RANDOMIZED, CONTROLLED, DOUBLE-BLIND TRIAL OF DAILY ORAL AZITHROMYCIN IN ADULTS FOR THE PROPHYLAXIS OF PLASMODIUM VIVAX MALARIA IN WESTERN THAILAND

D. GRAY HEPPNER, JR.,* DOUGLAS S. WALSH, NICHAPAT UTHAIMONGKOL, DOUGLAS B. TANG, SOMCHIT TULAYON, BARNYEN PERMANI, THEERA WIMONWATRAWAT, NIPHON CHUANAK, ANINITTA LAOBOONCHAI, PRASIT SOOKTO, THOMAS G. BREWER, PHILIP MCDANIEL, CHIRAPA EAMSILA, KOSOL YONGVANTICHIT, KATHLEEN UHL, DENNIS E. KYLE, LISA W. KEEP, ROBERT E. MILLER, AND CHANSUDA WONGSIRICHANALAI

Department of Immunology and Medicine, United States Army Medical Component, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; Walter Reed Army Institute of Research, Silver Spring, Maryland; Kwai River Christian Hospital, Sangkhlaburi, Kanchanaburi Province, Thailand; Research Division, Thai Component, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; United States Army Medical Materiel Development Activity, Fort Detrick, Frederick, Maryland

Abstract. We assessed the prophylactic efficacy of azithromycin (250 mg/day) against malaria in 276 adults in western Thailand in a randomized, double-blind, placebo-controlled trial. After antimalarial suppressive treatment, volunteers were randomized in a 2:1 ratio to either the azithromycin or placebo, respectively. Study medication was given for an average of 74 days. The azithromycin group (n = 179) had five endpoint parasitemias (1 Plasmodium vivax and 4 P. falciparum), and the placebo group (n = 97) had 28 endpoint parasitemias (21 P. vivax, 5 P. falciparum, and 2 mixed infections). Adverse events and compliance and withdrawal rates were similar in both groups. The protective efficacy (PE) of azithromycin was 98% for P. vivax (95% confidence interval [CI] = 88–100%). There were too few cases to reliably estimate the efficacy of azithromycin for P. falciparum (PE = 71%, 95% CI = –14–94%). We conclude that daily azithromycin was safe, well-tolerated, and had a high efficacy for the prevention of P. vivax malaria.

INTRODUCTION

Azithromycin is a macrolide antibiotic used extensively in adult and pediatric populations, and is not predicted to be harmful in human pregnancy (U.S. Food and Drug Administration [FDA], Category B). In standard murine malaria models, azithromycin proved comparable to doxycycline in antimalarial activity. Subsequently, the prophylactic efficacy of daily azithromycin against mosquito-borne malaria was demonstrated in malaria-naïve adults at the Walter Reed Army Institute of Research in the mid-1990s. In 1995, daily azithromycin showed an efficacy of 83% (95% confidence interval [CI] = 69–91%) in preventing Plasmodium falciparum malaria in highly immune adult males in western Kenya. In 1996, daily azithromycin was shown to be highly protective against P. vivax but not P. falciparum (protective efficacy [PE] = 99%, 95% CI = 93–100% and PE = 72%, 95% CI = 50–84%, respectively) in Irian Jaya, Indonesia. Here we describe a simultaneous prophylactic efficacy study of azithromycin in adults for the prevention of malaria conducted in 1996 along the Thailand-Myanmar (Burma) border, an area endemic for P. vivax and mefloquine-resistant P. falciparum malaria.

MATERIALS AND METHODS

Study design. The study was a prospective, randomized, double-blind, placebo-controlled trial of daily azithromycin for the prevention of malaria conducted from June to November 1996. The study was designed to test a hypothesis that a three-tablet loading dose of azithromycin (total = 750 mg), followed the next day by single tablet (250 mg daily doses) would prevent P. vivax and mefloquine-resistant P. falciparum malaria for a period of up to 140 days. Primary efficacy endpoints were the first instances of P. vivax parasitemia and the first instances of P. falciparum parasitemia as determined by standardized light microscopy performed on a Giemsa-stained blood smear. Secondary outcomes were safety, tolerability, and in vitro drug susceptibility profiles for P. falciparum parasites isolated at time of prophylaxis failure.

Ethical approval and study monitoring. The protocol was reviewed and approved by the Ethical Committee for Research in Humans of the Thai Ministry of Public Health and the Office of the U.S. Army Surgeon General (Washington, DC). The study was conducted according to Good Clinical Practices guidelines. Study monitoring in Thailand was conducted by the Quality Assurance Office, Armed Forces Research Institute of Medical Sciences (AFRIMS) and the U.S. Army Medical Materiel and Development Activity (Fort Detrick, Frederick, MD).

Study site and study center. The study was conducted in remote forest and scrub-covered foothills at the AFRIMS–Kwai River Christian Hospital (KRCH) field site in the Sangkhlaburi District in Kanchanaburi Province in western Thailand, along the border with Myanmar. The AFRIMS Malaria Research Unit on the campus of the KRCH provided infrastructure for a Good Clinical Practices compliant study.

Malaria epidemiology. Plasmodium falciparum along the western border of Thailand is mefloquine-resistant. Plasmodium vivax malaria remains highly susceptible to chloroquine throughout Thailand, with only rare instances of parasitemia after a standard chloroquine plus primaquine treatment regimen. Malaria is the most commonly diagnosed acute febrile illness at the KRCH, but leptospirosis, tuberculosis, dengue fever, Japanese encephalitis, and several rickettsioses are also endemic.

Recruitment and enrollment. Persons eligible for study registration were ethnic Thai, Mon, and Karen men and women 18–45 years of age living in villages within 12 km of the KRCH. Investigators met with village leaders, work site fore-
men, KRCH staff, and local Ministry of Public Health workers within the community to explain the study and enlist their support. Then using local interpreters and hospital staff at villages and work sites throughout the field site, written informed consent was obtained in the appropriate language before eligibility screening for enrollment into the study. Persons eligible for screening had given written informed consent and were willing to comply with study requirements. At pre-enrollment screening, each volunteer answered detailed medical history questions, and underwent a physical examination and laboratory screening that included hematologic (hematocrit and white blood cell and platelet counts) and biochemical laboratory tests (blood urea nitrogen, creatinine, and $\gamma$-glutamyl transferase; GGT), a blood smear for malaria assessment, and, for women, a urine $\beta$-human chorionic gonadotropin (HCG) test.

Exclusion criteria were pregnancy, nursing, mefloquine use within the past five weeks, hematocrit < 25%, chronic disease, weight < 45 kg, allergy to macrolide antibiotics, absence of a spleen, or any evidence of ill health.

Test articles. Azithromycin dihydrate (250 mg tablets) and identically appearing placebo tablets containing an inert substance were provided by Pfizer Central Research (Groton, CT). The Walter Reed Army Medical Center Pharmacy (Washington, DC) re-labeled study drugs in identical blister packs of 80 tablets each. Each tablet wrapper within a blister pack was labeled with the identical alphanumeric code from a master list supplied by the study statistician.

Interventions and assessment for malaria. Eligible volunteers were examined for malaria parasites by blood smear and received pre-randomization malaria treatment according to the results. Pre-randomization treatment was intended to suppress or eliminate blood-stage parasites, and did not aim to eliminate developing P. falciparum or P. vivax hepatic stages or P. falciparum hypnozoites. Volunteers with negative smears received presumptive treatment with oral artesunate (600 mg over a five-day period; Atlantic Pharmaceutical Company, Bangkok, Thailand) to eliminate any sub-patent blood stage of malaria. Volunteers with asexual P. vivax parasitemia (patient) were treated with chloroquine phosphate (25 mg base/kg over a three-day period; Sterling Winthrop Corporation, Collegeville, PA) and artesunate (600 mg over a five-day period), and volunteers with asexual P. falciparum parasitemia or mixed P. falciparum plus P. vivax parasitemia were treated with artesunate (600 mg over a three-day period) plus doxycycline (200 mg/day for 5 days; Rugby Laboratories, Rockville Center, NY). In volunteers with patent parasitemia, clearance of parasites was confirmed at the end of treatment by examination of at least one thick blood smear. The short half-lives of artesunate and doxycycline minimized the potential carryover of any significant prophylactic effect into the start of the double-blind study drug administration period. It was assumed that chloroquine treatment would exert a negligible prophylactic effect against mefloquine-resistant P. falciparum, and a transient effect against subsequent P. vivax.

Upon completion of malaria parasite clearance treatment, volunteers were randomized to receive a three-tablet loading dose of azithromycin (total = 750 mg) or placebo on day 1, and then one tablet daily thereafter (250 mg of azithromycin or placebo). Study drugs were administered with a biscuit under direct observation of study personnel. Rarely, study volunteers were allowed to self-administer drug during planned absences.

Duplicate malaria smears were obtained weekly or during any febrile illness and read according to standard operating procedure in which 200 thick smear oil-immersion fields ($\times$ 1,000) were examined before declaring a slide negative. Malaria infection was defined as the presence of Plasmodium asexual stage parasites on a thick blood smear. If asexual parasites were detected on the thick smear, they were enumerated per 500 white blood cells. When possible, speciation was confirmed on a thin blood smear. A second slide examiner read each positive slide independently and 10% of all negative slides. Discrepancies of speciation or $\geq$ 3-fold differences in parasitemia were resolved by the senior study microscopist (BP).

Volunteers developing P. vivax parasitemia continued taking the daily study drug and were treated with chloroquine phosphate (25 mg base/kg over a three-day period) and were considered to remain at risk for an endpoint (P. falciparum parasitemia due to pervasive high-level P. falciparum resistance to chloroquine). Volunteers reaching a P. falciparum parasitemia endpoint were censored from further efficacy analysis, and treated with a standard mefloquine and artesunate regimen.7,8 For P. falciparum, drug susceptibility profiles, field collection, cryopreservation, and determination of in vitro drug inhibitory concentrations by $^3$H-hypoxanthine uptake were performed as previously described.12

Safety and tolerability. Clinical hematologic and biochemical laboratory tests were repeated after one month and at the completion of daily dosing for available volunteers. Women underwent monthly urine $\beta$-HCG testing and were withdrawn from the study if the test result became positive.

During daily dosing, volunteers were asked if they were generally well, and all medical complaints were evaluated by a study physician. On a weekly basis, adverse events (AEs) were recorded using a structured questionnaire to capture symptoms of potential azithromycin side effects and of malaria. Oral temperature and non-study medication use were also recorded. Serious AEs, defined as those requiring hospital admission or withdrawal from the study, were independently coded by the medical monitor as to the likelihood of a causal relationship to study medication. When standards of care permitted, antibiotics without anti-malarial effect were used to treat inter-current, non-malarial infections. Upon completion of study drug (azithromycin or placebo) administration, available volunteers underwent weekly assessments using the standard structured AE questionnaire and malaria smears for up to four weeks.

Sample size. The goal of this study was to confirm the estimated PE of azithromycin of 85% with sufficient precision to rule out a PE < 50%. Based on historical data, the 20-week malaria attack rate was estimated to be 30% for P. vivax and 30% for P. falciparum. To increase the robustness of the study, sample size calculations were based upon a projected attack rate of 15%. Assuming a PE $\geq$ 85% (and enough precision to rule out a PE < 50%), a 15% attack rate in the placebo group, and an 80% study power (given $\alpha = 5\%$, one-sided), the minimum total sample size required was 300. To compensate for anticipated dropouts, it was planned to enroll additional replacement volunteers to maintain 300 volunteers on study. Unequal 2:1 allocation (azithromycin:placebo), with more volunteers assigned to the group expected
to have fewer events (parasitemias) was used to reduce the total required sample size to achieve the target power (80%).

Randomization, allocation, and concealment. Blocked randomization (computer generated) was used to provide 1:1 allocation for groups with ≤4 volunteers (block size 2) and 2:1 for groups with ≥5 (block size 6). Randomization occurred 24–48 hours before completing blood-stage antimalarial treatment, according to date of randomization and site location. At the time of randomization, investigators ranked volunteers by age and entered them sequentially into one of four master randomization lists stratified by sex and group size (≤4, ≥5). This plan allowed for continuing enrollment at multiple sites within the study area stratified by sex, balanced with respect to age, and increased the chance that both arms were allocated within smaller groups (defined by randomization date and site location).

Volunteers and trial personnel were unaware of study group assignment and the double-blind was maintained throughout the study until completion and the database was locked. The randomization list was prepared by the study statistician (DBT) who was not directly involved with the study and who also maintained the code linking each volunteer to assigned treatment.

Data management and statistical methods. Volunteer data were entered at time of collection onto source documents and then case report forms (CRFs). After review for accuracy and completeness by an investigator, CRFs were entered twice into a database for comparison. Database discrepancies were visually checked against source documents and verified. The interventions were then unblinded and the data were analyzed using StatExact version 4.01 for Windows (Cytel Software Company, Cambridge, MA) and Minitab version 14 (Minitab, Inc., State College, PA).

The protocol specified a maximum duration of daily study drug administration of 20 weeks, but no minimum. All randomized volunteers who received study drug and completed the initial weekly questionnaire and blood smear were included for AE and efficacy (intent-to-treat) analysis, respectively. All randomized volunteers who received study drug and remained in the study for completion of the one-month interim clinical laboratories were included for the analysis of safety.

The primary efficacy endpoint was the occurrence of a first instance of *P. falciparum* or *P. vivax* parasitemia during study drug administration. Follow-up time was measured from the first dose of study drug (day 0) to the date of drug failure (parasitemia), withdrawal from the study (physician or volunteer initiated), or termination of dosing (maximum of 20 weeks).

Crude attack rates (cases/number randomized) and incidence (density) rates (cases/follow-up time) were calculated based on the number of first instances of either *P. falciparum* or *P. vivax* or any parasitemia. The PE (azithromycin relative to placebo) was calculated both as the percentage reduction in attack rates (risk ratio) and incidence rates (rate ratio). The corresponding CIs for PE were calculated using the method of Koopman (risk ratio) and the exact conditional method based on the ratio of two Poisson variables (rate ratio). Cumulative incidence curves (Kaplan-Meier) were compared using the log rank test. Proportions were compared using Fisher’s exact test. All reported CIs are 95%, and all P values are two-sided.

Hematology and biochemistry laboratory values were recorded during a pre-study screening, after one month of dosing, and at the completion of dosing. Group treatment means were computed and compared within and across the two treatment groups using analysis of variance and t-tests (paired or unpaired, as appropriate), respectively. The AEs were summarized by study group as proportion of the number of events/number of reporting days (expressed in percentage) and as the percentage of persons having at least one reported AE episode during the periods of daily medication and the four-week post-dosing follow-up. To avoid confounding study drug-related AEs with malaria-related AEs during daily dosing, AEs reported on the date of malaria diagnosis and one week later were excluded. Likewise, during the four-week post-dosing period, all AEs at and after the time of malaria diagnosis were excluded. Statistical comparisons (P values) of AEs (and laboratory values) were not adjusted for multiple comparisons. The study was not designed to reliably estimate rates of low incidence or have sufficient power to detect small differences between the two groups.

RESULTS

Recruitment, randomization, and withdrawals. Enrollment started in May 1996 and continued through September, one month before the end of daily double-blind dosing. Figure 1A shows that of 378 volunteers who gave informed consent and were screened for enrollment eligibility, 86 were excluded, 292 were randomized, and 276 received ≥1 dose of study drug (179 azithromycin and 97 placebo). Unexpected local civil disturbances led to abrupt migrations, decreasing the expected enrollment and participation. Seven volunteers who received ≥1 dose of study drug withdrew and then were re-enrolled to the same double-blind medication code when they returned to the study site. Both enrollments were included in all analyses.

The two study groups closely matched for age, sex, malaria history, splenomegaly, hematologic indices, and malaria parasitemia detected during pre-study screening (Table 1). Analysis of randomization showed balanced allocation of azithromycin versus placebo among the enrollment sites. Figure 1B shows the number of participants and cases of parasitemia by study group during the four-week follow-up period after completion of daily study drug.

Efficacy. During daily double-blind dosing, there were 32 first instances of parasitemia: 27 occurred in the placebo group, of which 21 were *P. vivax*, 2 were mixed cases of *P. falciparum* and *P. vivax*, and 4 were *P. falciparum*. Five first instances of parasitemia occurred in the azithromycin group, of which 4 were *P. falciparum* and 1 was *P. vivax* (Figure 1A and Table 2). One placebo recipient, who developed azithromycin versus placebo during the enrollment sites. Figure 1B shows the number of participants and cases of parasitemia by study group during the four-week follow-up period after completion of daily study drug.

Azithromycin was highly protective for *P. falciparum* based on percent reduction in incidence density ratio are shown in Table 2. Estimates of PE based on percent reduction in crude attack rates were similar. Azithromycin was highly protective for *P. vivax*, but there were insufficient instances of *P. falciparum* parasitemia to
reliability determine protection against \textit{P. falciparum}. The corresponding Kaplan-Meier plots comparing the two study groups are shown in Figure 2.

\textbf{Safety and tolerability.} Five volunteers were withdrawn because of a serious AE, none of which were judged definitely or probably related to study drug. A placebo recipient had an asthma attack whose history of asthma had been missed at enrollment. Of four azithromycin recipients withdrawn, one developed pulmonary tuberculosis, one developed unspecific respiratory complaints, and two developed abnormal GGT levels (> 2 times the upper limit of the normal reference range) after two months of receiving study drug. Both volunteers with elevated GGT levels had slightly elevated levels at study entry (< 1.5 times the upper limit of the normal reference range) that remained unchanged at the one-month safety check. At withdrawal, both GGT-related withdrawals admitted alcohol use and one had recently begun treatment with isoniazid.

There were no clinically significant effects on clinical laboratory endpoints for either study group. In the azithromycin group, there were small, statistically significant decreases in mean white blood cell counts at one month and at study completion in comparison with pre-dosing values. At both time points, mean white blood cell counts were within the normal reference range, and no individual value decreased to less than 2,500/\mu L.

\begin{table}
\centering
\caption{Enrollment characteristics for volunteers receiving \geq 1 dose of study drug*}
\begin{tabular}{lcc}
\hline
 & Azithromycin & Placebo \\
\hline
Sex & & \\
Men & 126 (69) & 69 (71) \\
Women & 53 (31) & 28 (29) \\
Age in years (mean: ± SD) & 29.3 ± 8 & 29.1 ± 8 \\
Weight in kilograms (mean: ± SD) & 52.3 ± 8 & 51.8 ± 8 \\
Palpable liver & 10 (6) & 8 (6) \\
Palpable spleen & 23 (13) & 20 (10) \\
Any history malaria & 87 (49) & 46 (47) \\
Once in last 12 months & 24 (13) & 11 (11) \\
≥ 2 times in last 12 months & 6 (3) & 5 (5) \\
Parasitemic during screen & 35 (19)† & 22 (23) \\
\textit{P. vivax} & 10 (6) & 7 (7) \\
\textit{P. falciparum} & 21 (12) & 13 (13) \\
\textit{P. vivax} plus \textit{P. falciparum} & 3 (2) & 2 (2) \\
\hline
\end{tabular}
\begin{flushright}
*Except where indicated, values are no. (%) \\
†Includes one \textit{Plasmodium malariae} monoinfection.
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\end{table}

\begin{table}
\centering
\caption{Protective efficacy (PE) of azithromycin versus placebo}
\begin{tabular}{lcc}
\hline
Study group & Azithromycin & Placebo \\
\hline
Randomized (n) & 190 & 102 \\
Started trial (\geq 1 dose) (n) & 179 & 97 \\
Lost to follow-up (n) & 53 & 25 \\
Completed prescribed study drug (n) & 127 & 72 \\
Follow-up time (person-days) for & & \\
All species (first instance) & 13,976 & 6,390 \\
\textit{P. vivax} (first instance) & 13,976 & 6,382 \\
\textit{P. falciparum} (first instance) & 14,007 & 7,163 \\
Malaria endpoint parasitemias (n) & & \\
All species & 5 & 28 \\
\textit{P. vivax} & 1 & 21 \\
\textit{P. falciparum} & 4 & 5 \\
Mixed (\textit{P. vivax} plus \textit{P. falciparum}) & 0 & 2 \\
Incidence rate (per person-year)* & & \\
All species (first instance) & 0.13 & 1.60 \\
\textit{P. vivax} (first instance) & 0.03 & 1.32 \\
\textit{P. falciparum} (first instance) & 0.10 & 0.36 \\
Protective efficacy (95% CI)† & & \\
All species (first instance) & 91.8 (78.6, 97.5) & \\
\textit{P. vivax} (first instance) & 98.0 (87.8, 99.9) & \\
\textit{P. falciparum} (first instance) & 70.8 (−14.0, 93.7) & \\
\hline
\end{tabular}
\begin{flushright}
*For species-specific incidence rate and corresponding PE calculation for a placebo, \textit{Plasmodium vivax} (first instance), (n = 23); includes two mixed infections; b, placebo, \textit{P. falciparum} (first instance), (n = 7); includes two mixed infections and one first instance \textit{P. vivax} developing \textit{P. falciparum}. \\
†Percent reduction in incidence rates for azithromycin.
\end{flushright}
\end{table}
Drug susceptibilities were determined for isolates obtained from placebo (five of six) and azithromycin (four of four) recipients at the time of the *P. falciparum* endpoint. Isolates from azithromycin failures had slightly higher azithromycin median 50% and 90% inhibitory concentrations than those receiving placebo (4,816 nM versus 3,715 nM, and 23,873 versus 22,167 nM, respectively), but the differences were not statistically significant. In accordance with previous definitions and data, drug sensitivity testing for the nine *P. falciparum* isolates showed that all were chloroquine resistant (99% inhibitory concentration [IC$_{99}$] > 200 nM), eight were mefloquine resistant (IC$_{99}$ > 140 nM), and five were quinine resistant (IC$_{99}$ > 1,800 nM).[^1^][^2^][^3^]

**DISCUSSION**

Daily azithromycin demonstrated high efficacy for the prevention of *P. vivax* parasitemia in western Thailand. The high rate of protection against chloroquine-sensitive *P. vivax* (98%, 95% CI 87–100%) in our study is consistent with the previously reported high efficacy of azithromycin chemoprophylaxis against *P. vivax* malaria in Indonesia (99%, 95% CI = 93–100%), where chloroquine-resistant *P. vivax* is present. Although our trial was conducted in 1996, the results are relevant in that there have been no subsequent trials assessing the efficacy of azithromycin alone for the prophylaxis of malaria. A treatment study conducted in 2001 demonstrated that azithromycin (500 mg/day for three days) gave a consistent therapeutic response to 18 patients in Thailand with *P. vivax* parasitemia, suggesting that chemoprophylactic efficacy of azithromycin against *P. vivax* is explained by its action against blood-stage parasites.[^4^][^5^]

In contrast to *P. vivax*, the much lower than expected *P. falciparum* incidence rate did not allow a precise estimate of the PE of azithromycin against multdrug-resistant *P. falciparum*. The estimated PE of 71%, but with a wide 95% CI (14–94%), did not help to further define the previously reported estimates of efficacy in a highly malaria-exposed adult population in Kenya (PE = 83%, 95% CI = 69–91%) and in adults with presumably less immunity to malaria in Irian Jaya (PE = 72%, 95% CI = 50–84%).[^6^][^7^] It was unclear why the *P. falciparum* attack rate in our study was far below that expected. The occurrence of parasitemia at initial enrollment and screening, and later during the four-week post-study drug follow-up period suggests, but does not prove, that malaria exposure occurred during daily study drug administration in both the azithromycin and placebo group volunteers.

Two significant AEs, both elevations in GGT levels, were potentially related to azithromycin administration. Both volunteers, who appeared well but had modestly abnormal GGT values at study entry, were randomized to receive daily azithromycin. After approximately two months of study drug, both complained of malaise and had developed GGT levels more than twice the upper limit of normal. Both admitted to frequent alcohol use, and one of them had recently started treatment with isoniazid. Although alcohol and isoniazid toxicity may explain the malaise and the elevation in the GGT levels, a contributing role of azithromycin cannot be excluded. For other laboratory values, the only notable effect of azithromycin was a minor reduction in group mean white blood cell counts deemed to be not clinically significant. Safety reports indicate that azithromycin, like other mac-

**Tables 3 and 4 summarize the instances of fever (oral temperature > 37.5°C) and solicited non-serious AEs during weekly follow-up surveys for daily dosing and the four-week post-dosing follow-up period, respectively. During study drug administration, azithromycin recipients had a statistically significant lower frequency of diarrhea than the placebo group.**

**Four week follow-up period after dosing completion.** Figure 1b shows the number of volunteers entering the four-week post-dosing follow-up period and malaria parasitemias. There were 10 cases of malaria (1 *P. falciparum*, 2 mixed *P. falciparum* and *P. vivax*, and 7 *P. vivax*) among 121 volunteers in the azithromycin group versus 2 cases (both *P. vivax*) among 56 volunteers in the placebo group. For the azithromycin group, none of the *P. vivax* or mixed cases were *P. vivax* smear positive during the pre-study screen or while receiving study medication. For the placebo, both *P. vivax* cases had been smear positive for *P. vivax* during the pre-study screen.

*Plasmodium falciparum in vitro drug susceptibility assays.* Drug susceptibilities were determined for isolates obtained...
rolides, can be associated with a reduction in white blood cells in a small proportion of persons, but this is generally mild, transient, and without sequelae.20

Daily azithromycin was well tolerated as shown by the similar compliance rate and AE profiles. During four weeks of follow-up after completion of study drug administration, there were no differences in AEs, further supporting the tolerability of daily azithromycin. These findings are consistent with the two previous studies of daily azithromycin in malaria-exposed populations4,5,21 and with a now much broader experience for non-malarial indications.22,23

The reduction in self-reported diarrhea in this study and the reported efficacy of daily azithromycin for the prevention of dysentery24 does not substantively bear upon the merits of this drug for the prevention of malaria.

In summary, azithromycin alone, as prescribed in this

<p>| Table 3 |
| Frequency of solicited adverse events (AEs) and fever (oral temperature &gt; 37.5°C) at weekly surveys during daily medication dosing* |</p>
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Azithromycin/Placebo</th>
<th>Placebo/Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of days reported (%)†</td>
<td>No (%) with ≥ 1 AE episode</td>
<td></td>
</tr>
<tr>
<td>No. of surveys conducted/no. possible</td>
<td>No. of persons reporting/no. possible</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>99 (5) 50 (5)</td>
<td>63 (37) 32 (34)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (&lt; 1) 7 (&lt; 1)</td>
<td>9 (5) 7 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>220 (11) 97 (10)</td>
<td>95 (56) 45 (48)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20 (1) 16 (2)</td>
<td>15 (9) 13 (14)</td>
</tr>
<tr>
<td>Hearing difficulty</td>
<td>1 (&lt; 1) 6 (&lt; 1)</td>
<td>1 (1) 4 (4)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>106 (5) 62 (6)</td>
<td>51 (30) 30 (32)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>11 (&lt; 1) 8 (&lt; 1)</td>
<td>11 (6) 6 (6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>66 (3) 38 (4)</td>
<td>41 (24) 21 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (1) 21 (2)</td>
<td>14 (8) 17 (18)§</td>
</tr>
<tr>
<td>Itch</td>
<td>16 (1) 6 (&lt; 1)</td>
<td>9 (5) 5 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>30 (2) 8 (&lt; 1)</td>
<td>19 (11) 5 (5)</td>
</tr>
<tr>
<td>Tender glands</td>
<td>1 (&lt; 1) 2 (&lt; 1)</td>
<td>1 (1) 1 (1)</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>16 (&lt; 1) 16 (2)</td>
<td>13 (8) 14 (15)</td>
</tr>
<tr>
<td>Cough</td>
<td>44 (2) 30 (3)</td>
<td>30 (18) 20 (21)</td>
</tr>
<tr>
<td>Temperature &gt; 37.5°C</td>
<td>1,941 (1215) 946 (1,042)</td>
<td>170 (170) 93 (94)</td>
</tr>
<tr>
<td>No. of surveys conducted/no. possible</td>
<td>No. of persons reporting/no. possible</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>35 (9) 52 (6)</td>
<td>59 (35) 28 (30)</td>
</tr>
</tbody>
</table>

* AEs and temperature on day of parasitemia and for 7 days afterward (Plasmodium vivax cases only) were excluded.
† Over the past 7 days.
‡ For azithromycin vs. placebo (binomial, exact-conditional test [2-sided]): hearing difficulty, P = 0.012; diarrhea, P = 0.011.
§ For azithromycin vs. placebo (Fisher’s exact test [2-sided]): diarrhea, P = 0.03.

<p>| Table 4 |
| Frequency of solicited adverse events (AEs) and fever (oral temperature &gt; 37.5°C) at weekly surveys during the four week follow-up period after study medication dosing was completed* |</p>
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Azithromycin/Placebo</th>
<th>Placebo/Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of days reported (%)†</td>
<td>No (%) with ≥ 1 AE episode</td>
<td></td>
</tr>
<tr>
<td>No. of surveys conducted/no. possible</td>
<td>No. of persons reporting/no. possible</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>7 (2) 5 (2)</td>
<td>5 (4) 4 (7)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (&lt; 1) 0 (&lt; 1)</td>
<td>1 (1) 0 (&lt; 1)</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (7) 12 (6)</td>
<td>25 (21) 10 (17)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (&lt; 1) 2 (&lt; 1)</td>
<td>2 (2) 2 (3)</td>
</tr>
<tr>
<td>Hearing difficulty</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>7 (2) 3 (1)</td>
<td>6 (5) 2 (3)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>1 (&lt; 1) 3 (1)</td>
<td>1 (1) 3 (5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (3) 3 (1)</td>
<td>12 (10) 3 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (&lt; 1) 3 (1)</td>
<td>0 (&lt; 1) 3 (5)‡</td>
</tr>
<tr>
<td>Itch</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (&lt; 1) 1 (&lt; 1)</td>
<td>2 (2) 1 (2)</td>
</tr>
<tr>
<td>Tender glands</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
<td>0 (&lt; 1) 0 (&lt; 1)</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>5 (1) 0 (&lt; 1)</td>
<td>4 (3) 0 (&lt; 1)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (&lt; 1) 1 (&lt; 1)</td>
<td>1 (1) 1 (2)</td>
</tr>
<tr>
<td>Temperature &gt; 37.5°C</td>
<td>400 (470) 204 (256)</td>
<td>110 (170) 58 (65)</td>
</tr>
<tr>
<td>No. of surveys conducted/no. possible</td>
<td>No. of persons reporting/no. possible</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>35 (9) 12 (6)</td>
<td>21 (18) 10 (17)</td>
</tr>
</tbody>
</table>
study, was reliable for the prevention of P. vivax malaria, but incidence rates were insufficient to comment on its reliability for the prevention of highly drug-resistant P. falciparum malaria. The linkage of P. vivax malaria during pregnancy with maternal anemia and low birth weight, suggests that the azithromycin (U.S. FDA pregnancy category B) safety and efficacy profile might warrant its limited off-label use in pregnancy where chloroquine-resistant P. vivax is the sole or predominant threat. Importantly, this would require recognition by the prescribing physician and patient that azithromycin is only partially effective for the prevention of P. falciparum malaria in non-pregnant adults. Currently, plans are underway to assess the combination of azithromycin and chloroquine for the chemoprophylaxis of P. falciparum malaria in Kenya based upon recent findings that these two drugs are synergistic against P. falciparum in vitro and in a recent treatment study.

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Authors’ addresses: D. Gray Heppner, Jr., Douglas S. Walsh, Douglas B. Tang, and Dennis E. Kyle, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910, Telephone: 301-319-9414, Fax: 301-319-7358, E-mail: donald.heppner@na.amedd.army.mil, Nichapat Uthaimongkol, Somchit Tulyayon, Barnyen Permpamich, Theera Wimonwattrawatee, Niphon Chuanak, Anintita Laoboonchai, Prasit Sookto, and Kosol Yongvanichit, United States Army Medical Component, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, AP APO 96546. Thomas G. Brewer, Bill & Melinda Gates Foundation, P.O. Box 23530, Seattle, WA 98102, E-mail: thomasb@gatesfoundation.org, Philip McDaniel, 10805 SE Cherry Blossom Drive, Portland, OR 97216-3107, E-mail: philmcd@concentric.net, Chirapa Eamsila, Research Division, Thai Component, Armed Forces Research Institute of Medical Sciences, 315/6 Rajavithi Road, Bangkok 10400, Thailand, E-mail: chirapa.eamsila@amedd.army.mil, Kathleen Uhl, U.S. Food and Drug Administration Center for Drug Evaluation and Research, Office of New Drugs, 5600 Fishers Lane, HFD-020, Rockville, MD 20857, Telephone: 301-443-5157, Fax: 301-443-5515, E-mail: uhlik@ceder.fda.gov, Lisa W. Keep, Department of Preventive Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, E-mail: lkeep@suslhs.mil, Robert E. Miller, L-3 Government Services, Inc., 1003 West 7th, Suite 506, Frederick, MD 21701, E-mail: DrBob2@adelphia.net, Chansuda Wongrinchanalai, National Institute of Public Health/Naval Medical Research Unit 2 Laboratory, P.O. Box 131, Phnom Penh, Cambodia, E-mail: chansuda@namru2.med.navy.mil.

Reprint requests: D. Gray Heppner Jr., Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910.

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