# Pharmacokinetics of the antiviral drug ribavirin in Lassa fever treatment

<b>Submission date</b> 02/02/2020	Recruitment status  No longer recruiting	<ul><li>Prospectively registered</li><li>Protocol</li></ul>
Registration date 06/02/2020	Overall study status Completed	<ul><li>Statistical analysis plan</li><li>[X] Results</li></ul>
<b>Last Edited</b> 05/10/2022	Condition category Infections and Infestations	Individual participant data

#### Plain English summary of protocol

Background and study aims

Lassa fever (LF) is a severe and often fatal systemic disease in humans. It is caused by Lassa virus (LASV) which belongs to the segmented negative-strand RNA viruses of the family Arenaviridae. LF affects a large number of countries in West Africa. The currently used antiviral, which is also recommended by WHO, is ribavirin. However, evidence for ribavirin efficacy in LF patients is poor and pharmacokinetic (PK) data for currently used regimens are not available. This study will describe blood concentrations of ribavirin and will provide evidence for further dose optimization studies with the ultimate goal of improving patient care.

Who can participate?

Patients aged 18 years or older, suffering from Lassa fever.

What does the study involve?

Participants will receive ribavirin treatment using the Irrua hospital dosing regimen. Blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10.

What are the possible benefits and risks of participating?

Benefits: Participants will be provided with protein bars and long-lasting insecticide-treated bednets as compensation for taking part in this observational study.

Risks: Participants may experience side effects from taking the drug.

Where is the study run from?
Irrua Specialist Teaching Hospital (Nigeria)

When is the study starting and how long is it expected to run for? February 2020 to September 2021

Who is funding the study?
Federal German Ministry for Health (Germany)

Who is the main contact? Dr Mirjam Groger groger@bnitm.de

# Contact information

#### Type(s)

**Public** 

#### Contact name

Dr Mirjam Groger

#### **ORCID ID**

https://orcid.org/0000-0001-7375-3685

#### Contact details

Bernhard Nocht Institute for Tropical Medicine Hamburg Germany 20359 +49 4042818511 groger@bnitm.de

## Additional identifiers

#### EudraCT/CTIS number

Nil known

#### IRAS number

#### ClinicalTrials.gov number

Nil known

#### Secondary identifying numbers

v03 06DEC2019, amended version of v02 25OCT2019

# Study information

#### Scientific Title

Prospective observational study on the pharmacokinetic properties of the Irrua ribavirin regimen used in routine clinical practice in Lassa fever patients in Nigeria

#### Acronym

**PAIRR** 

#### **Study objectives**

Evaluating the pharmacokinetic (PK) characteristics of ribavirin when administered as per local standard in a national reference centre for treatment of Lassa fever (LF). Descriptive analysis of

drug exposure and viral kinetics will be performed to elucidate the PK/PD (pharmacodynamic) profile of ribavirin in the treatment of LF.

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Approved 07/11/2019, Human Research Ethics Committee of ISTH (Irrua Specialist Teaching Hospital, km87 Benin Auchi Road, Irrua, P.M.B. 8 Edo State, Nigeria; +234 815 299 8878; isth.rec. 2015@gmail.com), ref: ISTH/HREC/20190104/009

#### Study design

Prospective observational clinical study

#### Primary study design

Observational

#### Secondary study design

Longitudinal study

#### Study setting(s)

Hospital

#### Study type(s)

Treatment

#### Participant information sheet

Part of the informed consent form

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

Lassa fever

#### **Interventions**

Pharmacokinetic analysis of ribavirin treatment

Blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10 of ribavirin treatment using the Irrua dosing regimen. Additionally, blood will be collected during screening before the first dose of ribavirin. Blood samples will be centrifuged and the plasma supernatant will be frozen at -80° C within 2 h after blood sampling. Plasma samples will be inactivated using a validated protocol. The samples will then be shipped frozen to the bioanalysis site (Dept. of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Germany). Ribavirin plasma concentrations will be determined using liquid chromatography coupled to tandem mass spectrometry (LCMS/ MS).

#### PCR analyses

Blood for RT-PCR, LASV serology and metagenomic sequencing will be sampled at inclusion, 24 hours after first drug administration and then every second day until end of treatment. Two RT-PCR assays for the detection of LASV, Altona Diagnostics (Hamburg, Germany) and an inhouse assay will be used to determine the viral load. These analyses will be performed at site in Irrua.

#### Biochemistry and hematology

Blood for biochemical safety and tolerability will be collected every second day starting with

screening. Biochemistry and hematology analyses will be performed using automated systems at ISTH.

#### **Intervention Type**

Drug

#### **Phase**

Phase IV

#### Drug/device/biological/vaccine name(s)

Ribavirin

#### Primary outcome measure

Pharmacokinetic parameters (maximum concentration (Cmax), maximum time (Tmax), area under the curve (AUC), half-life time (T1/2), volume of distribution) using blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10 of ribavirin treatment using the Irrua dosing regimen

#### Secondary outcome measures

- 1. Safety and tolerability of the Irrua Ribavirin regimen measured using clinical, hematological, and biochemical parameters:
- 1.1. Clinical: every day from day 0 to day 10
- 1.2. Haematology: standarad full blood count (hb; wbc; pla; diff) every 48 hours
- 1.3. Biochemistry: creatinine; alt; ast; bun; ldh every 48 hours
- 2. Viral kinetics in patients measured using at day 0, 5, 10
- 3. LASV genome changes under the Irrua ribavirin regimen measured at day 0, 5, 10

#### Overall study start date

01/06/2019

### Completion date

01/09/2021

# **Eligibility**

#### Key inclusion criteria

- 1. Age ≥ 18 years
- 2. Lassa fever confirmed by RT-PCR
- 3. Written informed consent
- 4. Anticipated treatment with intravenous ribavirin

#### Participant type(s)

Patient

#### Age group

Adult

#### Lower age limit

18 Years

#### Sex

Both

#### Target number of participants

20

#### Total final enrolment

20

#### Key exclusion criteria

- 1. Inability to give consent (e.g. unconscious patients/ cognitively impaired patients)
- 2. Critical illness (based on investigator's clinical evaluation)
- 3. Severe malnutrition
- 4. Hemodialysis
- 5. History of hemophilia / bleeding disorder
- 6. Hematocrit <30 %
- 7. History of hemoglobinopathies (i.e., sickle-cell anaemia or thalassemia major)
- 8. Known intolerance to ribavirin
- 9. Known pregnancy
- 10. Women who plan to get pregnant within the upcoming 3 months
- 11. Patients who already received ribavirin within the last 7 days

#### Date of first enrolment

03/02/2020

#### Date of final enrolment

18/03/2021

#### Locations

#### Countries of recruitment

Nigeria

# Study participating centre Irrua Specialist Teaching Hospital

km87 Benin Auchi Road Irrua Nigeria P.M.B. 8 Edo State

# Sponsor information

#### Organisation

Bernhard Nocht Institute for Tropical Medicine

#### Sponsor details

Bernhard Nocht Strasse 74 Hamburg Germany 20359 +49 40 42818-930 GUENTHER@BNITM.DE

#### Sponsor type

Research organisation

#### Website

https://www.tropmed-hamburg.de

#### **ROR**

https://ror.org/01evwfd48

# Funder(s)

#### Funder type

Government

#### **Funder Name**

Bundesministerium für Gesundheit

#### Alternative Name(s)

Federal Ministry of Health, Germany, Federal Ministry of Health, BMG

#### **Funding Body Type**

Government organisation

#### **Funding Body Subtype**

National government

#### Location

Germany

#### **Results and Publications**

#### Publication and dissemination plan

All results will be published in agreement between the Sponsor and the PI in international peer-reviewed scientific journals with preference to open access journals.

#### Intention to publish date

01/06/2022

#### Individual participant data (IPD) sharing plan

Relevant data are within the manuscript and its supporting information files. The data underlying the results presented in the study are available from the corresponding author on reasonable request.

#### IPD sharing plan summary

Available on request, Published as a supplement to the results publication

#### **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	16/04/2020	21/04/2020	Yes	No
Results article	outcome measures	26/07/2022	05/10/2022	Yes	No