Pyronaridine–artesunate or dihydroartemisinin–piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomised, multicentre, open-label, longitudinal, controlled, phase 3b/4 trial

*The West African Network for Clinical Trials of Antimalarial Drugs (WANECAM)**

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Summary

Background Artemether–lumefantrine and artesunate–amodiaquine are used as first-line artemisinin-based combination therapies (ACTs) in west Africa. Pyronaridine–artesunate and dihydroartemisinin–piperaquine are potentially useful for diversification of ACTs in this region, but further safety and efficacy data are required on malaria retreatment.

Methods We did a randomised, multicentre, open-label, longitudinal, controlled phase 3b/4 clinical trial at seven tertiary centres in Burkina Faso, Guinea, and Mali. Eligible participants for first malaria episode and all retreatment episodes were adults and children aged 6 months and older with microscopically confirmed *Plasmodium* spp malaria (>0 to <200 000 parasites per μL of blood) and fever or history of fever in the previous 24 h. Individuals with severe or complicated malaria, an alanine aminotransferase concentration of more than twice the upper limit of normal, or a QTc greater than 450 ms were excluded. Using a randomisation list for each site, masked using sealed envelopes, participants were assigned to either pyronaridine–artesunate or dihydroartemisinin–piperaquine versus either artesunate–amodiaquine or artemether–lumefantrine. Block sizes were two or four if two treatments were allocated, and three or six if three treatments were allocated. Microscopists doing the parasitological assessments were masked to treatment allocation. All treatments were once-daily or twice-daily tablets or granules given orally and dosed by bodyweight over 3 days at the study centre. Patients were followed up as outpatients up to day 42, receiving clinical assessments on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42. Two primary outcomes were compared for non-inferiority: the 2-year incidence rate of all microscopically confirmed, complicated and uncomplicated malaria episodes in patients in the intention-to-treat population (ITT; non-inferiority margin 20%); and adequate clinical and parasitological response (ACPR) in uncomplicated malaria across all episodes (unadjusted and PCR-adjusted for *Plasmodium falciparum* and unadjusted for other *Plasmodium* spp) in the per-protocol population on days 28 and 42 (non-inferiority margin 5%). Safety was assessed in all participants who received one dose of study drug. This study is registered at the Pan African Clinical Trials Registry (PACTR201105000286876).

Findings Between Oct 24, 2011, and Feb 1, 2016, we assigned 4710 eligible participants to the different treatment strategies: 1342 to pyronaridine–artesunate, 967 to artemether–lumefantrine, 1061 to artesunate–amodiaquine, and 1340 to dihydroartemisinin–piperaquine. The 2-year malaria incidence rate in the ITT population was non-inferior for pyronaridine–artesunate versus artemether–lumefantrine (1·77, 95% CI 1·63–1·93 *vs* 1·87, 1·72–2·03; rate ratio [RR] 1·05, 95% CI 0·94–1·17); and versus artesunate–amodiaquine (1·39, 95% CI 1·22–1·59 *vs* 1·35, 1·18–1·54; RR 0·97, 0·87–1·07). Similarly, this endpoint was non-inferior for dihydroartemisinin–piperaquine versus artemether–lumefantrine (1·16, 95% CI 1·01–1·34 *vs* 1·42 1·25–1·62; RR 1·22, 95% CI 1·06–1·41) and versus artesunate–amodiaquine (1·35, 1·21–1·51 *vs* 1·68, 1·51–1·88; RR 1·25, 1·02–1·50). For uncomplicated *P falciparum* malaria, PCR-adjusted ACPR was greater than 99·5% at day 28 and greater than 98·6% at day 42 for all ACTs; unadjusted ACPR was higher for pyronaridine–artesunate versus comparators at day 28 (96·9% *vs* 82·3% for artemether–lumefantrine and 95·6% *vs* 89·0% for artesunate–amodiaquine) and for dihydroartemisinin-piperaquine versus comparators (99·5% *vs* 81·6% for artemether–lumefantrine and 99·0% *vs* 89·0% for artesunate–amodiaquine). For non-falciparum species, unadjusted ACPR was greater than 98% for all study drugs at day 28 and at day 42 was greater than 83% except for artemether–lumefantrine against *Plasmodium ovale* (in ten [62·5%] of 16 patients) and against *Plasmodium malariae* (in nine [75·0%] of 12 patients). Nine deaths occurred during the study, none of which were related to the study treatment. Mostly mild transient elevations in transaminases occurred with pyronaridine–artesunate versus comparators, and mild QTcF prolongation with dihydroartemisinin-piperaquine versus comparators.

Interpretation Pyronaridine–artesunate and dihydroartemisinin–piperaquine treatment and retreatment of malaria were well tolerated with efficacy that was non-inferior to first-line ACTs. Greater access to these efficacious treatments in west Africa is justified.

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Introduction

In west Africa, 355 million people are at risk of malaria, with an estimated 112 million cases and 218 000 deaths occurring annually.[1] Artemisinin-based combination therapy (ACT) is recommended for uncomplicated *Plasmodium falciparum* malaria.[2] Because at-risk individuals might have frequent malaria episodes throughout their lives, ACTs must be assessed on repeated treatments. Artemether–lumefantrine and artesunate–amodiaquine were adopted as first-line ACTs in west Africa following studies showing retreatment efficacy and acceptable safety.[3–7] Artesunate–amodiaquine for malaria treatment is currently discouraged for children aged 3–59 months in the Sahelian countries in Africa that have adopted seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine.[1,8] Thus, artemether–lumefantrine is the only ACT available for malaria treatment across much of west Africa.

Two more recently licensed ACTs—pyronaridine–artesunate[9–14] and dihydroartemisinin–piperaquine[15–22]—showed high efficacy and were well tolerated in randomised clinical trials. Both are prequalified by WHO and included in WHO's Essential Medicines List, and would potentially be useful for ACT diversification in sub-Saharan Africa. However, a higher incidence of non-symptomatic increases in hepatic transaminase concentrations has been noted with pyronaridine–artesunate versus comparator drugs.[2,9,23] Further data are needed to characterise the risk for hepatotoxicity, particularly in young children, and whether there is an increased risk after retreatment for malaria. Dihydroartemisinin–piperaquine is used extensively in Asia but less so in Africa. Piperaquine prolongs the QT interval by approximately the same amount as chloroquine[24] and further safety data on the retreatment risk of QT prolongation with piperaquine in African populations would be valuable. Dihydroartemisinin–piperaquine has been shown to reduce the risk of recurrent malaria versus artemether–lumefantrine.[25,26] However, the longitudinal effect on malaria incidence has not been investigated.

Therefore we undertook the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) longitudinal study to assess malaria incidence and pyronaridine–artesunate or dihydroartemisinin–piperaquine efficacy and safety when used repeatedly for consecutive clinical malaria episodes over a 2-year period, compared with artemether–lumefantrine or artesunate–amodiaquine. A smaller substudy of pyronaridine–artesunate hepatic safety after repeated treatment compared with artemether–lumefantrine over 12 months' follow-up has been published.[14] This report is on the complete 2-year follow-up period across all enrolled patients, malaria episodes, and treatment arms.

Research in context

Evidence before this study

Artemisinin-based combination therapy (ACT) is recommended for treatment of uncomplicated *Plasmodium falciparum* malaria. In west Africa, people often have repeated episodes of malaria and therefore ACTs should be safe and effective for malaria retreatment. In this region, artemether–lumefantrine and artesunate–amodiaquine were adopted as first-line ACTs, following studies showing they had retreatment efficacy and acceptable safety. Pyronaridine–artesunate and dihydroartemisinin–piperaquine are more recently approved ACTs that have shown high efficacy and acceptable safety in randomised clinical trials. However, data are needed regarding efficacy and safety for malaria retreatment.

Added value of this study

The 2-year incidence of malaria in the intention-to-treat population in three countries in west Africa was non-inferior for pyronaridine–artesunate or dihydroartemisinin–piperaquine versus comparators. Our study provides evidence of the efficacy and safety of pyronaridine–artesunate and dihydroartemisinin–piperaquine for the repeated treatment of malaria in this African population.

Implications of all the available evidence

At present, only artemether–lumefantrine and artesunate–amodiaquine are available for first-line treatment of malaria in west Africa. Recently, artesunate–amodiaquine use has become restricted in most of west Africa because of the adoption of seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine. This study supports the wider use of pyronaridine–artesunate and dihydroartemisinin–piperaquine in west Africa, which is a key development for health care in the region and provides new options for national malaria control programmes when planning malaria treatment strategies.

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For **WHO's Essential Medicines List** see http://www.who.int/medicines/publications/essentialmedicines/en/

Methods

Study design and participants

We undertook a phase 3b/4 comparative, randomised, multicentre, open-label, longitudinal clinical study over 2 years at seven tertiary centres in Burkina Faso (Bobo Dioulasso and Banfora-Niangoloko), Guinea (Maferenya), and Mali (Bougoula-Hameau, Djoliba, Kolle, and Sotuba). Ethical approval was obtained from local ethics committees for each site. The WANECAM study protocol version 12 (eight amendments) is available online. All protocol amendments are in the appendix.

For the **WANECAM study protocol** see www.wanecam.org

See Online for appendix

Eligible participants were adults and children aged 6 months and older of either sex with uncomplicated malaria and a bodyweight of at least 5 kg, with no clinical evidence of severe malnutrition. For the first 40 patients retreated with pyronaridine–artesunate (and comparators), enrolment was staged for bodyweight and age based on a review by a data safety monitoring board (appendix). For the first malaria episode and all retreatment episodes, eligibility criteria were fever (axillary temperature ≥37·5°C, or oral, or rectal, or tympanic temperature ≥38°C) or history of fever in the previous 24 h, and positive microscopy for *Plasmodium* spp (>0 to <200 000 parasites per μL of blood). All participants had to be able to swallow oral medication and remain in the study vicinity with no absence of more than 3 months.

Exclusion criteria for the first malaria episode were severe or complicated malaria, severe vomiting or diarrhoea, known history or evidence of any clinically significant disorders, a QTc value of more than 450 ms, haemoglobin of less than 7 g/dL, non-malarial febrile conditions, known drug hypersensitivity, antimalarial treatment within the previous 2 weeks or an investigational drug within 4 weeks, known or suspected alcohol abuse, known HIV-antibody positivity, hepatitis A IgM, hepatitis B surface antigen or hepatitis C antibody, alanine aminotransferase (ALT) concentration of more than twice the upper limit of normal (ULN), or significant renal impairment (creatinine >1·5×ULN). Pregnant or lactating women were excluded, and women aged 12 years and older required a negative pregnancy test and could not be planning a pregnancy during each 42-day period after treatment. All participants or their parent or guardian provided written informed consent, plus children able to understand the study gave assent.

For each retreatment episode, exclusion criteria were severe or complicated malaria, severe vomiting or diarrhoea, liver function test result of more than twice the ULN, significant arrhythmia or prolonged QTc of more than 450 ms during previous treatment or at presentation, active acute hepatitis A, B, or C, renal impairment (creatinine >1·5×ULN), an ongoing severe adverse event not related to study drug, parasite relapse before day 28, use of any other antimalarial drug, pregnancy, or breastfeeding.

Randomisation and masking

We assigned eligible participants to repeated therapy with either pyronaridine–artesunate (Shin Poong Pharmaceutical, Ansan, South Korea) or dihydroartemisinin–piperaquine (Alfasigma SpA, Pomezia, [RM], Italy) versus either artemether–lumefantrine (Novartis Pharma AG, Basel, Switzerland) or artesunate–amodiaquine (Sanofi, Paris, France), depending on study centre. There was no direct comparison between pyronaridine–artesunate and dihydroartemisinin–piperaquine. This was an open label study, although microscopists doing the parasitological assessments were masked to treatment allocation. A computer-generated randomisation list for each site within each country was used. To minimise the risk of investigators guessing treatment allocation, when there were two treatments to allocate the block size was randomly two or four and when there were three treatments to allocate the block size was randomly three or six. The University of Bamako data management team enclosed the randomisation code containing the study arm in sealed, opaque, sequentially numbered envelopes. The site investigator opened the envelopes in order and assigned treatment accordingly. Because recruitment criteria for age and bodyweight differed between treatments, a separate randomisation list was generated for each experimental drug.

Procedures

All treatments were dosed according to bodyweight (appendix). The following procedures were undertaken for every malaria episode: patients eligible for treatment were administered an ACT once daily (twice daily for artemether–lumefantrine; appendix). Adults received tablets with water and young children received pyronaridine–artesunate granules, artemether–lumefantrine dispersible tablets, dissolved artesunate–amodiaquine tablets or crushed dihydroartemisinin–piperaquine tablets, all given in water. There were no requirements or restrictions regarding food intake. Patients were treated as inpatients on days 1 to 3 and followed up as outpatients until day 42, except in Bougoula-Hameau (63 days' follow-up, data not shown). Clinical assessments were done on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42.

Patients with symptomatic parasitaemia at or after the day 28 visit were retreated with the ACT allocated at initial randomisation. For treatment failure before day 28, or if inclusion or exclusion criteria were not met for that episode, alternative rescue therapy was given. At the screening visit, a physical examination was done and a medical history was taken. Asexual parasites and gametocytes were identified and enumerated using standard protocols.[14,27] For parasite evaluation, we obtained blood samples at the start of each treatment episode, then every 12 h (range 10–14) up to 72 h or until two consecutive blood smears were parasite-negative, and at days 7, 14, 21, 28, 35, 42 at the time of withdrawal or if malaria was suspected. Slides were read by two qualified microscopists,

masked to treatment allocation, with any discordant results read by a third reader whose results were then accepted. Blood spots for *P falciparum* PCR genotyping were obtained at the same time as blood smears. *P falciparum* recrudescence was distinguished from reinfection using *msp1*, *msp2*, and microsatellite markers.[3,28]

Adverse events were assessed every 12 h after treatment start until 72 h and at all follow-up visits. Clinical chemistry and haematology samples were collected pretreatment on day 0, 72 h after treatment start (after the final dose), days 7 and 28, and at other times if hepatic tests were abnormal or if deemed necessary by the investigator. Digital 12-lead electrocardiographs were done on day 0 (pre-dose), day 2 (post-dose), and day 3 if clinically indicated. Criteria for permanent drug discontinuation were a drug-related serious adverse event, study drug hypersensitivity, drug-related QTc prolongation greater than 450 ms, active or chronic hepatitis B or C, known HIV antibody positivity, ALT greater than five times ULN (revised to >8×ULN, implemented at protocol version 12.0), Hy's criteria (ALT or aspartate aminotransferase [AST] >3×ULN and total bilirubin >2×ULN), travel outside the study area for more than 3 months, consent withdrawal, or any medical condition considered to jeopardise patient safety.

Outcomes

The two primary efficacy outcomes were (1) the 2-year incidence rate of all repeat malaria episodes (uncomplicated and complicated) irrespective of parasite species; and (2) the unadjusted and PCR-adjusted adequate clinical and parasitological response (ACPR) for *P falciparum* and unadjusted ACPR for other *Plasmodium* species (ie, *P ovale and P malariae*) at days 28 and 42. ACPR was defined as the absence of microscopically detectable parasitaemia until day 28 or 42, irrespective of axillary temperature, without previous early treatment failure, late clinical failure, or late parasitological failure.[27] PCR-adjusted treatment success excluded malaria episodes caused by PCR-confirmed *P falciparum* reinfection.[27,28]

Secondary endpoints were reinfection and recrudescence rates over 42 days, parasite clearance time (time from first dose until parasite negative, maintained for 48 h), gametocyte density and carriage, the difference in time to the second infection between treatments, and the difference in the mean interval between reinfections.

Safety outcomes were adverse event incidence and severity, coded using MedDRA (version 19.0), clinically significant laboratory results (hepatic safety criteria in appendix), changes in vital signs, potential QT or QTc interval prolongation and QTc change from baseline, and effects on the CNS.

Statistical analysis

For the primary efficacy endpoint of the all-malaria incidence rate over 2 years, we calculated the sample size based on the survival method,[29] using an estimated malaria incidence rate of 3·29 episodes per person over 2 years in the comparator arm (artemether–lumefantrine or artesunate–amodiaquine).[30] Assuming a non-inferiority margin of 20% for pyronaridine–artesunate or dihydroartemisinin–piperaquine versus control, a significance level of 5%, a power of 80%, and loss to follow-up of 15%, a total sample size of 4032 patients was needed. To achieve a power of at least 80%, a sample size of 370 patients per treatment arm was required for each comparison. For the primary efficacy endpoint of ACPR, assuming a 95% treatment success rate and 5% non-inferiority margin, we calculated that 4032 patients would provide 93% power. To achieve enough young children in the pyronaridine–artesunate arm, the recruitment target was increased to 4722 (1344 pyronaridine–artesunate, 968 artemether–lumefantrine, 1066 artesunate–amodiaquine, and 1344 dihydroartemisinin–piperaquine).

The safety population included all patients who received at least one dose of study therapy. The intention-to-treat (ITT) population included patients in the safety population with a day 0 pre-dose positive *Plasmodium* spp parasite count. The per-protocol (PP) population included all patients who completed a full course of study medication for any treatment episode with valid efficacy outcomes on day 28 or day 42 for that episode.

All outcomes were evaluated for non-inferiority of pyronaridine–artesunate versus artemether–lumefantrine or artesunate–amodiaquine, and non-inferiority of dihydroartemisinin–piperaquine versus artemether–lumefantrine or artesunate–amodiaquine. Because of the randomisation method, neither pyronaridine–artesunate versus dihydroartemisinin–piperaquine or artemether–lumefantrine versus artesunate–amodiaquine were valid comparisons.

The 2-year incidence of uncomplicated and complicated repeat malaria episodes was calculated for the ITT population using a Poisson regression model done separately for each treatment comparison. In the case of overdispersion of data (ie, if the variance was greater than the mean), negative binomial regression analysis was used. Analysis of the PP population was not planned for this outcome, as the aim was to capture all repeat malaria episodes occurring in all patients who received treatment for the initial malaria episode.

Unadjusted and PCR-adjusted ACPR at days 28 and 42 across all *P falciparum* uncomplicated malaria episodes was estimated using a generalised estimating equation (GEE) model with ACPR as a binary-dependent variable, randomised treatment group as a fixed effect, and the patient as a random effect.[14] Treatment-group estimates and estimates for the treatment differences with their associated 95% CI were derived. The PP population was used for the primary analysis of non-inferiority in ACPR, and the ITT population as a supporting analysis for this outcome. For non-falciparum species, descriptive statistics of unadjusted ACPR at days 28 and 42 by treatment episode were used. For both primary

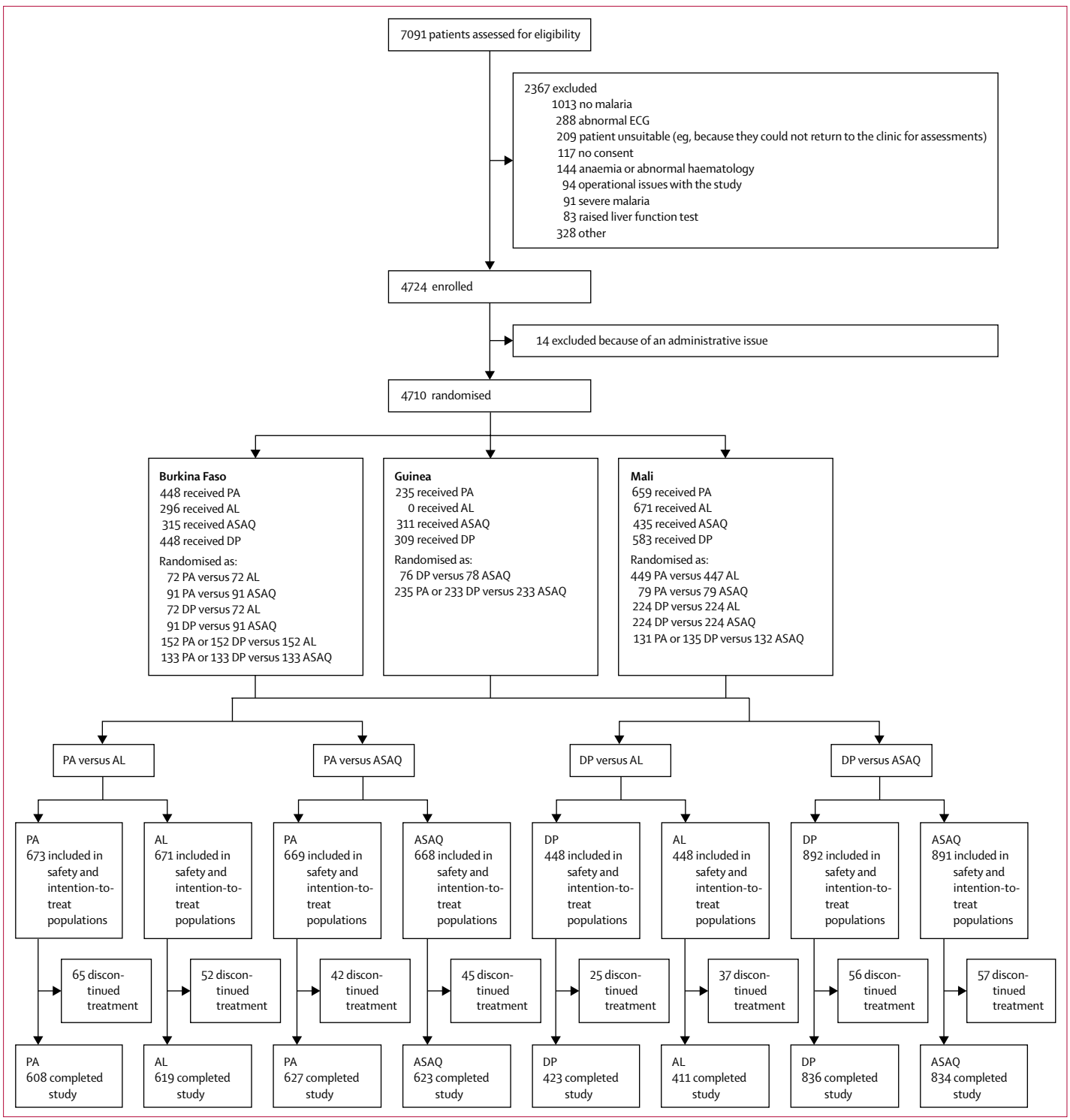

Figure 1: **Trial profile**
Data for recruitment by centre and country, reasons for study withdrawal and treatment discontinuation, reasons for exclusion from the intention-to-treat population, and day 28 or 42 per-protocol populations for each malaria episode are in the appendix. ECG=electrocardiogram. PA=pyronaridine–artesunate. AL=artemether–lumefantrine. DP=dihydroartemisinin–piperaquine. ASAQ=artesunate–amodiaquine.

endpoints, planned subanalyses were done based on country, age category, and bodyweight category.

All secondary efficacy outcomes were assessed in the ITT population. Recurrence rates for each *Plasmodium* species and recrudescence or reinfection rates for *P falciparum* over 42 days were calculated using Kaplan-Meier survival analysis, adjusted for repeated measures as appropriate. Patients were censored if they had an infection with another species than the one present at baseline, if they received a prohibited concomitant medication, if they did not receive the full course of study medication, or if they completed the study or discontinued prematurely. The time between the first and the second uncomplicated malaria episodes and the time between each two uncomplicated malaria episodes was summarised with descriptive statistics. Parasite clearance time was summarised using Kaplan-Meier estimates by treatment episode. Patients with no parasite clearance and those who received rescue therapy before parasite clearance were censored. Gametocyte clearance time was analysed similarly. The number of patients with gametocytes and gametocyte density were summarised using descriptive statistics.

Safety outcomes were assessed in the safety population and analysed using descriptive statistics. Statistical analyses used SAS (version 9.3). This study is registered at the Pan African Clinical Trials Registry, number PACTR201105000286876.

Role of the funding source

Authors associated with the funder of the study had a role in developing the protocol, study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 24, 2011, and Feb 1, 2016, we randomly assigned 4710 eligible participants to treatment: 1342 to pyronaridine–artesunate, 967 to artemether–lumefantrine, 1061 to artesunate–amodiaquine, and 1340 to dihydroartemisinin–piperaquine (figure 1). Nearly half of all randomly assigned patients were from Mali because of additional recruitment from this country while Guinea sites were closed during an epidemic of Ebola virus disease (figure 1, appendix). The possibility to recruit patients from other sites in the network had been included as a protocol amendment (appendix).

There were 326 withdrawals (7%) of 4710 patients throughout the study, with no major differences in the reason for withdrawal between the treatment comparisons (appendix). Reasons for exclusion from the PP population per malaria episode are also in the appendix. Baseline characteristics were similar between treatment comparisons (table 1). The 4710 patients included in the ITT population had 8640 repeat malaria episodes (7279 uncomplicated and 1361 complicated) over 2 years (appendix). 7119 episodes of repeated uncomplicated malaria was caused by *P falciparum*, 146 by *P malariae*, and 31 by *P ovale*, including 17 mixed infections.

For the primary outcome of repeat malaria (complicated and uncomplicated) incidence rate, because variance was greater than the mean we analysed data using negative binomial regression. The 2-year repeat malaria incidence rate (complicated and uncomplicated) in the ITT population was non-inferior for pyronaridine–artesunate versus artemether–lumefantrine (1·77, 95% CI 1·63–1·93 *vs* 1·87, 1·72–2·03) and versus artesunate–amodiaquine (1·39, 95% CI 1·22–1·59 *vs* 1·35, 1·18–1·54; figure 2) and also non-inferior for dihydroartemisinin–piperaquine versus artemether–lumefantrine (1·16, 95% CI 1·01–1·34 *vs* 1·42, 1·25–1·62) and versus artesunate–amodiaquine (1·35, 95% CI 1·21–1·51 *vs* 1·68, 1·51–1·88; figure 2). Two-year *Plasmodium* spp malaria incidence rates were higher in Burkina Faso and Mali versus Guinea, in children younger than 5 years versus adults, and in those with bodyweight of 20 kg or less versus heavier than 20 kg across all treatment groups (appendix). The study was not powered for subgroup comparisons of non-inferiority, but upper 95% CIs for pyronaridine–artesunate and dihydroartemisinin–piperaquine were greater than 1 for all comparisons based on country, age, and bodyweight (appendix).

In the PP population, PCR-adjusted or unadjusted ACPR estimated using a GEE model across all uncomplicated *P falciparum* episodes showed pyronaridine–artesunate to be non-inferior to artemether–lumefantrine or artesunate–amodiaquine (figure 2); similarly dihydroartemisinin–piperaquine was non-inferior to the two comparator ACTs (figure 2, appendix). All treatments met WHO efficacy criteria (>95% ACPR) for therapy adoption,[2] with PCR-adjusted ACPR in the PP population at least 99·5% at day 28 and at least 98·6% at day 42 (appendix). High PCR-adjusted ACPR rates were maintained across countries, and age and bodyweight categories (appendix). High rates of PCR-adjusted ACPR in the PP population were also sustained across all malaria retreatment episodes (appendix).

Unadjusted ACPR rates in the PP population were higher with pyronaridine–artesunate and dihydroartemisinin–piperaquine versus comparators (figure 2, appendix). Unadjusted ACPR in the ITT population was also higher for pyronaridine–artesunate and dihydroartemisinin–piperaquine versus comparators at days 28 and 42 (appendix). For non-falciparum species, in the PP population unadjusted ACPR was greater than 98% for all study drugs at day 28 and at day 42 was greater than 83% except for artemether–lumefantrine against *P ovale* (62·5%, 10/16) and *P malariae* (75·0%, 9/12; appendix).

Median time between any malaria episode was 175·5 days (IQR 65·3–319·0) for pyronaridine–artesunate versus 154·8 (58·0–298·5) for artemether–lumefantrine;

	Pyronaridine–artesunate versus artemether–lumefantrine		Pyronaridine–artesunate versus artesunate–amodiaquine		Dihydroartemisinin–piperaquine versus artemether–lumefantrine		Dihydroartemisinin–piperaquine versus artesunate–amodiaquine	
	Pyronaridine–artesunate (n=673)	Artemether–lumefantrine (n=671)	Pyronaridine–artesunate (n=669)	Artesunate–amodiaquine (n=668)	Dihydroartemisinin–piperaquine (n=448)	Artemether–lumefantrine (n=448)	Dihydroartemisinin–piperaquine (n=892)	Artesunate–amodiaquine (n=891)
Country								
Burkina Faso	224 (33%)	224 (33%)	224 (33%)	224 (34%)	224 (50%)	224 (50%)	224 (25%)	224 (25%)
Guinea	0	0	235 (35%)	233 (35%)	0	0	309 (35%)	311 (35%)
Mali	449 (67%)	447 (67%)	210 (31%)	211 (32%)	224 (50%)	224 (50%)	359 (40%)	356 (40%)
Female sex	328 (49%)	319 (48%)	350 (52%)	308 (46%)	219 (49%)	224 (50%)	427 (48%)	413 (46%)
Age (years)	11·8 (9·4)	11·7 (9·6)	7·3 (5·5)	7·0 (5·7)	9·6 (7·9)	9·1 (7·1)	7·6 (5·2)	7·5 (5·2)
Age group (years)								
<5	116 (17%)	129 (19%)	228 (34%)	249 (37%)	85 (19%)	102 (23%)	256 (29%)	264 (30%)
≥5 to <15	371 (55%)	341 (51%)	402 (60%)	386 (58%)	320 (71%)	299 (67%)	585 (66%)	589 (66%)
≥15	186 (28%)	201 (30%)	39 (6%)	33 (5%)	43 (10%)	47 (10%)	51 (6%)	38 (4%)
Weight (kg)	32·0 (17·7)	31·8 (18·2)	22·4 (11·9)	21·9 (12·2)	27·2 (13·8)	26·5 (13·7)	23·1 (12·1)	22·5 (11·2)
Weight group (kg)								
<20	213 (32%)	233 (35%)	359 (54%)	366 (55%)	161 (36%)	171 (38%)	447 (50%)	457 (51%)
≥20	460 (68%)	438 (65%)	310 (46%)	302 (45%)	287 (64%)	277 (62%)	445 (50%)	434 (49%)
Fever present	434 (64%)	397 (59%)	315 (47%)	360 (54%)	263 (59%)	265 (59%)	478 (54%)	497 (56%)
Body temperature (°C)	37·9 (1·1)	37·8 (1·1)	37·5 (1·1)	37·6 (1·0)	37·8 (1·1)	37·9 (1·1)	37·7 (1·1)	37·7 (1·1)
Plasmodium falciparum asexual forms	665 (99%)	663 (99%)	646 (97%)	652 (98%)	440 (98%)	443 (99%)	867 (97%)	869 (98%)
Median number of parasites per µL (IQR)	20 560 (4820–55 060)	24 860 (5380–56 620)	12 310 (1160–48 080)	17 100 (1170–50 140)	22 370 (4050–55 680)	23 940 (3278–56 980)	13 060 (1200–38 380)	15 360 (1020–43 520)
Plasmodium ovale asexual forms,	2 (<1%)	5 (<1%)	3 (<1%)	6 (<1%)	0	4 (<1%)	8 (<1%)	11 (1%)
Median number of parasites per µL (IQR)	2840 (2120–3560)	312 (120–4200)	1300 (80–4160)	1370 (480–2240)	0	1380 (350–3020)	1520 (460–2700)	480 (96–2260)
Plasmodium malariae asexual forms	15 (2%)	19 (3%)	36 (5%)	27 (4%)	15 (3%)	7 (2%)	46 (5%)	45 (5%)
Median parasite density per µL (IQR)	660 (100–2140)	540 (200–1420)	900 (312–2450)	1240 (560–4380)	800 (128–2040)	1900 (440–2240)	830 (400–3680)	960 (192–3720)
Patients with gametocytes								
P falciparum	13 (2%)	14 (2%)	16 (2%)	29 (4%)	15 (3%)	19 (4%)	21 (2%)	29 (3%)
P ovale	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
P malariae	1 (<1%)	0	3 (<1%)	2 (<1%)	5 (1%)	5 (1%)	0	1 (<1%)

Data are n (%) or mean (SD), unless stated otherwise. 152 patients receiving artemether–lumefantrine and 498 receiving artesunate–amodiaquine were randomly assigned to both pyronaridine–artesunate and dihydroartemisinin–piperaquine and so were included in both separate comparisons (figure 1).

Table 1: **Baseline demographic and clinical characteristics at the first uncomplicated malaria episode (in the intention-to-treat and safety population)**

162·0 days (59·0–285·0) for pyronaridine–artesunate versus 159·3 (62·0–269·5) for artesunate–amodiaquine; 195·3 days (96·0–344·5) for dihydroartemisinin–piperaquine versus 106·0 (47·0–307·0) for artemether–lumefantrine; and 157·5 days (85·0–269·0) for artemisinin–piperaquine versus 115·0 (56·0–232·0) for artesunate–amodiaquine (appendix).

Kaplan-Meier analysis of the first malaria episode, indicated a lower recurrence rate with pyronaridine–artesunate versus artemether–lumefantrine (p<0·0001; figure 2), but not versus artesunate–amodiaquine (p=0·67); and with dihydroartemisinin–piperaquine versus both comparators (p=0·0001; figure 2). Further analysis showed a lower *P falciparum* reinfection risk with pyronaridine–artesunate versus artemether–lumefantrine (p<0·0001) but not versus artesunate–amodiaquine (p=0·62), and for dihydroartemisinin–piperaquine versus both comparators (p<0·0001) (appendix). The risk of recrudescence was similar between study drugs (p>0·06; appendix).

Estimated across all uncomplicated malaria episodes, *P falciparum* parasite clearance time was slower with artemether–lumefantrine versus pyronaridine–artesunate (p<0·0001), and slower with artemether–lumefantrine versus dihydroartemisinin–piperaquine (p<0·0001; appendix). For the first episode, median parasite clearance time was 24·7 h (95% CI 24·3–26·1) with pyronaridine–artesunate versus 34·5 h (34·2–35·1) for artemether–lumefantrine (appendix). The proportion of patients with parasite clearance 24 h after the first dose was 253/665

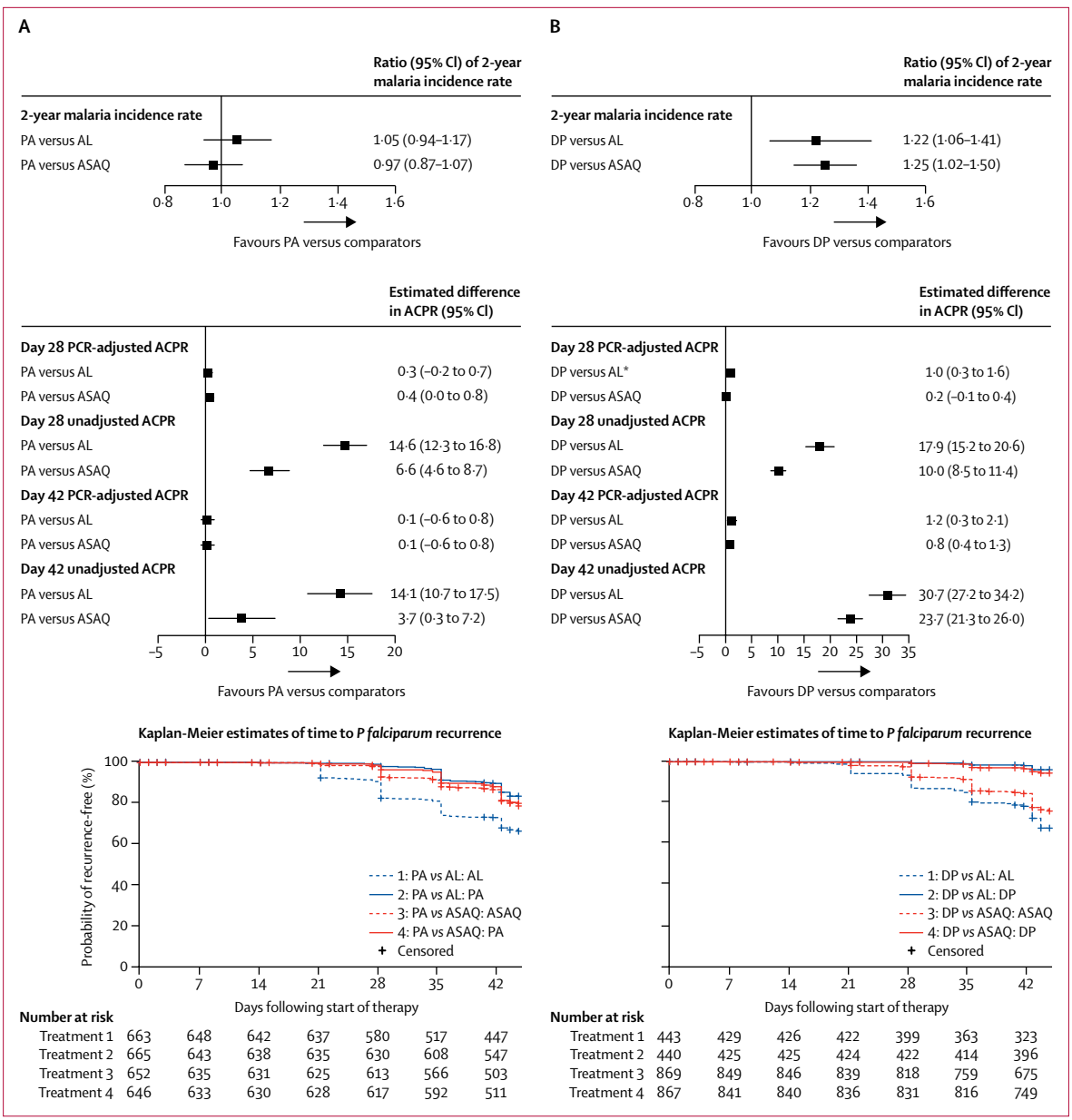

***Figure 2*: Treatment efficacy comparisons**

Data are for A) pyronaridine–artesunate versus comparators and B) dihydroartemisinin–piperaquine versus comparators. Forest plots are for the primary efficacy endpoints of 2-year incidence of *Plasmodium* spp malaria (uncomplicated and complicated), estimated using negative binomial regression in the intention-to-treat (ITT) population and the difference in adequate clinical and parasitological response (ACPR) across all *P falciparum* uncomplicated malaria episodes, estimated using a generalised estimating equation (in the per-protocol population). Kaplan-Meier estimates are shown for the time to *P falciparum* recurrence following treatment of the first malaria episode (in the ITT population). PA=pyronaridine–artesunate. AL=artemether–lumefantrine. ASAQ=artesunate–amodiaquine. DP=dihydroartemisinin–piperaquine. *P falciparum*=*Plasmodium falciparum*. *Based on raw incidence rate (not generalised estimating equation model) as ACPR was 100% in the dihydroartemisinin–piperaquine group.

(38·1%, 95% CI 34·3–41·8) for pyronaridine–artesunate versus 189/663 (29·0%, 25·0–31·9) for artemether–lumefantrine; appendix). *P falciparum* gametocytes were detected in 134 (3%) of 4606 patients at study enrolment, but data were too sparse to compare clearance rates.

For all uncomplicated *Plasmodium* spp malaria episodes, bronchitis and rhinitis were the most frequent adverse events of any cause across all treatment groups (table 2). There was no increase in the incidence of adverse events on repeated treatment for any study drug (appendix). Adverse events were more common in patients younger than 5 years and those with bodyweight less than 20 kg across all treatment groups, but there was no increase in the incidence of adverse

	Pyronaridine–artesunate versus artemether–lumefantrine		Pyronaridine–artesunate versus artesunate–amodiaquine		Dihydroartemisinin–piperaquine versus artemether–lumefantrine		Dihydroartemisinin–piperaquine versus artesunate–amodiaquine	
	Pyronaridine–artesunate (n=673)	Artemether–lumefantrine (n=671)	Pyronaridine–artesunate (n=669)	Artesunate–amodiaquine (n=668)	Dihydroartemisinin–piperaquine (n=448)	Artemether–lumefantrine (n=448)	Dihydroartemisinin–piperaquine (n=892)	Artesunate–amodiaquine (n=891)
Any adverse event	373 (55%)	411 (61%)	364 (54%)	391 (59%)	242 (54%)	226 (50%)	448 (50%)	406 (46%)
Any drug-related adverse event	203 (30%)	220 (33%)	138 (21%)	209 (31%)	142 (32%)	99 (22%)	205 (23%)	205 (23%)
Serious adverse events	13 (2%)	9 (1%)	10 (1%)	6 (<1%)	1 (<1%)	1 (<1%)	11 (1%)	5 (<1%)
Serious drug-related adverse events	3 (<1%)	2 (<1%)	4 (<1%)	2 (<1%)	1 (<1%)	0	4 (<1%)	1 (<1%)
Adverse events by preferred term								
Anaemia	33 (5%)	35 (5%)	15 (2%)	8 (1%)	31 (7%)	31 (7%)	11 (1%)	5 (<1%)
Monocytosis	13 (2%)	12 (2%)	0	0	22 (5%)	28 (6%)	0	0
Neutropenia	56 (8%)	64 (10%)	0	0	67 (15%)	71 (16%)	0	0
Abdominal pain	23 (3%)	25 (4%)	35 (5%)	37 (6%)	18 (4%)	16 (4%)	53 (6%)	53 (6%)
Vomiting	23 (3%)	17 (3%)	38 (6%)	58 (9%)	12 (3%)	6 (1%)	58 (7%)	82 (9%)
Bronchitis	115 (17%)	146 (22%)	156 (23%)	142 (21%)	101 (23%)	118 (26%)	179 (20%)	172 (19%)
Rhinitis	100 (15%)	103 (15%)	112 (17%)	110 (16%)	79 (18%)	67 (15%)	105 (12%)	135 (15%)
ALT increased	35 (5%)	11 (2%)	11 (2%)	4 (<1%)	6 (1%)	9 (2%)	13 (1%)	12 (1%)
AST increased	40 (6%)	17 (3%)	13 (2%)	6 (<1%)	8 (2%)	10 (2%)	13 (1%)	17 (2%)
QT prolonged	55 (8%)	99 (15%)	34 (5%)	91 (14%)	71 (16%)	36 (8%)	251 (28%)	195 (22%)
Abnormal ECG	4 (<1%)	4 (<1%)	0	0	29 (6%)	11 (2%)	0	0
Hypercreatininaemia	46 (7%)	51 (8%)	1 (<1%)	2 (<1%)	61 (14%)	55 (12%)	1 (<1%)	2 (<1%)
Headache	9 (1%)	12 (2%)	15 (2%)	14 (2%)	7 (2%)	9 (2%)	42 (5%)	45 (5%)
Cough	40 (6%)	42 (6%)	56 (8%)	54 (8%)	36 (8%)	34 (8%)	95 (11%)	108 (12%)

Data are n (%) of patients for events occurring in at least 5% of patients in any one treatment group. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ECG=electrocardiogram.

Table 2: **All-cause adverse events across all uncomplicated malaria episodes treated with study drugs (safety population)**

events on repeated treatment (appendix). Most adverse events were of mild to moderate severity (appendix). Drug-related adverse events are in the appendix.

There were nine deaths during the study, none of which were related to study treatment (appendix). Serious adverse events were uncommon and occurred mainly during the first malaria episode (table 2, appendix). Drug-related serious adverse events were associated mainly with increases in liver enzymes (appendix).

Mostly mild transient increases in liver enzymes occurred with pyronaridine–artesunate, which did not worsen on retreatment (appendix; table 2, figure 3). The incidence of hepatotoxicity events (defined as ALT >5×ULN or Hy's criteria: ALT or AST >3×ULN and total bilirubin >2×ULN) was 15 patients (2%) of 662 for pyronaridine–artesunate versus four (<1%) of 665 for artemether–lumefantrine, and seven (1%) of 661 for pyronaridine–artesunate versus four (<1%) of 659 for artesunate–amodiaquine (appendix). Hepatotoxicity events with pyronaridine–artesunate were more common in adults (five [4%] of 123) than in children younger than 5 years (seven [2%] of 332) or aged 5 to younger than 18 years (ten [1%] of 868), and more common in patients weighing at least 20 kg (14 [2%] of 765) than in patients less than 20 kg (eight [1%] of 558; appendix). None of the hepatotoxicity events were associated with any signs or symptoms, required any intervention, or resulted in any sequelae.

Exclusions from repeated treatment owing to hepatotoxicity events occurred in five (<1%) of 662 patients with pyronaridine–artesunate versus seven (1%) of 665 with artemether–lumefantrine; one (<1%) of 661 with pyronaridine–artesunate versus eight (1%) of 659 with artesunate–amodiaquine; five (1%) of 440 with dihydroartemisinin–piperaquine versus nine (2%) with artemether–lumefantrine; and four (<1%) of 885 with dihydroartemisinin–piperaquine versus 11 (1%) of 884 with artesunate–amodiaquine (appendix). Inadvertent redosing following hepatotoxicity events occurred in nine patients treated with pyronaridine–artesunate, three with artemether–lumefantrine, four with artesunate–amodiaquine, and two with dihydroartemisinin–piperaquine, but resulted in no clinical symptoms, worsening of liver function tests, or exacerbation of hepatotoxicity.

Overall, potential Hy's law cases occurred in three patients (0·22%) of 1342 receiving pyronaridine–artesunate, three (0·31%) of 967 receiving artemether–lumefantrine, one (0·09%) of 1061 receiving artesunate–amodiaquine, and two (0·15%) of 1340 receiving dihydroartemisinin–piperaquine (figure 3, appendix). Alkaline phosphatase was high in one patient receiving pyronaridine–artesunate and two receiving artemether–lumefantrine (appendix).

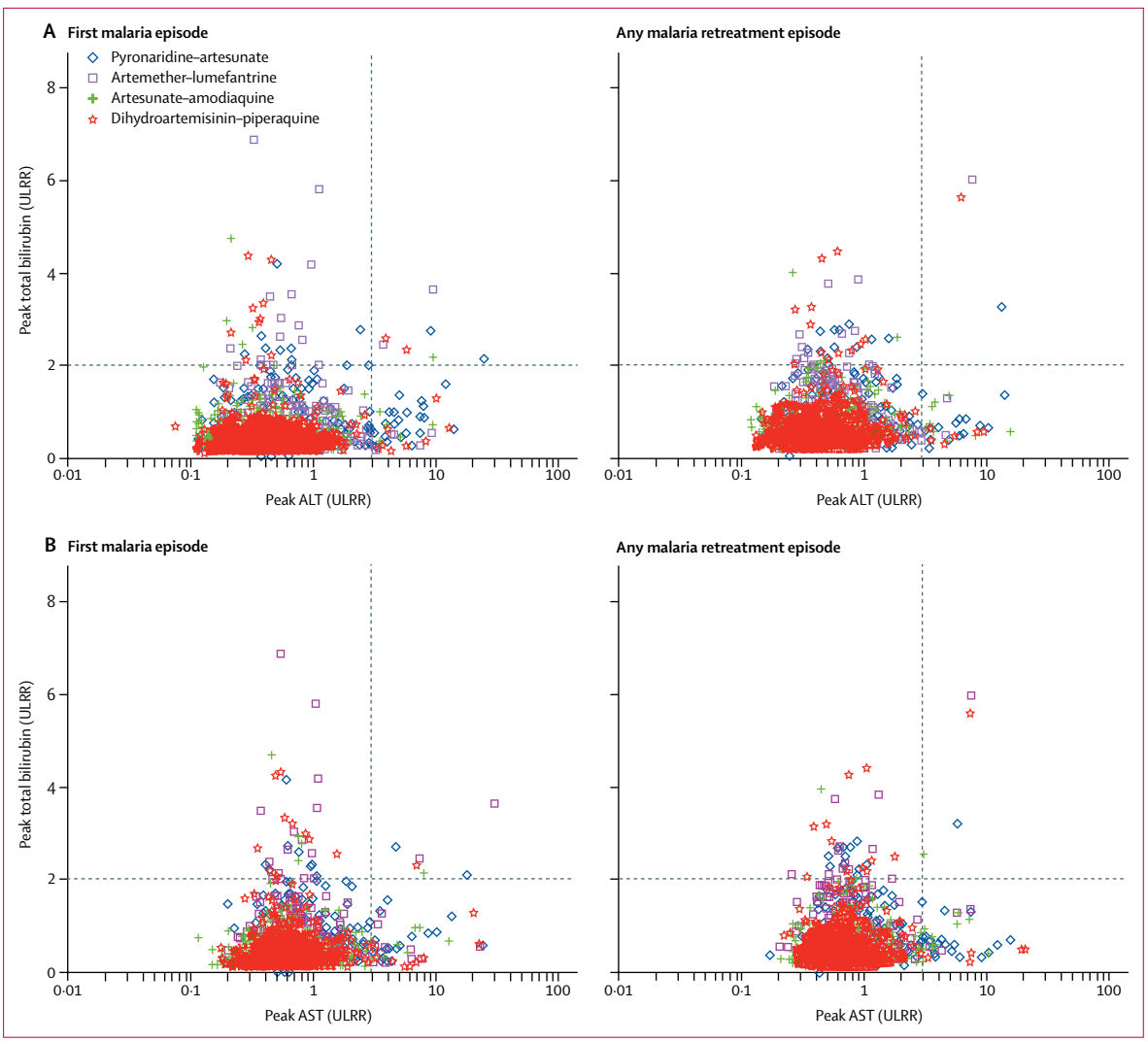

Figure 3: **Liver enzyme concentrations during the study**
Data are (A) peak alanine aminotransferase (ALT) concentrations versus total bilirubin concentration and (B) peak aspartate aminotransferase (AST) concentrations versus total bilirubin concentration. All available data after antimalarial drug treatment from day 3 until the end of observation following treatment of a first malaria episode or any uncomplicated malaria retreatment episode in the safety population. ULRR=upper limit of reference range.

Seven of the nine potential Hy's law cases occurred during the first treatment episode, and all cases resolved spontaneously without treatment or sequelae. There were no other notable differences between treatment groups in key haematological or biochemical laboratory measures (appendix).

Across all episodes, QTcF prolongation of more than 60 ms versus baseline occurred more frequently with dihydroartemisinin–piperaquine (31 patients [11%] of 288) than artemether–lumefantrine (five [3%] of 199), but in a similar proportion of patients for dihydroartemisinin–piperaquine (55 [11%] of 509) versus artesunate–amodiaquine (50 [12%] of 433; appendix). Overall, six patients (<1%) of 797 receiving dihydroartemisinin–piperaquine had any post-dose QTcF value longer than 500 ms (appendix). Although there were few data from retreatment episodes (68 for dihydroartemisinin–piperaquine *vs* 95 for artesunate–amodiaquine), there was no evidence that QTcF prolongation was more frequent following malaria retreatment (appendix). There was a trend for more frequent QTcF prolongation with dihydroartemisinin–piperaquine in patients aged 5–18 years than in adults or children younger than 5 years, but no difference based on bodyweight category (appendix). QTcF prolongation of more than 60 ms versus baseline was less frequent with pyronaridine–artesunate (in nine patients [2%] of 493) versus artemether–lumefantrine (12 [3%] of 400) and for pyronaridine–artesunate (three [2%] of 140) versus artesunate–amodiaquine (14 [12%] of 117; appendix). Overall, 226 patients (9%) of 2579 patients were excluded from repeated treatment because of QTcF prolongation (appendix).

Discussion

All treatment regimens tested in this study were highly efficacious and well tolerated in repeated treatment over 2 years. All study treatments had more than 99% efficacy in the PCR-adjusted PP population at days 28 and 42, similar to findings from previous studies in the region (>96% day 28 ACPR).[3,5] Analysis of *P falciparum* isolates obtained in this study from patients in Mali showed decreased susceptibility to both artemether and lumefantrine.[31] Although there was no effect on clinical efficacy, these findings highlight the potential risks of using a single ACT. Further investigations are ongoing, including *plasmepsin* 2 and *plasmepsin* 3 copy number and exonuclease polymorphisms as molecular markers of piperaquine resistance.[32]

Malaria incidence was high in the study area and most patients had at least two malaria episodes during the study. Repeated malaria is particularly concerning in young children, as it might affect their normal development, and the economic costs to families of frequent malaria episodes is substantial. For the first time, we showed the benefit of dihydroartemisinin–piperaquine on reducing 2-year *Plasmodium* spp malaria incidence rate following repeated treatment. This improvement might be explained by the long piperaquine half-life of around 4 weeks providing post-treatment prophylaxis.[33] However, this long half-life might also increase the risk of resistance selection.[34] In Cambodia and elsewhere in the Greater Mekong subregion, the emergence and spread of parasites resistant to both artemisinin and piperaquine has been rapid and profound, with high clinical failure rates.[35,36] Thus, widespread adoption of dihydroartemisinin–piperaquine in west Africa should be approached cautiously with assessment of treatment efficacy and monitoring of molecular markers of artemisinin and piperaquine resistance.[32]

Pyronaridine–artesunate has a terminal half-life of at least 13 days, compared with around 8–10 days for amodiaquine and 4 days for lumefantrine. The observed results for unadjusted ACPR and the risk of recurrence are thus consistent with the half-lives of the drugs, with pyronaridine–artesunate intermediate between dihydroartemisinin–piperaquine and artemether–lumefantrine. The 2-year *Plasmodium* spp malaria incidence rate for pyronaridine–artesunate was non-inferior to comparators, but there was no apparent effect of the limited post-treatment prophylaxis with pyronaridine–artesunate on reducing the malaria incidence rate versus comparators. We hypothesise that, as many factors contribute to malaria incidence rate, a longer period of post-treatment prophylaxis is needed to affect this outcome, as was noted with dihydroartemisinin–piperaquine. There is no evidence that historical pyronaridine monotherapy use has led to resistance emergence in Asia, though clinical efficacy of pyronaridine–artesunate in western Cambodia is lower than elsewhere in the region.[12,37] Consequently, there is currently no validated molecular marker for pyronaridine resistance.

Safety outcomes for malaria retreatment were consistent with the known safety profiles of the four ACTs.[3–5,9–21] Consistent with the interim analysis,[14] this larger dataset indicated no increased risk of liver injury on pyronaridine–artesunate retreatment.[9] Although pyronaridine–artesunate caused transient mild increased liver transaminases, the incidence of potential Hy's law events seemed to be low and no greater than with artemether–lumefantrine.[9,10,13,14] Although careful monitoring for liver enzyme increases was specified in the protocol, management of such a large study made this practically challenging and some patients with hepatotoxicity events on first treatment were retreated. None of these patients had hepatotoxicity events on repeated treatment. None of the patients with hepatic enzyme elevations had any clinical symptoms, required any intervention, or experienced sequelae.

The incidence of QTcF prolongation was higher following dihydroartemisinin–piperaquine versus comparators, although this was without clinical symptoms. This finding is consistent with those from a study in African patients after single treatment of uncomplicated malaria.[38] In the current study, QTcF prolongation also occurred with artesunate–amodiaquine. The incidence of QTcF prolongation did not appear to change on malaria retreatment, although there were few data for this outcome. Further analyses will examine the effect of the four ACTs on QTc interval during the first malaria episode (Cardiabase, Nancy, France).

This was a large and complex longitudinal study with several protocol amendments. The trial also required an amendment in design because of the outbreak of Ebola virus disease in west Africa from 2014 to 2016. Although this amendment was efficient in terms of time and resources, it increased complexity and the throughput of patients at the trial sites. One important caveat regarding the safety conclusions is that participants with pre-existing QTc prolongation or increased liver enzymes were excluded from the study. Additionally, participants with these adverse events occurring during the follow-up period for each episode were excluded. Thus, as is the case for all clinical trials, the safety data reported here reflect a selected population and careful pharmacovigilance will be needed to assess study drug safety in individuals potentially most at risk of these specific adverse events.

In many west African countries, artemether–lumefantrine is the only first-line ACT used. This is a fragile situation for a region which accounts for around half the world's malaria deaths, and reports of emerging artemether–lumefantrine resistance are concerning.[39,40] This study showed non-inferior efficacy and acceptable safety for both pyronaridine–artesunate and dihydroartemisinin–piperaquine for retreatment of uncomplicated

malaria in African populations compared with artemether–lumefantrine and artesunate–amodiaquine, and therefore pyronaridine–artesunate and dihydroartemisinin–piperaquine should be considered for diversifying ACT use across the region.

Contributors

ISa, AHB, IZ, ISo, ADic, FN, AAD, J-BO, and SBS contributed to the concept and design of the study and oversaw data acquisition in the field. BF, AT, ND, HD, AHT, SK, MK, SDa, SG, MDj, ABam, HM , BSi, FD, MC, MLA, HN, BSa, MDi, SC, DC, AFS, ASC, OBT, NDi, MJTK, YDC, SMO, ABar, DK, ADia, NH, HS, ECB, SBS, MMS, and MSD were involved in the acquisition of data. IT was involved with data management. IB-F, SP, SB, SDu, CJS, RMM, OKD, JS, JPG, and ABj contributed to the concept and design of the study. AAD was the coordinator of the programme and made substantial contributions to the concept and design of the study, oversaw data acquisition in the field, coordinated the writing of the manuscript and submitted the final draft. All authors critically reviewed the paper and approved the final version for submission.

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Declaration of interests

IB-F and SDu are employed by Medicines for Malaria Venture and JS is employed by Shin Poong Pharmaceutical Company. RMM consulted for Shin Poong during the study and is the Shin Poong qualified person for pharmacovigilance, responsible for providing interpretation of the safety data of this study and other studies involving pyronaridine–artesunate. All other authors declare no competing interests outside the stated funding sources for this study.

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References

1 WHO. World Malaria Report, 2016. Geneva: World Health Organization, 2016. http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf?ua=1 (accessed Jan 22, 2017).

2 WHO. Guidelines for the treatment of malaria, 3rd edn. Geneva: World Health Organization, 2015. http://www.who.int/malaria/publications/atoz/9789241549127/en/ (accessed Nov 17, 2016).

3 Sagara I, Fofana B, Gaudart J, et al. Repeated artemisinin-based combination therapies in a malaria hyperendemic area of Mali: efficacy, safety, and public health impact. *Am J Trop Med Hyg* 2012; **87:** 50–56.

4 Ndiaye JL, Faye B, Gueye A, et al. Repeated treatment of recurrent uncomplicated *Plasmodium falciparum* malaria in Senegal with fixed-dose artesunate plus amodiaquine versus fixed-dose artemether plus lumefantrine: a randomized, open-label trial. *Malar J* 2011; **10:** 237.

5 Adjei GO, Kurtzhals JA, Rodrigues OP, et al. Amodiaquine-artesunate vs artemether–lumefantrine for uncomplicated malaria in Ghanaian children: a randomized efficacy and safety trial with one year follow-up *Malar J* 2008; **7:** 127.

6 Ngasala BE, Malmberg M, Carlsson AM, et al. Efficacy and effectiveness of artemether–lumefantrine after initial and repeated treatment in children <5 years of age with acute uncomplicated *Plasmodium falciparum* malaria in rural Tanzania: a randomized trial. *Clin Infect Dis* 2011; **52:** 873–82.

7 Mavoko HM, Nabasumba C, da Luz RI, et al. Efficacy and safety of re-treatment with the same artemisinin-based combination treatment (ACT) compared with an alternative ACT and quinine plus clindamycin after failure of first-line recommended ACT (QUINACT): a bicentre, open-label, phase 3, randomised controlled trial. *Lancet Glob Health* 2017; **5:** e60–68.

8 WHO. WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization, 2012. http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf?ua=1 (accessed Jan 9, 2016).

9 Duparc S, Borghini-Fuhrer I, Craft CJ, et al. Safety and efficacy of pyronaridine–artesunate in uncomplicated acute malaria: an integrated analysis of individual patient data from six randomized clinical trials. *Malar J* 2013; **12:** 70.

10 Kayentao K, Doumbo OK, Penali LK, et al. Pyronaridine–artesunate granules versus artemether–lumefantrine crushed tablets in children with *Plasmodium falciparum* malaria: a randomized controlled trial. *Malar J* 2012; **11:** 364.

11 Poravuth Y, Socheat D, Rueangweerayut R, et al. Pyronaridine–artesunate versus chloroquine in patients with acute *Plasmodium vivax* malaria: a randomized, double-blind, non-inferiority trial. *PLoS One* 2011; **6:** e14501.

12 Rueangweerayut R, Phyo AP, Uthaisin C, et al. Pyronaridine–artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med* 2012; **366:** 1298–309.

13 Tshefu AK, Gaye O, Kayentao K, et al. Efficacy and safety of a fixed-dose oral combination of pyronaridine–artesunate compared with artemether–lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet* 2010; **375:** 1457–67.

14 Sagara I, Beavogui AH, Zongo I, et al. Safety and efficacy of re-treatments with pyronaridine–artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. *Lancet Infect Dis* 2016; **16:** 189–98.

15 Bassat Q, Mulenga M, Tinto H, et al. Dihydroartemisinin–piperaquine and artemether–lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. *PLoS One* 2009; **4:** e7871.

16 Grande T, Bernasconi A, Erhart A, et al. A randomised controlled trial to assess the efficacy of dihydroartemisinin–piperaquine for the treatment of uncomplicated falciparum malaria in Peru. *PLoS One* 2007; **2:** e1101.

17 Naing C, Mak JW, Aung K, Wong JY. Efficacy and safety of dihydroartemisinin–piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in endemic countries: meta-analysis of randomised controlled studies. *Trans R Soc Trop Med Hyg* 2013; **107:** 65–73.

18 Ratcliff A, Siswantoro H, Kenangalem E, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. *Lancet* 2007; **369:** 757–65.

19 Smithuis F, Kyaw MK, Phe O, et al. Efficacy and effectiveness of dihydroartemisinin–piperaquine versus artesunate–mefloquine in falciparum malaria: an open-label randomised comparison. *Lancet* 2006; **367:** 2075–85.

20 Smithuis F, Kyaw MK, Phe O, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Infect Dis* 2010; **10:** 673–81.

21 Valecha N, Phyo AP, Mayxay M, et al. An open-label, randomised study of dihydroartemisinin–piperaquine versus artesunate–mefloquine for falciparum malaria in Asia. *PLoS One* 2010; **5:** e11880.

22 Four Artemisinin-Based Combinations Study Group. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. *PLoS Med* 2011; **8:** e1001119.

23 Bukirwa H, Unnikrishnan B, Kramer CV, Sinclair D, Nair S, Tharyan P. Artesunate plus pyronaridine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst Rev* 2014; **3:** CD006404.

24 Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin–piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst Rev* 2014; **1:** CD010927.

25 Akpaloo W, Purssell E. Does the use of dihydroartemisinin–piperaquine in treating patients with uncomplicated falciparum malaria reduce the risk for recurrent new falciparum infection more than artemether–lumefantrine? *Malar Res Treat* 2014; **2014:** 263674.

26 Zongo I, Dorsey G, Rouamba N, et al. Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether–lumefantrine, and dihydroartemisinin–piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Burkina Faso. *Clin Infect Dis* 2007; **45:** 1453–61.

27 WHO. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Geneva: World Health Organization, 2003. http://www.who.int/malaria/publications/atoz/whohtmrbm200350/en/ (accessed Nov 17, 2016).

28 WHO. Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. Geneva: World Health Organization, 2008. http://www.who.int/malaria/publications/atoz/9789241596305/en/ (accessed Nov 17, 2016).

29 Friedman L, Furberg C, DeMets D. Fundamentals of clinical trials, 4th edn. New York: Springer-Verlag, 2010.

30 Sagara I, Fofana B, Sidibe B, et al. Évaluation de l'effet de différentes combinaisons thérapeutiques à base d'artémisinine, sur l'incidence du paludisme dans une zone hyperendémique de paludisme au Mali. *Rev Epidemiol Sante Publique* 2010; **58:** S85.

31 Dama S, Niangaly H, Ouattara A, et al. Reduced ex vivo susceptibility of *Plasmodium falciparum* after oral artemether–lumefantrine treatment in Mali. *Malar J* 2017; **16:** 59.

32 Amato R, Lim P, Miotto O, et al. Genetic markers associated with dihydroartemisinin–piperaquine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study. *Lancet Infect Dis* 2017; **17:** 164–73.

33 Ahmed T, Sharma P, Gautam A, et al. Safety, tolerability, and single- and multiple-dose pharmacokinetics of piperaquine phosphate in healthy subjects. *J Clin Pharmacol* 2008; **48:** 166–75.

34 Kay K, Hastings IM. Measuring windows of selection for anti-malarial drug treatments. *Malar J* 2015; **14:** 292.

35 Duru V, Witkowski B, Menard D. *Plasmodium falciparum* resistance to artemisinin derivatives and piperaquine: a major challenge for malaria elimination in Cambodia. *Am J Trop Med Hyg* 2016; **95:** 1228–38.

36 Thanh NV, Thuy-Nhien N, Tuyen NT, et al. Rapid decline in the susceptibility of *Plasmodium falciparum* to dihydroartemisinin–piperaquine in the south of Vietnam. *Malar J* 2017; **16:** 27.

37 Leang R, Canavati SE, Khim N, et al. Efficacy and safety of pyronaridine–artesunate for treatment of uncomplicated *Plasmodium falciparum* malaria in western Cambodia. *Antimicrob Agents Chemother* 2016; **60:** 3884–90.

38 Kabanywanyi AM, Baiden R, Ali AM, et al. Multi-country evaluation of safety of dihydroartemisinin/piperaquine post-licensure in african public hospitals with electrocardiograms. *PLoS One* 2016; **11:** e0164851.

39 Plucinski MM, Dimbu PR, Macaia AP, et al. Efficacy of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in Angola, 2015. *Malar J* 2017; **16:** 62.

40 Plucinski MM, Talundzic E, Morton L, et al. Efficacy of artemether–lumefantrine and dihydroartemisinin–piperaquine for treatment of uncomplicated malaria in children in Zaire and Uige Provinces, Angola. *Antimicrob Agents Chemother* 2015; **59:** 437–43.