Assessing the tolerability and safety of single low dose primaquine in African children with acute uncomplicated falciparum malaria and glucose 6 phosphate dehydrogenase deficiency

Short Study Title: Primaquine in African children (PAC)

Patient Information Sheet

Today you are being asked to allow your child (child under your care if you are the legal guardian) to participate in a research study of about 1600 children with malaria from Uganda and the Democratic Republic of Congo (DRC). In this leaflet, we will give you information about the study to help you decide whether or not you wish your child to participate.

Why is this research being done?

We are doing this research because we want to know if adding a drug called PRIMAQUINE to your child's treatment for malaria is safe. Normally, malaria is treated with a drug to get rid of the malaria parasites in the blood and make your child feel better. In this study we will use either ARTEMETHER-LUMEFANTRINE (also called COARTEM), the standard treatment for malaria in Uganda, or another drug called DIHYDROARTEMISININ PIPERAQUINE. Both drugs are very effective for treating malaria.

The primaquine is being added to try to stop malaria being transmitted to mosquitoes when they bite. We hope primaquine is safe so that if it is used in many people in the future, it will reduce the amount of malaria in our community.

Primaquine is well tolerated but in some people it can cause the red cells in the blood to break apart if they are weak. If many red cells break apart your child could become anaemic. Red cells need enzymes to work properly and weak red cells have low amounts of an enzyme called glucose 6 phosphate dehydrogenase (G6PD). In this study, we want to know if treating your malaria with primaquine will be safe for the red cells that do not have enough of the G6PD enzyme.

What will happen to my child in this study?

The study doctors will ask you some more questions about your child and examine him/her. We will also take blood from a finger and a vein. These blood will tests are to: (i) see how much malaria there is in the blood, (ii) check how much G6PD enzyme is in your child's red cells, (iii) measure your child's blood count, (iv) check the liver and kidneys are working well, and, if you agree, (v) measure the study drugs in your child's blood. We will also do genetic tests to see how the child's body deals with Primaquine and the type of G6PD deficiency the child has as well as other problems with your child's red blood cells.

Then, we will treat your child for malaria with either artemether lumefantrine or dihydroartemisinin piperaquine. We will decide this by a system programmed on a computer and predetermined by a researcher (statistician). For us to know what damage primaquine can do to the red cells in the blood, we will give your child either primaquine or a drug that looks like primaquine but has no effect on the red cells, a bit like a sugar pill. This is called a PLACEBO.

This is important because when children have malaria, they may be anaemic anyway. We will measure and compare how much anaemia children have when they receive primaquine or placebo. That way, we will be able to see if the primaquine causes more anaemia compared to the placebo. No one will know if your child has received primaquine or placebo and the chances of getting one or the other is 50 - 50; again, this is like tossing a coin.

So your child will receive any one of four possible treatments:

1. ARTEMETHER-LUMEFANTRINE (also called COARTEM) and PRIMAQUINE
2. ARTEMETHER-LUMEFANTRINE and PLACEBO
3. DHA-PIPERAQUINE and PRIMAQUINE
4. DHA-PIPERAQUINE and PLACEBO

We want to be careful with badly anaemic children with a lot of malaria in their blood, so we ask that you allow your child to stay in hospital for a few days so we can monitor him or her closely. After 100 of such children have been admitted, we will see if we can stop this practice and treat your child as an outpatient.

Taking extra blood to measure drugs in the blood in the first 24 hours

We would like to measure the drugs in your child's blood because we do not have information on primaquine in young children from Africa. Also, we will give primaquine with artemether lumefantrine or dihydroartemisinin piperaquine and the primaquine may affect these drugs.

We will need to take 8 samples of blood in the first 24 hours, so we will insert a small cannula into the vein of your child. This is a small piece of plastic through which we can obtain the blood. It will be removed after 24 hours.

The total amount of extra blood in 24 hours is 6 mL, a little more than one teaspoon.

This extra blood sampling is optional. It is your choice.

What will happen after my child leaves the hospital?

After the first 24 hours, if your child remains well they may leave hospital but will have to come back every day for 3 days for blood tests. Alternatively if you wish, your child can stay for up to 4 days.

You will be asked to return to the clinic on Day 7, 14, 21, 28, 35, and 42 with your child. At each visit, we will examine your child and take blood again from the fingertip and the vein (Days 3, 7 and 28). The visit will take about one hour.

For children who were not admitted into hospital, the follow up is very similar. Day 1, 2, 3, 7, 14, 21, 28, 35, and 42. Please note that in our study, Day 0 is the first day of treatment.

If at any time your child is unwell during the next 42 days you are requested to come directly to the research clinic or to contact us by phone. There will be someone at the study clinic every day and every night. Please do not buy drugs from a local pharmacy or see other doctors not involved in the study during the period of the study.

If at any time your child is not completely cured, the doctor will treat him/her with another effective drug against malaria. The doctor, throughout the study, will always do what is in your child's best interest.

In case you miss an appointment, the medical staff will contact you to find out why you missed the appointment. If we cannot contact you, we will visit you at home and ask that your child be brought to the clinic for assessment.

Does my child have to take part?

No. Your child should only take part if you decide he/she can. We want to give you enough information to help you make an informed decision and please ask us any questions you have while reading or being read to this information.

If you do not want your child to take part, he/she will still receive treatment for malaria. Also, if after your child has entered the study, you decide to take him/her out of the study, this will not affect your child's care. You will be referred to the hospital outpatient department where standard care for malaria is available.

What are the advantages of taking part?

Your child will receive clinical care from the medical officers and nurses of the project staff in the study clinic. This will include care for unscheduled sick visits. If we learn new information from this study that we think will benefit your child, we will inform you.

The knowledge gained from this study will contribute to the effort of eliminating malaria.

What are the disadvantages of taking part?

Side effects, like nausea, tummy upset, headache or dizziness, could occur after using antimalarial medicines but they are generally mild and short-lived. Your child will be treated with one of these drugs, even if they are not in the study.

Anaemia can develop following the use of primaquine in patients with G6PD deficiency and, if severe, a blood transfusion might be required. Malaria itself can also cause severe anaemia that may also require a blood transfusion.

The risk of drawing blood includes temporary discomfort from the needle stick and bruising. Your blood will be taken by an experienced laboratory technician to prevent and/or limit these problems.

If your child has any side effects from the study drugs or a minor illness unrelated to the study drugs, we will treat your child free of charge. The trial is insured, so in the unlikely event that your child is harmed as a direct result of participation in the study, compensation will be available.

How much blood will be taken?

The amount of blood removed will be too small to affect your child's health. If your child does not come into hospital, the total amount of blood is about 26 mL, a bit more than 5 teaspoonfuls over 6 weeks.

If your child is admitted into hospital and has extra blood taken to measure drugs, the total amount of blood is a little under 34 mL – about 7 teaspoons.

Do I have to pay for medical care received in the study?

No. If your child participates in the study you will not have to pay for treatment, medical tests or clinic visits. We will reimburse any transport costs incurred for the clinic visits and if you have to visit your child while he or she is in hospital. If you lose wages to look after your child in hospital, we will compensate you for these lost wages according to modest rates for daily wages set at Uganda Shillings 10,000 (ten thousand). Meals and soap for personal hygiene will be provided when your child is in hospital and we will compensate for lost wages.

Who will have access to my child's information?

All information collected in this study will be treated confidentially by the medical staff. To help this process your child will be assigned an identification number which will be used on all study forms and blood tubes.

Some samples will be transferred to a specialised laboratory outside of Uganda for the tests that we cannot perform here e.g. the drugs will be measured in Thailand. For some specialised malaria and blood tests, your blood may be sent to Kenya, Thailand and England.

The information collected will be reviewed only by authorised staff to ensure that your child safety and rights are protected while participating in the study. They will also treat the data confidentially.

The findings might be published in a medical journal and, if you agree, may be shared with other researchers, in the future. The study participants will never be identified by name.

The researchers and doctors who carry out this study guarantee that the study conduct and the results will not be influenced at any time by the funder of the study. After the study is completed, you may request an explanation of the study results.

Storing blood samples for future use

We will store some of your child's blood because we cannot do all the tests straightaway. We would like to confirm if and what type of G6PD your child has and look for other red blood cell problems. We will advise you if you have a serious problem with your red blood cells.

After the study tests are done, we would like to continue to store your child's blood in case we want to do further tests or new tests on the blood that will help us better understand G6PD, malaria and primaquine. If we wish to do more tests, we will give the details to the ethics committee and they will decide if these tests can be done.

Who is conducting this study and who has approved it?

This study is being done by doctors and scientists Mbale Regional Referral Hospital in collaboration with a hospital in the DRC. Two universities in England are also involved: (i) Imperial College in London, and (ii) Oxford University in Oxford.

The study is sponsored by and insured via the University of Oxford and funded by the Medical Research Council of England. This research has been reviewed by a committee of experts, known as the Research Ethics Committee, to protect your child rights and welfare.

Implication of your signature or thumbprint

If you give consent for your child to participate in this study you should sign the consent form (or you should place your thumbprint in case you cannot read and/or write). Your signature or thumb print below means that you have understood the information given to you about your child's participation in the study. You will be given a copy of this consent form for you to keep.

What if I have questions?

If you have any questions at this stage or if you have questions later during the research please feel free to ask the research staff with at this time.

If you have any other question or would like to understand more about this study please feel free to contact the following:

Dr. Peter Olupot-Olupot, Mbale Clinical Research Institute, P.O.Box 1966, Mbale, Uganda. Telephone Number 0772 457 217.

If you want to ask someone independent about this research please contact:

The Chairman, Mbale Regional Referral Hospital Research & Ethics Committee (MRRH-REC), Dr. John Stephen Obbo Olwenyi, P.O. Box 921, Mbale, Uganda. Telephone Number 0772 437 407.

WE THANK YOU FOR YOUR TIME

INFORMED CONSENT FORM FOR PARTICIPATION IN A RESEARCH PROJECT

STUDY NUMBER |__|__|__|__|-|__|__|__|

Study Title: Assessing the safety of low dose primaquine in *Plasmodium falciparum* infected African children with glucose 6 phosphate dehydrogenase deficiency, Primaquine in African children (PAC)

Principal Investigator: Dr. Peter Olupot-Olupot (Tel. 0772 457 217 or email: polupotolupot@yahoo.com)

I, _____ mother / father / legal representative (aged 18 or above) declare that I have understood the objectives and purposes of this study. I have had the opportunity to ask questions about the study and any questions I have been asked have been answered to my satisfaction.

I agree that my child _____, aged _____ years _____months, participates in this study. I am aware that I can withdraw my child from the study at any time without any consequence to my child or to me.

I allow ☐ / do not allow my child to have the extra blood taken for the drug measurements ☐

I allow ☐ / do not allow the blood of my child to be stored for future study ☐

I allow ☐ / do not allow the clinical data and results from blood analyses that are stored in the database to be shared with other researchers to use in the future ☐

I allow ☐ / do not allow the study to use the clinical and blood test data, if I take my child out of the study ☐

☐ The participant cannot read/write, but the researcher has read the document to him/her. He/she has listened and clearly understood. He/she hereby agrees to participate in this research study

Parent / Legal representative

Name_____ **Signature or Thumbprint** _____

Date |__|__|__|__|__|__|__|__| **Time** |__|__:__|__|

Impartial Witness (if participant cannot read/write)

Name_____ **Signature** _____

Date |__|__|__|__|__|__|__|__| **Time** |__|__:__|__|

Person Taking Consent

Name_____ **Signature** _____

Date |__|__|__|__|__|__|__|__| **Time** |__|__:__|__|