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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Zithromax[®]/Azithromycin hydrate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NCT NO: 00082576

PROTOCOL NO.: A0661134

PROTOCOL TITLE: A Phase 2/3, Randomized, Double-Blind, Comparative Trial of Azithromycin Plus Chloroquine Versus Mefloquine for the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Africa

Study Centers: Five centers in Africa

Study Initiation and Completion Dates: 28 June 2004 to 01 May 2006

Phase of Development: Phase 3

Study Objectives: The primary objective was to confirm the hypothesis that azithromycin plus chloroquine (AZCQ) is non-inferior to mefloquine for the treatment of symptomatic, uncomplicated malaria due to *P. falciparum*.

Secondary objectives included the following:

- Efficacy (asexual *P. falciparum* parasite clearance rate) of AZCQ at Day 28
- Safety and tolerability for all treatment regimens
- Resistance as measured by RI, RII, RIII
- Percent (%) early treatment failures (ETFs)
- Percent (%) late treatment failures (LTFs)
- Clinical cure rates at 3, 7, 28 and 42 days
- Asexual *P. falciparum* parasite clearance rate at 7, 14, 21, 35 and 42 days
- *P. falciparum* gametocyte clearance rate at 7, 14, 21, 28, 35 and 42 days
- Fever clearance time
- Asexual *P. falciparum* parasite clearance time

METHODS

Study Design: This was a multi-center, randomized, double-blind study comparing the efficacy and safety of AZCQ to that of mefloquine when used for the treatment of adults with uncomplicated, symptomatic *P. falciparum* malaria in Africa. The duration of study treatment was 3 days and each subject was asked to participate in the study for 42 days. All subjects were hospitalized and monitored closely for a minimum of 3 days until 3 consecutive blood smears were negative for asexual parasitemia and the investigator deemed discharge from the hospital appropriate. Post-therapy outpatient visits were conducted on Days 3, 7, 14, 21, 28, 35, and 42. Test of Cure was Day 28.

Number of Subjects (planned and analyzed): Of the 333 subjects planned 238 subjects (114 subjects in the 1000 mg AZCQ arm, 9 subjects in 500 mg AZCQ arm and 115 subjects in the 1250 mg mefloquine arm) were assigned to treatment. Subject disposition is given in Table S1.

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥ 18 years with symptomatic, uncomplicated, monoinfection with *P. falciparum* malaria indicated by the presence of blood smears positive for *P. falciparum* asexual parasitemia between 1000-100,000 parasites/ μ L and fever or history of fever ($\geq 38.5^{\circ}\text{C}/101.2^{\circ}\text{F}$ rectal or tympanic; $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ axillary or $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$ oral) within the prior 24 hours were included in the study. Subjects also had serum glucose ≥ 60 mg/dL or 3.3 mmol/L and rapid diagnostic test (Binax NOW™ ICT) positive for *P. falciparum*.

Study Treatment: All study drugs were administered orally as blinded therapy. Initially, subjects were randomized to 1 of the 3 active arms and received 1 of the following treatment regimens:

1000 mg AZCQ: Azithromycin 1000 mg (two 500 mg tablets) plus chloroquine 600 mg base, once daily for 3 days (Days 0, 1, 2) and matching placebo for mefloquine (3 placebo capsules initial dose followed by 2 placebo capsules 6 hours later) on Day 0; or

500 mg AZCQ: Azithromycin 500 mg (one 500 mg tablet and 1 matching placebo tablet) plus chloroquine 600 mg base, once daily for 3 days (Days 0, 1, 2) plus matching placebo for mefloquine (3 placebo capsules initial dose followed by 2 placebo capsules 6 hours later) on Day 0; or

1250 mg Mefloquine: Mefloquine 750 mg (three 250 mg capsules) initial dose followed by 500 mg (two 250 mg capsules) on Day 0 and matching placebo for azithromycin and chloroquine (2 azithromycin placebo tablets plus chloroquine placebo matching 600 mg base, once daily for 3 days [Days 0, 1, 2]).

After the 30 November 2004 decision to eliminate the 500 mg azithromycin-containing treatment arm, subjects were randomized to either the 1000 mg AZCQ arm or the 1250 mg mefloquine arm.

Study drug was not to be taken on an empty stomach and was administered with at least 8 oz (240 ml) of water. Any dose that was vomited within 30 minutes of administration was repeated once. If vomiting recurred, the subject was to be discontinued from therapy.

Efficacy Evaluations: The primary endpoint of the study was the asexual *P. falciparum* parasite clearance rate (adjusted for molecular testing determining recrudescence [true failures] from re-infection [true cures]) at Day 28 in the Parasitologic Per Protocol population (Evaluable at Day 28). Secondary endpoints included: asexual *P. falciparum* parasite clearance rate at Days 7, 14, 21, 28, 35 and 42; resistance as measured by RI, RII and RIII, asexual parasite clearance time, gametocyte clearance rate at Days 7, 14, 21, 28, 35 and 42, clinical response at Days 3, 7, 28 and 42, percent ETFs and LTFs, fever clearance time and chloroquine resistance testing.

Safety Evaluations: Subjects were monitored closely for clinical evidence of illness progression. Safety evaluations included adverse event (AE) and vital sign monitoring throughout the study, hematology and serum chemistry laboratory evaluations (Baseline and Day 3), and a complete (Day 0) and focused (Days 1, 2, 3, 7, 28) physical examination.

Statistical Methods:

Efficacy: The primary population of interest for efficacy analysis was the Parasitologic Per Protocol population (Evaluable at Day 28). The primary efficacy analysis of this study compared the rates of asexual parasite clearance in the 1000 mg AZCQ and mefloquine treatment arms at the Test of Cure Day 28 evaluation in the Parasitologic Per Protocol population. A 2-sided confidence interval (CI), using the appropriate confidence level, for the difference in asexual parasite clearance rates using normal approximation to the binomial was constructed. Non-inferiority was concluded if the lower boundary of the CI for the difference in cure rates (1000 mg AZCQ - mefloquine) was $\geq -10\%$. For the secondary objective of assessing the efficacy of the azithromycin combination arm, the asexual parasite clearance rates of this treatment regimen were estimated at the Test of Cure Day 28 evaluation in the Parasitologic Per Protocol population using a 95% 2-sided CI based on normal approximation to the binomial. Similar estimation was also done for the mefloquine arm.

Analysis of other efficacy endpoints included the comparisons of asexual parasite clearance rates at other time points as well as percentages of ETFs and LTFs, asexual parasite clearance time and fever clearance time. Comparisons for the clinical cure rates and gametocyte clearance rates were done at all time points. Differences in ETFs and LTFs, clinical cure rates and gametocyte clearance rates were estimated by constructing 95% CIs using normal approximation to the binomial distribution. Clearance time comparisons used the life table method.

Safety: Summary tabulations of AEs, deaths, discontinuations and laboratory data, and listings of subjects who discontinued, or had clinically significant laboratory abnormalities were presented for All Treated Subjects by treatment regimen. The incidence of AEs and the frequency of laboratory abnormalities were tabulated.

RESULTS

Subject Disposition and Demography: A total of 960 subjects were screened and 238 subjects were randomized and treated with study drug. Of the treated subjects, 201 subjects completed the study and 37 discontinued. The subject evaluation groups are summarized in Table S1.

Table S1. Subject Evaluation Groups

Number of Subjects	1000 mg AZCQ	500 mg AZCQ	1250 mg Mefloquine
	N (%)	N (%)	N (%)
Screened	960		
Assigned to Study Treatment	114	9	115
Treated	114	9	115
Completed	96 (84.2)	4 (44.4)	101 (87.8)
Discontinued	18 (15.8)	5 (55.6)	14 (12.2)
Related to Study Drug:	5 (4.4)	1 (11.1)	4 (3.5)
Adverse event	2 (1.8)	0	2 (1.7)
Lack of efficacy	3 (2.6)	1 (11.1)	2 (1.7)
Not Related to Study Drug:	13 (11.4)	4 (44.4)	10 (8.7)
Adverse event	1 (0.9)	0	1 (0.9)
Other	4 (3.5)	0	2 (1.7)
Subject defaulted	8 (7.0)	4 (44.4)	7 (6.1)
Analyzed for Efficacy			
Parasitologically Eligible	113 (99.1)	9 (100.0)	114 (99.1)
Evaluable at Day 7*	106 (93.0)	9 (100.0)	107 (93.0)
Evaluable at Day 28*	103 (90.4)	7 (77.8)	103 (89.6)
Analyzed for Safety			
Adverse events	114 (100.0)	9 (100.0)	115 (100.0)
Laboratory data**	109 (95.6)	8 (88.9)	108 (93.9)

*Evaluable for Parasitologic Response. A subject receiving an anti-malarial in presence of *P. falciparum* parasitemia remained evaluable for all the subsequent analysis days regardless of missing data.

**Laboratory data reported not analyzed for subjects who had 1 or more missing values.

N = number of subjects; AZCQ = azithromycin plus chloroquine.

All the subjects assigned to treatment in the study were Black, representing the local population of the study site areas. Of the treated subjects, 56.3% were males and 43.7% were females, with ages in the range of 18 to 68 years.

Efficacy Results:

Primary Evaluations

Based on the interim review of the entire program including South America and India by the data safety monitoring board (DSMB) in November 2004, the 500 mg AZCQ was found to be inadequate for eradication of *P. falciparum* and was discontinued. The study continued from that point forward with 1000 mg AZCQ and 1250 mg mefloquine treatment arms.

Azithromycin 1000 mg plus chloroquine satisfied the pre-specified criteria for non-inferiority to mefloquine with an overall efficacy of 98% at Day 28 in the Parasitologic Per Protocol

population. Determination of the non-inferiority of 1000 mg AZCQ was based on a 95.04% CI for the difference in cure rates using a normal approximation to the binomial distribution. There was no adjustment for centers. Evaluable subjects treated with 1000 mg AZCQ had a parasite clearance rate of 98.06% through Day 28 compared with 99.03% for subjects treated with mefloquine. The 95.04% CI for the difference in cure rates was (-5.23%, 3.29%) (Table S2). The lower limit of this CI was higher than the pre-specified -10% indicating that 1000 mg AZCQ therapy satisfied the criteria for non-inferiority to mefloquine therapy in the treatment of uncomplicated *P. falciparum* malaria in this study.

Table S2. Summary of Statistical Analysis of Asexual Parasite Clearance Rate (1000 mg AZCQ versus mefloquine) – Day 28 (Evaluable)

Number of Subjects	1000 mg AZCQ	1250 mg Mefloquine	Difference (%) [95.04% CI]
Evaluable at Day 28	103	103	
Eradicated*(%)	101 (98.06)	102 (99.03)	-0.97 [-5.23%, 3.29%]

*As defined by the Primary Response
 AZCQ = azithromycin plus chloroquine; CI = confidence Interval

The parasitologic clearance rate observed in the Parasitologically Eligible population was similar to the Evaluable population. The 1000 mg AZCQ treatment arm showed a clearance rate of 91.15% through Day 28 compared with 93.86% for mefloquine arm. Evaluable subjects in the 500 mg AZCQ arm had a parasite clearance rate of 85.71% on Day 28.

Statistical analysis of asexual parasite clearance rate of 1000 mg AZCQ arm versus mefloquine arm in Zambia showed parasite clearance rate of 100% through Day 28 compared with 99.08% for subjects treated with mefloquine. The 95.04% CI for the difference in cure rates was (-3.72, 7.57). The lower limit of this CI was higher than the pre-specified -10% indicating that 1000 mg AZCQ satisfied the criteria for non-inferiority to mefloquine therapy in the treatment of uncomplicated *P. falciparum* malaria in Zambia. In Ghana, Kenya, Mali and Uganda, the 95.04% CI for the difference of the asexual parasite clearance rates between the 1000 mg AZCQ and the mefloquine arm was not calculated because of insufficient number of subjects.

Secondary Evaluations

The asexual parasite clearance rates on Days 7, 14, 21, 28, 35 and 42 were similar for 1000 mg AZCQ and mefloquine treatment arms. Although, the 1000 mg AZCQ arm appeared to have had more treatment failures than the mefloquine arm, the 2 RIII failures in the 1000 mg AZCQ arm cleared subsequently and it was the delay in clearance that permitted the criteria for RIII to be met.

In a logistic regression model using baseline parasite count and weight (in mg/kg) as covariates, baseline parasite count was found to have no effect on parasite clearance rate. Analysis of parasite clearance rates on Day 28 (Evaluable population) based on median body weight showed that heavier subjects (weight greater than median body weight) in the 1000 mg AZCQ treatment arm had slightly lower eradication rates (96.22%; 51 of 53

subjects were eradicated) compared to 100% eradication rates seen in subjects weighing less than or equal to median body weight.

On Days 7, 14 and 21 the gametocyte clearance rate was overall similar for 1000 mg AZCQ and mefloquine treatment arms. On Day 28 and at subsequent visits, the mefloquine arm showed a slightly higher gametocyte clearance rate than 1000 mg AZCQ arm.

At Days 3 and 7, 99.07% of the evaluable subjects in the 1000 mg AZCQ arm had an investigator clinical response of cure as compared to 97.27% of the evaluable subjects in the mefloquine arm. The rates of investigator clinical response of cure (clinical cure rates) for the Evaluable population at Day 28 were similar in both the arms.

One each of ETF (0.97%) and LTF (0.97%) was observed in the mefloquine arm and only LTFs (4.85%) were observed in the 1000 mg AZCQ arm.

There was no significant difference in the time to fever clearance between the 1000 mg AZCQ and 1250 mg mefloquine treatment arms. Data in the Parasitologically Eligible population were similar to data in the Evaluable population.

Safety Results: There were no deaths or dose reductions due to AEs reported during the study. A total of 675 all causality treatment-emergent AEs (11 in 500 mg AZCQ arm, 327 in 1000 mg AZCQ arm and 337 in mefloquine arm) were reported in 219 subjects (106 subjects in 1000 mg AZCQ, 6 subjects in 500 mg AZCQ and 107 subjects in mefloquine treatment arms, respectively) during the study. Treatment-emergent AEs (all causality and treatment-related) are summarized in Table S3.

Table S3. Summary of Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events	1000 mg AZCQ N = 114	500 mg AZCQ N = 9	1250 mg Mefloquine N = 115
All-causality:	n (%)	n (%)	n (%)
Number of adverse events	327	11	337
Subjects with adverse events	106 (93.0)	6 (66.7)	107 (93.0)
Subjects with serious adverse events	1 (0.9)	0	2 (1.7)
Subjects with severe adverse events	2 (1.8)	0	3 (2.6)
Subjects discontinued due to adverse events	3 (2.6)	0	4* (3.5)
Subjects with dose reduced or temporary discontinuations due to adverse events	1 (0.9)	0	1 (0.9)
Treatment-related:	n (%)	n (%)	n (%)
Number of adverse events	175	7	150
Subjects with adverse events	89 (78.1)	4 (44.4)	71 (61.7)
Subjects with serious adverse events	0	0	2 (1.7)
Subjects with severe adverse events	1 (0.9)	0	3 (2.6)
Subjects discontinued due to adverse events	2 (1.8)	0	2 (1.7)
Subjects with dose reduced or temporary discontinuations due to adverse events	1 (0.9)	0	1 (0.9)

*One subject counted here was not a discontinuation due to adverse event. The subject was actually withdrawn from the study as the subject was not re-dosed within the time frame required in the protocol after vomiting on Day 0.

AZCQ = azithromycin plus chloroquine.

Five SAEs were reported in 3 subjects in the study (1 subject in 1000 mg AZCQ and 2 subjects in the mefloquine treatment arms). Three of the 5 SAEs were reported in the mefloquine arm and were considered treatment-related. The SAEs are listed in Table S4.

Table S4. Serious Adverse Events

Treatment Arm	Adverse Event (COSTART Preferred Term)	Onset Day*	Causality	Outcome
1000 mg AZCQ	Dyspnea	3	Not Related	Recovered
	Confusional State	3	Not Related	Recovered
1250 mg Mefloquine	Mental Disorder	3	Related	Recovered with sequelae
	Nephrotic Syndrome	19	Related	Not Recovered
	Blood Creatinine Increased	14	Related	Unknown

* Days are relative to the day of starting active therapy (Day 1)
 AZCQ = Azithromycin plus chloroquine

There were 6 permanent discontinuations due to AEs (3 each in 1000 mg AZCQ and mefloquine treatment arms) of which 4 (2 in each arm) were treatment-related. Vomiting was the most frequently reported AE (reported by 4 of the 6 subjects who discontinued) leading to discontinuation. Permanent discontinuations due to AE's are listed in Table S5.

Table S5. Permanent Discontinuations due to Adverse Events

Treatment Arm	Adverse Event (COSTART Preferred Term)	Related to Treatment
1000 mg AZCQ	Confusion, Dyspnea	No
	Vomiting	Yes
	Vomiting, Dizziness, Tinnitus	Yes
1250 mg Mefloquine	Vomiting	No
	Jaundice, Nausea, Vomiting, Bilirubinemia	No
	Fever, Hypotension, Hematuria	Yes
	Hypertension, Vomiting	Yes

AZCQ = Azithromycin plus chloroquine

There were no discontinuations from the study due to abnormal laboratory test values. The incidence of laboratory abnormalities was similar in the 1000 mg AZCQ and the mefloquine arms.

The majority of AEs reported in the 3 treatment arms of the study were mild. Five severe treatment-related AEs (3 were SAEs) were reported; 4 in the mefloquine arm and 1 in the 1000 mg AZCQ arm. The most frequently reported all causality AEs in subjects treated with 1000 mg AZCQ were pruritus (51.8%), headache (35.1%), vomiting (18.4%), dizziness (16.7%) and abdominal pain (15.8%), and with 1250 mg mefloquine were dizziness (33.9%), headache (30.4%), vomiting (25.2%), abdominal pain (21.7%) and nausea (17.4%). The incidence of the treatment-emergent AEs in ≥ 2 subjects in any 1 treatment arm is summarized in Table S6.

Table S6. Number (%) of Subjects With All Causality (≥2 Subjects in any 1 arm) and Treatment-Related Adverse Events by Body System and Treatment arm

Adverse Events (COSTART Preferred Term)	1000 mg AZCQ N=114		500 mg AZCQ N=9		1250 mg Mefloquine N=115	
	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Body as a Whole:						
Abdominal Pain	18 (15.8)	8 (7.0)	2 (22.2)	1 (11.1)	25 (21.7)	13 (11.3)
Asthenia	10 (8.8)	6 (5.3)	1 (11.1)	0	17 (14.8)	11 (9.6)
Back Pain	1 (0.9)	0	0	0	2 (1.7)	1 (0.9)
Chest Pain	9 (7.9)	2 (1.8)	0	0	3 (2.6)	0
Chills	9 (7.9)	3 (2.6)	0	0	11 (9.6)	1 (0.9)
Fever	6 (5.3)	1 (0.9)	0	0	13 (11.3)	2 (1.7)
Flu Syndrome	2 (1.8)	0	0	0	4 (3.5)	0
Headache	40 (35.1)	15 (13.2)	0	0	35 (30.4)	11 (9.6)
Infection	1 (0.9)	0	0	0	5 (4.3)	0
Malaise	4 (3.5)	1 (0.9)	0	0	1 (0.9)	1 (0.9)
Pain	4 (3.5)	2 (1.8)	0	0	2 (1.7)	2 (1.7)
Cardiovascular:						
Hypertension	2 (1.8)	0	0	0	4 (3.5)	2 (1.7)
Palpitation	4 (3.5)	3 (2.6)	0	0	8 (7.0)	7 (6.1)
Digestive:						
Anorexia	8 (7.0)	4 (3.5)	1 (11.1)	0	4 (3.5)	2 (1.7)
Diarrhea	14 (12.3)	6 (5.3)	0	0	12 (10.4)	5 (4.3)
Dyspepsia	4 (3.5)	3 (2.6)	1 (11.1)	1 (11.1)	4 (3.5)	3 (2.6)
Enteritis	0	0	0	0	2 (1.7)	0
Flatulence	2 (1.8)	1 (0.9)	0	0	0	0
Nausea	11 (9.6)	9 (7.9)	0	0	20 (17.4)	13 (11.3)
Stools Loose	3 (2.6)	3 (2.6)	1 (11.1)	1 (11.1)	0	0
Tooth Disorder	1 (0.9)	0	0	0	2 (1.7)	0
Vomiting	21 (18.4)	18 (15.8)	2 (22.2)	1 (11.1)	29 (25.2)	12 (10.4)
Musculoskeletal:						
Arthralgia	4 (3.5)	2 (1.8)	0	0	1 (0.9)	0
Arthritis	3 (2.6)	0	0	0	1 (0.9)	0
Nervous:						
Dizziness	19 (16.7)	11 (9.6)	0	0	39 (33.9)	26 (22.6)
Insomnia	2 (1.8)	2 (1.8)	0	0	3 (2.6)	3 (2.6)
Respiratory:						
Bronchitis	2 (1.8)	0	0	0	1 (0.9)	0
Cough Increased	11 (9.6)	0	0	0	9 (7.8)	0
Dyspnea	2 (1.8)	1 (0.9)	0	0	0	0
Pharyngitis	0	0	0	0	3 (2.6)	0
Respiratory Tract Infection	11 (9.6)	0	0	0	9 (7.8)	0
Rhinitis	1 (0.9)	0	0	0	4 (3.5)	2 (1.7)
Sputum Increased	2 (1.8)	0	0	0	3 (2.6)	0
Skin and Appendages:						
Folliculitis	0	0	0	0	3 (2.6)	0
Herpes Simplex	7 (6.1)	0	0	0	5 (4.3)	0
Pruritus	59 (51.8)	58 (50.9)	2 (22.2)	2 (22.2)	11 (9.6)	11 (9.6)
Rash	2 (1.8)	2 (1.8)	0	0	2 (1.7)	0
Skin Disorder	0	0	0	0	2 (1.7)	0
Sweating	3 (2.6)	0	0	0	6 (5.2)	2 (1.7)
Special Senses						
Abnormal Vision	2 (1.8)	2 (1.8)	0	0	0	0
Conjunctivitis	2 (1.8)	1 (0.9)	0	0	0	0
Eye Pain	2 (1.8)	2 (1.8)	0	0	2 (1.7)	2 (1.7)
Taste Perversion	2 (1.8)	2 (1.8)	0	0	4 (3.5)	4 (3.5)
Tinnitus	3 (2.6)	1 (0.9)	0	0	1 (0.9)	1 (0.9)

AZCQ = Azithromycin plus chloroquine

Pruritus (50.9%) followed by vomiting (15.8%) and headache (13.2%) were the most commonly reported treatment-related AEs with 1000 mg AZCQ. The most frequently reported treatment-related AEs with 1250 mg mefloquine was dizziness (22.6%) followed by abdominal pain (11.3%), nausea (11.3%) and vomiting (10.4%).

CONCLUSION:

- Treatment with azithromycin 500 mg plus chloroquine was determined to be inadequate for the eradication of *P. falciparum* and this arm was removed from the study at the request of the DSMB.
- The hypothesis that 1000 mg AZCQ is non-inferior to 1250 mg mefloquine was confirmed in this study. Azithromycin 1000 mg plus chloroquine satisfied the pre-specified criteria for non-inferiority to 1250 mg mefloquine for the treatment of adults with uncomplicated *P. falciparum* malaria in Africa with an overall efficacy of 98% on Day 28 and also on Days 7, 14, 21, 35 and 42. Genotyping of the failed subjects indicated that re-infection with new strains occurred in this study.
- Azithromycin in combination with chloroquine was well tolerated. No new safety concerns emerged from this study.