NHREC Approval Number: NHREC/01/01/2007-14/09/2021
Date of NHREC approval: 14/09/2021
This approval will elapse on: 13/09/2022

This Informed Consent Form is for men and women who attend Irrua Specialist Teaching Hospital (ISTH), and who we are inviting to participate in research on Lassa Fever. The title of our research project is as follows.

Title of the research: Pharmacokinetics, tolerability and safety of favipiravir compared to ribavirin for the treatment of Lassa fever: A randomized controlled open label phase II clinical trial

Name(s) and affiliation(s) of researcher(s) of applicant(s): This study is being conducted by Dr. Peter Akhideno (Principal Investigator) of the Irrua Specialist Teaching Hospital (ISTH) in Edo State, Nigeria and by Dr. Cyril Erameh (Co-Principal Investigator) of the Irrua Specialist Teaching Hospital (ISTH) in Edo State, Nigeria, and Prof. Stephan Günther of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany.

Sponsor(s) of research: The sponsor of this study is the Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany. The sponsor representative is Prof. Stephan Günther, Department of Virology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany.

Funding: The research is funded by the German Federal Ministry of Health.

Introduction: The ISTH and the Bernhard-Nocht-Institute for Tropical Medicine in Germany as well as the Federal Medical Center of Owo (FMCO) Ondo State, Nigeria, the Institut national de la santé et de la recherche médicale (Inserm), France and the Alliance for International Medical Action (ALIMA), France, are doing research on the treatment of Lassa fever. You have been diagnosed with Lassa fever. Therefore, you are being invited to volunteer as a participant in this research being conducted by ISTH. The same study is also conducted at FMCO. Before you decide whether you want to participate in this research or not, it is important for you to understand why the research is being done and what it will involve. You will have sufficient time to consider whether or not you would like to participate in the research. Please read through the following information carefully and feel free to ask any questions if it is not clear or to

discuss it with anyone you wish. There may be some words that you do not understand. Please feel free to ask the research physician (investigator) who is informing you about this study. There will be time to explain all details, to address all your questions and time for you to consider your participation.

Purpose(s) of research: Lassa fever is an acute febrile illness with bleeding and organ failure. The Lassa virus, which is spread by rodents, is responsible for this illness. There is no vaccination available against the Lassa virus. There is only one drug known for treatment of Lassa fever which is called ribavirin. The knowledge of the efficacy of this drug in Lassa fever treatment is poor. Favipiravir is a drug candidate that showed efficacy against Lassa fever in non-human research. It has also been evaluated for use during the West-African Ebola outbreak and is approved for the treatment of widespread influenza virus infections in Japan. In order to evaluate the efficacy of favipiravir in Lassa fever, it is necessary to compare this new treatment candidate to the standard of care. We therefore conduct a randomized study with two treatment arms. This means that one of two treatment options will be allocated to you by chance.

Participation selection: We are inviting all (if female: non-pregnant) adults with Lassa fever who attend ISTH to participate in this research. Pregnant women, minors and cognitively impaired patients will be excluded from the research because, as a vulnerable population, they should not be exposed to the additional burden of an interventional study. Furthermore, intravenous ribavirin is not suitable for children and pregnant women. In case you are not able to take oral drugs (favipiravir will be administered orally) you may not be eligible.

Voluntariness: Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you choose not to participate in this research project, you will be offered the standard of care for Lassa fever treatment which is ribavirin. This treatment is routinely offered in this hospital for the treatment of Lassa fever. You also may change your mind later and stop participating even if you have agreed earlier.

Alternatives to participation: If you choose not to participate, this will not affect your treatment in this hospital in any way.

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Procedure of the research, what shall be required of each participant and approximate total number of participants that would be involved in the research: If you decide to participate in the study, one of the following treatment options will be allocated to you by chance:

1. Intravenous ribavirin standard treatment
2. Oral favipiravir

You will further be asked to provide blood. In total there will be 10 additional blood draws. 75 ml blood will be drawn in addition to the routine care which corresponds to approximately 5 tablespoons of blood. The routine care includes at least 8 blood draws and 49 ml of blood (corresponding to approximately 3.5 tablespoons) which will be withdrawn. Sampling will stop at discharge. The sampling frequency is planned as follows: To determine the ribavirin or favipiravir blood levels, blood collection will take place at 0.5, 1, 3, 5, 8 and 12 hours after as well as before the first drug administration. Furthermore, blood collection for determination of ribavirin or favipiravir blood levels will be performed once daily on day 2, 4, 6, 8, 10 and three times daily on day 7. On day 1 and 7 the blood may be taken with the help of a venous catheter which will stay in your vein for up to 13 hours on these days so that there will be less punctures and the blood is easier accessed. Blood for viral load measures will be taken at recruitment, before and 24 hours after first drug administration and on the 4^{th}, 6^{th}, 8^{th} and 10^{th} day of drug administration. Blood for general analyses (biochemical and haematology) will be collected every other day starting with screening. Whenever possible, collecting blood for research purposes is done in conjunction with routine blood collection to prevent additional interventions. If blood will be taken without a venous catheter, it will be taken with a syringe and needle. In total 124 ml blood will be drawn from you which corresponds to 8.5 tablespoons of blood. The additional amount of blood which is taken for research purposes amount to 75 ml (= 5 tablespoons) and is included in this 124 ml. Sampling will stop at day 10.

The blood will be tested in the laboratory for several parameters to find out how the drugs works in your body. In addition, your symptoms along the disease/your stay at the hospital will be

recorded, vital signs and body temperature will be measured regularly, ECG measurements as well as physical examinations will be performed and your urine will be analysed.

The research is conducted by staff of the Institute of Lassa Fever Research and Control at ISTH in collaboration with your doctor, as well as specialized laboratories. Part of your blood will also be sent to and tested by our German collaboration partners at the Bernhard-Nocht-Institute for Tropical Medicine, Hamburg and at the Institute of Pharmacy, University of Hamburg. This blood will be shipped according to the respective regulations. Your blood will be shipped in a pseudonymized manner (there will be no link to your name). Please see also the chapter "Confidentiality".

A total of 40 evaluable patients with Lassa fever are expected to participate (20 per treatment option).

What happens to your blood samples: The biologicals materials are to be stored at the Bernhard-Nocht-Institute for Tropical Medicine, BNITM, Hamburg, Germany and used at the laboratories of the BNITM and collaborators under BNITM's direct or delegated supervision as specified in the research protocol approved by the Institutional HREC. The blood samples will be stored securely for up to 10 years. It may become necessary to redo the analysis at a later time to confirm the results. The remaining blood samples will be destroyed according to the institutions' Standard Operating Procedure as well as to applicable regulations.

In order to improve the general health of the population and help the countries to put in place the right preventive measures, it could also occur that your blood may be needed to perform more analysis for Lassa fever and/or for other diseases that you might have been exposed to (it is possible to know this by testing the blood you gave along the study). These additional analyses would be conducted following internationally accepted standards (e.g. approval by ethics committee if applicable) and your identifier would be removed from your identifiable blood samples. That way your blood samples could be used without your additional informed consent.

Expected duration of research and of participant(s)' involvement: The enrolment period corresponds to the 10-day treatment period which is the common duration for Lassa fever treatment. The study itself started in August 2021 and is supposed to end in December 2022.

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Risk(s):

Favipiravir has never been used for the treatment of Lassa fever in humans but there is evidence from laboratory and animal studies suggesting that it is active. Therefore, it is not known whether and at which dose it is beneficial for the treatment of Lassa fever. The dose used in this study is a dose estimate based on previous studies in humans and in animal models. The most frequent side effects of favipiravir are decreased liver function, diarrhoea, decrease of white blood cells, decrease of neutrophils, increased blood uric acid and increased blood triglycerides. There may also be a temporary effect on the conduction system of the heart. To minimize this risk, repeated investigations of the heart will be performed by ECG.

Administration of ribavirin is standard of care for Lassa fever patients and therefore there is no additional risk associated with ribavirin. The most frequent side effects of ribavirin are pain, swelling and soreness at the injection site, nausea, flu-like symptoms, tiredness, fever, chills or shaking, headache, mood changes, irritability, muscle pain, stomach pain, vomiting and loss of appetite.

The total amount of blood is 124 ml taken over 10 days and does not pose a particular risk for your health. The minimal risks of blood drawing are possible discomfort like painful swelling of the skin or local infection. Any bleeding can be stopped by putting pressure on the puncture site. There might be the risk of infection or, in rare cases, damage of nerves caused by insertion of catheters for repeat blood draws, but this risk is also very low. Before the start of the study, the personnel will receive trainings in Good Clinical Practice (GCP), research ethics, study procedures and blood drawing. The study team will consist of personnel which is trained in supportive care of Lassa fever patients.

Modality of providing treatments and action(s) to be taken in case of injury or adverse event(s): If you suffer any injury as a result of your participation in this research, you will be treated at ISTH and the research will bear the cost of this treatment. There will also be an insurance covering all trial related injuries. You will receive the insurance certificate as well as the policy. This proceeding will not have any influence on your legal rights.

Costs to the participants, if any, of joining the research: Your participation in this research will not cost you anything.

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Benefit(s):

There is benefit to your community anticipated from participation in this research. Benefits to the community may be a new and more effective treatment for Lassa fever. This will help to better treat Lassa fever in the future.

Confidentiality:

All data collected in this study will be kept confidential. Information about you that will be collected during the research will be put away and no-one, but the researchers, will be able to see it. Any information about you and all your samples will have a number on it instead of your name (pseudonymized data). Only the researcher will know what your number is and will lock that information up with a lock and key. It will not be shared or given to anyone except designated persons. As part of our responsibility to conduct this research properly, officials from ethics committees, NAFDAC (National Agency for Food and Drug Administration and Control) and from the sponsor will have access to the medical records for verification of correctness.

Data from the research will be reported and may be published but will **never** include your name or identify any individual participants when shared with third parties (e.g. regulatory authorities, clinical trial registries as Nigeria Clinical Trial Registry or scientific journals).

Due inducement(s): No costs will occur to you regarding your treatment of Lassa Fever (hospitalization, examinations, drugs) as long as you participate in the study. The sponsor of this research will bear these costs. You will not be paid any fees for participating in this research. You will receive one impregnated mosquito net as further incentive for taking part in the research.

Consequences of participants' decision to withdraw from research and procedure for orderly termination of participation: You can choose to withdraw from the research at any time. This will not affect medical care given to you. If you withdraw from the study, you will be asked whether information that has been obtained about you before you chose to withdraw may be used for analysis and hence may be included in reports and publications. If you also

withdraw your consent for data processing, all obtained data from you will be excluded from further analysis and deleted.

What if new information arises during this research project: Sometimes during the course of a research project, new information becomes available about the treatment/the disease that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your research doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

What happens to research participants and communities when the research is over: During the course of this research, you will be informed about any information that may affect your continued participation or your health. The outcome of the research will be shared with the scientific community to improve future management of Lassa fever. You may also request to be informed about the outcome of the study at any time.

Statement about sharing of benefits among researchers and whether this includes or exclude research participants: This research will not lead to commercial products.

Any apparent or potential conflict of interest: None of the researchers (neither the PI, the sponsor, nor ISTH) declare conflict of interest. None of the researchers has any relationship that may affect the integrity of any aspect of the research. We are not aware of any other information that may cause the researchers not to do their work with fear or favor.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form to keep for myself. I have further received a copy of the insurance certificate and policy.

DATE: _____ SIGNATURE: _____

NAME: _____

PARTICIPANT RESEARCH IDENTIFIER

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

DATE: _____WITNESS' SIGNATURE (if applicable):_____

WITNESS' NAME (if applicable): _____

_____

AND

THUMB-PRINT OF PARTICIPANT

Detailed contact information including contact address, telephone, fax, e-mail and any other contact information of researcher(s), institutional NHREC and head of the institution:

This research has been approved by the National Health Research Ethics Committee of Nigeria (NHREC) and the Chairman of this Committee, Prof. Zubairu Iliyasu, NHREC, can be contacted via info@nhrec.net and +234 9 523 8367. This research has also been approved by the Health Research Ethics Committee of ISTH and the Chairman of this Committee, Prof. M.A.C. Odike, can be contacted at ISTH REC/IEC Irrua, Nigeria. The phone number is +234 815 299 8878. In addition, if you have any question about your participation in this research, you can contact the principal investigator, Dr. Peter Akhideno or the co-principal investigator Dr. Cyril Erameh at address: Irrua Specialist Teaching Hospital (ISTH), Km 87, Benin Auchi Road, P.M.B. 8. The phone number is +2348037048831/+2348032413382, the e-mail address is: ehideno@yahoo.co.uk/ cyrilerameh@gmail.com

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT