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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Jeevan Scientific Technology Ltd B-17, TIE, Phase II, Balanagar Hyderabad, 500 037 India
Name and Address of Bioanalytical Research Site	Jeevan Scientific Technology Ltd Plot No. 1&2, Sai Krupa Enclave Near Lanco Hills, Golconda Post, Hyderabad, 500 008 India
Name and address Statistical Site	Jeevan Scientific Technology Ltd Plot No. 1&2, Sai Krupa Enclave Near Lanco Hills, Golconda Post, Hyderabad, 500 008 India
GPS coordinates	Clinical site Latitude: 17.472276 Longitude: 78.444644 Bioanalytical site: Latitude: 17.413429 Longitude: 78.366327
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA 772** Bioequivalence study of Atazanavir and Ritonavir tablets 300 mg/100 mg **WHO application no: CV009** Bioequivalence study of Molnupiravir capsules 200 mg **WHO application no: CV017** Bioequivalence study of Nirmatrelvir tablets 150 mg (150 mg x 2 tablets) and Ritonavir tablets 100 mg tablets

Inspection details	
Dates of inspection	14-17 March 2023
Type of inspection	Routine
Introduction	
Summary of the activities	Jeevan Scientific Technology Limited, hereafter referred to as JSTL, has been designed to provide a range of clinical research services in Bioavailability and Bioequivalence Studies (Clinical, Bioanalytical & Statistical Phase), Clinical Trials, and Pharmacovigilance for pharmaceutical and biotech industries across the globe.
General information about the company and site	JSTL, established on 2 Feb 1999 as Jeevan Softech Private Limited in Hyderabad, India, is a global management consulting, technology services, and outsourcing company providing education, staffing, and information technology services. On 12 Jan 2000, the company's legal structure was changed from Jeevan Softech Private Limited to Jeevan Softech Limited. Later, on 24 Mar 2011, the company name was changed to Jeevan Scientific Technology Limited to offer clinical research services. It started its services with medical writing and expanded to full CRO with a portfolio of BA/BE, clinical trials, and pharmacovigilance Services in 2014. JSTL is divided into two locations for BA/BE study operations.
History	Since 2015, the CRO has been inspected by USFDA, MHRA & CDSCO. WHO previously inspected the CRO in March 2019.
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	N/A

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 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
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

A presentation was provided explaining the organization's activities in detail, including changes from previous WHO inspections. The changes included:

- Shifting the clinical pathology laboratory from the Bioanalytical & Corporate facility to the Clinical facility in February 2021.
- The addition of a Cold walk-in chamber on the 4th floor of the Bioanalytical & Corporate facility in Aug 2021.
- Changes in the organogram of the organization.

JSTL Clinical Pharmacology Centre was approved by CDSCO on 26 Dec 2019 for conducting bioequivalence studies. The company was also accepted by Telangana State Pollution Control Board. Approval letters were attached as Annexure – 2 to the site's CROMF.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organization chart was dated 1 Feb 2023, authorized, and kept up to date. The Head of QA was reporting directly to the CEO.

There was a job description for each employee, including 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 responsibilities 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 master service agreement between the CRO and the sponsors was available.

A full-time working day commonly was from 9:30 to 18:30. Every other Saturday was also considered a working day.

2. Computer systems

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

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.

Changes to the network, including the temporary addition or removal of systems from the network, were documented through the change request procedure.

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

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

The software programs used to perform key steps were reviewed to be suitable and validated for the intended use. The qualification and/or validation certificates were provided under the user's supervision to ensure the appropriate development of software systems in a controlled manner following the QA system. The qualification of the following systems was reviewed:

- A software system used to record the volunteer registration, and screening activities, including QC and QA review and approval process to provide a selected list of volunteers to be recruited for the clinical research studies, maintain an audit trail of data and archived data in line with the requirements.
  The data from the decommissioned volunteer registration system was migrated to the new system. The installation of the new system was controlled through the change control procedure, i.e., SOP for Change requests. IQ, OQ, and PQ of the software system with the recent version were completed on 28 Nov 2022. The vendor provided the qualification documentation, which was internally reviewed and authorized by the CRO team.
- The LIMS, i.e., a Laboratory Information Management System used to transfer the analytical results from the pathology analyzers' equipment and generate the respective laboratory reports.
- The software associated with the hematology analyzer.
- The software system associated with clinical biochemistry Analyzer.
- The software associated with the ECG machine. The respective user access rights and privileges, together with the transmission of data through LAN cable were investigated. The audit trail report was reviewed for the period of the selected studies in the scope of the inspection.

The specific user requirements, regulatory/guideline requirements for BE studies, the operating environment in which the system was used, and the usage of the system in the studies were considered in the qualification of the systems. The practice was defined in the Validation Master plan. SOPs for the usage of each software program used to perform activities of a BE study were available.

Computer systems related to instruments and data evaluation processes were evaluated for system integrity every two years per the validation master plan to confirm that they remain validated. In that context, a review schedule for validated software systems was provided with information about the software name and the due date of the software validation.

The Software programs used, data storage, the procedure for backup of all relevant electronic data, and restoration of data, including frequency of backup, were specified in SOP for Data Backup and Restoration. The data related but not limited to LC-MS/MS instruments, SAS, Pharmacy, Volunteer Database, temperature monitoring system, PK application, and any other data were synchronized into the file server. Backup was performed continuously as incremental and full back-up on tapes. Incremental backup was done daily, and full backup was done every fortnightly. Data restoration check was done on a half-yearly basis. For LC-MS/MS systems, data was transferred every six hours automatically from the source (Local Drive) to the destination (Server) by using a designated software. Daily logs were checked to ensure data transfer was adequately working. JSTL was located at two locations, each site acting as backup for the other site continuing the operations. In case of disaster, the crisis management team would handle such incidents and plan for disaster recovery as per the policy. The last restoration document was available on 27 Sep 2022 and reviewed. The form was issued in a controlled manner, and the size of the folders was verified.

Networks, including the full client/server architecture and interfaces such as laboratory information management systems, were designed, qualified, managed, and controlled, as illustrated in a network diagram.

Observations regarding computerized systems were effectively addressed in the 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. The current relevant SOPs were provided on a USB for the inspectors' review at the time of inspection. The historical versions were provided upon specific request.

A Quality manual was provided. The manual described Quality Management System for clinical research services with BA/BE operations at JSTL. A Quality Manual was prepared individually for other operations of the Clinical Pathology Laboratory, pharmacovigilance, and Clinical Trial.

JSTL had a Quality Assurance (QA) function independent of the rest of the operations. QA functioned as a separate department, and the Head-QA reported directly to the management. QA was responsible for implementing, maintaining, overseeing, and continually improving quality standards and procedures to meet sponsors, regulatory and in-house requirements. QA maintained the master copy of SOPs, controlled the documents, and distributed the controlled copies in the organization. QA conducted internal audits (study audits & system audits).

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed.

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

The company defined the audit trail queries or reports to be used for different systems and different purposes in an SOP. It was specified which data was required to be reviewed, however; the QA was recommended to provide more information and, most likely, training on how the data and any possible modifications were presented in the audit trail and which data changes were acceptable in the routine use of the system. It should be described what justifications were required and acceptable in these instances and how/where these should be documented.

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

4. Archive facilities

The archive facility was located on the fourth floor. The CRO had sufficient and appropriately secure storage space for archiving the trial-related documentation. The facility was protected by a fire-rated door. Relative humidity was controlled, and adequate measures were in place to control pests.

The archiving activities were managed following the SOP for Archives activities.

Access to archive storage areas was controlled and restricted to authorized personnel. A list of authorized personnel was displayed at the entrance of the facility.

Records of document access and return 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 the financing of the archiving.

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

5. Premises

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

The clinical facility consisted of the Clinical Pharmacology Centre (CPC), occupied with an area of approximately 20,000 sq. ft. on the building's 2nd, 3rd, and 4th floors. The Clinical Pathology Laboratory occupied a total area of roughly 1400 sq. ft on the 1st floor of the building, which was located on the opposite side of the clinical pharmacology centre.

The facilities were kept at a satisfactory level of cleanliness at the time of inspection and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

Clinical trials were carried out under conditions that ensured the safety of the subjects. The site selected was appropriate to the potential risk involved.

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.

Security was available round the clock at the facility. The volunteers' mobility was under CCTV surveillance, and all restricted areas were equipped with access-controlled doors. All staff was required to access the rooms in the facility with their access card. Any entry to and exit from the facility was recorded. The Emergency evacuation was ensured.

Sites where 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 was available for samples, standards, solvents, reagents, and records.

Laboratory premises were designed to protect employees and authorized external personnel, including inspectors or auditors.

Staff was trained to use the firefighting equipment, including fire extinguishers and fire blankets; a checklist for emergency exits in case of a fire alarm was available and verified during the Fire Mock Drill. The activity was recently performed on 29 Apr 2022. Staff was instructed to wear laboratory coats or other protective clothing, including eye protection. A room in the laboratory for sample processing was equipped with a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings whenever appropriate.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. First-aid materials, fire blankets, and a spill kit were provided at the laboratory.

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 certified fume hoods or air extractors, and safety and eye showers were available in the laboratory.

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

The diesel generator and UPS were available and adequately maintained.

Observations concerning the Premises were satisfactorily addressed.

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 152 (permanent employees) at the time of inspection. At all trial stages, including at night, there were qualified and trained personnel to ensure that the subject's rights, safety, and well-being 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 clinical Pharmacology Centre had a capacity of 132 beds with 4 CPUs (Clinical Pharmacology Units) and two special care units (3 beds each). Systems were in place in the accommodation facilities so 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. An alarm was installed in Lockable toilets.

The clinical site consisted of:

- subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- CPU;
- subjects' recreation;
- pharmacy;
- room for the administration of the investigational products and sample collection;
- sample processing (e.g., plasma separation) and storage (freezer);
- archive facility;
- preparation of standardized meals and a dining hall;
- ICU

Provisions were made for the urgent transportation of subjects to the hospital.

Access to the randomization list was restricted to the pharmacist in charge of the study. The list was transferred in a sealed envelope, a log was provided, and their distribution was documented.

The equipment used was appropriately calibrated at predefined intervals. Emergency-use equipment's adequate function and performance were verified at appropriate intervals.

Observations related to the clinical phase were addressed in the CAPA plan.

8. Clinical laboratory

A suitable clinical laboratory located at No. S-13, TIE, Phase II, Balanagar, Hyderabad-500 037, Telangana, India, was used for analyzing samples. The laboratory was accredited in accordance with ISO 15189:2012. The accreditation was valid until 3 May 2023.

JSTL also employed external pathology laboratory services as a backup, which were used to analyze the volunteer screening samples and the subject's safety samples. JSTL would send the samples to the outsourced pathology laboratory, along with the test requisition form and sample collection.

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. The samples used for screening activities were once labelled with a specific barcode at the time of collection. The barcode was generated in the applicable software system. Another barcode with a specific lab-identification number was generated using another application.

The CRO received information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges, and the accreditation certificate of the laboratory.

The current and signed curricula vitae of the Head of the Clinical Laboratory were reviewed.

The laboratory created individual reports for each subject through the software application and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic or paper formats.

Data integrity requirements were ensured for all tests related to the study through adequately validated systems used for sample analysis.

9. Ethics

Trials were approved by the independent ethics committee (IEC) before any study was conducted. This Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation.

The insurance policy covered the study period by the Insurance company. 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.

Informed consent form

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

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

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

In the informed consent form of study CV009, the CRO declared that this study was a clinical research project. Still, no part of it was of an experimental nature, and the intake of both test and reference drug was not risk associated. However, the statement was removed from the recent studies' ICF, and the procedure was amended after the recent US FDA inspection and the respective observation.

The certificate of translation of the informed consent was reviewed.

An observation related to the ICF was identified which was addressed in the CAPA plan.

10. Monitoring

The study was monitored by the sponsors' representative. A pre-and post-study visit and monitoring visits for study periods were performed, except for study CV009, for which the monitor covered only one study period. The monitoring included verifying the use of correct procedures for completing CRFs and verifying the accuracy of data obtained. The visits of monitors were confirmed.

The monitors prepared a written report after each site visit only if there were any observations and communicated the issues to the CRO and the sponsor in a timely manner. The respective communications and corrective actions were documented.

11. Investigators

The principal investigator (PI) was responsible 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 investigational products' receipt, storage, handling, and accountability 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 in stability chambers. The temperature, humidity, and access to the chambers were controlled using the datalogger system, which was reviewed during the inspection.

Randomization was performed following the respective SOP to generate a randomization list for clinical studies. The records were maintained, including the randomization list and seed. The biostatistician generated the randomization schedule through the respective procedure using a software. Equal allocation of subjects in each sequence (T-R or R-T) was ensured. Thus, the random allocation of drug products (or formulations) was balanced over the period and sequence. The randomization list was accessible only to the person who generated it, a dispensing pharmacist, and the statistician.

The IPs were properly labelled. Compliance of all labels with the randomization list was verified once they were printed and before the labelling of the containers. Labels were pasted onto the container to ensure 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 them by using labels with a tear-off portion. Labels were designed to have two identical labels to have one portion to be pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The empty containers were labelled separately for the test and the reference investigational products. They 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 requirements.

The surface on which the product was handled was thoroughly cleaned before bringing bottles of the product into the area. Any product containers (full or empty), labelling materials, contaminants, dirt, and debris were removed from the area. A second person verified that the surface area/line was clear and clean before bringing in and opening product containers. The IMPs were handled with appropriate utensils. Tablets were distributed into each container following the randomization list for the comparator or the test product as appropriate. The two products, i.e., Test & Reference, were handled at different times. This also applied to the labelled containers. Every step was recorded sequentially in detail. The surface upon which the product was handled, and its surroundings were cleared and cleaned immediately before and after initiating the dispensing of the following product, also in the same study.

Investigational product accountability and dispensing records were always maintained. Each activity was documented when performed, including records of doses administered and returned or destroyed and records of verification by a second person of each step.

Dosing was carried out in accordance with the corresponding SOP under the supervision of the investigator and qualified staff member to whom this task was explicitly delegated in writing. The time of dosing was documented on the CRF's designated page.

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 specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained, according to SOP for Retention of investigational products.

13. Case report forms

Randomly selected CRFs from the studies CV009 & CV017were reviewed. The respective CRFs were in paper form.

The data collected on each volunteer was specified in the trial protocol. The screening-related data was directly recorded in Medical Screening Records, and the study-related data generated during the conduct of the study were directly recorded in the respective CRF, which were considered as source data and were kept along with other source data (e.g., X-ray reports, ECG, laboratory reports). The Principal Investigator and the Project In-charge were responsible for data custody until transfer to archives.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about inclusion /exclusion criteria and all procedures required by protocols was recorded in the CRFs. Documentation regarding IMP administration and blood sample collection was available. The investigators verified patients' eligibility and adequately documented the approval process. The quality of documents was sufficient, and ALCOA principles were generally followed. All CRFs were readily available and provided in a timely manner upon the request of the inspection team.

14. Volunteers, recruitment methods

Procedures for registration of volunteers who were intended to participate in clinical studies were specified in SOP for the Registration of volunteers. A database was maintained on volunteers to avoid cross-participation and specify a minimum time that should elapse 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.

Identification of volunteers and subjects was ensured through a biometric system using the right and left thumb and index fingers.

The 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 software system was used to determine whether any of the subjects had participated in a previous trial at any CROs in the district. Participation data was uploaded to this central repository to prevent over-volunteering.

A testing kit was used for both alcohol and drug test, at the time of screening and check-in.

15. Food and fluids

Meals were standardized and adequately controlled and scheduled during the study days. The CRO arranged standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol. JSTL outsourced the catering services to a catering company to provide meals to study volunteers as per the meal menu. The respective invoice records for study CV009 were verified.

Timing, duration, and amount of food and fluids consumed were recorded. Before samples were obtained from ambulatory subjects, they were asked about their food and drink consumption. A dietitian with appropriate qualifications, training, and experience designed standardized meals.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of a 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. Intake of any concomitant medication was documented in the CRF, when applicable.

Bioanalytical section

The inspection focused on studies CV009 & CV017, including the associated validation projects. Spot checks were also performed for study HA772. More specifically, the following records & activities were investigated:

- 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 interruptions in the injected sequences or between the analytical runs were verified. The reasons for the study sample repeat analyses and randomly selected instrument failures were reviewed. The documentation of the reinjection of subject samples and ISTD trending analysis was also confirmed.

The inspection team received adequate support from well-informed and transparent personnel to review the study documentation. The inspectors were provided with access to a copy of the electronic raw data, including audit trails generated by the chromatography data management software.

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

The method development process was described in the SOP and documented, and the usage of IS was justified based on the relevant literature. After method development, an analytical plan was provided as a basis for the method validation. A stable isotope-labelled internal standard was used in the MS methods, and anticoagulant usage was verified. A certificate of analysis was available for the reference standards, with correct stability. The selection of the regression model was described in the respective SOPs.

During the method validation as per SOP for Bioanalytical Method Validation, a run was performed to determine the batch with a predefined number of samples of QCs and CCs (so-called Analytical Batch size experiment) comparable in length to those expected to be used for analysis.

The sample processing was documented in the respective forms. 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, which was performed before the issuance of the study reports.

The review of the method validation included precision and accuracy testing (P&A), selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, 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. Pooled plasma documentation used for method validation of study CV009 was reviewed. The plasma was purchased from a service provider center. The respective screening reports were provided and available. An Excel sheet was provided for each study before the inspection, indicating the entire method validation experiments.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. A second person documented and verified the pre-defined exact processing sequence. 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 were done before the start of runs on each day in accordance with SOP for Equipment response check and stabilization runs. Acceptance criteria were calculated using a validated Excel sheet which was validated in accordance with a Working Instruction.

The IS response plots of the analytical runs in study CV017 exhibited inconsistent responses in some batches, e.g., subjects 03, 10, 15, 17, and 19. In some analytical runs, the calibrators exhibited different behaviour compared to the study samples (e.g., subjects 08 and 47). The validity of the respective runs was discussed. ISTD acceptance criteria and ISTD trend analysis were described in the respective SOP. The acceptance criteria and trending applied to intra-batch results. When the IS response plots of the runs exhibited inconsistency and started behaving differently, the analyst recorded the trend, and a decision was made to clean/maintain the instrument. After observing inconsistency in Internal Standard Metrics, internal maintenance was carried out for the respective

instrument LC-MS/MS, after analysis of subject 3 and subject 10. However, the response-dropping issue was still observed on the same instrument in subjects 15, 17, and 19. The stabilization run performed on 29 Oct 2022 demonstrated instability in the instrument, and the Project manager decided to call for a service engineer on 31 Oct 2022. An equipment report record was provided and reviewed on 1 Nov 2022. Mass Spectrometer – Triple Quad 4500 was calibrated on 31 Oct 2022. The dropping issue in the IS Peak area would not trigger maintenance if the sample concentrations fell along with QC and CCs and the rest of the acceptance criteria were met. The respective audit trail from 29 Oct to 31 Oct, including the engineer log-in records, was checked.

The number of samples for ISR was governed by the study design. The basis of sample selection was a representative cross-section of samples from different subjects within the analytical range. The acceptance criteria were clearly defined in the SOP for Incurred Sample Reanalysis.

A software system audit trail review was implemented in accordance with the respective SOP, effective 31 Jan 2022, to define the procedure for reviewing audit trails of the software systems used at the CRO.

The sequence of samples in the autosampler was verified for their sample name, plate position, vial position, data file, and acquisition method by the analyst and a second person, dated and signed through a stamp on the sequence documentation.

When the subject samples were processed, they could be stored in the refrigerator before being transferred to the autosampler. The processing documentation of samples exceeding the benchtop stability period was reviewed to verify their correct stability.

None of the chromatograms of the analytical runs related to the studies in the scope of inspection underwent a manual integration.

18. Sample collection, storage and handling of biological material

The specification of samples (blood plasma), sampling method, volume, and the 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 occurred per the SOP for Receipt and Handling of Biological Samples & the SOP for Handling of biological samples at the clinical facility.

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.

The 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. The shipment documentation for study CV009 and the respective record of the datalogger during the shipment were reviewed.

The study samples, QC samples, and pooled matrix were discarded in accordance with SOP for Receipt and Handling of biological samples for Study sample management. Moreover, the biological fluids were discarded/retained in accordance with the predefined provisions in the service agreement between the CRO and the sponsor. The biological matrix used for pooled plasma was recorded in a form for the Usage of Biological matrix related to the applicable SOP. The issue details and usage of plasma were recorded for each study, kept together with the respective screening reports, with information about the type of anticoagulant, LOT ID, collection, and expiry date. The forms were issued in a controlled manner.

19. Data processing and documentation

Integration settings were science-based and justified. The smoothing factor was kept low enough not to mask possible interferences and changes in peak geometry.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. The calibration range was adequately truncated. Internal standard variations were trended and used as part of the verifications of result validity.

Full audit trails were always 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).

All audit trail files were retained (e.g., results table audit trail, project audit trail, and instrument audit trail).

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.

The reconciliation of the forms was checked and verified. All templates were issued in a controlled manner under the supervision of QA.

20. Good laboratory practices

A tour of the facility was performed on Day 2 to verify its suitability of the facility 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 the samples and refrigerators for storage of the Reference standards were qualified, calibrated, and maintained. There was an alarm system associated with the digital thermometer to trigger a call from security personnel to the custodians responsible for the maintenance of the facility. The automatic alarm system associated with Deep Freezer at the CPU III was tested during the inspection to verify its functionality. The daily monitoring and all the alarm checks were documented. The datalogger temperature records were provided, together with the alarm logs. The alarms were received and acknowledged by the custodian in the system. The records were adequate.

For the purpose of qualification verification, the temperature mapping of the Deep Freezer located at the CPU III _ sample processing room, dated 24 Jan 2022 & 18 Jan 2023 was reviewed to verify the location of the hotspot and 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, equipment, and instruments used during a trial were periodically calibrated and verified before use to be fit for 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 random review of the equipment, such as Micro Balance, and UHPLC used in study-related activities. Equipment and its components were labelled with the respective ID number, calibration date, and next calibration date. The analytical sheets and the respective logbooks for instrument usage adequately documented the equipment usage. The use of columns was recorded in the logbook for the usage of chromatography instruments.

Safety data sheets were available to staff before testing was carried out and it was documented whether the staff were trained on how to use the data.

An observation related to Good Laboratory Practices was identified and later addressed in the CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The biostatistician provided a presentation explaining the biostatistician's role, sample size estimation, generation of randomization schedule, data handling, and pharmacokinetic & statistical analyses.

The means of performing pharmacokinetic and statistical calculations (both software and scripts) were specified in the study protocol and/ or a pharmacokinetic analysis plan and a statistical analysis plan. Data analysis conformed to these requirements.

Generation of randomization list and statistical analysis were performed using the designated software. The assigned Pharmacist requested the randomization schedule through PI authorized “Randomization Schedule Request template” form as per the SOP.

Pharmacokinetic analysis was carried out using software system for PK analysis per the study-specific protocol and the applicable SOP. Individual and mean concentration tables and individual and mean pharmacokinetic parameters data were saved in a study-specific folder in .xpt and excel formats. Statistical analysis was performed using software application in accordance with the study-specific protocol and the respective SOP. Once the statistical analysis was completed, the generated output was saved in .rtf and .pdf formats in study specific folder. The obtained results from SAS software were cross verified against results to ensure accuracy and reliability. The final results were forwarded to the PI and Project Management (PM) team.

The Biostatistician was required to lock the concentration data after receipt of QA clearance while documenting the details in the "Concentration Data Lock/Unlock" form to be confirmed by QA personnel. After the lock of the concentration data, no changes were allowed. If any changes were required, then the biostatistician should document the details in the "Concentration Data Lock/Unlock" form and receive approval from the PI/designee and clearance from the QA unit to unlock the concentration data.

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 (raw) 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 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. 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 Site Master Files issued on 17 Feb 2023 for the clinical site and the bioanalytical sites were available.
Annexes attached	Not applicable

Part 3	**Inspection conclusion**

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 guidelines at ***Jeevan Scientific Technology Ltd***, located at the following addresses:

Clinical site: ***B-17, TIE, Phase II, Balanagar, Hyderabad, 500 037, India***
Bioanalytical site: ***Plot No. 1&2, Sai Krupa Enclave - Near Lanco Hills, Golconda Post, Hyderabad, 500 008, 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. 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. 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***
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

5. 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://www.who.int/publications/i/item/9789241502948

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

7. 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

8. 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)

9. 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
   chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf

10. 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

11. 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

12. 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

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

14. 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

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4
https://apps.who.int/iris/handle/10665/43443
ring-practices-guidelines-on-validation