THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

CLINICAL TRIAL PUBLIC INSPECTION REPORT FOR
Study Trial and Site: Evaluation of Pharmacokinetics and Safety/Tolerability of Higher Doses of Rifampicin in Children with Newly Diagnosed, Uncomplicated Tuberculosis – KCRI Kilimanjaro

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Swaswa Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz, **Website:** www.tmda.go.tz
Toll-free: 080011008

Part 1: GENERAL INFORMATION ABOUT THE TRIAL

Clinical trial details	
Clinical Trial Registration number	TZ20CT0003
Title of the study	Evaluation of Pharmacokinetics and Safety/Tolerability of Higher Doses of Rifampicin in Children with Newly Diagnosed, Uncomplicated Tuberculosis
Protocol Number	HIGHRIF C, Version 6.0
Ethical Clearance Number/ Date of Approval	02/10/2021
TMDA Approval Date	20/03/2020
Name of Investigational Product or Intervention	Rifampicin
Name (s) of Comparator Product (where applicable)	N/A
Name and address(es) of the Sponsor	Kilimanjaro Clinical Research Institute under EDCTP Project P.O.BOX 2236 Moshi, TANZANIA Email: kcriadmin@kcri.ac.tz
Name and address(es) of the Principal Investigator (PI)	Dr. Hadija H. Semvua Sokoine Road, Longuo Street, Moshi, Kilimanjaro Tel: +255 272754377 Mob: +255 754 377 777 E-mail: h.semvua@kcri.ac.tz
Name and address(es) of the Inspected Study Site	**KCMC-Hospital Kilimanjaro Clinical Research Institute (KCRI),** Sokoine Road, Longuo Street, Moshi, Kilimanjaro, Tanzania.
Inspection details:	Routine inspection to verify whether the trial is being conducted in line with the approved

	protocol and acceptable guidelines including Good Clinical Practices and applicable regulations. **Inspection method:** • Walk through different sections of the study sites • Face-to-face interviews with the study team members on different aspects of the conduct of the clinical trial. • Review of the essential documents.
Date of inspection:	2nd – 3rd March 2022
Type of inspection:	Follow-up inspection.
Brief description of trial and trial site	
Brief information about the site:	Study Site: KCMC – Hospital Kilimanjaro Clinical Research Institute (KCRI). Participants: Recruited from Kibong'oto Infectious Disease Hospital, Mawenzi, Majengo, Kibosho and Pasua Hospital. KCMC-KCRI has: • administrative offices, • outpatient area, • clinicians' rooms, • counselling room, • Consenting area, • Phlebotomy area, • wards (for in-patient participants) • Laboratory. The Investigational products were kept at the KCRI Pharmacy.
General information about the trial	Open-label assessing pharmacokinetics and safety/tolerability of higher doses of rifampicin when co-administered with other TB drugs (isoniazid, pyrazinamide and ethambutol) in children who are newly diagnosed with

	uncomplicated TB. • The trial is sponsored by Kilimanjaro Clinical Research Institute under EDCTP Project. • By the time of site inspection, 25 participants were screened and 17 were recruited. • The study was approved by TMDA and ethical clearance certificate before the initiation of the study, • The trial was regularly monitored by the sponsor's representative.
Study design:	An open-label trial assessing pharmacokinetics and safety/tolerability of higher doses of rifampicin when co-administered with other TB drugs (isoniazid, pyrazinamide and ethambutol) in children who are newly diagnosed with uncomplicated TB.
Objectives of the trial (primary, secondary, explorative objectives etc.)	Primary objective: To assess which higher rifampicin doses in children yield similar exposures in plasma to those achieved in adults who received 35 mg/kg rifampicin daily, as it is thought that similar exposures in plasma will yield similar responses. Secondary objectives: - i. To describe the steady-state pharmacokinetics of increasing doses of rifampicin when administered in combination with isoniazid, pyrazinamide and ethambutol in children who are newly diagnosed with uncomplicated TB; ii. To establish the incidence and severity of adverse events (safety/tolerability) of increasing dosages of rifampicin administered in combination with isoniazid, pyrazinamide and ethambutol in children who are newly diagnosed with uncomplicated TB; and

	iii. To assess possible relationships between pharmacokinetic parameters of rifampicin and adverse events (pharmacodynamics of rifampicin about toxicity).
A brief report of the activities undertaken at the site	
Areas inspected	• clinician rooms, • sample collection room, • Investigational Product (IP) • storage room, • sample archive and • the Clinical Laboratory
Restrictions (if any)	No
Out of scope	NA
Abbreviations	**Meaning**
AE	Adverse Event
BE	Bioequivalence
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiography
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IP/IMP	Investigational (Medicinal) Product
IRB	Institutional Review Board
NatHREC	National Health Research Ethics Committee
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMDA	Tanzania Medicines and Medical Devices Authority
TMF	Trial Master File

Part 2: SUMMARY OF THE FINDINGS AND COMMENTS

1. Personnel, Organization and Management

The site was confirmed to have qualified and sufficient personnel to undertake various activities conducted in support of this study. The organization of facility was divided into various operational units that were headed by unit leads who were confirmed to be of adequate qualification in fulfilling their designated roles and responsibilities. The principal investigator's curriculum vitae supports the qualification declared and expected for an individual in this role.

Key staff members were medical doctors, pharmacists, nurses, laboratory scientists, laboratory technologists, laboratory assistants, data managers and clerks, all of whom provided their current curriculum vitae. All members of this team were confirmed to operate under descriptive instructions, in line with GCP principles and as delegated by the principal investigator. The same was verified following a review of the active and up-to-date delegation logs.

2. Facilities and Equipment

The facility was confirmed to have sufficient rooms for conducting all the expected activities, including, clinical procedures, counselling and areas for storage. Emergency facilities, necessary equipment and medication were also confirmed to be readily available.

Rooms used for the study were locked and access was restricted to only study personnel. Materials, equipment and source documents were also locked inside the cabinets (with lock and key) in the secured rooms.

The pharmacy unit was spacious enough to store medicinal products (including the investigational product). All products were confirmed to be stored in a well-monitored, temperature and humidity-regulated, and secured environment. Equipment used for storage, such as fridges and freezers were confirmed to be in good operational status.

3. Management of Investigational Medicinal Product(s)

The investigational medicinal products (IMPs) received from the sponsor were stored under the manufacturer's storage recommendations, in a well-secured, restricted access area by the pharmacist in charge. Logs for storage, receiving and issuing of the same were confirmed to reflect adequate control of the product. Importation documents including permits were verified and observed to be in line with the requirements.

4. Review of Patient's Data and Informed Consent

Patient data were categorized in the form of source data, case report forms (CRFs) and signed consent forms. A review of all the above confirmed that GCP requirements were adhered to since alignment with the trial protocol requirement was maintained.
Both approved versions of Swahili and English consent forms were available on-site.

5. Assessment of Efficacy and Safety Data

The efficacy and safety data recorded in the CRF were reviewed and found to agree with the source data obtained during the trial. Data related to endpoints were compared with source documents and were adequate.

All medications issued were documented in the protocol and were recorded in the patient's CRF and source documents.

6. Documentation

All essential documents stipulated in the ICH-GCP and TMDA guidelines were observed on the site. A scrutinized review was done on the following;

- Trial Protocol,
- Screening and Enrollment Logs,
- Case Report Forms (CRFs),
- Patient Information Sheets,
- Source Documents,
- Informed Consent Forms,
- Delegation/Signature Log,
- Subject Visit Logs,
- Investigational Product Inventory Records,
- Study memos and sponsor letters,
- Ethical Papers and Agreements,
- Ethical Committee Approvals,
- Communicational Documents (with a sponsor, TMDA, IRB, etc.) and, Training/Qualification Documents.

The completeness, accuracy and authenticity of the aforementioned documents were ascertained.

7. Computerized system

All data documented in the case report forms and other site data records were recorded in a computerized database system and information was sent to the sponsor.

Evidence of system maintenance, necessary modifications and the system's capability in data archiving, retrieving and transmission was adequately observed. The sponsor also maintains a backup of the trial data.

8. Monitoring and Auditing

Monitoring of the study was conducted by the Investigator and it was observed that an auditing plan was developed, confirmed to be followed through and audit reports were well documented. Based on the scope of monitoring, adequacy and implementation of corrective actions recorded, it can be confirmed that every operational aspect of the site allows the proper conduct of the required study.

9. Clinical Laboratory

The site uses the KCMC laboratory for processing samples used in this study.

The laboratory was confirmed to be spacious enough to potentially avoid mix-ups, contamination and interference, the same was also well partitioned.

For operational status, the laboratory was fully aided by up-to-date SOPs, operational records and activity logbooks, whereas, the equipment used was confirmed to be qualified (operational status acceptable and calibrated) and well maintained.

The laboratory setting was confirmed to be under well-controlled environmental conditions, well-ventilated and installed with fully operating temperature and humidity regulating devices. Hazard maintenance and safety of the personnel were guaranteed by in-place SOPs and guidelines for the prevention of accidents, safety training sessions, presence of safety personnel, first aid kits, emergency eye wash areas, fire alarms and sufficiently maintained fire extinguishers.

Laboratory personnel were also qualified and adequately trained on trial-related procedures and Good clinical laboratory practice (GCLP) as evidenced by their up-to-date CVs and training records. Each personnel were subject to a proficiency testing scheme conducted on a scheduled basis to ensure consistency in GCLP practices. Personnel medical records were reviewed, and it was observed that each personnel crosschecked and that procedures were undertaken to prevent the contraction of laboratory-acquired infections.

Following a review of the internal and external quality audit reports of the quality assurance system of the laboratory, it was confirmed that the laboratory is guided by a well-established quality system, that guarantees proper maintenance of all records generated within, and adequately operates under GCLP principles.

Part 3: CONCLUSION

Based on the findings of the inspection conducted on the 2nd to 3rd of March 2022, regarding the trial titled "Evaluation of Pharmacokinetics and Safety/Tolerability of Higher Doses of Rifampicin in Children with Newly Diagnosed, Uncomplicated Tuberculosis", TMDA considers that the activities conducted by the KCMC-Kilimanjaro Clinical Research Institute (KCRI) located in Kilimanjaro, complied with TMDA GCP guidelines, ICH – GCP/GCLP, Tanzania Medicines and Medical Devices Act Cap 219 and its related Clinical Trials Control Regulations, 2013.

This CTPIR will remain valid for two (2) years from the date of inspection of the trial in question provided that the outcome of any inspection conducted during this the period is positive.

Part 4: REFERENCES

1. Tanzania Medicines and Medical Devices (Clinical Trials Control) Regulations, 2013.
2. Guidelines for application to conduct clinical trials in Tanzania.
3. Guidelines for reporting safety data in clinical trials in Tanzania.
4. Guidelines for insurance and indemnity of clinical trials in Tanzania.
5. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996).
6. World Health Organization, Guidelines for good clinical practice (ICH-GCP) for trials on pharmaceutical products.
7. World Health Organization, Good Clinical Laboratory Practice
8. ICH - Tripartite Guideline, Guideline for Good Clinical Practice.
9. World Medical Association Declaration of Helsinki.
10. Protocol Number HIGHRIF C, Version 6.0.
11. Tanzania Medicines and Medical Devices Act, Cap 219.
12. Trial Master File