ISRCTN14750348 https://doi.org/10.1186/ISRCTN14750348

A multicentre phase III trial to evaluate the safety, tolerabilty, and efficacy of a combination of three antimalaria drugs (artemether-lumefantrine+atovaquone-proguanil) versus two malaria drugs (artemether-lumefantrine) +placebo in African children aged 6 months to ≤ 10 years with an uncomplicated malaria infection

Submission date
17/11/2021

Recruitment status
No longer recruiting

Registration date
24/11/2021

Overall study status
Completed

Last Edited
18/09/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] 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.

Artemether-lumefantrine (AL) is widely used and shows high efficacy and good safety in Africa. However, in case of an emergence or spread of ACT-resistant parasites, an additional partner drug is required to increase its lifespan as first-line antimalarial and ideally also to block transmission. Atovaquoneproguanil (AP) is highly efficacious, safe and registered for the use in young children. AP targets multiple parasite stages - liver and blood stages of P. falciparum in the human host, and mosquito stages - by a mode of action independent from other clinical antimalarials. These features limit the risk of crossresistance with current ACTs, may provide an increased post-treatment prophylactic effect and features transmission-blocking activity in mosquitoes. As parasites resistant to AP or AL are apparently not detected at high rate in Africa,

except cycloguanil/pyrimethamine resistance, combining these two drugs could offer a timely new treatment.
The overall aim of this phase III clinical trial(main study = study II) is to develop a readily deployable highly efficacious, safe and well tolerated antimalarial triple combination therapy for young children.

Who can participate?
Children aged 6 months to ≤10 years 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), twice 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), pharmacokinetics, 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 young children. The uncertainty of safety in patients is a foreseeable risk in participating in the study. However, this drug combination was tested in the pilot study in adolescents and adults.

Where is the study run from?
Kwame Nkrumah University of Science and Technology (Ghana)

When is the study starting and how long is it expected to run for?
March 2019 to April 2024

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

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
R2017MC-2022, Study II

Study information

Scientific Title
A multicentre phase III non-inferiority trial to evaluate safety, tolerability and efficacy of artemether+lumefantrine + atovaquone-proguanil tri-therapy versus artemether-lumefantrine bi-therapy for the treatment of uncomplicated malaria in African children aged 6 months to ≤ 10 years

Acronym
ASAAP study II to V

Study objectives
Day-28 efficacy of AL+AP and AL+placebo for the treatment of uncomplicated P. falciparum malaria in African children aged 6 months to ≤10 years defined as PCR-adjusted adequate clinical and parasitological response (ACPR) excluding reinfections, in the per-protocol (PP) population.
Day-28 efficacy of AL+AP and AL+placebo for the treatment of uncomplicated P. falciparum malaria in African children aged 6 months to ≤10 years defined as PCR-adjusted ACPR excluding reinfections, in the modified intention-to-treat (mITT) population.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 16/08/2021, Le comité d'éthique de l'Université des Sciences, des Techniques et des Technologies de Bamako (BP 1805, Bamako, Mali; +233 20 22 52 77; no email provided), ref: N° 2021/198/CE/USTTB
2. Approved 02/11/2021, Comité national d'éthique pour la recherche en santé (08 BP 882, Cotonou, Bénin, +229 21 33 2178; sante.infos@gouv.bj), ref: N°127/MS/DC/SGM/CNERS/SA
3. Approved 05/10/2021, National Research Ethics Committee of Gabon (BP 2217 Libreville, Gabon; +241 (0)7791200; email not available), ref: N°0057/2021/P/SG/CNER
4. Approval pending, Research & Development Division, Ghana Health Service (P. O. Box MB 190, Accra-Ghana;+233-0302681109; ghserc@gmail.com)

Study design
Two-arm randomized comparator-controlled participant- observer- and analyser-blind multicentre phase III non-inferiority clinical 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 African children aged 6 months to ≤10 years

Interventions
Treatment will be randomly assigned (block randomization) to the participants using a 1:1 ratio. Participants will receive one of the following treatments following a weight-based treatment algorithm:
Experimental: Artemether lumefantrine twice daily + atovaquone proguanil twice daily, over 3 consecutive days, oral administration
Control: Artemether lumefantrine twice daily + placebo twice daily, over 3 consecutive days, oral administration

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), pharmacokinetics, hematology and biochemistry. Clinical examinations will be carried out.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
1. Day-28 efficacy of treatment defined as PCR-adjusted adequate clinical and parasitological response (ACPR) excluding reinfections, in the per-protocol (PP) population.
2. Day-28 efficacy of treatment defined as PCR-adjusted ACPR excluding reinfections, in the modified intention-to-treat (mITT) population.

Secondary outcome measures
Current secondary outcome measures as of 18/09/2024:
1. PCR-unadjusted day-28 ACPR by treatment arm in both the PP and the mITT population overall and in age subgroups (aged 6 to 59 months and from 60 months to ≤10 years)
2. PCR-adjusted and unadjusted day-42 ACPR by treatment arm in both the PP and in the mITT population overall and in age subgroups (aged 6 to 59 months and from 60 months to ≤10 years)
3. PCR-adjusted day-28 ACPR by treatment arm in both the PP and the mITT population in age subgroups (aged 6 to 59 months and from 60 months to ≤10 years);
4. Cure rate at days 14, 21, 28, 35 and 42 by treatment arm to evaluate post-treatment prophylactic efficacy in both PP and mITT populations
5. Types, proportion, severity and causality of adverse events (AEs) during treatment follow-up by the treatment arm as measures of tolerability and safety
6. Day-7 lumefantrine and desbutyl-lumefantrine plasma concentrations by treatment arm
7. Day-7 atovaquone, proguanil and its metabolite (cycloguanil) plasma concentrations when the treatment is AL +AP
8. Day 3 positivity rate by treatment arm in both PP and mITT day 3 positivity rate is defined as the proportion of patients who were still parasitaemic on day 3 after initiation of treatment

Previous secondary outcome measures:
1. PCR-unadjusted day-28 ACPR by treatment arm in both the PP and the mITT population. Percentages will be reported along with 95% exact Clopper-Pearson confidence intervals;
2. PCR-adjusted and unadjusted day-42 ACPR by treatment arm in both the PP and in the mITT population. Percentages will be reported along with 95% exact Clopper-Pearson confidence intervals;
3. Unadjusted cure rate (including reinfections) at days 14, 21, 28, 35 and 42 by the treatment arm to evaluate post-treatment prophylactic efficacy (PTP) in both PP and mITT populations. Time-to-event analyses will be performed to assess the association between treatment and the duration of PTP;
4. Types, proportion, severity and causality of AEs during treatment follow-up by the treatment arm as measures of tolerability and safety;
5. Day-7 lumefantrine and d-LF plasma concentrations by treatment arm;
6. Day-7 atovaquone, proguanil and its metabolite (CG) plasma concentrations when the treatment is AL +AP;
7. Day 3 positivity rate by treatment arm in both PP and mITT; day 3 positivity rate is defined as the proportion of patients who were still parasitaemic on day 3 after initiation of treatment

Overall study start date
01/03/2019

Completion date
02/04/2024

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 18/09/2024:
1. Children between the ages of 6 to ≤10 years
2. Body weight ≥5.0kg
3. Fever (≥37.5°C axillary or 38.0°C oral, rectal or tympanic body temperature) or history of fever in the preceding 24 hours
4. Uncomplicated P. falciparum mono-infection with equal or more than 1,000 and less than 200,000 asexual P. falciparum parasites per microliter of blood.
5. Signed written informed consent from the child’s legal representative
6. Ability to comply with study procedures and follow-up schedules
7. Willing to stay in the study area during the period of follow-up
8. Ability to take oral medication

Previous participant inclusion criteria:
1. Children between the ages of 6 to 59 months
2. Body weight ≥5.0kg
3. Fever (≥37.5°C axillary or 38.0°C oral, rectal or tympanic body temperature) or history of fever in the preceding 24 hours
4. Uncomplicated P. falciparum mono-infection with equal or more than 1,000 and less than 200,000 asexual P. falciparum parasites per microliter of blood.
5. Signed written informed consent from the child’s legal representative
6. Ability to comply with study procedures and follow-up schedules
7. Willing to stay in the study area during the period of follow-up
8. Ability to take oral medication

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
10 Years

Sex
Both

Target number of participants
1664

Total final enrolment
1664

Key exclusion criteria
1. Presence of severe malaria following WHO definition
2. Reported intake of any antimalarial drug within the previous 28 days
3. Intake of drugs with antimalarial activity or contraindicated drugs within the previous 28 days
4. Administration of strong inducers or inhibitors of CYP3A4 such as rifampin, carbamazepine, phenytoin, millepertuis/St. John's wort/
hypericum perforatum, grapefruit within the previous 28 days
5. Known history or evidence of clinically significant medical disorders as determined by the investigator
6. Severe malnutrition assessed by middle upper arm circumference (< 115 mm) according to WHO standard
7. Screening hemoglobin level <7 g/dL
8. Known hypersensitivity or contraindications to any AL and/or AP components
9. Known QT prolongation
10. Previous participation in a malaria vaccine study
11. Participation in the ASAAP study during the previous 42 days
12. Participation in other interventional studies within the previous 28 days
13. Patients that the investigator considers would be at particular risk if participating in the study

Date of first enrolment
01/10/2021

Date of final enrolment
18/02/2024

Locations

Countries of recruitment
Benin

Gabon

Ghana

Mali

Study participating centre
Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR); Kwame Nkrumah University of Science and Technology (KNUST)
UPO
PMB
Kumasi
Ghana
-

Study participating centre
Institut de Recherche Clinique du Benin (IRCB)
01 BP 1114
Abdomey Calavi
Benin
-

Study participating centre
Centre de Recherches Médicale de Lambaréné (CERMEL)
BP 242
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Study participating centre
Malaria Research and Training Centre (MRTC), Université des Sciences, des Techniques et des Technologies de Bamako (USTTB)
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Sponsor information

Organisation

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ROR
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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.

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

Intention to publish date
31/12/2025

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

Available on request, Stored in repository