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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**VerGo Pharma Research Pvt. Limited (Division-VerGo Clinicals)** Plot No 24/1, D1 Mologa-De-Orora, Corlim Tiswadi Goa-403110 India
Name and Address of Bioanalytical Research Site	**VerGo Pharma Research Pvt. Limited (Division-VerGo Clinicals)** Plot No 24/1, D1 Mologa-De-Orora, Corlim Tiswadi Goa-403110 India
Name and address Statistical Site	As mentioned above
Corporate address of the Organization	As mentioned above
GPS coordinates	Longitude: 15.50503° N Latitude: 73.93540° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA691** Bioequivalence study for Co-Trimoxazole Tablet BP 960 mg **WHO application no. CV013** Bioequivalence study of Molnupiravir Capsules 200 mg **WHO application no. HA783-0** Bioequivalence study of Sulfamethoxazole/Trimethoprim tablet 800mg / 160mg **WHO application no. TB360**

	Bioequivalence study of Fixed dose combination of Rifampicin/Isoniazid Dispersible Tablets 75 mg/50 mg **WHO application no. TB400** Bioequivalence Study of Fixed-Dose Combination of Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150 mg Dispersible Tablets **WHO application no. HA785** Bioequivalence Study of Dolutegravir 10 mg Tablets for Oral Suspension **WHO application no. TB393** Bioequivalence study of Rifapentine tablet 300 mg **WHO application no. TB394** Bioequivalence study of Rifapentine and Isoniazid tablet 300 mg/300 mg
Inspection details	
Dates of inspection	22-26 January 2024
Type of inspection	Routine
Introduction	
Summary of the activities	The facility had the capacity to conduct bioequivalence/bioavailability studies in healthy human volunteers. Various types of studies and activities could be performed including: • Single-dose crossover • Multiple-dose crossover • Single-dose parallel • Steady State Studies • Food interaction
General information about the company and site	VerGo is a private limited company that was registered in September 2010 under "The Companies Act 1956" and commenced its operations in February 2013.
History	The CRO was previously inspected by WHO during 24-27 May 2022 by WHO. Since the last inspection, the US FDA also conducted an onsite inspection from 4 Jul 2022 to 8 Jul 2022.

Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing, and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with the comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Not applicable

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original, and accurate
BA	bioanalytical
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice

GMP	good manufacturing practice
HPLC	high-performance liquid chromatography
LC-MS/MS	liquid chromatography-mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	international council for harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
ISF	investigator study file
ISR	incurred sample reanalysis
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

PART 2	**SUMMARY OF THE FINDINGS AND COMMENTS**

General Section

1. Organization and management

At the opening meeting, a presentation was provided that explained the activities of the organization and the changes since the last inspection in detail.

The CRO's organizational chart, depicting key positions and the names of responsible persons, was updated on 12 Dec 2023. It was randomly verified that every job description was signed and dated by the staff member to whom it applied. The list of signatures of the authorized personnel performing tasks during each study was available and verified.

The Good Laboratory Practices principles had already established the responsibilities for test facility management. The CRO management recognized that, since the investigator was a CRO employee, some of the investigator's responsibilities also applied to CRO management, as noted in the previous inspection report. Management ensured the implementation and adherence to appropriate and technically valid SOPs, with a well-organized historical file of all SOPs in place.

The service agreement and project agreement between the CRO and the sponsor were made available.

It was confirmed that the previous CAPA plan had been implemented as intended.

2. Computer systems

An inventory of all computerized systems on the network was readily accessible, with clear identification of those subject to GxP regulations. Any modifications to the network, including temporary additions or removals of systems, were documented.

Procedures for Computer System Validation were established to ensure that computerized systems were deemed suitable for their intended purposes and were validated, operated, and maintained in accordance with the principles of GCP and GLP. The procedure was discussed with the IT department.

Sufficient computers were available for data entry and handling, with the required capacity and memory. The network diagram, along with the list of WIFI, GxP systems, and server configuration, was provided in an SOP.

Access to trial-related software systems was controlled, specifying the method of access, and maintaining a list of authorized users. Individual-specific identifiers and secure passwords were used.

Software programs used for key steps were validated. Validation certificates, supervised by the user, were intended to ensure proper development in line with a QA system. Qualification of the randomly selected systems was reviewed on risk-based approach.

In the Performance qualification, considerations were made regarding specific user requirements, regulatory/guideline requirements for BE studies, the operating environment in which the system was utilized, and the system's usage in the studies. A risk assessment was conducted on software functionalities. SOPs were in place for each software program used in the execution of BE study activities. Regular updates to key software programs were carried out as necessary, based on a risk assessment of their potential impact on current data and validation status. The frequency of updates was determined by a scoring system based on the respective risk assessment.

The procedure for backing up and archiving all relevant electronic data was outlined in the SOP for Backup and Restoration of Electronic Data, which included details about the frequency of backups. The configuration of the computers and servers responsible for data backup, as well as that of the backup server, could be found in 'Configuration of Computers and Servers for Backup'. As part of this procedure, backups were periodically overwritten, and data from previous backups were archived. Electronic data was backed up at regular intervals, as stipulated in this SOP. To ensure their reliability and completeness, these backups undergo annual verification based on a plan. Data was retained on the backup server for a period of 2 years, while data on Backup tapes will be retained for 15 years, with a tape validity of 5 years. The SOP provided a backup network flowchart. Regarding restoration activities, the last evidence performed on 19 Jul 2023 was reviewed and verified.

Configuration and transfer of Window’s event logs were specified in the applicable SOP.

Observations related to the Computerized systems were adequately addressed in the respective CAPA plan.

3. Quality management

The CRO had established appropriate Quality Assurance (QA) and Quality Control (QC) systems with documented SOPs to ensure that clinical trials were conducted, data were generated, documented, and reported in accordance with the study protocol, GCP, GLP, GMP, and relevant regulatory requirements. The current and applicable SOPs were promptly delivered to the inspectors on the first day, stored on a USB stick memory upon request

QA personnel were not directly involved in trial-related activities. Both in-process and retrospective QA verifications (e.g., in bioanalysis, during the preparation and testing of samples and standards) were carried out following the applicable version of the respective SOP. The documentation for the study related to WHO application CV013 was readily available and subject to review.

Internal audits were conducted in compliance with the applicable SOP, with an annual schedule provided, including details about the audited department, delegates, audit date, and signatures upon audit completion.

The company had outlined specific audit trail queries or reports in various applicable SOPs, such as SOP for the Conduct of In-Process and Retrospective Audits of Bioequivalence/Bioavailability (BA/BE) Studies. The audit trail review and its outcomes were systematically documented in respective forms and logbooks dedicated to audit trail reviews for each system.

Regarding the review of audit trails, there was a notable change in the CRO's practice. Initially, during the time of studies within the scope of the inspection, the BA team provided the QA reviewer with electronic data, including the audit trail record for QA review. However, this practice was revised in November 2023, allowing the QA reviewer to have direct access to the software for audit trail review and the detection of any gaps or discrepancies. This change was reflected in the logbook for "User audit trail reviews of the VIMS software system," along with the logbook for audit trail reviews of ongoing projects in the bioanalytical laboratory. Additionally, the Event log for the Windows application was scrutinized and tested under different scenarios by the Inspection team to understand system limitations and possibilities. Furthermore, the audit trail of the volunteer registration system was thoroughly examined.

A list of reviewed and verified SOPs, as well as all SOPs utilized for study activities, were requested and provided to the inspectors on the first day of the inspection. The SOP pertained to the Issuance and Control of Documents, was assessed. Each template was assigned a specific number under the supervision of the QA department, an application. These assigned numbers were chronologically recorded in the respective logbook, which was available and reviewed. Moreover, the reconciliation of templates used for BA activities in the study related to WHO application CV013 was performed, and any unused templates were discarded and documented by the QA department.

Observations concerning the Quality Management System (QMS) were adequately addressed in the respective CAPA plan.

4. Archive facilities

We visited the newly established Archive Facility. The CRO had established a secure storage facility dedicated to archiving trial-related documents. This facility was equipped with fireproof measures, temperature and humidity control systems, and effective pest control measures.

The management of archiving activities was described in the SOP.

Access to the archive storage areas is meticulously controlled and limited to authorized personnel. The list of authorized individuals was displayed at the facility's entrance.

Records of document access and returns were maintained. The duration for which study documentation, encompassing raw data, should be retained in the archive was defined within the contract between the sponsor and the CRO, as well as outlined in the study protocol.

The procedures governing the archiving of trial-related documentation were confirmed during the inspection, with successful retrieval and traceability of the documents serving as validation of the robust archiving process.

5. Premises

During the inspection, it was verified that:

- The facility was clean, well-lit, and had proper ventilation and environmental controls.
- Clinical trials prioritized participant safety by selecting suitable sites.
- The CRO had sufficient space and well-equipped facilities for study activities.

Specifically at Clinic IV:

- Access was controlled through keycards and biometrics.
- Emergency evacuation procedures were in place.
- Entry and exit were documented.
- Emergency doors in the CPU area were tested for release in case of a fire incident, and their functionality was confirmed in line with the applicable SOP, with evidence from 29 Dec 2023. It was noted that there was a manual option to open the emergency door in case of malfunction.

The pharmacy had two distinct sections. The first section was dedicated to storing IMP. Temperature and humidity in this section were controlled using a digital thermometer. The second section was used for dispensing activities and had a hygro-thermometer to monitor temperature and humidity. Additionally, the pharmacy diligently maintained entry and exit records for every visit. During the inspection, random checks were performed on the temperature and humidity records in the IMP storage section, and the associated alarms were reviewed to ensure compliance.

Laboratory premises were designed to suit the operations to be carried out in them. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Adequate storage space was available for samples, standards, solvents, reagents, and records.

The laboratory premises were designed to prioritize the safety of both employees and authorized external personnel. Prior to conducting tests, safety data sheets were provided to the staff, ensuring their familiarity with the chemicals and solvents they used. In addition, regular training was provided on the proper utilization of firefighting equipment, including fire extinguishers and fire blankets, and personnel were instructed to wear laboratory coats and eye protection. To maintain safety standards, all chemical containers were appropriately labeled. It is also recommended to ensure that the necessary equipment for handling broken glassware is easily accessible within the laboratory.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Staff was aware of the need to avoid working alone in the laboratory. First-aid materials were provided, and the staff was instructed in first-aid techniques and emergency care.

Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were closed with an appropriate seal. Volatile organic chemicals were handled under fume hoods or air extractors, and safety and eye showers were available in the laboratory.

Premises had suitable systems in place to dispose of waste, treat fumes, and protect the environment in conformance with local or national regulations.

6. Personnel

A competent team of medical, paramedical, technical, and clerical staff was available to support the trial and respond to expected emergencies. The inspection team randomly reviewed the current resumes and training records of co-investigators involved in trial activities to confirm their qualifications.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted at the CRO's premises. On Day 3, the inspectors conducted a facility tour, focusing on the expanded areas.

The CPUs were equipped with 166 beds, and during our visit, we specifically explored Clinic IV. Accommodation facilities were equipped with systems that allowed subjects to alert CRO staff when needed. Facilities for changing and storing clothes, as well as for washing and toilet purposes, were clean, well-organized, easily accessible, and suitable for the number of users. Lockable toilets were equipped with alarms, and their doors were designed to be opened from the outside in case of a medical emergency.

The clinical site comprised various areas, including subjects' registration and screening, obtaining informed consent while maintaining privacy, the CPU, spaces for subjects' recreation, a pharmacy, a room for administering investigational products and collecting samples, sample processing areas (such as plasma separation) and storage (freezer), an archive facility (with the addition of a new one), a kitchen for preparing standardized meals, a dining hall, and an ICU. X-ray services were outsourced.

Access to the randomization list was limited to the study's responsible pharmacist. These documents were securely stored in hard copy, and their distribution was documented.

All equipment used underwent regular calibration as scheduled. At appropriate intervals, the proper functioning and performance of emergency-use equipment, such as defibrillators, were verified.

8. Clinical laboratory

A certified clinical laboratory was established for sample analysis, accredited in accordance with ISO 15189:2012, and valid until 20 Jul 2024. The laboratory was equipped with the appropriate instruments, including a hematology analyzer, electrolyte analyzer, biochemistry analyzer, and urine analyzer.

Sample labeling, receipt, and chain of custody procedures were in place to ensure complete traceability and sample integrity. Labels were generated at the clinic during sample collection, including volunteer ID, initials, and age, which were manually recorded on the label. In the laboratory, the system-generated assigned number was also added to the label.

The CRO received information regarding the laboratory's analytical methods, a dated list of laboratory normal ranges, and the laboratory's accreditation certificate.

The laboratory generated individual reports for each subject and included them in the CRFs. Source or raw data for all tests conducted were archived by the laboratory, either electronically or in paper format, depending on their source and the laboratory's storage capacity.

Data integrity for all study-related tests was ensured using validated systems for sample analysis.

9. Ethics

While reviewing the pertinent documentation for study related to WHO application CV013, it was confirmed that the trials had received approval from the independent ethics committee (IEC) before the study commenced. The independence of this committee from the sponsor, investigator, and CRO was established through the examination of the member list. Detailed minutes of the IEC meetings were maintained, including discussions, recommendations, and decisions made during these meetings. The IEC was afforded ample time to review protocols, informed consent forms (ICFs), and associated documentation.

Informed consent form

Study participants were provided with information in their vernacular languages, including Hindi, Marathi, and English. This information was presented both orally and in written form, ensuring it was comprehensible to them.

Informed consent was obtained in writing and through video recording from each subject before initiating any trial-related activities. The provided information explicitly conveyed that participation was entirely voluntary, and subjects had the right to withdraw from the study at any time without providing a reason. Reasons for withdrawal were duly recorded in the study records.

Regarding insurance and compensation procedures, in the event of injury or disability resulting from participation in the trial, details were available through the Insurance policy.

Volunteers or subjects, along with their nominated individuals, had the opportunity to consult with a physician to address any concerns about potential side effects or reactions to the investigational products prior to their participation in the trial.

The certificate of translation and back translation for the informed consent documents were also reviewed.

10. Monitoring

The presence of monitors, along with their corresponding reports and responses, was accessible and reviewed for the study related to WHO application CV013. The monitoring of the study was carried out by the sponsor's representative.

11. Investigators

The principal investigator (PI) had overall responsibility for the clinical aspects of the study, including the study's design, administration of the investigational products, interactions with local authorities and the ethics committee, as well as the signing of both the protocol and the final study report. The qualifications and training of co-investigators were subject to random verification.

12. Receiving, storage, and handling of investigational drug products

In the review of randomly selected documentation for the study related to WHO application CV013 and the study related to WHO application no. HA785, the comprehensive handling, and accountability of investigational products throughout the trial were recorded. This included details related to shipment, delivery, receipt, storage conditions, dispensing, administration, and reconciliation.

The pharmaceutical products were stored according to the sponsor's provided official product information, ensuring appropriate conditions were maintained. Monitoring of these conditions was carried out using a Eurotherm digital thermometer.

The study's randomization adhered to the relevant SOP, and records were maintained, including the randomization list and seed. Access to the randomization list was restricted to the person who generated it, a dispensing pharmacist, and the statistician.

The IPs were labeled to ensure compliance with the randomization list. Prior to attaching labels to the containers, verification was conducted to confirm their accuracy. Labels were affixed to the containers to prevent information loss upon opening the lid.

To maintain a robust system, effective routines for labeling and documenting IP administration were established. Each subject's receipt of the dispensed product was verified. Labels were designed in duplicate, with one of the label portions retained in the plastic bag used for dispensing, to be later attached to the relevant CRF section. Empty containers for the test and reference investigational products were labeled separately. They were stored separately and under lock to prevent any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were executed in adherence to the prescribed requirements. The relevant SOPs included the SOP for the administration/dosing of solid oral investigational products, the SOP for the administration/dosing of liquid investigational products and reconstituted preparations, and the SOP for dispensing.

The handling of IMPs followed the applicable procedures:

- The working surface was thoroughly cleaned before introducing product bottles, and any containers, dosage forms, labeling materials, contaminants, dirt, and debris were removed.
- A second person confirmed the cleanliness of the surface area before introducing and opening product containers.
- IMPs were managed using appropriate utensils. Tablets were distributed into containers as per the randomization list for either the reference or the test product, with the two products handled separately.
- Detailed records were maintained for each step, including the cleaning of the working surface before and after handling each product in the same study.
- Investigational product accountability and dispensing records were kept, documenting each activity, including doses administered, returned, or destroyed (when applicable). A second person verified each step.
- Dosing was documented, confirming the supervision of the investigator and designated qualified staff member. The exact dosing time was noted in the designated section of the CRFs.
- In the case of solid oral dosage forms, a mouth check was conducted to ensure that the subject had swallowed the IP, and it was directly recorded in the CRFs.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for possible confirmatory testing for at least one year after the expiry date of the newest product. Sample retention was defined and described in the protocol and was specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

13. Case report forms

Randomly selected CRFs from the studies were reviewed. These CRFs contained data that corresponded to the trial protocol, detailing the information collected from each volunteer.

Furthermore, the CRFs included copies of clinical laboratory reports and all electrocardiograms (ECGs) for each subject. Study information was also documented within the CRFs as per the study requirements.

14. Volunteers, recruitment methods

An SOP outlined the procedure for recruiting volunteers and detailed various methods used by the CRO for this purpose. To ensure proper management, a software database was maintained to prevent cross-participation and specify minimum time intervals between volunteers' involvement in different studies. Access to this database was

password-controlled to protect confidential volunteer information. A biometric system was deployed using fingerprints for secure verification.

Separate Informed consent was obtained from potential subjects for registration, screening procedures, and participation in the research phase of the study. The clinical trial protocol provided criteria for subject selection and screening procedures (inclusion and exclusion criteria). A centrally accessible software system was used to check if subjects had participated in previous trials conducted by other CROs, preventing over-volunteering by centralizing participation data.

ECGs were conducted using an ECG machine isolated from any network connection. An IT personnel held custody of the SD card, and usage was logged in the ECG logbook. Daily time correction was recorded in the logbook.

Alcohol and drug abuse tests were conducted at the clinic using specific kits to analyze volunteers' urine.

15. Food and fluids

During the study, meals were controlled and standardized, following a set schedule. The CRO utilized its kitchen to provide study subjects with standardized meals, snacks, and beverages, as outlined in the clinical trial protocol. A dedicated dietician was hired full-time to oversee food preparation.

The study recorded details such as the timing, duration, and quantity of food and fluids consumed by the subjects.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, and conducted to ensure an acceptable safety profile for the volunteers. A medical doctor was responsible for making medical decisions in case of adverse events, and the relevant health authorities, sponsor, and ethics committee were notified, particularly in the case of serious adverse events.

Emergency preparedness was maintained with first-aid equipment and rescue medication readily accessible in the ICU at the study site. The treatments administered to subjects were documented, including entries in the CRF, and supporting documentation within the ICU.

Additionally, the CRO had incorporated adverse event registration and reporting forms as part of the CRF.

The inspection primarily focused on studies related to WHO applications CV013 & HA691, along with their associated validation projects. Spot checks were additionally carried out for the remaining studies within the scope of the inspection. In particular, the following records and activities were subject to investigation:

- Source documentation and raw data for validation of the bioanalytical methods.
- Analysis of subject plasma samples as well as the respective electronic data.
- Audit trails for electronic data capture and handling related to the BE studies.
- Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs, along with the chromatograms generated from the analytical runs.
- Preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were verified. The reason for the study sample repeat analyses and all instrument failures was reviewed. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions.

The inspection team received support from knowledgeable and transparent personnel during the review of the study documentation. The inspectors were granted access to the relevant studies within the scope of inspection through the chromatography software application and were provided with access to the respective Windows Event logs.

17. Method development, Method validation & Analysis of study samples

The process of method development was sufficiently outlined and documented in compliance with the applicable. The decision to use an internal standard (IS) was proved with reference to applicable literature, for which a copy was provided. Following method development, a Standard Test Procedure (STP) was prepared as the foundation for method validation. In MS methods, when applicable, a stable isotope-labeled internal standard was consistently incorporated, and the appropriate anticoagulant was applied as per protocol.

In accordance with the respective SOP, the method validation included a run aimed at identifying a batch with a sufficient number of QC and CC samples. This "Extended batch determination" matched the expected sample length for the subsequent analysis.

The sample processing was documented using dedicated forms designed for each activity. When applicable, a note-to-file was maintained to record any unexpected activities during sample processing.

Data confirming sample stability under specified conditions and storage periods was available prior to the start of the studies, except for long-term stability, which was conducted before the issuance of study reports.

The review and verification activities related to method validation for randomly selected studies covered various analytical runs, including precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), hemolytic effect, recovery, and reinjection reproducibility. Partial validation was conducted as per requirements. The matrix employed for analytical method validation aligned with the matrix of the study samples, encompassing anticoagulants. Additionally, the purchase documentation for the study related to WHO application CV013 plasma from the supplier, covering receipt, storage, retrieval, preparation, and consumption of pooled plasma, was reviewed and discussed.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact sequence of processing was defined and documented. All samples collected from a given subject during all trial periods were analyzed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. A system suitability and a stabilization test were done prior to the start of runs on each day.

Of the first 1000 samples, 10% were used to run Incurred Sample Reanalysis (ISR), and of the subsequent samples, 5% were used for ISR. The samples were selected with a concentration around Cmax and in the elimination phase. The acceptance criteria were clearly defined in the SOP.

The system audit trail review was carried out at the time of the studies in the scope of the inspection.

The observations pertaining to the Method validation were adequately addressed in the respective CAPA plan.

18. Sample collection, storage, and handling of biological material

The clinical trial protocol and information provided to volunteers clearly outlined the specifications of blood plasma samples, including the sampling method, volume, and quantity. The collection, preparation, transport, and storage of these samples adhered to relevant SOPs, notably SOP for Receipt, Handling, Storage, and Disposal of Biological Samples.

Actual sampling times were recorded, including any deviations from the pre-specified times, which were accounted for when calculating pharmacokinetic parameters.

Labeling of collected samples was designed for clarity to ensure accurate identification and traceability. Stringent control, monitoring, and recording of storage conditions, including freezer temperatures, were maintained throughout storage and transportation. Detailed records of sample storage and retrieval were upheld. Samples were duplicated in aliquots and stored separately, with both aliquots transferred from the clinical department to the BA department simultaneously and stored independently.

In accordance with the applicable SOP, the handling and retention of study samples, QC samples, and pooled matrices were carried out as per the protocol or the agreement with the respective sponsor.

19. Data processing and documentation

The integration settings in use were based on scientific principles and were thoroughly justifiable. Smoothing factors were maintained at a low level to prevent the masking of potential interferences and changes in peak geometry.

Clear criteria for the acceptance and exclusion of CC and QC samples, as well as batch acceptance, were defined in the applicable SOP. Source data for all analytical runs included comprehensive information regarding the initial evaluation of runs, containing all CCs whenever analysis was repeated. The calibration range was appropriately truncated, and variations in internal standards were monitored and incorporated into result validity checks.

Audit trails were consistently activated on all analytical instruments, covering periods before, during, and after both method validation and the studies of interest.

Original analytical raw data, such as chromatograms and associated audit trails, were documented in a manner ensuring traceability, including sample number, equipment used, date and time of analysis, and the technician's name(s). Various audit trail files were retained, including results table audit trails, project audit trails, and instrument audit trails.

Each data point was traceable to specific sample details, encompassing sample number, collection time, centrifugation time, freezer placement time, and sample analysis time. This comprehensive traceability facilitated the identification of any potential anomalies caused by sample mishandling.

20. Good laboratory practices

A tour of the facility on Day 4 took place to verify the laboratory's suitability in terms of arrangement and safety.

The bioanalytical portion of BE studies complied with the general principles of Good Laboratory Practice, supported by an appropriate QA system.

The deep freezers used for sample storage and refrigerators for storing Reference standards were adequately qualified, calibrated, and well-maintained.

For qualification verification, a review of the temperature mapping of a randomly selected Deep Freezer was conducted to confirm the accuracy of the Hot spot and the sensor's location. This mapping process was found to be properly executed during the inspection.
Balances, measuring devices, and various equipment and instruments used in the trials underwent periodic calibration and verification before use to ensure their fitness for the intended purpose.

The operation, calibration, checks, and preventive maintenance of equipment were outlined in respective SOPs. Records were diligently maintained in accordance with applicable requirements. These activities were subject to random reviews of the equipment used in study-related tasks. Equipment and its components were appropriately labeled with their respective ID numbers, calibration dates, and next calibration dates. Additionally, equipment usage was thoroughly documented in analytical sheets and the relevant logbooks dedicated to instrument usage. The usage of columns was also recorded in the logbook for column usage.

The performance verification documentation of the randomly selected was reviewed.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The sample size was determined based on molecule-specific guidelines and existing literature. SAS software, following the corresponding SOP, was employed for this purpose. Once the calculations were complete and the methodology chosen, the statistical analysis plan (SAP) was integrated into the study protocol.

The study protocol explicitly outlined the methods for conducting both pharmacokinetic and statistical calculations, including the software to be utilized.

Regarding randomization, the process began with a request from the pharmacist, which had to be approved by the Principal Investigator (PI) or Co-investigator (CI). Randomization was executed using SAS program, incorporating a seed number generated from a combination of the study number and the protocol version number. The resulting randomization details were compiled into a PDF document, printed using a dedicated printer for the Statistician, sealed in an envelope, and delivered to the pharmacist. The pharmacist conducted verification of the randomization process.

Concentration data was securely uploaded to a designated folder with restricted access by the Bioanalytical Department.

All calculations, including those for pharmacokinetic (PK) analysis, were conducted using the respective software. Quality Assurance procedures were carried out to verify the accuracy of data input, aligning with the applicable SOPs. Following PK analysis, graphical representations were generated.

It's important to note that the study data were locked before initiating any statistical analysis.

22. Study report

The process of study report writing was verified during the last inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies were identified between the results stated in the report and the original (raw) data during the inspection.

The study report included a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and a report on the validation of this method. The Principal Investigator approved the clinical study reports before data transfer to the statistical department. The responsible staff and management also approved the bioanalytical reports. Monitoring and audit reports were available before the release of the final study report.

Miscellaneous	
Samples taken	***Not applicable***
Assessment of the CRO master file	The CRO Master File, effective 6 Feb 2023, was submitted and reviewed.
Annexes attached	***Not applicable***

Part 3	**Conclusion – inspection outcome**

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at ***VerGo Pharma Research Pvt Limited (Division-VerGo Clinicals)***, located at ***Plot No 24/1, D1, Mologa-De-Orora, Corlim, Tiswadi, Goa-403110; India***.

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for three years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	**List of guidelines referenced in the inspection report**

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***WHO TRS 996, Annex 9***

2. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
   Short name: ICH M10

3. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
   Short name: WHO TRS No. 1025, Annex 4

4. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
   Short name: WHO TRS 1033, Annex 4

5. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
   Short name: WHO TRS No. 1019, Annex 3

6. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
   Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***

7. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP

8. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP

9. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***

10. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
    Short name: WHO Ethics Committee Guidance

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
    Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***

12. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
    Short name: Glove use information leaflet

13. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6

14. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).
Short name: Declaration of Helsinki

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Frothiest report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4