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Assessing the safety and tolerability of artemether-lumefantrine+atovaquone-proguanil tri-therapy for malaria treatment in adults and adolescents in Gabon

Submission date
30/09/2020

Recruitment status
No longer recruiting

Registration date
06/10/2020

Overall study status
Completed

Last Edited
11/12/2020

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Malaria is a mosquito-borne infectious disease caused by the parasite Plasmodium. Artemisinin-based combination therapies (ACTs), combining a fast-acting artemisinin derivative with a longer half-life partner drug, are currently the first-line treatment for malaria. Their effectiveness has declined in South-East Asia because of the emergence of parasite resistance that has the potential to spread through Africa. Although susceptibility to ACTs remains high among the African Plasmodium falciparum population, previous first-line antimalarials have been lost quickly due to the spread of resistant parasites. To mitigate this risk and to have a highly effective, safe and well-tolerated treatment for uncomplicated malaria at hand in the foreseeable scenario of ACT resistance in Africa, more effective antimalarial drug combinations need to be explored urgently for quick deployment in Africa. Artesunate-amodiaquine (ASAQ) is widely used and shows high effectiveness and good safety in Africa. However, in case of a spread of ACT-resistant parasites in Africa, an additional partner drug is required to increase its lifespan as the first-line antimalarial and ideally also to block transmission. Atovaquone-proguanil (AP) is highly effective, safe and registered for the use in young children. Parasites resistant to AP or ASAQ are not circulating in Africa. AP targets multiple parasite stages - the liver and blood stages of P. falciparum in the human host, and mosquito stages by a mode of action independent from primaquine. These features limit the risk of cross-resistance with current ACTs, may provide an increased post-treatment prophylactic effect and features transmission-blocking activity in mosquitoes. The aims of this study are to assess the frequency and severity of adverse events in the two treatment groups (i.e., AL+AP and AL), and to report the exploratory effectiveness at Day 28 and Day 42.

Who can participate?
Adolescents and adults aged 15 and older with uncomplicated P. falciparum malaria

What does the study involve?
Participants are randomly allocated to be treated with artemether-lumefantrine + atovaquone-

proguanile or artemether-lumefantrine + placebo (dummy drug), once daily over 3 consecutive days. Participants will be followed up until day 42. Blood will be sampled throughout the follow-up for malaria microscopy, dried blood spots (for genotyping in case of the reappearance of parasites), hematology and biochemistry. Clinical examinations will be carried out.

What are the possible benefits and risks of participating?
Expected benefits include the treatment of malaria and follow up of any arising health issues during the study period. Patients will benefit from another antimalarial treatment in case of safety issues or treatment failure. Blood sampling may cause discomfort but has a very low risk. The combination of AL + AP has not been studied in patient populations. The uncertainty of safety in patients is a foreseeable risk in participating in the study.

Where is the study run from?
Centre de Recherches Médicales de Lambaréné (CERMEL) (Gabon)

When is the study starting and how long is it expected to run for?
October 2020 to March 2021

Who is funding the study?
European and Developing Countries Clinical Trials Partnership (EDCTP)

Who is the main contact?
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Study website
https://asaap-malaria.org/

Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RIA2017MC-2022 Study I, PACTR202010540737215

Study information

Scientific Title
Assessing the safety and tolerability of artemether-lumefantrine+atovaquone-proguanil tri-therapy for malaria treatment in adults and adolescents in Gabon: a two-arm randomized, placebo-controlled, participant, observer and analyser blinded mono-centre, Phase IIb clinical pilot trial

Acronym
ASAAP study I

Study objectives
Primary objective: To assess the frequency and severity of adverse events by treatment arm in general and related to the administered study drugs in adolescents and adults aged 15 years and older.

Secondary objective: To report the exploratory efficacy in terms of adequate clinical and parasitological response of participants treated with AL+AP and participants treated with AL for uncomplicated P. falciparum malaria.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/09/2020, National Research Ethics Committee of Gabon (BP 2217 Libreville, Gabon; +241 (0)7791200; email not available), ref: N°005/2020/CNER/SG/P

Study design
Two-arm randomized placebo-controlled participant observer and analyser blinded mono-centre Phase IIb clinical pilot trial

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 contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Treatment of uncomplicated malaria in adults and adolescents

Interventions
Treatment arms will be randomized in blocks of 6 participants with a 1:2 ratio of control and experimental treatments. Participants will receive one of the following treatments following a weight-based treatment algorithm:
1. Experimental: artemether-lumefantrine twice daily + atovaquone-proguanil, once daily over 3 consecutive days
2. Control: artemether-lumefantrine twice daily + placebo, once daily over 3 consecutive days

Artemether-lumefantrine: 80 mg/480 mg artemether/lumefantrine as a single dose twice daily for 3 consecutive days (1 standard tablet [80 mg/480 mg] per time point)
Atovaquone-proguanil: 1,000 mg/400 mg atovaquone/proguanil as a single dose once daily for 3 consecutive days (4 standard tablets [250 mg/100 mg] per time point)
Placebo: single dose once daily for 3 consecutive days (4 tablets per time point)

Participants will be followed up until day 42.

Intervention Type
Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)
Artemether, lumefantrine, atovaquone, proguanil

Primary outcome measure
Frequency and severity of adverse events measured using the incidence of adverse events at day 42 of follow-up by treatment arm. Coding of adverse events will be based on the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).

Secondary outcome measures
1. Exploratory efficacy outcomes will be reported in terms of Adequate Clinical Parasitological Response (ACPR) by treatment group. ACPR will be assessed according to the WHO guideline and is defined as the absence of parasitaemia on day 28 and 42, irrespective of axillary temperature, in participants in the PP population who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure. The uncorrected cure rates will be reported following experimental treatment with AL+AP and control treatment with AL for uncomplicated P. falciparum malaria.
1.1. The PCR-uncorrected ACPR is the proportion of participants that have no evidence of asexual parasitaemia as detected microscopically, independent of whether any parasitaemia is due to re-infection or recrudescence. PCR-uncorrected ACPR on day 28 and day 42 will be reported by treatment arm. Percentages will be reported along with 95% exact Clopper-Pearson confidence intervals.
2.2. The PCR-corrected ACPR is the proportion of participants that have no evidence of recrudescence as determined microscopically and genotypically as an absence of the same asexual parasitaemia (clone) as the original infection. PCR-corrected ACPR on day 28 and day 42 will be reported by treatment arm. Percentages will be reported along with 95% exact Clopper-Pearson confidence intervals.

Overall study start date
01/03/2019

Completion date
31/03/2021

Eligibility

Key inclusion criteria
1. Adults and adolescents aged 15 years and older
2. Body weight ≥40 kg
3. Fever (≥37.5°C axillary body temperature) or history of fever in the preceding 24 hours
4. Uncomplicated P. falciparum monoinfection with equal or more than 1,000 and less than 200,000 asexual P. falciparum parasites per µl of blood
5. Signed written informed consent
6. Ability to comply with study procedures and follow-up schedules
7. Ability to take oral medication

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
60 participants: 40 participants for the intervention arm AL+AP, 20 participants for the control arm AL+placebo

Key exclusion criteria
1. Reported intake of any antimalarial drug including halofantrine within the previous month
2. Intake of drugs with some antimalarial activity or that interference with tolerability assessment (including cotrimoxazole/bactrim, tetracyclines, quinolones and fluoroquinolones, and azithromycin) within the previous month
3. Presence of severe malaria following WHO definition (see Annex 2: WHO definitions for severe malaria)
4. Known history or evidence of clinically significant medical disorders
5. Severe malnutrition assessed by BMI
6. Previous participation in a malaria vaccine study
7. Screening haemoglobin level <7 g/dL
8. Known hypersensitivity or contraindications to any AL+AP components
9. Administration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, millepertuis/St John's wort (hypericum perforatum)
10. Known QT prolongation (e.g. hypokalaemia, hypomagnesemia)
11. Pregnant or lactating women
12. Participation in other interventional studies

Date of first enrolment
01/09/2020

Date of final enrolment
28/02/2021

Locations

Countries of recruitment
Gabon

Study participating centre
Centre de Recherches Médicales de Lambaréné (CERMEL)
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Sponsor information

Organisation
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Sponsor type
University/education

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ROR
https://ror.org/00cb23x68

Funder(s)

Funder type
Government

Funder Name
European and Developing Countries Clinical Trials Partnership (EDCTP)

Results and Publications

Publication and dissemination plan
A scientific committee will be formed with the responsibility for the presentations and/or publications of the results. The results of the study will be submitted to the Project Steering Committee (PSC) before each publication. Each subsequent presentation or publication should be approved by the scientific board.

The final decision on the publication of a manuscript/summary/presentation will be taken by the PSC in order to allow for an internal review and the possibility of providing comments.

No country-level dissemination is foreseen for the pilot study results. However, the Ministry of Health and other applicable regulatory bodies will be informed of the findings to allow a smooth transition to the main trial. Release of results and findings to the Ministry of Health shall be agreed by all parties involved in the study via written approval.

The study protocol, informed consent forms and the clinical study report will be available.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
In line with the funding conditions, IPD is to be shared. However, this will be de-identified IPD that is used to generate the results reported (text, tables, figures and appendices). IPD sharing will begin after the primary publication. IPD will be available for a period which is aligned with the data-sharing agreements approved by the research ethics committees of the counties/sites participating in the trial. The IPD shall be made available via a request and evaluation process to investigators whose proposed research has received IRB approval. All investigators to whom this IPD is made available will be required to be part of the execution of a data use agreement.
The researchers aim to use the CDISC standard. The repository name and weblink are yet to be created as data collection is yet to begin. The process of requesting access etc is yet to be concluded and approved by the consortium and will be made available prior to the repository being put online. Participants consent process includes information on data sharing as this is a requirement of the funder. There are no known ethical or legal restriction on this.

IPD sharing plan summary
Stored in repository