4h post-dose. The Cmax (2.8 mcg/mL), t1/2 (13.6 h), and the AUCinf (44.3 mcg*h/mL) for this treatment were all higher or longer than the means for the entire study population (2.3 mcg/mL, 12.4h, 34.4 mcg*h/mL, respectively). It appears that the half-life in this patient was shorter in Period 1 (9.2 h) than in the succeeding periods (>13.6 h). The QTc change from baseline around the quinine Tmax (4h) was also smaller in Period 1 (-6 msec) than in Period 2 (14 msec) and Period 3 (16 msec). Figure 21 compares the time course of plasma quinine concentrations from the three treatments in this particular subject. Figures 22 A to C provide an overlay of the time courses of plasma quinine concentrations and the QTc change from baseline for this subject following the three treatments.

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✓ Trade Secret / Confidential

Draft Labeling

Deliberative Process

2. Study R04-0376

Title: A Dose Proportionality Study of Quinine Sulfate Capsules Under Fasting Conditions

Objective:
To compare the dose-proportionality of the applicant's 324 mg Quinine sulfate capsules following a single oral dose of 1 capsule and 2 capsules in healthy adult volunteers when administered under fasting conditions

Study Design:
This was a randomized, single-dose, two-way crossover study, under fasting conditions.

Study Population:
Twenty-four (24) healthy subjects (13 males, 11 females) entered the study. All but 1 (Native American) were Caucasians and were 19 to 61 years old (inclusive; mean = 33 years old). All were evaluable for PK except one subject (male Caucasian) who left for military duty during Period II of the study.

Dosing and Administration:
Following an overnight fast of at least 10 hours, volunteers received a single dose of the following two treatments, separated by at least a 7-day washout period.

Treatment A: 1 x 325 mg Quinine sulfate capsule, Mutual Pharmaceuticals
Treatment B: 2 x 325 mg Quinine sulfate capsule, Mutual Pharmaceuticals

Pharmacokinetic Sampling and Assay:
Blood samples were collected in EDTA vacutainers at -1, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours post-dose. Blood samples were centrifuged and the plasma was stored at -20°C until shipment and subsequent assay by HPLC-MS-MS (LOD=50 ng/mL).

Pharmacokinetic and Statistical Analysis:

Safety Evaluation:
Vital signs (BP, HR) and QT intervals were monitored prior to and at designated times following each dose

RESULTS:

Pharmacokinetics
Figure 23 shows the time course of the mean plasma quinine concentrations following a single dose of 1 capsule and 2 capsules of 324 mg Quinine sulfate.

Table 50 summarizes the results of the statistical analyses performed on the pharmacokinetic parameters comparing dose-adjusted Treatment A and Treatment B.

The 90% confidence intervals about the ratio of the dose-adjusted Treatment A geometric mean to the Treatment B geometric mean are within the 80 – 125% limits for the AUC but not for the Cmax of the ln-transformed data. The results indicate that the doses tested were not dose-proportionate with respect to Cmax.

FIGURE 23

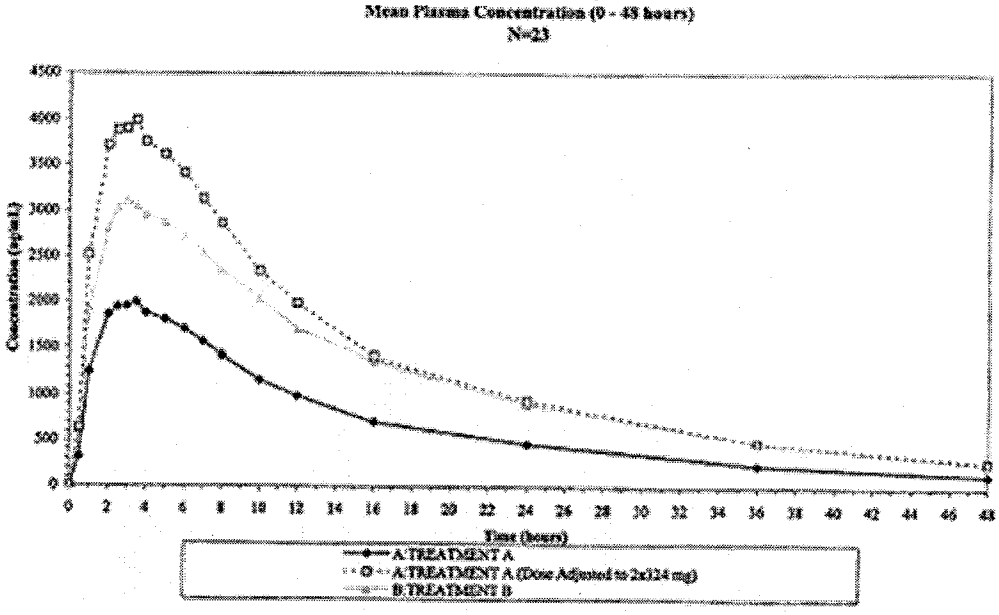


TABLE 50

Quinine	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Dose Adjusted Treatment A Geometric Mean	4126.31	61186.53	66715.41
Treatment B Geometric Mean	3174.89	54440.26	59166.93
% Ratio	129.97	112.39	112.76
90% Confidence Interval	(122.15, 138.29)	(106.56, 118.54)	(105.69, 120.3)

Quinine	C_{max}	AUC_{0-t}	AUC_{inf}
Dose Adjusted Treatment A Least Squares Mean	4247.02	64277.02	70886.14
Treatment B Least Squares Mean	3243.11	56394.65	61817.27
% Ratio	130.96	113.98	114.67
90% Confidence Interval	(123.28, 138.63)	(108.03, 119.93)	(107.37, 121.97)

Quinine	T_{max}	k_{elim}	$t_{1/2}$
Dose Adjusted Treatment A Least Squares Mean	2.78	0.0592	12.76
Treatment B Least Squares Mean	2.80	0.0572	12.80
% Ratio	99.25	103.48	99.67
90% Confidence Interval	(84.8, 113.7)	(94.67, 112.28)	(85.69, 113.66)

Concomitant Medications:
The table below provides the details of medication use over the course of this study. None of these medications were considered to have compromised the outcome or the validity of the study findings.

TABLE 51

Event No.	Subject No.	Subject Init.	Adverse Event	Medication	Average Daily Dose	Study Day(s)
01	10		Menstrual Cramps	Ibuprofen	200 mg	02
02	17		Tonsillitis	Acetaminophen	1300 mg	02
03	17		Tonsillitis	Cephalexin	1000 mg	02 through 08
04	17		Tonsillitis	Halls Mentho-Lyptus Drops	4 Drops	02 through 05

Safety:
Laboratory values
In general, the clinical laboratory values were unremarkable over the course of the study.

Electrocardiogram:
The mean QTc values and change from baseline are shown in Table 2. As shown in the table, an increase in mean QTc value corresponds with the peak quinine plasma concentration, which is reached in an average of 2.4 to 4.4 hours after oral administration. Additionally, increases are higher with a single dose of 648 mg as compared to 324 mg, however, there is substantial overlap. Prolongation of QTc to intervals beyond 450 msec occurred in 7 subjects: 3 subjects following a dose of 648 mg, 1 subject following a dose of 324 mg, and 3 subjects following both doses (Table 52).

TABLE 52

Mean QTc Measurements and Change from Baseline Over 24-hours Following a Single Oral Dose in Patients in Mutual-Sponsored Dose Proportionality Study R04-0376

Statistic	QTc (msec)					
	Baseline	2 hr	4 hr	6 hr	12 hr	24 hr
	Quinine Sulfate Capsules USP, 1 × 324 mg					
Mean ± SD N=23[1]	404 ± 20	415 ± 26	414 ± 26	411 ± 21	411 ± 24	409 ± 24
Change from Baseline[1] ± SD	–	10.4 ± 18.8	9.1 ± 17.4	6.4 ± 13.9	5.2 ± 15.3	4.8 ± 11.9
	Quinine Sulfate Capsules USP, 2 × 324 mg					
Mean ± SD N=24	410 ± 26	422 ± 29	422 ± 30	419 ± 25	417 ± 24	412 ± 23
Change from Baseline ± SD	–	12.3 ± 17.7	12.0 ± 14.8	9.3 ± 14.8	7.5 ± 14.4	2.8 ± 14.4

Source: ECG data for R04-0376
[1] Subject 10 has no baseline value, thus 22 subjects contributed data to the baseline mean and change from baseline

TABLE 53

Patients with QTc > 450 Msec and Baseline and Within 24 hours Following a Single Oral Dose in Patients in Mutual-Sponsored Dose Proportionality Study R04-0376

Subj. No.	Dose (mg)	QTc					
		Baseline	2 Hours	4 Hours	6 Hours	12 Hours	24 Hours
3	648	**454**	449	**453**	442	443	433
7	324	411	448	**454**	422	421	439
11	648	398	**456**	430	439	445	431
15	324	402	**459**	434	443	435	401
	648	431	444	**460**	442	442	437
16	324	437	432	436	441	421	**463**
	648	439	**463**	**461**	**453**	443	435
19	648	405	**463**	405	403	420	416
20	324	439	445	**458**	434	441	432
	648	437	**458**	**470**	**463**	**458**	438

Source: ECG data for R04-0376

Adverse Events:

Thirty (30) adverse events were reported by 13 subjects over the course of the study. None of the AEs were considered serious. The AEs with incidence >2 were: dizziness, headache, nausea, and syncope. These adverse events are summarized in the following table.

TABLE 54

Event No.	Subject No.	Init.	Event	Relationship to Study Drug	Study Drug
01	17		Appetite lost (Loss of appetite)	4	B
02	20		Diarrhoea (Diarrhea)	1	B
03	20		Dizziness (Dizzy spells x 5)	4	B
04	24		Dizziness (Dizzy)	1	B
05	13		Dizziness (Light-headed)	2	B
06	10		Dysmenorrhoea (Menstrual cramps)	4	B
07	17		Generalized pain (Body aches)	4	B
08	2		Headache	4	B
09	11		Headache	3	B
10	15		Headache	2	A
11	19		Headache (Slight headache)	2	A
12	21		Joint injury (Swollen right knee)	4	A
13	20		Myalgia in extremities (right and left leg muscle aches)	1	A
14	7		Nausea	1	B
15	11		Nausea	1	B
16	17		Nausea	4	B
17	15		Night sweats	2	A
18	15		Pain in extremity (Leg pain – right)	3	B
19	20		Pallor	4	B
20	23		Pallor	4	A
21	17		Pharyngolaryngeal (Sore throat)	4	B
22	17		Rigors (Chills)	4	B
23	22		Skin laceration (Right index finger laceration)	4	B
24	24		Stomach discomfort (Upset stomach)	1	B

Event No.	Subject No.	Init.	Event	Relationship to Study Drug	Study Drug
25	20		Sweating increased (sweating)	4	B
26	23		Syncope	4	A
27	23		Syncope	4	A
28	24		Tinnitus (Ringing in ears)	1	B
29	17		Tonsillitis	3	B
30	17		Upper respiratory tract infection	4	A

Legend: Relationship to Study Drug: 1 = Probable; 2 = Possible; 3 = Remote; 4 = Unrelated
Study Drug: Treatment A = 1 x 324 mg Quinine Sulfate Capsules [Mutual Pharmaceutical Co., Inc.]
Treatment B = 2 x 324 mg Quinine Sulfate Capsules [Mutual Pharmaceutical Co., Inc.]
Clarification: The general description in parenthesis is at the request of the PRACS IRB to avoid the occasional misleading terminology of MedDRA.

Of the 30 reported AEs, 11 were either probably or possibly related to study medication. None of these were considered of serious nature.

There were no clinically significant changes in the clinical laboratory parameters over the course of the study which could be reasonably associated with the test formulations.

REVIEWER'S COMMENTS:

1. The literature reports that the Tmax and the half-life of quinine sulfate do not change with increasing doses of quinine sulfate and that the Cmax and AUC increase with the dose. From 250 mg to 1000 mg quinine (as free base), the Cmax ranges from 1.73 to 6.09 mcg/mL and the AUC ranges from 28.05 to 110.79 mcg*h/mL.(Babalola et al, 1997). Between the 250mg dose and the 500mg dose, the increase in mean Cmax was about 30% lower than expected as compared to the Cmax at the lower dose; the increase in the AUC at the 500mg dose was about 9% lower than expected from that from 250mg.

2. From the findings of the dose-proportionality study conducted for the sponsor, it appears that Treatment B (2 x 324 mg of quinine sulfate capsules) produced a quinine Cmax that was 24% lower than expected as compared to that produced from the 324mg capsule. However, the quinine $AUC_{(0-t)}$ following the administration of the higher test dose was only 12.5% lower than expected. Since the Tmax values and the half-lives of elimination were similar for the two test doses, the lower than expected systemic exposure at the 648 mg quinine dose could likely be due to decreased absorption. This decrease in absorption could be related to limited solubility and/or decreased quinine transport by absorptive organic cation transporters (OCTs) at the higher dose. Given the aqueous solubility of quinine sulfate, [redacted] is expected to dissolve in 250 mL water with a concentration of about [redacted] (as free quinine); even lower amounts of about [redacted] quinine sulfate dissolves in a phosphate buffer of the same pH as intestinal fluid (pH 6.8; see Figure 15, General Biopharmaceutics Section). According to the literature, quinine is an inhibitor of the organic cation transporter (OCT) that is expressed in the intestines and other tissues; the IC_{50} is 5.0 μM as free quinine.

3. Regardless of relationship to study treatment, the number of reported adverse events were more than 2-fold greater for 2 capsules of 325 mg quinine sulfate compared to 1 capsule only (n = 21 versus n = 9). For only those AEs which were judged by the investigators to be probably/possibly related to study treatment, 2 capsules of quinine sulfate produced a 50% greater AE rate than 1 capsule (n = 7 versus n = 4). A similar trend was observed in regard to the number of patients complaining of adverse events. These observations are consistent with the statement in the package insert: *"Most toxic reactions [of quinine sulfate] are dose-related."* The fact that the Cmax increased in a less-than-dose proportional manner at the higher dose can probably explain why the adverse events were numerically less than 2-fold compared to that after the lower dose. Table 55 below provides a comparison of the incidence rates of AEs for the two doses of quinine sulfate investigated.
It was interesting to note that only 7 of the 23 PK-evaluable subjects this study demonstrated a dose-proportional increase in quinine sulfate Cmax and AUC, namely Subject nos. 7, 13, 15, 19, 20, 21, 22 & 24. Some (5 of 8) of these patients were reported to have experienced AEs during treatment with the higher test dose.

TABLE 55

Number of Adverse Events	Treatment **A** (**1** x 325 mg Quinine sulfate capsule)	Treatment **B** (**2** x 325 mg Quinine sulfate capsule)
Regardless of relationship to study treatment	9	21
Only those judged to be possibly/probably related to study treatment	4	7
Number of Subjects with Adverse Events		
Regardless of relationship to study treatment	6	11
Only those judged to have experienced AEs possibly/probably related to study treatment	3	5

4. **Relationship between QT prolongation effect and quinine concentration/dose.** As shown in Table 52 above and Figure 24 below, there appears to be a direct (temporal) relationship between QT prolongation effect and quinine concentration. The mean values for QTc change from baseline appear to be highest at 2 to 4 hours post-dose around the Tmax of quinine. In the sponsor's analysis, the maximum QTc change from baseline was 10.4 ± 18.8 msec for the 324 mg dose and 12.3 ± 14.8 msec for the 648 mg dose. These average maximum QTc change from baseline values were similar to those calculated by the reviewer as shown in Table 56 below and represent not more than 3% increase from baseline. The magnitude of the QT-effect (as mean maximum QTc change from baseline or mean area under the QTc change curve (AUQTcC) was also consistently greater with the 648 mg dose than the 324 mg dose, but the overlap between the two doses was substantial.

FIGURE 24
Time Course of Mean Plasma Quinine Concentration and Mean QTc Change From Baseline

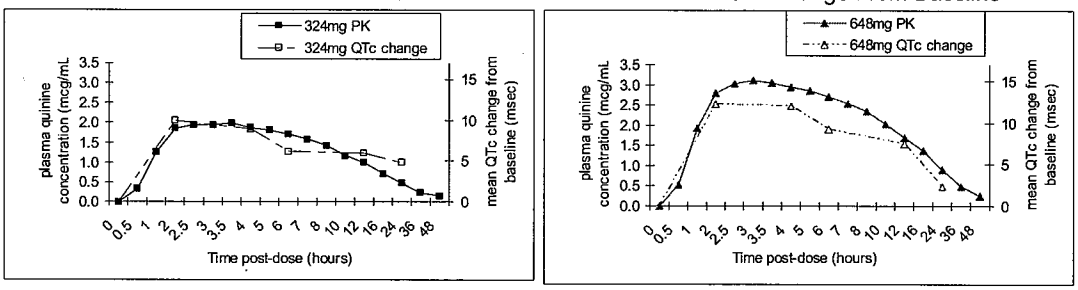


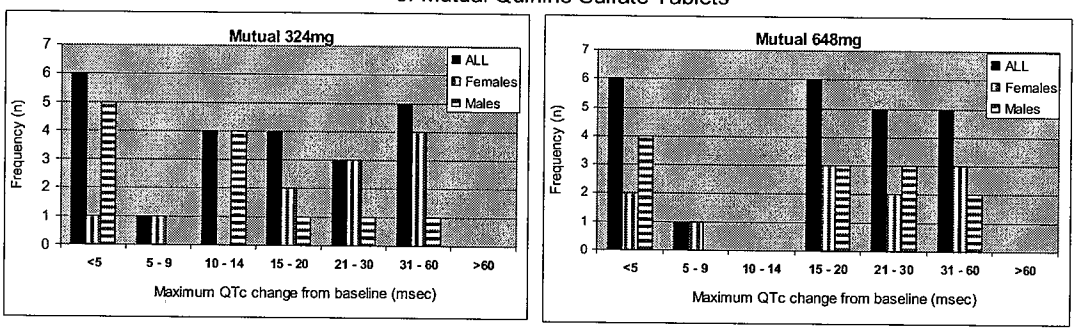
TABLE 56
Mean ± SD QTc Parameters Following a Single Dose of
324 mg and 648 mg Quinine Sulfate Tablets in Healthy Volunteers

QT PROLONGATION PARAMETER	QUININE SULFATE DOSE	
	324 mg (N=23)	**648 mg** (N=24)
Maximum QTc change from baseline (msec)	10.0 ± 18.5	12.3 ± 17.7
Area under the QTc change Curve (msec*h)	146 ± 266	167 ± 292

5. **Maximum QTc change from baseline and Quinine Sulfate Dose.** Figure 25 provides the maximum QTc change frequency histograms for the Mutual Quinine Sulfate capsule at the 324mg and 648mg doses. A comparison of the frequency distribution curves suggest that in the 324mg dose, there was an equal proportion of subjects with QTc change of < 15msec and QTc change of ≥15 msec; more of the subjects with max QTc >15 msec were females.

At the 648mg dose, there was a 2-fold greater number of subjects with QTc change of ≥15msec and QTc change of <15 msec. Between the two test doses, there was an equal proportion of subjects with a maximum QTc change of >20 msec and >30 msec. None of the subjects in this crossover study showed a QTc change of >60 msec nor a QT interval of >500 msec.

FIGURE 25
Frequency Histograms for Maximum QTc Change from the 324mg and 648mg doses of Mutual Quinine Sulfate Tablets



6. The QT prolongation effect of quinine sulfate in malaria patients may be of equal or lesser magnitude than that observed in these healthy subjects because the fraction of unbound or free quinine in the plasma of healthy subjects is about 2x to 3x higher compared to that in malaria patients.

7. **Relationship between QT effect and quinine Cmax, AUC and half-life.** Figures 26A and 26B are plots of quinine Cmax versus the maximum QTc change from baseline following a 324mg and a 648 mg dose of quinine sulfate in healthy volunteers. Figure 27A and 27B are plots of quinine AUC_{inf} versus the maximum QTc change following single doses of 324mg and 648mg tablets, respectively. Figure 28A and 28B are plots of quinine elimination half-life versus the maximum QTc change from baseline following a 324mg and a 648 mg dose. Based on these figures, there appears to be a trend of increasing QT prolongation effect as the quinine exposure (Cmax, AUC) increases, as well as when the elimination half-life of quinine is prolonged, following single dose administration of a 324mg quinine sulfate tablet. The strongest PK-PD correlation was between maximum QTc change from baseline and AUC_{inf} (r^2 = 0.2646) and between maximum QTc change and half-life (r^2 = 0.339) at the 324mg dose. These trends were not observed with the higher dose (648mg); it is not known whether erratic absorption and limited solubility at higher quinine doses play a role in this anomaly.

FIGURE 26 A and B

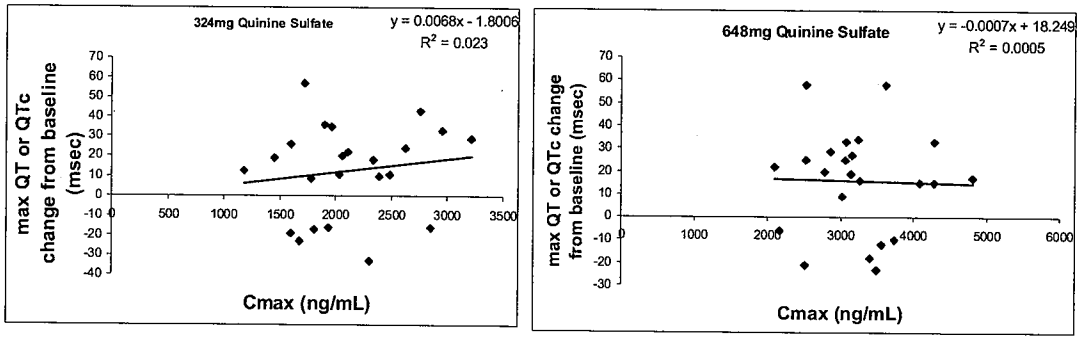


FIGURE 27 A and B

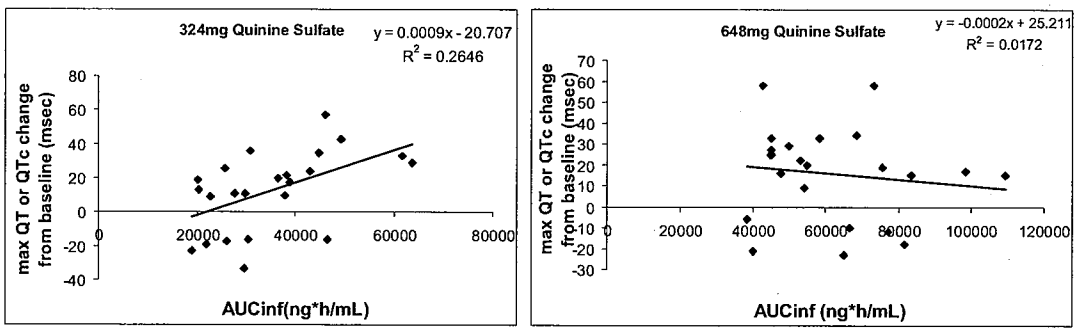
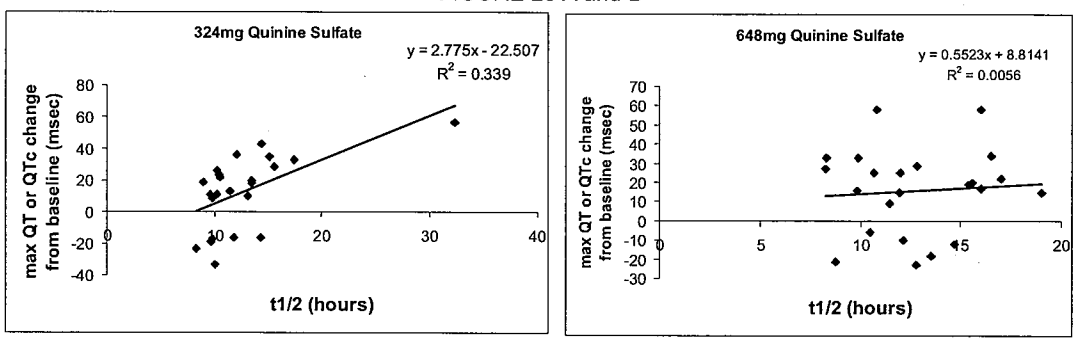


FIGURE 28 A and B



8. Table 57 below compares the mean QTc change from baseline data on subjects with QTc >450 msec at 324 mg versus 648 mg quinine doses as reported by the sponsor; Table 58 compares the average quinine Cmax, Tmax, and $AUC_{0\text{-}24h}$ and elimination half-life values for this same subset of subjects at the two test doses. The weak correlation between quinine PK parameters and maximum QTc change from baseline following 324 mg and 648 mg quinine in this subpopulation are illustrated in Figure 29 below; the correlation coefficients with QT effect were 0.1012, 0.2602, and 0.2153 for Cmax, AUC_{inf}, and $t_{1/2}$ respectively.

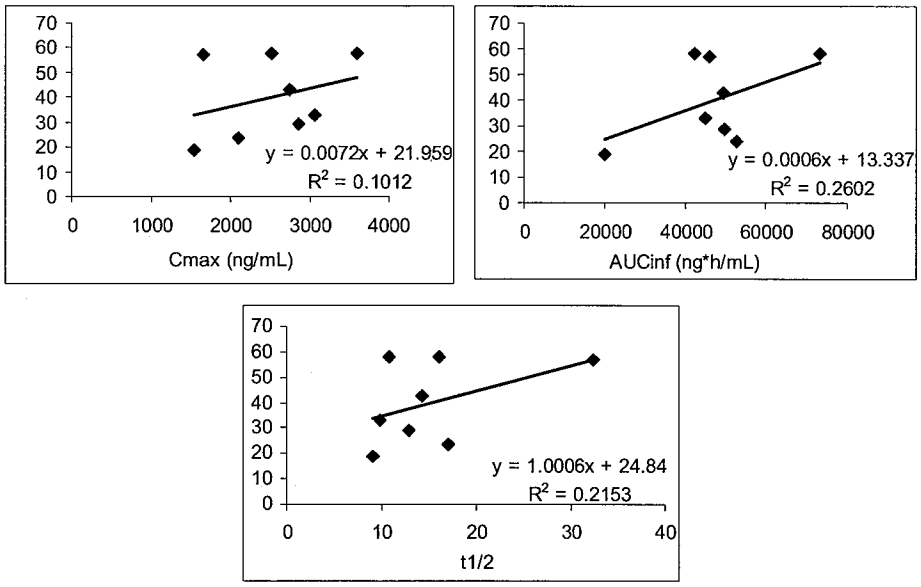
TABLE 57
Mean QTc Change from Baseline Over 24 hours Following a Single Oral Quinine Dose in Dose-Proportionality Study R04-0376: Subjects with QTc >450 msec

Dose (mg)	Quinine Sulfate Capsules (324 mg) n = 4	Quinine Sulfate Capsules (2 x 324 mg) n = 6
Time post-dose (hours)		
2.0	23.8 ± 28.4	28.2 ± 25.2
4.0	23.3 ± 18.9	28.5 ± 18.5
6.0	12.8 ± 19.9	21.3 ± 21.9
12.0	7.3 ± 20.3	18.3 ± 21.6
24.0	11.5 ± 18.1	7.5 ± 20.7

TABLE 58
Mean Quinine Pharmacokinetic Parameters Following a Single Oral Quinine Dose in Dose-Proportionality Study R04-0376: Subjects with QTc >450 msec

Dose (mg)	Quinine Sulfate Capsules (324 mg) n = 4	Quinine Sulfate Capsules (2 x 324 mg) n = 6
Tmax (h)	2.63 ± 0.76	2.83 ± 0.52
Cmax (ng/mL)	1880.7 ± 590	2953.1 ± 586.7
$AUC_{0\text{-}t}$ (ng*h/mL)	29787.3 ± 10528.5	51469.6 ± 12251.3
t½ (h)	16.5 ± 10.8	13.5 ± 2.9

FIGURE 29
Maximum Mean QTc Change from Baseline (msec)
as a Function of Quinine Cmax, $AUC_{0\text{-}inf}$ and half-life



9. At the 324 mg dose, the maximum mean QTc change from baseline was statistically significantly different between subjects who experienced a QTc>450 msec and those who did not (p=0.0405). The mean quinine PK values for this subset were not statistically significantly different from the mean values for the rest of the population. A scrutiny of the demographic characteristics of the QTc>450 msec subpopulation indicates that compared to the rest of the study population, these subjects were of comparable body weight, body surface area, but were older (mean age: 42 versus 29 years), and were mostly females (proportion 71% versus 38%). Table 59 provides a statistical comparison of the demographics, mean quinine QTc increase from baseline and mean PK parameters of the QTc>450 msec subpopulation versus the rest of the study population.

TABLE 59
Mean ± SD Demographic Characteristics, Maximum QTc Change from Baseline, and Pharmacokinetic Parameters: Subjects with QTc >450 msec versus the subjects with normal QTc interval

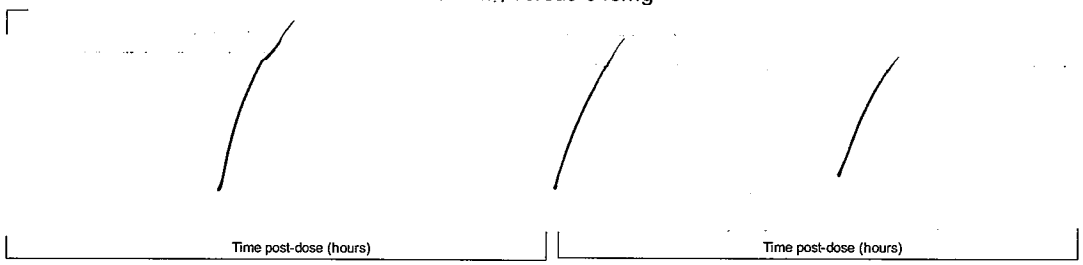
PARAMETER	Subjects with QTc>450 msec	Subjects with QTc <450 msec	P value[a]
N	7	16	
Age (years)	41.6 ± 13.5	29.3 ± 13.3	0.0541
Weight (lbs)	158.3 ± 14.5	165.3 ± 26.7	0.5234
BSA (m^2)	1.8 ± 0.1	1.9 ± 0.2	0.2769
Gender (% females)	71%	38%	
324 mg			
Cmax (ng/mL)	1957.87 ± 613.0	2190.8 ± 473.9	0.3219
$AUC_{0\text{-}24}$ (ng*h/mL)	30703.8 ± 10004.3	32496.7 ± 10882.6	0.7137
AUC_{inf} (ng*h/mL)	34739.8 ± 12439.2	35400.3 ± 13180.6	0.9116
t½	14.5 ± 8.1	11.9 ± 2.6	0.2632
Maximum QTc change from baseline (msec)	28.6 ± 15.8	5.8 ± 23.1	0.0276
Area under the QTc (change) Curve (msec*h)	254.7 ± 227.4	92.3 ± 274	0.2016
648 mg			
Cmax (ng/mL)	3217 ± 880.3	3254.2 ± 616.0	0.9081

AUC_{0-24} (ng*h/mL)	56428.1 ± 17239.2	56097.6 ± 15551.1	0.9642
AUC_{inf} (ng*h/mL)	62712.3 ± 20715.1	61070.4 ± 19327.0	0.8561
t½	13.9 ± 2.8	12.3 ± 3.1	0.2495
Maximum QTc change from baseline (msec)	29.6± 24.3	10.7 ± 19.0	0.0540
Area under the QTc (change) Curve (msec*h)	286 ± 372	118 ± 249	0.2056

[a] ANOVA, single-factor, assuming equal variance

10. **Clinical adverse events that signal proarrhythmic risk.** Two syncope episodes were reported in Subject #23 — which occurred at 3 and 4 hours after a 324mg dose of quinine sulfate in Period 1. At 2 and 4 hours post-dose, the QTc interval increased to 11 and 9 msec, from 385 msec to 396 and 394 msec, respectively. Quinine plasma concentration at 2 and 4 hours post-dose was slightly higher in this subject than the mean values for the study population. Figures 30A and B provide an overlay of the time courses of the quinine concentrations and the QT change from baseline at the 324mg and the 648mg doses. A remarkable observation for this subject is that the increase in QT parameters (maximum QTc change and AUQTcCC) at 648mg was dose proportional.

FIGURE 30A and B
Time courses of Plasma Quinine Concentration and QTc Change from Baseline in Subject #23 —
324mg versus 648mg

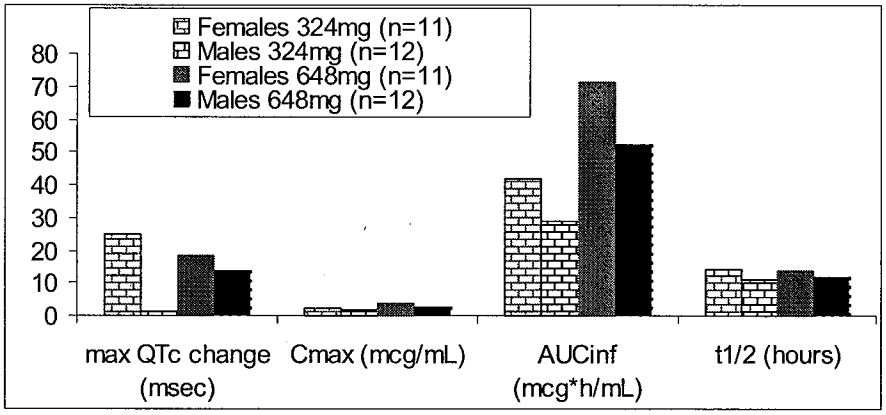


11. **Effect of covariates on PK and QT prolongation parameters of quinine.** Exploratory analyses were conducted to evaluate the influence of age, gender, body weight, and body surface area on quinine exposure (Cmax, AUC), elimination half-life, and maximum QTc change from baseline in healthy subjects who received 324 mg and 648 mg quinine sulfate.

Gender

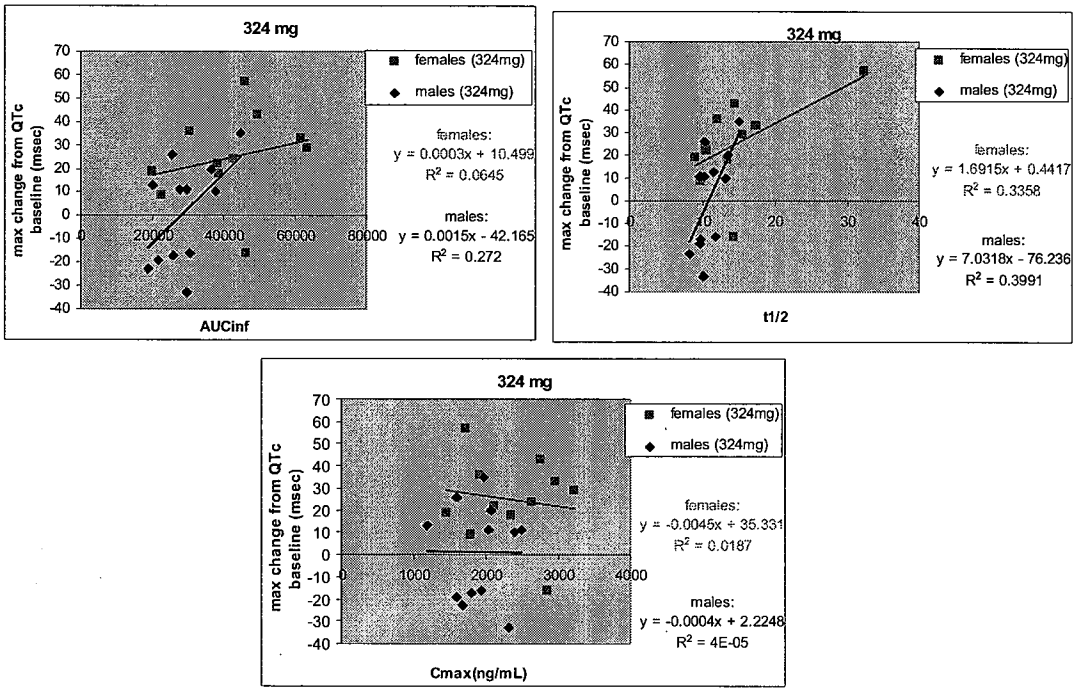
Figure 31 compares the PK and QT prolongation parameters of quinine in males and females who received the two test doses. Compared to males, in females there was a trend of a higher mean quinine Cmax and AUC_{0-inf}, a slightly longer mean elimination half-life and consequently, a higher maximum QTc change from baseline, regardless of the quinine dose. A scrutiny of the demographics of these gender groups indicated that compared to the male subjects, female subjects in the study were generally older (mean age: 39 versus 28 years old), of lower bodyweight (152 versus 174 lbs) and lower body surface area (1.75 versus 1.97 m^2). It is possible that any of these demographic factors could have confounded the findings in relation to gender influence on quinine PK and QT effect.

FIGURE 31
Influence of Gender on Quinine PK and QT effect



The following figures plot maximum QTc change as a function of quinine PK parameters measured in patients following the 324 mg dose. At the 324 mg dose, a trend of increased maximum QTc change from baseline was observed with increasing AUC_{inf} (moreso with males than females) and increasing half-life but not with increasing Cmax; these same trends were not observed following the 648 mg dose.

Figure 32A to C
Maximum QTc change from baseline as a function of Quinine AUCinf, $t_{1/2}$, and Cmax following 324 mg quinine sulfate dose in female and male subjects



<u>Age</u>
Figure 33A compares the PK and QTc effect of quinine in <50 year-old patients and 50 to 61 year-old patients. There was a trend of slightly higher quinine mean Cmax and $AUC_{0\text{-}inf}$, as well as a higher average maximum QTc increase from baseline in older patients than in younger patients at 324mg and 648mg. In addition, a slight prolongation in mean elimination half-life was

evident in older patients who received the higher dose (648 mg). A comparison of the two age groups indicate that the gender distributions were not similar;100% of the ≥50 year-old patients were females versus only 33% in the <50 year old group.

As shown in Figure 33B, with increasing age, there was a trend of increasing QTc effect of quinine although the correlation with age was not strong ($r^2 \leq 0.1805$).

FIGURE 33A
Influence of Age on Quinine PK and QT effect

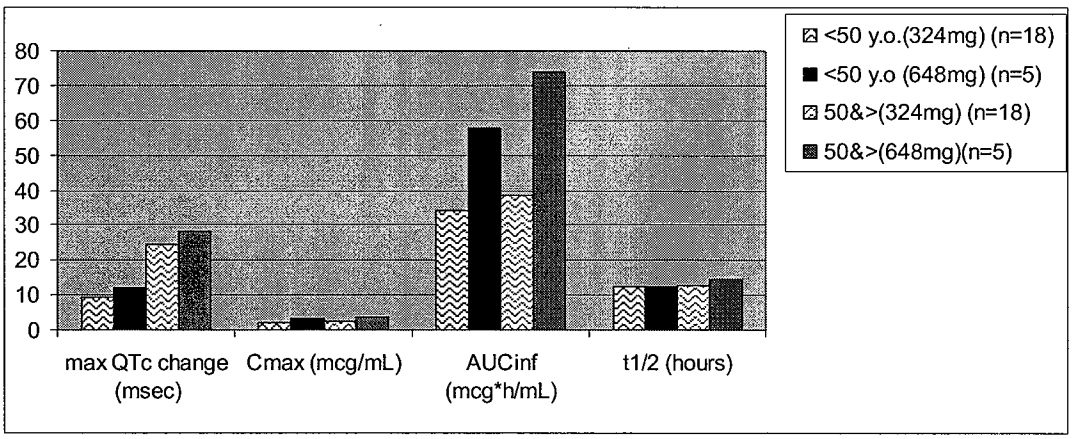
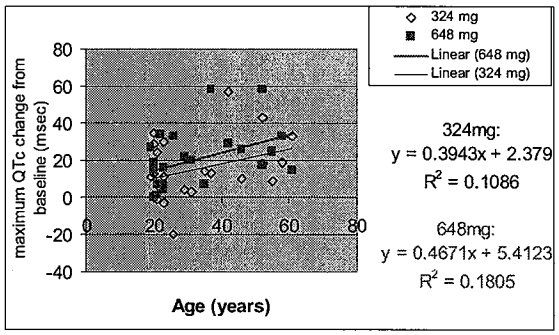


FIGURE 33B
Maximum QTc Change From Baseline As A Function Of Age:
324 mg Versus 648mg Quinine Sulfate



Body Weight

Figure 34 plots maximum QTc change from baseline as a function of body weight following single doses of 324 mg and 648 mg quinine sulfate. It appears that only at the higher dose (648 mg) was there somewhat a trend of decreasing QT prolongation effect of quinine with increasing body weight. This observation may be, at least in part, attributed to a higher mg/kg quinine dose received by lower body weight subjects, which results in a numerically lower Cmax, AUCinf, without affecting the elimination half-life of quinine following a single dose (Figures 35A to C). At the lower dose, neither the QT effect nor the PK parameters (Cmax, AUCinf, t½) of quinine appears to have been influenced by body weight.

FIGURE 35
Mean QTc Change from Baseline as a Function of Body Weight and Quinine Sulfate Dose

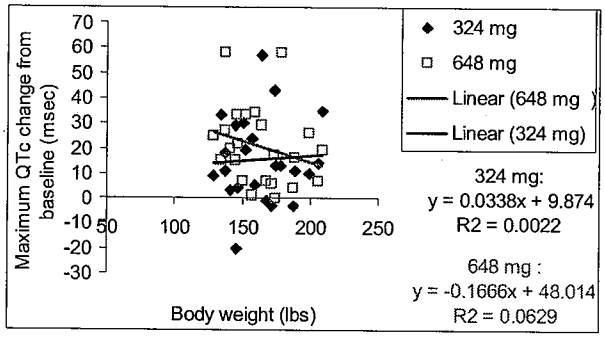
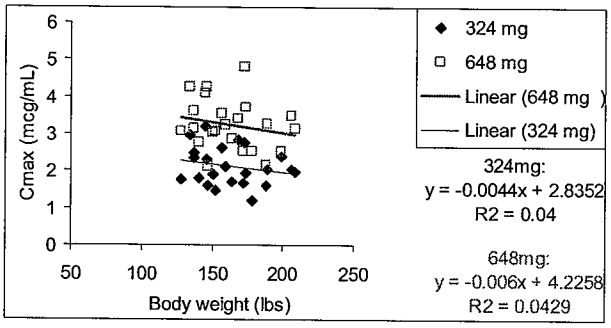


FIGURE 35A to C
Quinine Cmax As a Function of Body Weight and Quinine Sulfate Dose



Quinine AUCinf As a Function of Body Weight and Quinine Sulfate Dose

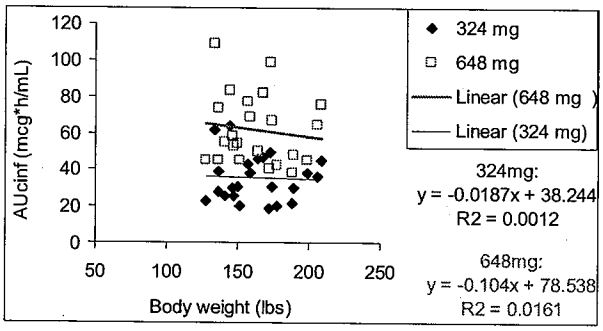
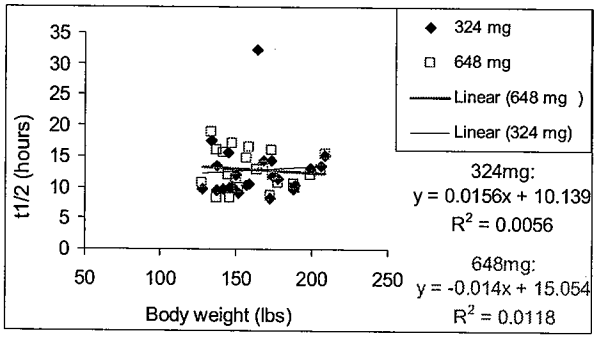
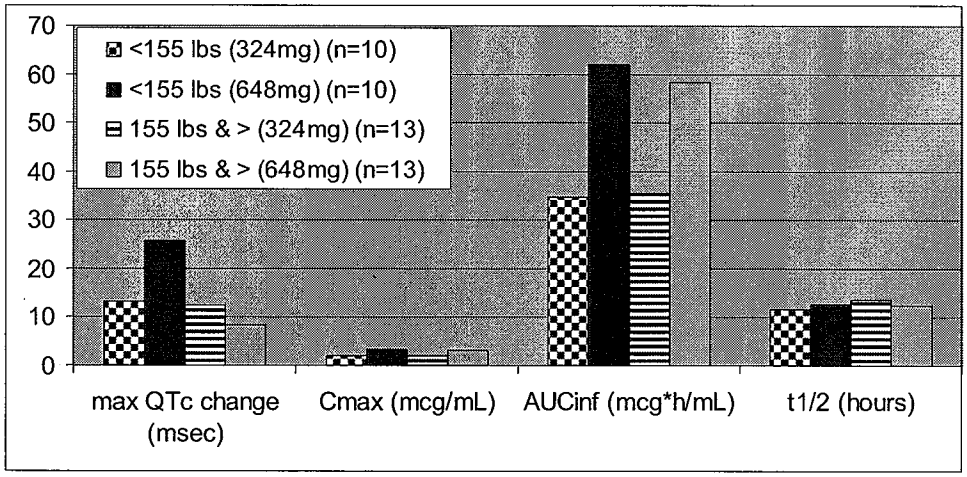


FIGURE 35C
Quinine Elimination Half-life As a Function of Body Weight and Quinine Sulfate Dose



The influence of body weight (as a categorical variable) on quinine PK and QT effect was also explored. Figure 36 provides a comparison of quinine PK and QTc parameters in subjects weighing <155 lbs and in subjects with BW from155 to 209 lbs. At the higher (648mg) quinine dose, higher BW subjects experienced a lower mean QTc change from baseline as compared to the lower BW group, consistent with the slight decreases in mean quinine AUCinf and Cmax in higher BW subjects as compared to lower BW subjects. At the 324mg dose, there were no BW-category related differences in mean PK and QT prolongation parameters.

FIGURE 36
Influence of Body Weight (as a categorical variable) on the QT effect and PK of Quinine



Body Surface Area

The following figures compare the 324mg and 648mg doses in terms of the QT effect of quinine and the resulting quinine exposure, as a function of body surface area. Following single doses of 324mg and 658mg quinine sulfate tablets, with increasing body surface area (BSA), a trend of decreasing maximum QTc increase from baseline, as well as a decrease in quinine exposure (Cmax, AUC_{inf}) was observed although these correlations were not robust (Figures 37 and 38A through C). These observations could be attributed to at least in part, the lower mg/m^2 quinine doses received by the higher BSA subjects. Following single doses of 324mg and 658mg quinine sulfate, the elimination half-life of quinine did not change as a function of dose and body surface area.

FIGURE 37
Mean QTc Change from Baseline as a Function of Body Surface Area and Quinine Sulfate Dose

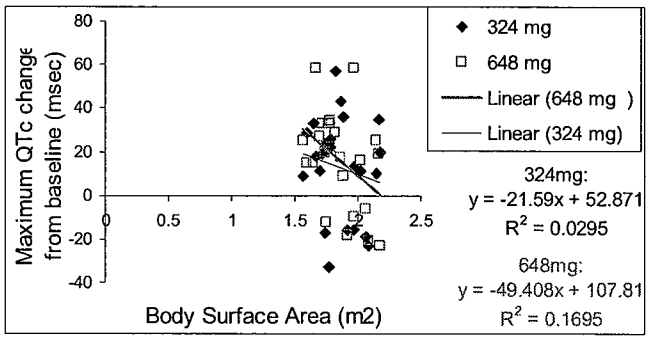
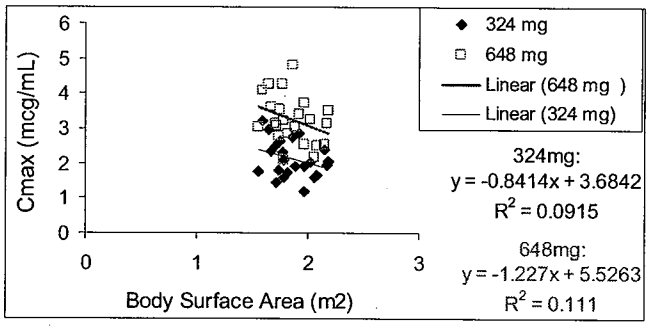
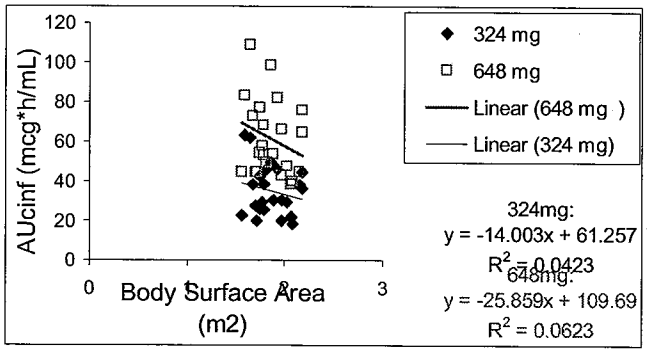


FIGURE 38A to C

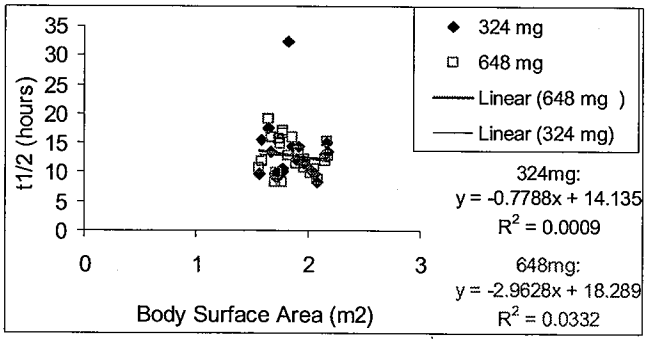
Quinine Cmax As a Function of Body Surface Area and Quinine Sulfate Dose



Quinine AUC_{inf} As a Function of Body Surface Area and Quinine Sulfate Dose



Quinine Elimination Half-life As a Function of Body Surface Area and Quinine Sulfate Dose



C. Consult Review (including Pharmacometric Reviews)

None.

D. Cover Sheet and OCPB Filing/Review Form

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

13 October 2004

Renata Albrecht, M.D., Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research/ HFD-590
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Confidential, Commercial Trade Secret Information Exempt from Disclosure Under FOI Act

Re: New Drug Application 21-799
Quinine Sulfate Capsules 324 mg

Dear Dr. Albrecht:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and in accordance with provisions of 21CFR 312, Mutual Pharmaceutical Company, Inc. of Philadelphia, Pennsylvania is submitting this New Drug Application (NDA 21-799) for its product, Quinine Sulfate Capsules. The product is available as immediate release capsules for oral administration in a 324-mg dosage strength. The proposed indication is the treatment of uncomplicated *Plasmodium falciparum* malaria. Mutual Pharma's quinine product has been granted Orphan Designation for this proposed use.

The safe and effective use of quinine as a treatment for malaria is well established in the published literature, reviewed extensively herein. Included with this review is a comprehensive SAS dataset of efficacy results in the format requested by the FDA statistical reviewer. These studies, together with the long history of clinical use, have resulted in the inclusion of quinine in treatment guidelines published by both the Centers for Disease Control and Prevention and the World Health Organization. The indication and dosing recommendations, two capsules three times daily for — 7 days, are consistent with these guidelines.

As discussed in Pre-IND and Pre-NDA meetings, bioequivalence of the Mutual Pharma product and a representative product in clinical use, including in published clinical trials, has been documented. Dose proportionality and the effect of food have also been studied. These studies are supported by an extensive literature on the pharmacokinetics of quinine in healthy subjects as well as the target patient population.

As was requested at the Pre-NDA meeting, this NDA is being submitted primarily in an electronic format, in compliance with the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations (October 2003)." An overview of the sections that are electronic (and their contents) and the sections that are paper is given below. For further details, please see the NDA Table of Contents.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-799 (N-000)**	**Brand Name**	
OCPB Division (I, II, III)	**DPEIII**	**Generic Name**	**Quinine sulfate capsules**
Medical Division	**HFD-590 (DSPIDP)**	**Drug Class**	
OCPB Reviewer	**Gerlie C. De Los Reyes**	**Indication(s)**	**Treatment of uncomplicated *Plasmodium falciparum* malaria**
OCPB Team Leader	**Philip M. Colangelo**	**Dosage Form**	
		Dosing Regimen	**2 capsules three times daily for 7 days**
Date of Submission	**13 October 2004**	**Route of Administration**	
Estimated Due Date of OCPB Review		**Sponsor**	
PDUFA Due Date		**Priority Classification**	**Standard (10 months)**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**	**2**	**2**	
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	Fasting (1)		**1 capsule versus 2 capsules**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		**Reference tablet (GPO, Thailand)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	58		
Total Number of Studies		2+1	2+1	

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gerlie Gieser
8/12/05 11:50:10 AM
BIOPHARMACEUTICS

Phil Colangelo
8/12/05 11:56:46 AM
BIOPHARMACEUTICS