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Radical cure for vivax malaria in Indonesia 2

Submission date	Recruitment status	[X] Prospectively registered
09/03/2013	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
20/03/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
16/12/2015	Infections and Infestations	

Plain English summary of protocol

Background and study aims
This study aims to measure the efficacy of primaquine against relapse when administered with one of two ACT therapies likely to replace chloroquine as the companion blood schizontocide with primaquine for radical cure of vivax malaria. The study also examines safety and tolerability of these therapies.
The findings will assess current first line therapy, will guide rational decisions about new first-line therapies and will inform strategy concerning the development of new pairs of therapies for radical cure of vivax malaria in Indonesia.

Who can participate?
180 participants from Indonesian Army Batallion 408 Sragen, East Java, Indonesia, returning from 6 months deployment at Papua, who have vivax malaria based on microscopic examination, will participate

What does the study involve?
All study participants are asked to stay on the base for at least 28 days. They are randomly allocated to one of three treatments: (i) artesunate first followed by primaquine (AS+PQ), (ii) Pyronaridine Tetraphosphate-Artesunate combined with primaquine (PYR-AS) or (iii) Dihydroartemisinin-Piperaquine Phosphate (DHA-PQP) plus primaquine. The follow up will be for one year. The participants will be closely observed by routine clinical and laboratory investigations including the measurement and recording of vital signs, complete blood counts, and blood chemistries, along with measurement of peripheral blood methaemoglobin level and also ECG examinations. The total amount of blood taken is about 150 ml from 9 blood draws and 20 finger pricks.

What are the possible benefits and risks of participating?
There are two main risks in this study: drug toxicity and the risk of a recurrent bout of malaria. In general, these drugs are well tolerated, although in some cases adverse reaction could occur. This study will provide on-site clinic for 24 hours and 7 days a week. If participants have recurrent malaria, they will receive immediate standard therapy. The main benefit is that all participants will be given safe and effective drugs and will be closely monitored for safety until completely recovered and well beyond.

Where is the study run from?
This study is run by the Faculty of Medicine University of Indonesia, Eijkman Institute for Molecular Biology in Jakarta, the Eijkman Oxford Clinical Research Unit and the Indonesian Army Medical Corps.

When is the study starting and how long is it expected to run for?
March 2013 to July 2014.

Who is funding the study?
This study is sponsored by the ALERTAsia Foundation (Indonesia) and funded by Medicines for Malaria Venture (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Vivax-primaquine-ACT-AS/EOCRU.2012.002

Study information

Scientific Title

Randomized, open-label trial of the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetraphosphate-artesunate or dihydroartemisinin-piperquine phosphate for radical cure of acute Plasmodium vivax malaria in soldiers

Study objectives
The first treatment arm, AS+PQ administered consecutively, will test the hypothesis that primaquine administered after a rapidly excreted blood schizontocide may offer protection against relapse.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Medical Research Ethics Committee of Faculty of Medicine, University of Indonesia, 14/01 /2013, ref: 13/H2.F1/ETIK/2013
2. Medical Research Ethics Committee of Faculty of Medicine, University of Indonesia, Amendment Approval of Protocol v3 dated 11/03/2013, No. 247/H2.F1/ETIK/III/2013 2. OXTREC Approval of Protocol v3 dated 15/03/2013

Study design
Single-center randomized open-label clinical trial of primaquine efficacy against relapse

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Malaria

Interventions
1. AS+PQ= One tablet of artesunate contains 50 mg base. Artesunate alone will use the same artesunate tablet from co-blister of Arsuamoon™ used by Ind MoH for malaria therapy. Arsuamoon™ manufactured by Guilin Pharmaceutical, China. This will be administered on days 0-6 (200 mg day 0; 100 mg days 1-6). After a 48hr pause, 0.5 mg/kg primaquine in tablets containing 26.3 mg of primaquine phosphate (15 mg base) daily for days 8 to 21. Primaquine manufactured by Sanofi, France.

2. PYR-AS+PQ=One tablet of PYR-AS contains 180 mg of pyronaridine tetraphosphate & 60 mg artesunate. Dosing is daily for 3 days and by weight per EMA recommendations:
- 24 kg to <45 kg - 2 tablets
- > 45 kg to <65 kg - 3 tablets
- >65 kg - 4 tablets
The target doses are 7.2 to 13.8 mg/kg PYR and 2.4 to 4.6 mg/kg AS. These tablets (Pyramax™) will be supplied by the manufacturer, Shin Poong Pharmaceuticals (South Korea). This will be administered on days 0-2 concurrently with 0.5 mg/kg primaquine in tablets containing 26.3 mg of primaquine phosphate (15 mg base) daily for days 0 to 13. Primaquine manufactured by Sanofi, France.

3. DHA-PQP+PQ=One tablet of DHA-PQP contains 40 mg of DHA and 320 mg of PQP.
Dosing is daily and by weight:
- < 75 kg - 3 tablets
- ≥ 75 kg - 4 tablets
These tablets ((Eurartesim™) will be supplied by the manufacturer, Sigma Tau (Italy). This will be administered on days 0-2 concurrently with 0.5 mg/kg primaquine in tablets containing 26.3 mg of primaquine phosphate (15 mg base) daily for days 0 to 13. Primaquine manufactured by Sanofi, France.

Follow up was for 365 days, counting the first day of study drug administration as Day 0.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Primaquine, Pyronaridine Tetraphosphate-Artesunate, Dihydroartemisinin-Piperquine Phosphate

Primary outcome measure
To obtain independent, high precision estimates of the efficacy of standard primaquine therapy when combined with PYR-AS or DHA-PQP for radical cure of acute malaria caused by P. vivax.

Efficacy of relapse is calculated as:
(natural relapse rate - relapse rate post-PQ) / natural relapse rate x 100%

Measured by following up for 365 days, counting the first day of study drug administration as Day 0

Secondary outcome measures
Measure the efficacy of the blood schizontocides against acute vivax malaria, documenting safety and pharmacokinetic characteristics of the drug regimens, and their tolerability through monitoring adverse events.

Measured by following up for 365 days, counting the first day of study drug administration as Day 0

Overall study start date
28/03/2013

Completion date
01/07/2014

Eligibility

Key inclusion criteria
1. Age 18 years or older, but younger than 65 years
2. Travelled for >1 month to northeastern Papua within the past 12 months
3. Body weight >40 kg and ≤ 90 kg
4. A diagnosis of P. vivax parasitemia, mono- or mixed-species infection of any density and confirmed by a second microscopist
5. Written informed consent provided by participants
6. Glucose-6-phosphate dehydrogenase (G6PD) normal using the NADPH qualitative fluorescent spot test (Trinity Biologicals, USA)
7. Able to swallow oral medication

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
60 participants per arm, total 180 participants.

Key exclusion criteria
1. Patient confirmed as having Plasmodium falciparum mono infection
2. Patient requires hospitalization for any reasons
3. Haemoglobin <7 g/dL.
4. G6PD deficient according to NADPH spot test
5. Definite plans for an absence of 5 consecutive days or more from the base within 28 days of being enrolled, if the destination of travel exceeds 100km from the study site.
6. Known history of clinically significant disorders, such as:
6.1. Cardiovascular
6.2. Respiratory including active tuberculosis
6.3. Hepatic
6.4. Renal
6.5. Gastrointestinal
6.6. Immunological
6.7. Neurological, including hearing impairment
6.8. Endocrine
6.9. Infectious
6.10. Malignancy
6.11. Psychiatric

6.12. Recent head trauma
6.13. Any other clinically significant finding that the investigator judges will place the patient at risk or interfere with the study results.
7. Laboratory evidence of clinically significant disorders, such as:
7.1. A corrected QT interval (QTc) >450 ms*.
7.2. Active Hepatitis A, e.g. by detection of anti HAV-IgM.
7.3. Hepatitis B surface antigen (HBsAg) carrier.
7.4. Hepatitis C antibody (HCV Ab).
7.5. Liver function tests (AST/ALT levels) more than 2.5 times the upper limit of normal range.
7.6. Renal impairment as indicated by abnormal creatinine clearance of <60 ml/min, measured using Cockcroft-Gault formula.
8. Known history of hypersensitivity, allergy or adverse reactions to primaquine, artesunate, dihydroartemisinin (DHA), pyronaridine or other artemisinins.
9. Previous participation in the present clinical trial, i.e., subjects experiencing relapse may not be enrolled and randomized as a new subject.
10. Have received any investigational drug within the past 4 weeks.
11. Anyone of the following contra indications of DHA-PQP, such as:
11.1. Family history of sudden unexplained death.
11.2. Known congenital QTc prolongation.
11.3. Known presence of a medical condition known to prolong the QT interval: myxoedema, cardiomyopathies, recent myocardial infarction.
11.4. History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
11.5. Cardiac illnesses predisposing to arrythmias e.g. hypertension, left ventricular hypertrophy, cardiomyopathies, cardiac failure with reduced ejection fraction.
11.6. Presence of an electrolyte disturbance particularly hypokalaemia, hypocalcaemia, hypomagnesaemia.
11.7. On any drug known to prolong the QTc interval, including:
11.7.1. Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
11.7.2. Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine) and antidepressive agents.
11.7.3. Certain antimicrobial agents, including agents of the following classes: macrolides (e.g. erythromycin, clarithromycin), fluoroquinolones (e.g. moxifloxacin, sparfloxacin), imidazole and triazole antifungal agents and also pentamidine and saquinavir.
12. Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Eurartesim is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

* We will use the Fridericia formula (QTcF=QR/(RR)0.3 or Bazetts formula (QTcF=QR/(RR)0.5 whichever is lower.

Date of first enrolment
28/03/2013

Date of final enrolment
01/07/2013

Locations

Countries of recruitment

Indonesia

Study participating centre
University of Indonesia
Jakarta
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Sponsor information

Organisation
ALERTAsia Foundation (Indonesia)

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Sponsor type
Research organisation

ROR
https://ror.org/04fhhgs91

Funder(s)

Funder type
Research organisation

Funder Name
Medicines for Malaria Venture

Alternative Name(s)
MMV

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Switzerland

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	11/12/2015		Yes	No