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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of inspected Site (Clinical, Bioanalytical & Statistical site)	VerGo Pharma Research Pvt Limited (Division-VerGo Clinicals) Plot No 24/1, D1 Mologa-De-Orora, Corlim Tiswadi Goa-403110 India
Corporate address of Organization	VerGo Pharma Research Pvt Limited (Division-VerGo Clinicals) Plot No 24/1, D1 Mologa-De-Orora, Corlim Tiswadi Goa-403110 India
GPS coordinates	15.50503° N 73.93540° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. NT010** Bioequivalence Study of Albendazole Chewable Tablets 400 mg **WHO application no. HA731** Bioequivalence Study of Dolutegravir tablets 50mg. **WHO application no. MA169:** Bioequivalence study of Amodiaquine Dispersible Tablets 150 mg **WHO application no. TB375** Bioequivalence study of Isoniazid Tablets 300 mg **WHO application no. NT011** Bioequivalence study of Praziquantel tablets 600 mg
Inspection details	
Dates of inspection	24 - 27 May 2022
Type of inspection	Routine

Introduction	
Summary of the activities	The facility had the capacity to perform bioequivalence/bioavailability studies in healthy human volunteers. Various types of studies/activities could be carried out as below: • 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 registered in September 2010 under "Companies Act 1956" and commenced its operations in February 2013.
History	The CRO was inspected by various regulatory authorities such as: • DCGI (Drug Controller General of India), • NPRA (Malaysia), • MHRA, UK and • US FDA. The company was previously inspected by WHO in April 2018.
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 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
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CDMS	chromatography data management system
	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 chromatograph
	LC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form
	ICH	International Conference on Harmonization
	(I)EC	(Independent) Ethics Committee
	IMP	investigational medicinal product
	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

A presentation was provided explaining the activities of the organization in detail.

The CRO had an organogram depicting key positions and the names of responsible persons. The organogram was authorized and kept up to date.

There was a job description for each employee, including a description of their responsibilities. It was randomly verified that every job description was signed and dated by the staff member to whom it applied.

A list of signatures of the authorized personnel performing tasks during each study was available and verified.

The principles of Good Laboratory Practices had sufficiently established the responsibilities of the test facility management. The CRO management was aware that as the investigator was an employee of the CRO, some of the duties usually assigned to the investigator would, in a similar way, reside with the CRO management.

It was ensured by the management that appropriate and technically valid SOPs were implemented and followed. Maintenance of a historical file of all SOPs was adequately organized.

The contract between the sponsor and VerGo was signed. The Master service agreement was reviewed.

The ownership, confidentiality provisions, retention of records and biological samples' specifications, monitoring rights, and insurance reliability were all addressed in the agreement.

The Company's core time working hours were from 9-18, with two different shifts covering the respective activities.

2. Computer systems

A list of software and computerized systems used in the studies was provided.

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and were validated, operated, and maintained in accordance with the principles of GCP and GLP, as appropriate.

An inventory of all computerized systems on the network was available, with a clear identification of those GxP regulated.

There were enough computers to enable personnel to perform data entry and handling, required calculations, and compilation of reports. Computers had the adequate capacity and memory for the intended use.

The access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of people who had access to the database was maintained. Secure and unique, individual-specific identifiers and passwords were used.

The software programs used to perform key steps of the studies in the scope of this inspection were validated for the intended use. The qualification evidence was provided under the user's supervision to ensure that the software was validated for its intended use and that it was developed in a controlled manner in accordance with a QA system.

Regular updates to key software programs, whenever required, following a risk assessment on the potential impact that it could have on current data and qualification or validation status, were carried out in accordance with the respective SOP.

Qualification/requalification of the selected systems was reviewed to be verified. Risk assessment reports were available for both software systems, identifying eight risks with specific RPN numbers.

The database for registration of volunteers were designed by the third-party vendor and validated by the inhouse IT. The system was equipped with an audit trail.

Quality Risk Management was applied when deciding which components needed to be validated. SOPs or usage of each software program used to perform activities of a BE study was available.

Software programs used, frequency of virus testing, storage of data, and the procedure for backups and long-term archiving of all relevant electronic data were specified in the SOP for Backup and restoration of electronic data, and SOP for Audio-visual recording during the informed consent process was reviewed to discuss the CD/DVD records, and SOP for Submission, archival, retention, retrieval and re-storage of study project specific and non-study specific documents, including frequency of the backups.

Electronic data was backed up at regular intervals in accordance with the respective SOP. The reliability and completeness of these backups were verified daily through the logs generated in the system. The form for data restoration verification was available.

The backup software systems were reviewed in detail. The backup software was used to generate backups stored on the file server. The file server had a virtualization option, and two virtual machines were defined, one for the operating system and one for the data storage. The virtual machines were established as RAID level 1 for the operating system and RAID level 5 for the data storage.

Excel spreadsheet validation was carried out by SOP for Preparation, Qualification, Validation, Usage, and Control of Excel Spreadsheets.

The Mock drill plan and the respective safety inspection per department were carried out according to the respective procedure. A mock drill form was also available for medical emergencies.

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

3. Quality management

The CRO had appropriate QA and QC systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP and the applicable regulatory requirements.

A Quality manual was provided. The purpose of the Quality Manual was to:
1) communicate quality management plan
2) communicate information regarding quality procedures, control, and assurance
3) provide evidence of conformity to the National and International regulatory requirements
4) share knowledge
5) provide evidence of management's commitment to quality

QA personnel were not directly involved in trial-related activities, and an in-process audit by QA personnel did not replace oversight by another person when required. The QA Head was directly reporting to CMD (Chairman and Managing Director)

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed. The BA templates issued by QA were reconciled using the template for requisition and reconciliation form related to the applicable SOP.

The quality management system included root cause analysis, tracking trends, ensuring all aspects of data integrity, and implementing appropriate corrective and preventive actions (CAPA).

SOP for Management review meeting was reviewed, together with the last Management Review documentation:
- Attendance sheet
- Agenda
  - Status of previous meeting – actions taken
  - Discussion points – Procedure for taking print of chromatograms was stopped and it was now saved as electronic format.
  - Action plan was available

Business continuity plan was available to define:
- Possible risks
- Risk control
- Communication and arrangement
- Risk review
- Risk reporting
- Risk assessment and risk mitigation
- List of instrument vendors with contact number and email IDs.

Change control activities were recorded in a logbook for Change Control registration. The change control was available and reviewed for installation of Dropbox software, and the same was validated.

Templates were issued with a unique number that could be linked to a logbook for registration of the templates. Each template was associated with an SOP, starting from 00001. The numbering was continued until the next revision of the respective SOP.

Audit activities for 2021, including audit plan, reporting, actions, and respective checklists and procedures, were reviewed and discussed.

SOP for Handling deviations, Incident Investigation, CAPA implementation, and the respective logbook for registration of deviations were available and reviewed.

A list of vendors and service providers with information about the vendor and the respective service was associated with SOP. The vendors were audited in accordance with an annual vendor audit schedule, with the scheduled date, allocation, and audit date. The audit reports included the vendor's general information, a summary of the audit, observations, a conclusion, and a list of documents reviewed during the audit. An audit agenda was also provided to the auditee in advance.

4. Archive facilities

The CRO had a new archive facility on the ground floor. The facility was accessed by authorized personnel using a digital key card and was equipped with a relative humidity hygrometer, fire extinguisher sprinkles, and a fire detector. Pest control was regularly carried out and documented in the respective Entry/Exit logbook. The folders were protected in plastic bags. A list of authorized personnel was displayed at the entrance of the facility.

The archiving activities were managed in accordance with the respective SOP.

Records of document access and retrieval of documentation were maintained. The length of time for which study documentation, including raw data, should be kept in the archive, was defined in the SOP. This period was also specified in the contract between the sponsor and the CRO, which included provisions for financing the archiving.

The archiving procedures of the trial-related documentation were verified through successful retrieval and traceability of the documents during the inspection.

Observation related to the Archive facility was adequately addressed in the respective CAPA plan.

5. Premises

A facility tour was conducted during the inspection on Day 2 and Day 3.

The facilities were kept clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site had adequate facilities, including laboratories and equipment. Entry to the facility was restricted and controlled through digital key cards. The entry doors to the CPUs were locked to detect the exit of subjects from clinical facilities. Any entry to and exit from the facility were documented at the gate security by recording the activity in separate logbooks for entry and exit.

Sites where the clinical activities took place, included a pharmacy where investigational products were stored under appropriate conditions with entry and exit restricted by access control. Proper entry/exit records of each visit to the pharmacy were maintained.

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 suitable for samples, standards, solvents, reagents, and records was available.

Laboratory premises were designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Safety data sheets were available to staff before testing was carried out. The staff working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals. Staff was instructed to wear laboratory coats or other protective clothing, including eye protection. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison,” “flammable,” or “radioactive”) whenever appropriate.

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

The temperature and humidity of the facility were monitored by using thermo-hygrometers. The max-min temperature and related humidity were read and documented twice daily.

There was a Diesel Generator for backup of the power supply. Three UPS were available. Usage of diesel was recorded daily and topped up when the level was half.

Synchronized clocks were located throughout the facility to document study activities' exact times.

The observation related to the Premises was taken care of in the respective CAPA plan.

6. Personnel

There was enough medical, paramedical, technical, and clerical staff with the appropriate qualifications, training, and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies. The number of staff members counted to 127 at the time of inspection. At all trial stages, including at night, there were qualified and trained personnel to ensure that the rights, safety, and well-being of the subjects were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities.

Randomly selected current curricula vitae and training records of personnel involved in trial activities for full-time and contract workers were reviewed to be verified.

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO.

The CPU was equipped with 100 beds. Systems were in place in the accommodation facilities so that subjects could alert CRO staff in case of need.

Facilities for changing and storing clothes and for washing and toilet purposes were clean, well-ordered, easily accessible, and appropriate for the number of users. Lockable toilets were alarmed, and doors were designed to ensure they could be opened from the outside should a medical emergency occur.

The clinical site consisted of

- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- CPU I, II & III
- Subjects' recreation;
- Pharmacy;
- Room for administration of the investigational products and sample collection;
- Walking cold room

- Archive facility;
- Facility for preparation of standardized meals (kitchen) and a dining hall;
- ICU

Provisions were made for the urgent transportation of subjects to the designated hospital. The service agreement was signed. The notification was sent to the hospital in advance, and automated feedback was received to verify the receipt of the notification.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified at appropriate intervals and specifically before check-in activities.

There was a Master calibration plan and schedule for both clinical and bioanalytical laboratory departments associated with the applicable SOP, in addition to the Master list of instruments with information about name, model, serial number, area, and ID, associated with the respective SOP.

8. Clinical laboratory

A suitable clinical laboratory was used for analyzing samples. The laboratory was accredited by NABL in accordance with ISO 15189:2012. The scope of accreditation was also provided.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol.

Sample labelling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

Information about the analytical methods used in the laboratory and a list of laboratory normal ranges were available during inspection. The current and signed curricula vitae of the Head of Clinical Laboratory were reviewed.

The laboratory created individual reports for each subject and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic or paper formats, depending on their source and the laboratory's storage capacity.

Data integrity requirements were ensured for all tests related to the study through validated systems used for sample analysis. Repeat and additional examinations were possible for haematology, clinical biochemistry, and serological tests if a request was received within a period of retention of examined samples in accordance with SOP for Repeat examination of test parameters.

9. Ethics

Trials were approved by an independent ethics committee (IEC) before the conduct of the studies. The Committee's independency from the sponsor, the investigator, and the CRO was verified through the respective member list. Detailed minutes were kept of the discussions, recommendations, and decisions of the IEC meetings. The IEC was given sufficient time for protocols, informed consent forms (ICFs), and related documentation review.

The insurance documentation for the period of 8 Mar 2019 to 07 Mar 2020 was provided through an insurance company.

Informed consent form

Information for study participants was given to them in vernacular language, i.e., Marathi and Hindi, and at a level of complexity appropriate to their understanding, both orally and writing.

Informed consent was given by the subject and documented in writing before starting any trial-related activities. Informed consent was also recorded by video. The information was clear: participation was voluntary, and the subject had the right to withdraw from the study on his or her initiative at any time without giving a reason. The reasons for withdrawal from the study were included in the study records.

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through the Insurance policy.

The volunteers or subjects were allowed to discuss their concerns regarding potential side effects or reactions from using the investigational products with a medical officer before participating in the trial.

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

10. Monitoring

It was verified that the monitors were the sponsor representatives with appropriate qualifications. Their primary responsibility of the monitor was to ensure that the study was conducted in accordance with the protocol, GCP, and applicable ethical and regulatory requirements through verification of the usage of correct procedures for completion of CRFs and verification of the accuracy of data obtained.

The presence of monitors during the monitoring visits was documented in the respective visitor logbooks. Monitoring reports were adequately provided and communicated with the CRO. One of the monitoring reports related to the first period of one of the studies was shared with the CRO after the completion of the second period. However, due to the absence of any observation/deficiency, it was found acceptable.

11. Investigators

The principal investigator (PI) had the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee, and signing of the protocol and the final study report.

12. Receiving, storage and handling of investigational drug products

The information concerning the receipt, storage, handling, and accountability of investigational products at every trial stage was recorded. The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products were also verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through Thermo hygrometers for room temperature and a Eurotherm digital thermometer system for the refrigerator and walk-in stability chamber.

Randomization was performed in accordance with SOP for Generation of Randomization and records were maintained, including the randomization list and seed number. The randomization list was accessible to the statistician who generated it, PI and QA for verification purposes, and the pharmacist for the respective dispensing.

The IPs were properly labelled. Compliance of all labels with the randomization list was verified once they were printed and before labelling the containers. Labels were pasted onto the container to ensure that the information was not lost once the lid was removed.

Adequate routines for labelling and documenting the administration of the IP were established to verify that each subject did receive the product dispensed for him or her by using labels with a tear-off portion. Labels were designed to have two identical labels to have one portion pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The empty containers were separately labelled for the test and the reference investigational products and remained segregated in a secure area under lock and key to avoid the risk of any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were performed in accordance with the applicable requirements. Dosing was performed in accordance with the applicable SOPs under the supervision of the investigator and qualified staff member to whom this task was explicitly delegated in writing. The exact time of dosing was documented on the CRF's designated page. A mouth check was performed by looking under the tongue, under the lips, in the corners of the mouth, and between gums and cheeks, using a tongue depressor or a spatula and a penlight, in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. Dosing was directly documented in the CRFs.

Samples of the product in the original container were retained for possible confirmatory testing in the future for at least one year after the expiry date of the newest product. Sample retention was defined and described in SOP for Handling of Investigational Products and was specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

Observation related to the handling of Investigational Products was adequately addressed in the respective CAPA plan.

13. Case report forms

Randomly selected CRFs from the studies in the scope of inspection were reviewed.

The data collected on each volunteer was specified in the trial protocol & the respective SOPs.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about screening, pre-check-in activity, intake of the meal, vital exam records, blood sample collection record; including scheduled and actual time, IMP dosing administration, subject withdrawal/dropout, clinical examination at the time of checkout, breath alcohol record, adverse event (serious) was recorded in the CRFs. All the CRFs were signed and verified by the respective study coordinator and the investigator.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers specified in SOP for Mobilization and Recruitment of the Prospective Volunteers and included a description of the potential methods that the CRO used for this purpose. The database for registration of volunteers was maintained to avoid cross-participation and specify a minimum time between a volunteer's participation in one study and the next. Access to the database was password controlled to secure confidential information on volunteers or subjects.

A biometric system using the thumb and index finger ensured the identification of volunteers and subjects. The biometric system was verified every year.

The screening-specific informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study. The clinical trial protocol described criteria for subject selection (inclusion and exclusion criteria) and screening procedures. A central repository software system was used to determine whether any of the subjects had participated in a previous trial. Participation data was uploaded to this central repository to prevent over-volunteering.

The screening procedures were reviewed and discussed, including registration, Informed Consent process, Inclusion – exclusion criteria check, Physical exam, ECG, Alcohol test, Blood sampling, and urine sampling.

15. Food and fluids

Meals were standardized, supervised, and scheduled during the study days. The CRO was able to arrange for standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol in their in-house kitchen.

Timing, duration, and amount of food and fluids consumed were recorded in the respective CRF. Prior to samples being obtained from ambulatory subjects, they were asked about their food and drink consumption. Standardized meals were designed and planned by a dietitian with appropriate qualifications, training, and experience.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and for notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of serious adverse event.

First-aid equipment and appropriate rescue medication were available in the ICU and ready for emergency use at the study site. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the ICU.

The CRO had adverse event registration and reporting forms as part of the CRF.

Bioanalytical section

The inspection included the audit of source documentation and raw data for validation of the bioanalytical methods and analysis of subject plasma samples, a review of the 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 were inspected, along with the chromatograms generated from the analytical runs. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited.

Chromatograms and their integration, absence of signals in the blank samples, and absence of any unexplained interruptions in the injected sequences were verified. The reason for the study sample repeat analyses and all instrument failures were 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.

For a review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. A copy of the electronic raw data was provided to the inspectors on a laptop having the relevant version of the relevant software installed.

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

The process of method development of randomly selected studies in the scope of inspection was adequately described and documented. The usage of IS was justified based on the applicable literature. After method development, an analytical validation plan was provided as a basis for the method validation. A stable isotope-labelled internal standard was always used in the MS methods, and K_2EDTA was applied as an anticoagulant.

During the method validation of the analyte in the scope of inspection as per the applicable SOP, a run was performed to determine the batch with 124 samples of QCs and CCs (so-called batch size evaluation) comparable in length to those that were expected to be used for analysis. The LLOQ of the applied method was found adequate to identify the presence of 5% of C_{max} concentration of analyte in pre-dose samples of study subjects.

The sample processing was documented in the respective forms. Sample handling, equipment, materials, and reagents were documented in forms associated with the SOP method. A note to file was also provided to record any unexpected activity during sample processing, when applicable.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the studies, except for the long-term stability performed before the issuance of the study reports.

The review of the entire method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), recovery and reinjection reproducibility. Partial validation was performed according to the requirements. The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. The purchase documentation of the plasma from qualified vendors, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed and discussed.

During study sample analysis, 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 analysed 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 stabilization test was done before the start of runs on each day.

For study related to WHO application no. NT010, 414 samples out of a total of 5935 samples were used to run Incurred Sample Reanalyses (ISR). A total of five independent analytical ISR runs were carried out. The samples were selected with concentrations around C_{max} and in the elimination phase. The acceptance criteria were clearly defined in SOP for Incurred Samples Reanalysis.

The site did not implement procedures for audit trail review. Nonetheless, the availability and completeness of the audit trails for study related to WHO application no NT010 were verified. The analytical instruments used for study sample analyses were inspected. Audit trails (result table, project, and instrument audit trail) of the software system were verified. In addition, the audit trails of all other instruments were confirmed for the relevant period (June to December 2019).

Observations related to Sample analysis were adequately addressed in the respective CAPA plan.

18. Sample collection, storage and handling of biological material

The specification of samples (blood plasma), sampling method, volume, and number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport or shipping, and storage of samples were in accordance with the respective SOP.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were to be considered when calculating the pharmacokinetic parameters.

Labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots, shipped, and stored separately.

As per the applicable SOPs, the study samples, QC samples, and pooled matrix were discarded. The preparation and purchase of pooled plasma and the reconciliation and preparation of bulk spiking of QC and CCs of a study in the scope of inspection were reviewed and discussed. The records and logbooks were appropriately documented.

The refrigerator and freezers' temperature was monitored using a Eurotherm digital thermometer. The hotspots of the storage facilities were identified through regular temperature mapping.

The retention time of blood samples was defined in the agreement with the respective sponsor.

19. Data processing and documentation

Integration settings were science-based and fully justifiable. The smoothing factor was kept low enough not to mask possible interferences and changes in peak geometry. The retention times were found to be sufficiently stable throughout the runs analysed for the individual studies.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were defined in the applicable SOP. The acceptance criteria for reinjection of runs were defined in the SOP.

When the analysis was repeated, the source data for all the analytical runs contained all information about the original, first evaluation of runs (containing all calibration samples). The calibration range was truncated correctly. Internal standard variations were trended and used as part of the verifications of result validity.

Full audit trails were activated on all analytical instruments before, during, and after the method validation and the studies of interest.

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented in a manner that ensured traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). Audit trail files were generally retained (e.g., results table audit trail, project audit trail, and instrument audit trail) at the site.

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, the time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

Observation related to data processing was adequately addressed in the respective CAPA plan.

20. Good laboratory practices

A tour of the facility was performed to verify the suitability of the laboratory in terms of arrangement and safety. The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE studies, with an established appropriate QA system.

Deep freezers for storage of samples and refrigerators for storing the Reference standards were adequately qualified, calibrated, and maintained. The digital thermometer triggered notifications to the custodians responsible for the maintenance of the facility and gate security. The automatic alarm system was tested during the inspection to verify its functionality.

For qualification verification, the temperature mapping documentation of the Deep Freezer in the sample processing room and the refrigerator used for storage of spiking solutions was reviewed to verify the Hot spot and the location of the respective sensor. The temperature mapping process was adequately carried out at the time of inspection. Transfer of samples to equivalent storage units was appropriately considered under maintenance and repair.

Balances, other measuring devices and equipment, and instruments used during a trial were periodically calibrated and verified before use to fit their intended purpose.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. These activities were verified by a random review of the equipment used in study-related activities. Equipment and its components were labelled with the respective ID number, date of calibration, and date of next calibration. The equipment usage was adequately documented in the analytical

sheets and the respective logbooks for instrument use. The usage of columns was recorded in the logbook for the usage of columns.

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

Due to the time constraints, this part was not inspected.

22. Study report

The process of study report writing was verified during the 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 data.

The study report included a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and a report of the validation of this method.

The Principal Investigator approved the clinical study reports before data was transferred to the statistical department. The responsible staff and management also approved the bioanalytical reports.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The Contract Research Organization Master File was provided in accordance with the applicable requirements.
Annexes attached	N/A

Part 3	**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 guideline 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 3 years, provided that the outcome of any inspection conducted during this period is positive.

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

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9. ***Short name: WHO BE guidance*** or ***TRS996 Annex 9***
   https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y

2. 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
   https://apps.who.int/iris/handle/10665/44092
3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137). ***Short name: WHO GCP***
   https://www.who.int/publications/i/item/9241208503

4. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. Short name: ***WHO TRS 1010, Annex 9***
   https://www.who.int/publications/m/item/trs-1010---annex-9-who-good-practices-for-desk-assessment-of-compliance-with-good-manufacturing-practices-good-laboratory-practices-and-good-clinical-practices-for-medical-products-regulatory-decisions

5. 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***
   https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en

6. 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***
https://apps.who.int/iris/handle/10665/44783

7. 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***
https://www.who.int/publications/i/item/WHO_TRS_957

8. 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***
https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y

9. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised). ***Short name: Glove use information leaflet***
https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009)

10. 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***
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf

11. 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***
https://apps.who.int/iris/handle/10665/331814

12. 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***
https://apps.who.int/iris/handle/10665/340323

13. 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***
https://apps.who.int/iris/handle/10665/268312

14. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf.

15. 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
https://www.who.int/publications/m/item/trs-1019---annex-3-good-manufacturing-practices-guidelines-on-validation