Efficacy, Safety and Tolerability of Pyronaridine-artesunate in Asymptomatic Malaria-infected Individuals: a Randomized Controlled Trial

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Summary:

This randomized study in The Gambia and Zambia evaluated pyronaridine-artesunate as full or incomplete treatment in individuals with asymptomatic *Plasmodium falciparum* infection. High efficacy and good tolerability suggest that pyronaridine-artesunate could be useful in mass drug administration campaigns in Africa.
Abstract

**Background.** Pyronaridine-artesunate (PA) is a registered artemisinin-based combination therapy, potentially useful for mass drug administration campaigns. However, further data are needed to evaluate its efficacy, safety and tolerability as full or incomplete treatment in asymptomatic *Plasmodium falciparum*-infected individuals.

**Methods.** This phase II, multi-center, open label, randomized clinical trial was conducted in The Gambia and Zambia. Participants with microscopically confirmed asymptomatic *P. falciparum* infection were randomly assigned (1:1:1) to receive a 3-day, 2-day, or 1-day treatment regimen of PA (180:60 mg), dosed according to bodyweight. The primary efficacy outcome was PCR-adjusted adequate parasitological response (APR) at day 28 in the per-protocol population.

**Results.** A total of 303 participants were randomized. Day 28 PCR-adjusted APR was 100% for both the 3-day (98/98) and 2-day regimens (96/96), and 96.8% (89/94) for the 1-day regimen. Efficacy was maintained at 100% until day 63 for the 3-day and 2-day regimens, but declined to 94.4% (84/89) with the 1-day regimen. Adverse event frequency was similar between the 3-day (51.5% [52/101]), 2-day (52.5% [52/99]), and 1-day (54.4% [56/103]) regimens; the majority of adverse events were of grade 1 or 2 severity (85% [136/160]). Asymptomatic, transient increases (>3xULN) in alanine transaminase/aspartate transaminase were observed for 6/301 (2.0%) participants.

**Conclusion:** PA had high efficacy and good tolerability in asymptomatic *P. falciparum*-infected individuals, with similar efficacy for the full 3-day and incomplete 2-day regimens. Although good adherence to the 3-day regimen should be encouraged, these results support the further investigation of PA for mass drug administration campaigns.

**Keywords.** pyronaridine-artesunate; malaria; asymptomatic; pediatric; randomized controlled clinical trial.

**Clinical Trials Registration.** ClinicalTrials.gov: NCT03814616.
Abbreviations

ACT, artemisinin-based combination therapy; APR, adequate parasitological response; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-RDT, hyper-sensitive rapid diagnostic test; MDA, mass drug administration; m-ITT, microbiological intention-to-treat; PA, pyronaridine-artesunate; PCR, polymerase chain reaction; PP, per-protocol; RDT, rapid diagnostic test; ULN, upper limit of normal; WHO, World Health Organization.
Introduction

In 2015, the World Health Organization (WHO) Global Technical Strategy set ambitious goals for reducing malaria mortality and incidence rates by at least 90%, and achieving malaria elimination in at least 35 countries by 2030 [1]. Eleven countries worldwide, ten of them in sub-Saharan Africa, contribute about 70% of global malaria morbidity and mortality [2]. Even in areas with high coverage of control interventions, malaria transmission persists and has become increasingly heterogeneous [3-5]. Innovative tools and strategies are needed to reduce malaria transmission and promote elimination.

A major challenge for malaria elimination is transmission from asymptomatic malaria-infected individuals carrying low density infections [6-8]. Interventions targeting the human transmission reservoir, such as mass drug administration (MDA), can reduce malaria prevalence and transmission [9-16]. Effective MDA requires high coverage and good adherence to treatment [17-19], and there is a need for efficacious, well tolerated, and affordable treatment for this purpose.

Pyronaridine-artesunate (PA) is a fixed-dose artemisinin-based combination therapy (ACT) shown to be highly efficacious and well tolerated for the treatment of uncomplicated falciparum malaria [20-32]. This study is the first to evaluate PA efficacy, safety, and tolerability in individuals with asymptomatic Plasmodium falciparum infection. To assess the potential impact of sub-optimal adherence on parasitological efficacy, PA was administered at the full therapeutic dose (once daily for three days) and as incomplete treatment (once daily for 2-days or 1-day).

Methods

Ethics statement

The protocol was approved by the Gambian Government/MRC Joint Ethics Committee in The Gambia, the Tropical Diseases Research Centre (TDRC) Ethics Review Committee and the National Health Research Ethics Board in Zambia, and the Ethics Committee of the London School of Hygiene and Tropical Medicine. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable national regulations. Written informed consent was obtained from all patients or their parents/guardians if aged under 18 years; documented assent was obtained from children aged 12–17 years.

Study design and participants

This phase II, multi-center, open label, randomized clinical trial was conducted in Basse (Upper River Region), Eastern Gambia, and Nchelenge (Luapula Province), Northern Zambia, between 2nd October 2018 and 16th May 2019. Trial sites were in areas of moderate-to-high malaria transmission. Potential study participants were identified by systematic pre-screening for malaria infection in local communities and schools until the required sample size was reached.

Inclusion criteria were confirmed P. falciparum mono-infection with a parasite density between 20 and 50,000/µL, no clinical malaria signs or symptoms for the past 72 hours, age >5
years, body weight >20 kg, and the ability to swallow oral medication. Participants were excluded if they had a hemoglobin level <7 g/dL, evidence of severe malnutrition, known allergy to the study drugs. Complete eligibility criteria are described in Supplementary Methods 1.

Study drug

Pyronaridine-artesunate (180/60 mg) fixed-dose combination tablets (Shin Poong, Pharmaceutical, Co, Ltd) were given orally, once daily, according to body weight: 20 to <24 kg, 1 tablet; 24 to <45 kg, 2 tablets; 45 to <65 kg, 3 tablets; and ≥65 kg, 4 tablets. Treatment was administered for 3 days (3-day regimen), two days (2-day regimen), or one day (1-day regimen). All doses were directly supervised. Vomiting within 30 minutes prompted repeat dosing. Vomiting of the repeat dose resulted in participant withdrawal and rescue treatment as per local recommendations.

Randomization and masking

Participants were randomized (1:1:1) to receive the PA 3-day regimen, 2-day regimen, or 1-day regimen according to a computer-generated randomization list provided by the study sponsor. Treatment allocation was in sealed envelopes sequentially numbered with the study participant’s unique code. Participants were allocated in enrolment order to the treatment in the next available envelope. Participants and clinical staff were not masked to treatment regimen; microscopists responsible for reading malaria smears remained blinded to treatment allocation throughout the study.

Procedures

Pre-screening for malaria infection was done using a standard rapid diagnostic test (RDT; SD Bioline Malaria Ag Pf, Standard Diagnostics Inc.) or hypersensitive (HS)-RDT (Alere Malaria Ag Pf, Standard Diagnostics, Inc.) in Zambia and HS-RDT in The Gambia, with confirmation by microscopy. Eligible participants received their first PA dose on day 0; a blood slide was collected 4–8 hours after the first dose. Participants returned on days 1, 2, 3, 7, 14, 21, 28, 35, 42, and 63, or at any time if they felt unwell. Insecticide-treated bed nets were provided to all participants on day 0. The assessment schedule is shown in Table 1.

Giemsa-stained thick and thin blood smears for parasite identification and quantification were examined independently by two microscopists using standard methods [33]. Any discordant blood smears or those with >30% variance in parasite density were reviewed independently by a third microscopist, with external quality control on approximately 4% of slides. To distinguish between recrudescence and re-infection, blood spots were obtained for P. falciparum polymerase chain reaction (PCR) genotyping. Recrudescence was defined as at least one matching allelic band in all markers (P. falciparum genes msp 1, msp 2, and glurp) between samples from baseline and recurrence [34].
Demographic characteristics were recorded, and a medical history taken at screening. Physical examination, vital signs, malaria signs and symptoms and adverse events were assessed throughout the study and categorized using the Medical Dictionary for Regulatory Activities (version 22.1). Blood samples were collected for hematology and clinical chemistry.

Outcomes

The primary efficacy outcome was day 28 PCR-adjusted adequate parasitological response (APR), defined as a microscopically negative slide at Day 28, irrespective of axillary temperature, in participants without previous treatment failure. Secondary efficacy endpoints were: i) PCR-adjusted APR at days 7, 14, 21, 35, 42, and 63; ii) PCR-unadjusted APR at days 7, 14, 21, 28, 35, 42, and 63; iii) recurrence, re-infection and recrudescence incidence rate until day 63; iv) the proportion of participants parasite-free by microscopy between 4–8 h post first PA dose and by day 1, 2, and 3 post-first dose; and v) gametocyte carriage up to Day 14, by microscopy.

Safety outcomes were adverse event frequency, and abnormal vital signs, hematological parameters, or clinical chemistry values. Serious adverse events were defined as death, life-threatening, requiring hospitalization or prolongation of hospitalization, congenital abnormalities, or birth defects, persistent or significant disability or incapacity, or Hy's law (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 times the upper limit of normal [xULN] plus a serum total bilirubin >2xULN [>35% direct bilirubin], in the absence of alkaline phosphatase ≥2xULN or biliary injury).

Sample size

The 3-day regimen was assumed to have similar efficacy against P. falciparum in asymptomatic carriers as in patients with uncomplicated malaria, i.e. ≥97% at day 28 [20, 31, 32]. With a sample size of 90 participants, assuming an efficacy of 97.8% for the 3-day regimen, the lower limit of the one-sided Clopper–Pearson 90% confidence interval (CI) was 94.2%. The efficacy of the 2-day and the 1-day regimen was assumed ≥94%, providing reasonable precision given that the minimal acceptable efficacy for an MDA treatment is >90% [15]. Assuming 10% loss to follow-up, 100 participants per arm were needed to demonstrate ≥90% efficacy with 90% power.

Statistical analysis

For this exploratory study no formal statistical testing was planned. The primary efficacy endpoint was evaluated in the per-protocol (PP) population (Figure 1), with one-sided (lower) 90% and 95% CI (Clopper–Pearson) calculated for each treatment arm. Two-sided exact 95% CI for the difference in day 28 APR between each pairwise comparison were calculated, i.e. 3-day regimen versus 1-day regimen, 3-day regime versus 2-day regimen, 2-day regimen versus 1-day regimen (Wilson method without continuity correction). Statistical analysis was performed using SAS Version 9.4 or higher. A
supportive analysis was conducted for the microbiological intention-to-treat (m-ITT) population (Figure 1).

Recrudescence rate and re-infection rate over 63 days were evaluated using Kaplan–Meier analysis in the m-ITT population. Participants with no recurrence event were censored at the last available parasite assessment date and those with major protocol deviations at the time of the protocol deviation. The proportion of parasite-free participants was determined for the PP population. Gametocyte carriage was determined as area under the gametocyte density–time curve (AUC) calculated according to the trapezoidal rule for all participants having at least one positive gametocyte count in the PP population.

**Results**

**Participants**

Overall, 303 participants with confirmed *P. falciparum* mono-infection were enrolled (Figure 1). Baseline characteristics were generally comparable across the treatment arms (Table 2). Geometric mean parasite density was 573.9 µL⁻¹, and 18.8% (55/292) of evaluable participants had baseline gametocytes detectable by microscopy.

**Efficacy**

For the primary outcome, day 28 PCR-adjusted APR in the PP population was 100% (98/98) for the 3-day regimen, 100% (96/96) for the 2-day regimen, and 96.8% (91/94) for 1-day regimen; the lower limit of the 95% CI exceeded 90% for all regimens (Table 3). There was no significant difference in day 28 PCR-adjusted APR across the three study arms (Figure 2). Efficacy was maintained until day 63 for the 3-day and 2-day regimens but declined for the 1-day regimen (Table 3). The m-ITT analysis supported the primary analysis (Supplementary Table 1, Supplementary Figure 1). In the Kaplan–Meier analysis, there were no recrudescences through day 63 for the 3-day and 2-day regimens (Figure 3A). Re-infections were more frequent in the shorter treatment regimens (Figure 3B).

The proportion of participants without infection as determined by microscopy between 4–8h post first PA dose and day 3 was similar for the three treatment groups (Figure 4A). The mean $\log_{10}$ AUC gametocytes until day 14 was similar for all three regimens (Figure 4B). However, all baseline gametocytes were cleared by day 21 with the 3-day regimen but persisted until day 28 with the 2-day and 1-day regimens, re-appearing in one participant at day 63 with the day-1 regimen (Supplementary Table 2).
Safety

Adverse event frequency was similar between the 3-day (51.5% [52/101]), 2-day (52.5% [52/99]), and 1-day (54.4% [56/103]) regimens, though with some differences, i.e. a lower incidence of cough with the 2-day regimen, and a higher incidence of neutropenia and abdominal pain with the 2-day and 1-day regimens versus the 3-day regimen (Figure 5). Most adverse events were grade 1 or 2 in severity (85% [136/160]); grade 3+ adverse events were more common in the day-2 (8.1% [8/99]) and day-1 (12.6% [13/103]) regimens versus the day-3 regimen (2.0% [2/101]) (Supplementary Table 3). The frequency of treatment-related adverse events was lower for the 3-day regimen (6.9% [7/101]) versus the 2-day (12.1% [12/99]) and 1-day (12.6% [13/103]) regimens (Supplementary Table 4), as was the frequency of malaria-related adverse events (2.0% [2/101], 6.1% [6/99], and 6.8% [7/103]), respectively (Supplementary Table 5). There were two serious adverse events, one death of a 12-year-old male by drowning at day 30 (day-3 regimen), and a missed abortion in a 35-year-old female at day 149 resolved by a vacuum aspiration at day 152 (2-day regimen); neither was considered treatment related.

Most laboratory abnormalities were grade 1 or 2 and resolved by day 28 (Supplementary Tables 6 and 7). Post-baseline hemoglobin declines >2 g/dL were observed in 3.7% (11/297) of participants, but hemoglobin levels were >8 g/dL in all participants by day 28 (Table 4). Asymptomatic, transient increases in ALT/AST >3xULN were observed in 6/301 (2.0%) participants, three of whom had increases >5xULN. All values had normalized by day 28 (Table 4). There were no Hy’s Law cases.

Discussion

This study evaluated PA efficacy in asymptomatic individuals infected with \textit{P. falciparum}. In addition, the potential consequences of poor adherence to the full 3-day regimen during MDA campaigns were evaluated by administration of 2-day and 1-day regimens. It is important to stress that this study was not designed to support any change to the 3-day PA regimen for the treatment of uncomplicated malaria, nor does it support abbreviated dosing to clear parasitemia in asymptomatic individuals. The reason of investigating incomplete treatment regimens was to determine PA efficacy when given for community-based interventions aiming at reducing the human reservoir of malaria infection, e.g., mass drug administration or mass testing and treatment. In these circumstances, when treatment may not be directly supervised, treated individuals may take only one or 2 days of treatment. Therefore, it is reassuring the day-28 efficacy was similar across the three treatment regimens and that efficacy for the 3-day and 2-day regimens was maintained until day 63.

Single-dose PA had unexpectedly good efficacy in this population. In a murine blood-stage malaria model, single-dose pyronaridine was shown to reduce parasitemia more rapidly and completely than artesunate, chloroquine, or amodiaquine [35]. This potent effect may have been sufficient to suppress and/or clear parasites after only one dose in most individuals with low parasite density. Although there was no significant difference in PCR-adjusted day-28 APR, recrudescence occurred in the 1-day regimen group from day 7. Recrudescence drives resistance development [36]. Thus, there is a concern that the 1-day regimen would increase the risk or rapidity of resistance...
emergence to PA. In the Greater Mekong Sub-region, PA has been shown to be efficacious in regions where dihydroartemisinin-piperaquine and/or mefloquine-artesunate have been abandoned as first-line therapy for uncomplicated *P. falciparum* malaria owing to multi-drug resistance [21, 24-26]. Therefore, adherence to full treatment for PA is extremely important, given this combination might be an alternative option in case of emerging resistance to other ACTs [37]. With the 3-day and 2-day regimens, PCR-adjusted efficacy was maintained at 100% through day 63, with one-sided 95% CIs exceeding 96% in both arms. Such an high efficacy probably reflects the low baseline parasite density (geometric mean 573.9, μL⁻¹ blood); in contrast, African patients with uncomplicated malaria, have mean parasite densities typically above 15,000 μL⁻¹ blood [20, 22, 27, 28, 30, 32].

Re-infections were more frequent with the 2-day and 1-day versus the 3-day PA regimen and occurred earlier; from day 7 with the 1-day and 2-day regimens versus day 14 for the 3-day regimen. This was expected given that a larger dose of pyronaridine will result in a longer half-life for the pyronaridine component, providing an extended period of post-treatment protection [30, 38]. Although the half-life of pyronaridine is about 14–18 days, the effect of this early difference in re-infection could still be observed at day 63.

Parasite clearance by day 3 was 99.0% for both the 3-day and 2-day regimens and slightly lower (97.9%) for the 1-day regimen. Similar rapid parasite clearance has been previously demonstrated for 3-day PA in patients with uncomplicated *P. falciparum* malaria [22, 29, 30, 32]. Only a small proportion of patients were parasitemic at day 3 following the 1-day PA regimen. However, because the half-life of artesunate and its active metabolite dihydroartemisinin is short (up to 1.5 h) [39], these parasites will be exposed to pyronaridine monotherapy. As these parasites may be also those least susceptible to artesunate, any subsequent recrudescence increases the risk for the selection of artesinin-resistant strains.

Clinical studies in patients with uncomplicated *P. falciparum* malaria indicate that ACTs have limited efficacy in clearing gametocytes, which is dependent primarily on the non-artesinin component [40, 41]. Pyronaridine is thought to have limited efficacy against gametocytes, with conflicting *in vitro* data [42-45]. In Kenyan children with uncomplicated *P. falciparum* malaria treated with PA, quantitative reverse-transcription PCR indicated that 25.3% (20/79) of patients harbored gametocytes at day 14 [46]. In the current study, though the AUC values with all three regimens were similar, microscopically determined gametocytemia persisted to day 14 with the 3-day regimen, and to day 63 following the 1-day regimen. Thus, co-administration of PA and single low-dose primaquine may be needed if MDA is to rapidly clear gametocytes from asymptomatic individuals infected with falciparum malaria, as has been demonstrated with artemether-lumefantrine/primaquine and dihydroartemisinin-piperaquine/piperaquine [14, 47, 48].

PA was generally well tolerated, with adverse events consistent with previous studies of 3-day treatment of patients with uncomplicated malaria [20, 22, 24-32, 49]. There was a trend for fewer adverse events with the 3-day versus the 2-day and 1-day regimens. Although the study population was asymptomatic for malaria, falciparum infection is not necessarily benign, being associated with immune system dysregulation and inflammation [50]. The full therapeutic dose may have been more effective in resolving the more subtle health impacts of malaria infection, and emergent malaria symptoms were observed more frequently with the abbreviated regimens. Consistent with the known safety profile for PA [20, 31, 32], transient, asymptomatic increases in
ALT and AST were observed for six participants (2.0%). Notably, post-baseline ALT or AST >5 xULN only occurred with the 2-day and 1-day regimen.

A limitation of this study was the selection of participants based on microscopy, whereas individuals with sub-patent infection are an important component of the transmission reservoir [6, 7]. Nevertheless, given the lower parasite densities, PA efficacy is likely to be similar, if not higher against sub-microscopic infections. Moreover, we could not exclude the possibility of low-level residual parasitemia in PA-treated participants. In Kenyan children with uncomplicated *P. falciparum* malaria treated with either PA or artemether-lumefantrine, residual parasitemia at day 7 detected by quantitative PCR was not associated with parasite recurrence at day 28 or day 42 [51]. Given study participants were followed up until day 63 post-treatment in our study, it is unlikely that any recrudescence was missed. Nevertheless, it is possible that infections acquired during follow up may have had sub-patent densities at day 63 and may have been missed by microscopy. A further limitation of this study was the lack of an ACT comparator.

This study indicates the potential of PA for community-based malaria control interventions, in conjunction with other tools. The finding that the 2-day and 3-day regimens had similar efficacies in this population is reassuring given the challenges related to treatment adherence during MDA, as treatment is unlikely to be supervised for 3 days. However, this does not negate the importance of adherence to the 3-day regimen when used for acute malaria. This study supports further investigation of PA in comparative operational studies to examine adherence and outcomes in asymptomatic *P. falciparum* infection.
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Conflicts of interest

IBF, and SD are full time employees of Medicines for Malaria Venture and JS is employed by Shin Poong Pharmaceutical Company, Ltd. and is an employee of Medicines for Malaria Venture. RM consulted for Shin Poong during the study and is the Shin Poong qualified person for pharmacovigilance; RM is a full-time employee at Artemida Pharma Limited and is responsible for safety aspects of pyronaridine-artesunate on behalf of Shin Poong. SAB is a full-time employee at Artemida Pharma Limited and responsible for project oversight for pyronaridine-artesunate on
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**Figure legends**

**Figure 1.** Participant disposition.

Populations: safety population, all randomized participants who received at least one dose of study medication; microbiological-intention-to-treat (m-ITT) population, all randomized patients who received at least one treatment dose and who had confirmed positive parasitemia before treatment; per-protocol (PP) population, all randomized patients who completed their treatment, had outcome data for the primary efficacy end point, and complied with the protocol.

Abbreviations: PA, pyronaridine-artesunate.

**Figure 2.** Adequate parasitological response at day 28 in the per-protocol population.

Abbreviations: APR, adequate parasitological response.

**Figure 3.** Kaplan–Meier estimates of (a) recrudescence; and (b) re-infection in the microbiological intention-to-treat population.

**Figure 4.** Parasite clearance in the per-protocol population: (a) Proportion of participants with asexual parasite clearance until day 3; and (b) Mean (SD) log₁₀ area under the curve for gametocytes up to day 14 in participants with or without baseline gametocytes.

Abbreviations: AUC, area under the gametocyte density–time curve.

**Figure 5.** Most common treatment-emergent adverse events of any cause in the safety population.

Adverse events occurring in >1 participant in any one treatment group. Values are percentage frequency. Participants may have had more than one adverse event.
Table 1. Assessment schedule.

| Assessment                                      | Study day/ visit |
|------------------------------------------------|------------------|
| Demographics, medical history                   | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Urine pregnancy test                            | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Physical examination<sup>b</sup>                 | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Thick/thin blood smears                          | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Blood spot (PCR genotyping)<sup>c</sup>          | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Hematology/biochemistry                          | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Adverse events                                   | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Concomitant medication                           | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
| Study drug administration                        | BL, D1, D2, D3, D7, D14, D21, D28, D35, D42, D63, EW, UV |
|<sup>a</sup> 4–8 h                               |                  |

<sup>b</sup>Physical examination, malaria signs and symptoms, vital signs and body temperature.

<sup>c</sup>Increases in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total or conjugated bilirubin >3 times the upper limit of normal (xULN) prompted collection of an additional sample within 24 h and repeated sampling at 48-h intervals until values were ≤2xULN.

<sup>d</sup>Assessment was only done in the event of recurrent infection.

Abbreviations: BL, baseline; ET, early withdrawal; UV, unscheduled visit.
Table 2. Baseline Characteristics

| Characteristics                  | Pyronaridine-artesunate treatment group | Overall (n = 303) |
|----------------------------------|----------------------------------------|------------------|
|                                  | 3-day regimen (n = 101)                | 2-day regimen (n = 100) | 1-day regimen (n = 102) |
| Country, n (%)                   |                                        |                  |                       |
| The Gambia                       | 51 (50.5)                              | 50 (50.0)        | 52 (51.0)             | 153 (50.5) |
| Zambia                           | 50 (49.5)                              | 50 (50.0)        | 50 (49.0)             | 150 (49.5) |
| Sex, n (%)                       |                                        |                  |                       |
| Male                             | 60 (59.4)                              | 39 (39.4)        | 49 (47.6)             | 148 (48.8) |
| Female                           | 41 (40.6)                              | 60 (60.6)        | 54 (52.4)             | 155 (51.2) |
| Age, years, mean (SD) [range]    | 15.0 (8.3) [6–48]                      | 15.9 (9.9) [6–60] | 16.6 (11.5) [6–64]    | 15.8 (10.0) [6–64] |
| Age group, n (%)                 |                                        |                  |                       |
| 5–≤12 years                      | 48 (47.5)                              | 49 (49.5)        | 48 (46.6)             | 145 (47.9) |
| >12–18 years                     | 32 (31.7)                              | 24 (24.2)        | 25 (24.3)             | 81 (26.7)  |
| Age Group | Weight by age group, kg, mean (SD) [range] |
|-----------|------------------------------------------|
|           | 21 (20.8) | 26 (26.3) | 30 (29.1) | 77 (25.4) |
| 5–≤12 years | 29.0 (8.2) [20.7–65.2] | 27.4 (6.3) [20.2–51.2] | 26.1 (4.4) [20.6–40.1] | 27.5 (6.6) [20.2–65.2] |
| >12–18 years | 42.8 (7.5) [33.2–62.4] | 46.5 (11.7) [27.8–72.0] | 40.2 (6.7) [29.3–56.1] | 43.1 (8.9) [27.8–72.0] |
| ≥18 years | 58.8 (11.6) [37.1–87.3] | 56.7 (10.5) [44.4–94.0] | 57.40 (10.7) [42.7–96.3] | 57.50 (10.8) [37.1–96.3] |
| Asexual parasites, µL-1, geometric mean (range) | 592.7 (20–38960) | 579.6 (24–47600) | 550.6 (16–33020) | 573.9 (16–47600) |
| Participants with gametocytes, n/N (%) | 17/99 (17.2) | 20/97 (20.6) | 18/96 (18.8) | 55/292 (18.8) |
Table 3. Adequate Parasitological Response in the Per-protocol Population

| APR, n/N (%) [one sided 95% CI] | Pyronaridine-artesunate treatment group |
|---------------------------------|----------------------------------------|
|                                 | 3-day regimen (n = 99) | 2-day regimen (n = 97) | 1-day regimen (n = 96)* |
| PCR-adjusted                    |                         |                         |
| Day 7                           | 99/99 (100) [97.0]      | 97/97 (100) [97.0]      | 95/96 (99.0) [95.2]    |
| Day 14                          | 99/99 (100) [97.0]      | 96/96 (100) [96.9]      | 94/95 (98.9) [95.1]    |
| Day 21                          | 98/98 (100) [97.0]      | 96/96 (100) [96.9]      | 92/95 (96.8) [92.0]    |
| Day 28                          | 98/98 (100) [97.0]      | 96/96 (100) [96.9]      | 91/94 (96.8) [92.0]    |
| Day 35                          | 96/96 (100) [96.9]      | 93/93 (100) [96.8]      | 89/92 (96.7) [91.8]    |
| Day 42                          | 96/96 (100) [96.9]      | 92/92 (100) [96.8]      | 88/91 (96.7) [91.7]    |
| Day 63                          | 93/93 (100) [96.8]      | 86/86 (100) [96.6]      | 84/89 (94.4) [88.6]    |
| PCR-unadjusted                  |                         |                         |
| Day 7                           | 99/99 (100) [97.0]      | 96/97 (99.0) [95.2]     | 94/96 (97.9) [93.6]    |
| Day 14                          | 98/99 (99.0) [95.3]     | 96/97 (99.0) [95.2]     | 94/96 (97.9) [93.6]    |
| Day 21                          | 98/99 (99.0) [95.3]     | 96/97 (99.0) [95.2]     | 91/96 (94.8) [89.4]    |
| Day 28                          | 97/99 (98.0) [93.8]     | 94/97 (96.9) [92.2]     | 89/96 (92.7) [86.7]    |
| Day 35                          | 96/98 (98.0) [93.7]     | 92/96 (95.8) [90.7]     | 88/96 (91.7) [85.5]    |
| Day 42                          | 94/98 (95.9) [90.9]     | 90/96 (93.8) [88.0]     | 86/96 (89.6) [83.0]    |
| Day 63                          | 91/97 (93.8) [88.2]     | 85/93 (91.4) [85.0]     | 81/96 (84.4) [77.0]    |

Abbreviations: PCR, polymerase chain reaction; APR, adequate parasitological response.

*aIn the PCR-adjusted analysis, all treatment failures on or before day 42 and 4/5 on day 63 were late parasitological failures (parasitemia plus temperature <37°C), the remaining treatment failure on day 63 was a late clinical failure (parasitemia plus temperature ≥37°C).
### Table 4. Changes in Hemoglobin, Alanine Aminotransferase and Aspartate Aminotransferase.

| Parameter                                      | Time point | Pyronaridine-artesunate treatment group |
|------------------------------------------------|------------|----------------------------------------|
|                                                |            | 3-day regimen (n=101) | 2-day regimen (n=99) | 1-day regimen (n=103) |
| Change in hemoglobin from baseline >2 g/dL, n/N (%) | Post-baseline | 3/99 (3.0) | 6/97 (6.2) | 2/101 (2.0) |
|                                                | Day 1      | 2/98 (2.0) | 3/95 (3.2) | 1/98 (1.0) |
|                                                | Day 7      | 2/97 (2.1) | 3/95 (3.2) | 2/98 (2.0) |
|                                                | Day 28     | 1/97 (1.0) | 3/96 (3.1) | 0/95      |
| Mean hemoglobin (SD) [range], g/dL             | Baseline   | 11.9 (1.5) [7.6–16.1] | 12.1 (1.6) [7.3–17.4] | 11.8 (1.6) [7.1–16.9] |
|                                                | Day 1      | 11.6 (1.8) [7.2–19.2] | 11.6 (1.5) [8.0–16.4] | 11.5 (1.7) [6.9–19.0] |
|                                                | Day 7      | 11.3 (1.4) [7.8–15.0] | 11.6 (1.6) [8.5–19.9] | 11.4 (1.8) [7.7–21.8] |
|                                                | Day 28     | 12.0 (1.2) [8.2, 15.6] | 12.2 (1.2) [9.1, 16.2] | 12.0 (1.3) [8.6, 15.6] |
| Post-baseline ALT or AST >3xULN, n/N (%)       | Day 1      | 1/101 (1.0) | 4/97 (4.1) | 1/98 (1.0) |
|                                                | Day 7      | 0/101      | 2/99 (2.0) | 0/100     |
|                                                | Day 28     | 0/99       | 0/98       | 0/95      |
| Post-baseline ALT or AST >5xULN, n/N (%)       | Day 1      | 0/101      | 2/97 (2.1) | 1/98 (1.0) |
|                                                | Day 7      | 0/101      | 0/99       | 0/100     |
|                                                | Day 28     | 0/99       | 0/98       | 0/95      |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; xULN, times the upper limit of normal.
Figure 1

Screened for eligibility (n = 408)
211 The Gambia
197 Zambia

Randomized (n= 303)
153 The Gambia
150 Zambia

Not enrolled (n = 105)
102 Inclusion criteria not met
1 Declined to participate
2 Other reasons

PA 3-day regimen (n = 101)
Safety and m-ITT population (n = 101)
Day 28 PP population (n = 99)
Reasons for exclusion (n = 2):*
1 Drug administration error
2 Incorrect number of days dosed
1 Unknown efficacy outcome
Completed study (n = 98)
Premature withdrawals (n = 3):
1 Death
1 Lost to follow-up
1 Withdrawal by subject

PA 2-day regimen (n = 100)
Safety and m-ITT population (n = 100)
Day 28 PP population (n = 97)
Reasons for exclusion (n = 3):*
1 Drug administration error
3 Incorrect number of days dosed
2 Unknown efficacy outcome
Completed study (n = 93)
Premature withdrawals (n = 7):
3 Lost to follow-up
4 Withdrawal by subject

PA 1-day regimen (n = 102)
Safety and m-ITT population (n = 102)
Day 28 PP population (n = 96)
Reasons for exclusion (n = 6):*
2 Incorrect number of days dosed
1 Parasitemia outside limits
1 Full dose not given
Completed study (n = 100)
Premature withdrawals (n = 2):
1 Lost to follow-up
1 Withdrawal by subject

*Participants may have had >1 reason for exclusion from the PP population.
Figure 2

Comparison

**PCR-adjusted day 28 APR**
- Difference 3-day vs 2-day regimen: 0.0 (−3.8, 3.8)
- Difference 3-day vs 1-day regimen: 3.2 (−1.1, 9.0)
- Difference 2-day vs 1-day regimen: 3.2 (−1.2, 9.0)

**PCR-unadjusted day 28 APR**
- Difference 3-day vs 2-day regimen: 1.1 (−4.4, 6.9)
- Difference 3-day vs 1-day regimen: 5.3 (−1.0, 12.4)
- Difference 2-day vs 1-day regimen: 4.2 (−2.5, 11.5)
Figure 3

(a) Cumulative risk of recrudescence (%) vs. Study day for different treatment groups: 3-day regimen, 2-day regimen, and 1-day regimen. Each line represents a different treatment group with numbers at risk shown in the table below.

(b) Cumulative risk of re-infection (%) vs. Study day for different treatment groups.

| Treatment group          | Day | 0  | 7  | 14 | 21 | 28 | 35 | 42 | 49 | 56 | 63 |
|--------------------------|-----|----|----|----|----|----|----|----|----|----|----|
| 3-day regimen            | 101 | 100| 99 | 99 | 99 | 98 | 95 | 92 | 90 | 87 | 81 |
| 2-day regimen            | 100 | 98 | 96 | 96 | 96 | 93 | 92 | 87 | 87 | 81 | 81 |
| 1-day regimen            | 102 | 101| 98 | 98 | 95 | 93 | 92 | 90 | 83 | 83 | 83 |
Figure 4

a

Proportion of aparasitic participants, %

Time point after first dose

3-day regimen (n=99)
2-day regimen (n=97)
1-day regimen (n=96)

48h Day 1 Day 2 Day 3 48h Day 1 Day 2 Day 3 48h Day 1 Day 2 Day 3

b

Mean (SD) log_{10} AUC for gametocytes, count.day/μL

No baseline gametocytes (n=38)
1-day regimen (n=11)
2-day regimen (n=14)
3-day regimen (n=13)

Baseline gametocytes (n=55)
1-day regimen (n=18)
2-day regimen (n=20)
3-day regimen (n=17)
Figure 5

| Condition                      | 3-day regimen (n=101) | 2-day regimen (n=99) | 1-day regimen (n=103) |
|-------------------------------|-----------------------|----------------------|-----------------------|
| Nasopharyngitis               | 15.8                  | 14.1                 | 12.6                  |
| Headache                      | 7.9                   | 13.1                 | 7.8                   |
| Cough                         | 10.9                  | 2.0                  | 9.7                   |
| Abdominal pain                | 2.0                   | 7.1                  | 10.7                  |
| Neutropenia                   | 2.0                   | 5.1                  | 9.7                   |
| Vomiting                      | 5.0                   | 2.0                  | 2.9                   |
| Diarrhea                      | 2.0                   | 1.0                  | 3.9                   |
| P. falciparum infection       | 1.0                   | 3.0                  | 2.9                   |
| Anemia                        | 2.0                   | 2.0                  | 0                     |
| Influenza                     | 2.0                   | 2.0                  | 0                     |
| Limb injury                   | 2.0                   | 0                    | 1.9                   |
| Schistosomiasis               | 1.0                   | 2.0                  | 1.0                   |
| Gastroenteritis               | 2.0                   | 1.0                  | 0                     |
| Pyrexia                       | 0                     | 1.0                  | 1.9                   |
| Respiratory tract infection   | 2.0                   | 0                    | 1.0                   |
| Skin ulcer                    | 0                     | 1.0                  | 1.9                   |
| Thrombocytopenia              | 0                     | 2.0                  | 1.0                   |
| Toothache                     | 2.0                   | 0                    | 1.0                   |
| Transaminases increased       | 0                     | 3.0                  | 0                     |
| Furuncle                      | 0                     | 0                    | 2.0                   |
| Procedural pain               | 0                     | 0                    | 1.9                   |