A Randomized Controlled Double-Blind Trial for Prevention of Recurrent Ischemic Priapism in Men with Sickle Cell Disease: A Pilot Study

September 20, 2020

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Institutional Review Board Informed Consent Document for Research

Principal Investigator: Dr. Michael R. DeBaun **Revision Date:** 20/09/2020
Site Investigator: Dr. Ibrahim M. Idris
Shortened Title: Priapism in Nigeria (PIN) trial **Institution/Hospital:** Aminu Kano Teaching Hospital
Coordinating Center: Vanderbilt University Medical Center

Name of participant _____ Age _____

The following is given to you to tell you about this research study. Please read this form carefully and ask any questions you may have about this study to prevent recurrent priapism. Your questions will be answered. Also, you will be given a copy of this consent form to study on your own. You do not have to be in this research study. You may choose not to be in this study to prevent recurrent priapism and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because we would like to determine if a drug named tadalafil could prevent recurrences of painful erections in men with sickle cell anemia. At the moment, there is no evidence-based medical treatment of recurrent painful, unwanted erections (priapism) in men with sickle cell anemia. The drug we are researching has shown some promise in a small clinical trial conducted in the United States. We believe that:

1. Hydroxyurea approved for use in Nigeria, will be beneficial in the treatment of recurrent priapism
2. Tadalafil, which is approved for use in Nigeria, is a drug typically used to prevent erectile dysfunction, may have some benefit in preventing recurrent priapism.
3. But do not know that hydroxyurea treatment and tadalafil treatment may work better to prevent recurrent priapism than hydroxyurea therapy alone (standard therapy).

As a pilot, we plan to enroll and follow between 30 and up to 200 mend with SCD and recurrent priapism Aminu Kano Teaching Hospital and Murtala Muhammad Specialist Hospital for a period of 15months. The information obtained from this trial will help us to understand if tadalafil, in combination with hydroxyurea, maybe a more practical approach for preventing this feared complication (priapism) of sickle cell anemia. You will have an equal chance of getting either hydroxyurea therapy for recurrent priapism or hydroxyurea plus tadalafil treatment for a total of 12 months. The therapy and laboratory monitoring will be provided free of charge with monthly research visits for 15 months.

2. What will happen and how long will you be in the study?

Before entry into the study, we will explain the risks, benefits, and alternatives to the study and ask you to sign this informed consent form. If you choose to participate, we will do the following:

1. Take baseline history and physical examinations, which will be repeated during every study visit (four weekly)
2. Assess sexual function using the International Index of Erectile Function (IIEF), PROMIS Erectile function, Sexual Activity and Satisfaction, at baseline and study exit.
3. Assess priapism impact using a validated patient self-report tool (Priapism Impact Profile)
4. Do baseline laboratory assessment of renal and liver function
5. Assess Hemoglobin F and hemolysis marker (LDH), at baseline and study exit, month 12.
6. Assess blood level (complete blood counts and reticulocyte) at baseline and every four weeks of study follow up.
7. Assay serum testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin, at baseline and study exit.
8. Administer trial medications adherence questionnaire every study visit

You will be given $10 (3000 naira) for completing the study procedures and during monthly clinic follow up. You will be randomly (by chance) assigned to either a treatment group that consists of tadalafil plus hydroxyurea or a placebo group that consists of non-pharmacologically active substance and hydroxyurea (as a standard care). This assignment into either treatment or placebo group will be done unbiased by the study statisticians, and you have an equal chance of being assigned to either of the groups. However, only the study pharmacist will know the treatment you are on for dose adjustment.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study. All study procedures (tests and drugs) will be covered by the funds earmarked for this trial. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness that is not related to this trial. This includes treatments and tests you would need even if you were not in this study. You have the right to ask what it may cost you to take part in this study. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the trial. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs, and your doctor will discuss other treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:

I. Blood Draw: A small sample of blood (about 6 ml) will be taken at the start of the study and every four weeks during the study. This process may cause mild pain or a small bruise at the site. Patients may also feel lightheaded or pass out.

***II. Hydroxyurea (HU) Therapy*:** HU. has been studied in sickle cell disease since 1984. The study standard of care will include HU therapy at 20 mg/kg/day. HU therapy will be provided to each study participant at no cost to the participant and family. We will have a detailed plan in the protocol on how to deal with serious adverse events that may arise secondary to HU therapy. Sometimes HU is associated with:

- Feeling sick to one's stomach and throwing up
- Low sperm count

- Risk of infection
- Skin darkening
- Mouth sores
- Constipation
- Diarrhea
- Rash
- Hair loss
- Worsening of chronic leg ulcers

As a participant, you will receive a HU handbook that will provide an overview of the medicine, side effects, benefits, and latest literature on the use of the medicine among individuals with SCD.

Tadalafil: The drug is being used for treating erectile dysfunction. It has never been used in a trial of SCD-related priapism, but another drug similar to it, Sildenafil, has been used in a trial with no serious adverse effect. However, in a different trial for treating pulmonary hypertension, Sildenafil (which is in the same class with tadalafil) was reported to cause acute pain. As a participant, you may receive tadalafil 2.5-5 mg/day morning doses or a placebo. We will use PRO CTCAE to track the adverse effects of tadalafil. Occasionally, tadalafil has been associated with the following possible adverse effects:

- Hypotension
- Flushing
- Headache
- Nasal congestion
- Visual disturbance

There is a theoretical risk of tadalafil (a drug originally licensed for treatment of erectile dysfunction), precipitating priapism as an adverse effect. Although this adverse effect is very rare (the previous clinical trials in patients with sickle cell disease reported no single priapism from the use of Sildenafil), to prevent this potential adverse effect, this clinical trial is designed to use a small dose of tadalafil (2.5-5 mg) that is very unlikely to be associated with such type of adverse effect. We will also carefully monitor for pain, including pain-related hospital admissions, and malaria, as a safety measure and stopping rule for the pilot clinical trial.

6. Payment in case you are injured because of this research study:

If it is determined by the study site and the investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you, your insurance, or both will not have to pay for the cost of immediate medical care provided by **AKTH** to treat the injury. Based on the available evidence, there is only a remote chance that the treatment approved by the Nigerian government that we are using in this study will cause any reason for hospitalization

There are no plans for the research fund to pay for any injury caused by the usual care you would typically receive for treating your illness or the costs of any additional care unrelated to this research.

7. Good effects that might result from this study:

This trial may provide an evidence-based preventive strategy for recurrent priapism. Participants and other patients suffering from this complication will benefit from this finding.

8. Other treatments you could get if you decide not to be in this study:

If you chose not to participate in this study, this would not affect the routine care that you receive from your hematologist for treatment of your sickle cell disease and other medical conditions.

9. Payments for your time spent taking part in this study or expenses:

You will be paid $10 (3000 naira) for your participation. You will be compensated for monthly study visits with $10 (3000 naira). However, you will not be compensated for your regular medical care.

10. Reasons why the study doctor may take you out of this study:

If you have any contraindication to tadalafil or hydroxyurea, then you may be taken out of the study for your own safety.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding not to be part of the study will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel that taking part in this study has hurt you, please feel free to call the site investigator, Dr. Ibrahim Musa, at 08039685753.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to contact the AKTH Health Research and Ethics Committee (+234-8065669777) or call the Vanderbilt University Institutional Review Board Office at 1-615-322-2918 or toll-free at 1-866-224-8273.

13. Confidentiality:

With any clinical study, there is a small risk that your confidentiality may be violated, which could potentially affect your future ability to obtain employment or medical, disability, or life insurance. In order to prevent this, all key personnel involved in the design or conduct of this study will receive mandatory education on the protection of human research participants. In addition, a study code will be attached to your medical information for de-identification purposes. The key and charts connecting patient names and study codes will be kept in secure, locked sites, or a secure computer separate from the study records in order to prevent unauthorized access to your personal medical information.

The institutions affiliated with this project (Aminu Kano Teaching Hospital and Vanderbilt University Medical

Center may share your information, including date of birth, without identifiers, with others, or use it for other research projects not listed in this form. These institutions, Dr. DeBaun (the principal investigator of the study) and his staff, and Dr. Idris (the local site investigator), will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Researchers at Aminu Kano Teaching Hospital will share data with Dr. DeBaun (the Principal Investigator) at Vanderbilt University Medical Center (VUMC) in Nashville, TN, USA. VUMC will collaborate with the team in Kano to collect and analyze data for this research study.

14. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been, gathered or kept by your healthcare providers as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure"), such data must follow privacy rules. By signing the consent for this study, you agree ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you also agree to let the study team use and share your PHI as described below.

As part of the study, Dr. Idris, Dr. DeBaun, and the study team may share the results of your study and/or non-study linked imaging studies, as well as parts of your medical record, with other groups. These groups may include people from the US Federal Government Office for Human Research Protections and the Vanderbilt University Institutional Review Board, and the AKTH Health Research Ethics Committee. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private. The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Michael DeBaun in writing and let him know that you withdraw your consent. His mailing address is Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Michael DeBaun in writing and let him know that you withdraw your consent. His mailing address is:
2525 West End Ave, Ste 750 VIGH
Nashville, TN 37203
Phone: 615-875-3040

The health data that we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to participate in this research study, it will not affect your treatment, payment, or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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Revision date: 20/09/2020

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY I have read this consent form, and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____

Signature of patient Date

_____ _____

Printed Name Time