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Efficacy, safety and population pharmacokinetics of artesunate-mefloquine combination for the treatment of uncomplicated falciparum malaria in African children versus artemether-lumefantrine

Submission date
27/07/2010

Recruitment status
No longer recruiting

Registration date
26/08/2010

Overall study status
Completed

Last Edited
28/03/2017

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
We are conducting a study on a new malaria combination drug called artesunate-mefloquine. This drug will be used by sick children who are able to take the drug orally. Available information about this drug, which comes mostly from the use of this drug in East Asia and Southern American countries, indicates that the artesunate-mefloquine combination is better and safe for children. However, we need to understand more about the safety of this combination drug in the African continent, where this information is rare. It is for this reason that this study is conducted.

Who can participate?
Children aged between 6 and 59 months, either sex, with uncomplicated falciparum malaria.

What does the study involve?
Patients will be divided into two groups to ensure that each participant has an equal chance of being in either group (like a lottery). Half of the children will be given the trial drug artesunate-mefloquine (ASMQ) and the other half will be given a combination drug with a known efficacy (i. e. artemether-lumefantrine, AL) in order to be able to compare the results of the current malaria drug and the new drug. At the first visit your child will be seen by a doctor and a small amount of blood (less than a teaspoon) will be drawn from her/his hand to verify if the child has malaria parasites and to check the health status. This initial investigation will help us to know if your will be able to participate or not. Following this stage, your child will receive treatment based on the assigned group as described above. Blood from a finger prick to follow the malaria parasites will be taken every eight hours until the malaria parasites are not seen. Your child will be admitted in the ward not less than 3 days until she/he receive the last dose of malaria drug. A blood sample will be taken once again from the finger at days 1, 2, 3, 7, 14, 21, 28, 35, 42,49, 56 and 63 when the child will be brought for follow up. The doctor will see and examine your child during all

these 12 visits. An extra blood sample will be taken during the investigation of your child on days 7, 28 and 63 and any other sample will be taken only if it is needed for the childs treatment. Also, on day 0 (i.e. before the first dose) and day 7, a sample will be taken from every child to test the amount of drug in the childs body, as well as the last day if the child has recurrence of parasitemia. A total of 100 children (50 in each group, ASMQ and AL) will be selected out of the 940 for follow up of drug levels in the childs body. For the 50 children in ASMQ group, four additional samples will be taken on day 0 (after the first dose), day 2 (after the third dose), day 3, and either on day 28, 35, 42, 49, 56 or 63. For the 50 patients in the AL group, two additional samples will be taken on day 3 and either on day 28, 35, 42, 49, 56 or 63. You may stay with your child during the treatment, follow-up and in all stages. The child will be in the study for a total of nine weeks. In case of recurrent parasitaemia during the efficacy follow-up period (63 days), your child will be treated with the investigational product of the other arm. For example, if your child has received Coartem he would receive ASMQ, and vice versa, and follow-up of 63 days will recommence after the day of failure in order to supervise the progression. Three visits will be performed during this follow-up: at 7, 28 and 63 days. The following assessments will be done during these three visits and any other day if you return spontaneously: blood from a finger prick to follow the malaria parasites and recording of eventual adverse effects and concomitant medications.

What are the possible benefits and risks of participating?
If you agree for your child to participate in this study, you may have the following benefits: the child will be watched closely for a period of more than six weeks and in case of any sickness during that period, she/he will be given treatment without any cost. Also, participating in this study could help to understand if the combination drug artesunate-mefloquine is better and safe for African children and this will facilitate availability of this drug in African countries where children are dying of malaria.Incentives will not be provided to persuade people to participate in this study; however, to value your time and recognize your participation in this study; we will pay the treatment costs for your child in this hospital during the study period. Moreover, you will be paid for travel costs during the follow-up days. During the time you are admitted in the ward, you will be provided with food from the hospital cafeteria and at discharge you will be given an insecticide-treated bed net. When participating in this study, there is a possibility of discomfort to your child during examination and frequent blood sampling. Also in participating in this investigation there is a possibility of increased nausea and vomiting. We will try to reduce the possibility of discomfort, and in case of any problem your child will be provided with appropriate medical care without any cost. The sponsor will have an insurance policy which will be in place prior to the start of the trial.

Where is the study run from?
1. Centre National de recherche et de Formation sur le paludisme (CNRFP), Burkina Faso.
2. NIMR, Dar Es Salaam, Tanzania.
3. NIMR Korogwe, Korogwe, Tanzania.
4. Ifakara Health Institute, Bagamoyo, Tanzania.
5. KEMRI, Nairobi, Kenya.

When is the study starting and how long is it expected to run for?
October 2010 to October 2013

Who is funding the study?
Drugs for Neglected Diseases initiative (DNDi) (Switzerland)

Who is the main contact?
Dr Sodiomon Bienvenu Sirima
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
DNDi-ASMQ-AF09

Study information

Scientific Title
Efficacy, safety and population pharmacokinetics of artesunate-mefloquine combination for the treatment of uncomplicated falciparum malaria in African children versus artemether-lumefantrine: an open label prospective randomised controlled clinical trial

Study objectives
1. To evaluate efficacy of artesunate-mefloquine fixed-dose combination in children with uncomplicated falciparum malaria, by determining the proportion of patients achieving a negative parasitemia without recrudescence by 63 days
2. To measure the parasite reduction ratio on Day 1, 2 and 3
3. To compare the proportion of patients with parasitaemia on Day 2 and 3
4. To compare the proportion of patients with fever on Day 2 and 3
5. To compare the gametocyte carriage at Day 2 and 3, and Day 28, 42 and 63
6. To evaluate cure rate at 28 and 42 days
7. To evaluate the population pharmacokinetics of artesunate-mefloquine and lumefantrine in under-5 children
8. To evaluate the incidence and severity of adverse events
9. To evaluate the incidence of serious adverse events and adverse events leading to treatment discontinuation
10. To analyse the time description of time course and vomiting frequency

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Burkina Faso: Ministry of Health approved on 07/07/2010
2. Tanzanian ERB approval on 12/07/2010, 15/05/2012
3. Tanzania Food and Drugs Authority (TFDA) approval on 24/02/2011, 02/05/2012
4. Kenyan ERB approval on 22/02/2011
5. Kenyan ECCT/PPB (Expert Committee on Clinical trials- Pharmacy and Poisons Boards) approval on 04/03/2011

Primary study design
Interventional

Study design
Open-label prospective randomised controlled non-inferiority multicentre clinical trial

Study type(s)
Treatment

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

Interventions
All patients recruited into the study will be given full, supervised treatment with either:
1. Artesunate-mefloquine (ASMQ) co-formulation (25/55 mg), administered orally for 3 consecutive days according to the following dosing schedule:
1.1. 6 to 11 months a single tablet once daily
1.2. 12 to 59 months of age, 2 tablets once daily
2. Artemether-lumefantrine (AM-LM) (Coartem® dispersible, Novartis Pharma), 6 doses at 0, 8, 24, 36, 48 and 60 hours will be administered orally to patients. Doses will be as follows:
2.1. 5 to less than 15 kg body weight (BW): 1 tablet at inclusion, again 8 hours later and then twice daily on each of the following 2 days (total course comprises 6 tablets)
2.2. 15 to less than 25 kg BW: 2 tablets at inclusion, again 8 hours later and then twice daily on each of the following 2 days (total course comprises 12 tablets)

Total duration: 3 days of treatment and 60 follow-up days.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Artesunate-mefloquine, artemether-lumefantrine

Primary outcome(s)
Cure rate as determined by polymer chain reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) on Day 63. Treatment success or failures will be classified according to WHO Guidelines 2003.

Key secondary outcome(s)

1. Safety, measured on day 0, 1, 2, 3, 4, 7, 14, 21, 28, 35, 42, 49, 56, 63:
1.1. Frequency of adverse events by intervention
1.2. Detailed description of time course and vomiting frequency
1.3. Frequency of serious adverse events and adverse events leading to treatment discontinuation by intervention
2. Pharmacokinetics: population pharmacokinetic parameters for artesunate (AS), its main metabolite, dihydroartemisinin (DHA), mefloquine (MQ) and lumefantrine in a sub-set of 50 randomly selected patients. Drug levels for MQ and lumefantrine will be obtained for all patients on day 0 and day 7 and correlated with clinical response. Measured on day 0, 2, 3, 7, 28, 35, 42, 49, 56, 63.

Furthermore, for all patients with recurrence of parasitemia, a blood sample will be collected on the day of failure, in order to know the drug level at that specific time point.

Completion date
01/10/2013

Eligibility

Key inclusion criteria
1. Aged between 6 to 59 months, either sex
2. Presence of acute uncomplicated P. falciparum mono-infection confirmed by:
2.1. Axillary temperature greater than 37.5°C, and
2.2. Positive microscopy of P. falciparum with parasite density between 2,000 and 200,000 asexual parasites/µl
3. Written informed consent from parent/guardian

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 Months

Upper age limit
59 Months

Sex
All

Key exclusion criteria
1. Patients with signs and symptoms of severe/complicated malaria requiring parenteral treatment according to the World Health Organization Criteria 2000
2. Weight less than 5 kg
3. Inability to tolerate oral medication (presence of any of the following danger signs: unable to

drink or breastfeed, severe vomiting, recent history of convulsions, lethargic or unconscious state, unable to sit or stand up)
4. Mixed Plasmodium infection
5. Presence of febrile conditions caused by diseases other than malaria
6. Known history of hypersensitivity, allergic or serious adverse reactions to mefloquine, quinine, quinidine, artesunate or other artemisinins
7. History of use of any anti-malarial agent within 2 weeks prior to start of the study (except mefloquine and piperaquine within 4 weeks)
8. Prior participation in a therapeutic trial within 3 months

Date of first enrolment
01/10/2010

Date of final enrolment
01/10/2013

Locations

Countries of recruitment
Burkina Faso

Kenya

Tanzania

Study participating centre
Centre National de recherche et de Formation sur le paludisme (CNRFP)
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Sponsor information

Organisation
Drugs for Neglected Diseases initiative (DNDi) (Switzerland)

ROR
https://ror.org/022mz6y25

Funder(s)

Funder type
Research organisation

Funder Name
Drugs for Neglected Diseases initiative (DNDi) (Switzerland)

Results and Publications

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	01/10/2016		Yes	No