

WHO Prequalification Unit – 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	Cohance Lifesciences Limited, Clinical Research & Biosciences Division Plot No. 26 & 27, TIE, Balanagar Hyderabad - 500037, Telangana India
Name and Address of Bioanalytical Research Site	Cohance Lifesciences Limited Clinical Research & Biosciences Division Plot No. 26 & 27, TIE, Balanagar Hyderabad - 500037, Telangana India
Name and address Statistical Site	Cohance Lifesciences Limited Clinical Research & Biosciences Division Plot No. 26 & 27, TIE, Balanagar Hyderabad - 500037, Telangana India
Corporate address of Organization	Cohance Lifesciences Limited Clinical Research & Biosciences Division Unit No - 202, 2nd Floor, B Wing, Galaxy Towers Plot No-1, Hyderabad Knowledge City TSIIC, Raidurg, Panmaktha Serilingampally Mandal Rangareddi District Hyderabad - 500 081, Telangana India
GPS coordinates	17.47035° N 78.4442° E
WHO product numbers covered by the inspection/ Product names/ Study	WHO application no. TB389 Bioequivalence study of Linezolid Dispersible Tablets 150 mg WHO application no: MA188 Bioequivalence study of Artemether and Lumefantrine Tablets 20 mg / 120 mg WHO application no: CV014 Bioequivalence study of Molnupiravir Hard Capsules 200 mg

Cohance Lifesciences Limited, Hyderabad, CRO

31 January to 3 February 2023

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Contact: prequalinspection@who.int

numbers/ Study titles	
Inspection details	
Dates of inspection	31 January to 3 February 2023
Type of inspection	Routine
Introduction	
Summary of the activities	The facility provides comprehensive services for various clinical research activities, including medical writing, regulatory bioanalysis, biostatistics, data management, patient-based clinical and PK end-point studies, and phase trials.
General information about the company and site	<p>RA Chem Pharma Limited has merged into "Cohance Lifesciences Limited" (formerly known as AI Pharmed Consultancy India Limited), via a scheme of amalgamation approved by the Honorable National Company Law Tribunal by order dated September 30, 2022. RA Chem Pharma Limited was founded in 2003 after acquiring the API manufacturing unit at Jaggaiahpetta. In 2007, the CRBiosciences division (CRBio) was established.</p> <p>Cohance Lifesciences Limited is a vertically integrated company with manufacturing facilities for Active Pharmaceutical Ingredients (APIs), API Intermediates, Pharmaceutical Formulation Intermediates (PFIs), Finished Dosage Forms (FDFs), and CRBio (Bioequivalence/Bio-Availability studies) with a workforce over 2200 employees.</p> <p>The services that the CRO provided to its sponsors included, but were not limited to:</p> <ul style="list-style-type: none"> • Medical writing (Protocol, Informed Consent Document, CRFs, Ethics committee approval, Integrated/clinical report preparation according to ICH GCP E6 and ICH E3) • Clinical phase execution (both on Healthy and Patient Based Population) • Bioanalytical analysis • Pharmacokinetic and Statistical Services • eCTD submissions • Quality Assurance • Clinical Trials co-ordination • Regulatory Submission
History	The national regulatory authority (DCGI), as well as USFDA, UK MHRA, the Ministry of Health - Turkey, the Ministry of Health Malaysia (BPFK), the Ministry of Health - UAE, and GCC (Gulf Cooperation Council), inspected the CRO to ensure compliance with GCP & GLP for the Bioavailability and

	<p>Bioequivalence (BA/BE) studies submitted. A summary of the inspections and approvals can be found in Attachment 2 of the CROMF.</p> <p>WHO PQ last inspected the CRO (former RA Chem) in Feb 2018, and a desk review was carried out in Sep 2020.</p>
Brief report of inspection activities undertaken	<p>The following scope and study-related activities were reviewed:</p> <p>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.</p> <p>Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.</p> <p>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.</p>
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
ICD	informed consent document
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 activities of the organization in detail.

The CRO had an organizational chart depicting key positions including the names of responsible persons. The organization chart was dated 5 Jan 2023, authorized, and kept up to date.

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 in accordance with the respective SOP.

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. Maintenance of a historical file of all SOPs was adequately organized.

The facility was accredited by national regulatory authorities for the conduct of BA/BE studies (all phases) on healthy populations as well as patients, in accordance with GCP and applicable GLP principles in accordance with CT-09 form. An application to declare the new acquisition and the respective name change was submitted to the authorities, and it was approved by DCGI on 18 Jan 2023.

There was a project agreement between the CRO and the sponsor / third party with details about outsourced activities.

The CRO's business hours were from 9:00 a.m. to 6:00 p.m., Monday to Friday, as well as every other Saturday.

2. Computer systems

A list of software and computer systems used in the studies was submitted. A new inventory log with information about the purpose of the systems and the equipment associated with the software application was prepared during the inspection.

The chromatography software systems were used in bioanalytical laboratory for operations, acquisition, and quantification purposes of the studies in the inspection scope. All the concentrations of known and unknown samples reported, were calculated in the applicable software system.

Procedures for computerized system validation, i.e., SOP for System validation and management of user IDs, 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.

A flowchart for the computer networking illustrating the interaction between computing devices and servers and data transfer was provided during the inspection. The CRO did not exchange information between software systems through interface.

There were a sufficient number of computers enabling personnel to perform data entry and 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 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, were required to be suitable and validated for the intended use. In general, the qualification and/or validation certificates were 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 the QA system. The qualification of the randomly selected systems was reviewed.

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 performance qualification.

SOP for Authorization in LC-MS/MS related software system described the procedure for assigning privileges in LC-MS/MS related software systems to authorized users.

Electronic data was backed up at regular intervals in accordance with the applicable SOP. The daily backup was carried out using the onsite NAS system, and the weekly backup was administered using the offsite NAS. The reliability and completeness of these backups were verified every six months in accordance with the respective SOP. The anti-virus testing was incorporated into the company's global procedure.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.), were designed to prevent errors. The data entry process was specified in each respective SOP.

SOP for Crisis management was reviewed. A risk mitigation plan for crisis management was required to be implemented. The risk assessment was performed, and the risks were addressed in the respective SOPs.

The issues concerning the computerized systems were appropriately dealt with in the corresponding CAPA plan.

3. Quality management

The CRO had 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 presented, and it described the Quality Management System (QMS) of Cohance Lifesciences Limited, Clinical Research and Biosciences Division (CRBio), and provided guidance for writing policies and procedures for the organization.

The QA unit functioned independently and directly reported to Chief Quality & Compliance Officer, who was reporting to the CEO & MD. The procedure for the preparation of organograms was defined in the applicable SOP.

The QA unit was responsible for

- Review of SOPs, protocols, method validation, bioanalytical, clinical, and integrated study reports.
- Control and distribution of SOPs, validation reports, method SOPs, and study-related forms.
- Oversee staff training on applicable SOPs, GCPs, and GLPs.
- Perform system and facility audits at regular intervals.
- In-process and retrospective audit of the clinical and bioanalytical phases.
- Co-ordinate with the sponsor's auditors and regulatory inspectors.
- Providing a compliance report to the sponsor, customer, and regulatory authority.
- Perform vendor qualification audits at regular intervals.

Both in-process and retrospective QA verifications were performed.

An annual audit plan was available. The documentation related to the BA facility audit in February 2022 was reviewed. The quality management system included root cause analysis, ensuring data integrity, and implementing appropriate corrective and preventive actions (CAPA).

Although a risk analysis was not performed to identify the non-related study forms that needed to be issued in a controlled manner, the QA had practices in place to ensure the reliability and integrity of general forms by associating the forms with controlled documents or other types of evidence.

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

4. Archive facilities

The CRO had sufficient and appropriately secure storage space for archiving the trial-related documentation. The Archive facility was located on the 2nd floor, it was fireproof, the relative humidity was controlled, and there were pest-control measures in place,

The archiving activities were managed following SOP for Archival, retention, retrieval, and restoration of data.

Access to archive storage areas was controlled and restricted to authorized personnel using access control systems. 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, protocol, and the service agreement between the CRO & sponsor. The CRO had also an agreement with offsite archive facility for long-term storage. The facility was audited by the CRO.

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

5. Premises

During the inspection, a facility tour was conducted.

The building was spread over approximately 30,000 sq. ft. made up of five floors, including the Ground floor.

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 adequacy of the safety conditions during clinical trials was discussed with the management. The necessity of risk analysis by a qualified constructor was highlighted.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site had adequate facilities, including equipment.

Entry to the facility was restricted and controlled through keycards. Therefore, any access to and exit from the facility were recorded.

The site 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 provide protection to the 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. Staff working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff was trained to use the firefighting equipment, including fire extinguishers and gas masks.

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. The employees were aware of the need to avoid working alone in the laboratory. First-aid materials were provided, and the staff was instructed in first-aid techniques, emergency care, and antidotes.

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. Employees were trained on procedures for handling broken glass; however, they were only adequate for small glass devices.

The following utilities supported the facility for intended purposes:

Diesel Generator
Nitrogen Gas plant
UPS
Air Compressor

The CRO addressed all observations about the premises properly, following the appropriate 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 106 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 were reviewed to be verified. There were logbooks for personnel training in each employee binder where the employee could document their attendance in the respective training.

Clinical section**7. Clinical phase**

The clinical phase of the studies was performed on the premises of the CRO, which was visited on day 2 of the inspection.

The CPU was equipped with a total of 114 beds spread across four independent clinics (Located on the 2nd floor (54 beds) and 3rd floor (60 Beds)). Systems were in place in the accommodation facilities to allow the subjects to alert CRO staff in case of need.

Facilities for changing and storing clothes and washing and restrooms were relatively clean & well-ordered, easily accessible, and appropriate for the number of users. Lockable restrooms 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
- Ambulatory sample collection room
- CPU; along with sample processing areas, and storage
- Subjects' recreation & change room
- Pharmacy
- Room for the administration of the investigational products and sample collection
- Archive facility
- Dining hall
- ICU
- X-ray facility

The X-ray facility was not in use since 6 Jan 2022 due to the breakdown of the In-house X-ray digitizer. Therefore, the external facilities were used for volunteers who did not have a valid X-ray image within 12 months before the screening of study in the scope of inspection.

Provisions were made for the urgent transportation of subjects to the hospital. The hospital was notified in due course about the date of initiation, the number of subjects, and the study information.

Access to the randomization list was restricted to the pharmacist in charge of the study. The document was kept in the pharmacy under the supervision of the pharmacist.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) were also verified following the same procedure.

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

8. Clinical laboratory

A suitable clinical laboratory was used for analysing samples. The laboratory was accredited in accordance with ISO 15189:2012 by NABL.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol. An RT PCR for SARS COV2 COVID-19 was also performed for studies conducted during the Pandemic.

Sample labelling, receipt, storage, and chain of custody ensured full traceability and sample integrity. The subjects' information, i.e., volunteer registration number and date of birth, were recorded on the label.

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

The signed curricula vitae (22 Sep 2022) of the Head of the Clinical Laboratory was reviewed.

The laboratory created individual reports for each subject which were included in the CRFs. The laboratory archived source or raw data for all tests in paper formats.

An observation related to the Clinical laboratory was properly handled in the corresponding CAPA plan.

9. Ethics

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

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 in the presence of a witness 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 their 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 was available through the Insurance. A policy schedule for clinical trials' liability insurance was available. The insurance documentation covering the period during 30 Sep 2021 - 29 Sep 2022 was reviewed and verified.

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

The certificates of translation and back translation of the informed consent provided by Translation services were reviewed. The ICD was provided in vernacular languages, i.e., Hindi and Telugu.

10. Monitoring

The study was monitored by a sponsor representative. The monitor ensured that the study was conducted in accordance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. This included verifying the use of correct procedures for completing CRFs and verifying the accuracy of data obtained.

A site initiation visit, a monitoring visit during the trial and a close-out meeting were performed. The monitor prepared a written report after each site visit and communicated any issues to the CRO and the sponsor. The respective communications were documented and kept in the study file. The monitoring visits were documented in the respective logbook and a visit log and were archived in the study binder.

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.

List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study was included in the study report and the information was randomly verified.

12. Receiving, storage and handling of investigational drug products

The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products was recorded. The records were randomly 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 the stability chambers as specified in the official product information provided by the sponsor. The conditions were monitored through digital monitoring systems for temperature and humidity control.

Randomization was performed in accordance with the SOP for Randomization generation for bioavailability/bioequivalence studies. Records were maintained, including the randomization list and seed. The randomization list was accessible to the statistician, a dispensing pharmacist, and the QA responsible staff.

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 to avoid the risk of any potential mix-ups until the dispensing stage.

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 from the QA department 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 in accordance with 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, returned, or destroyed and records of verification by a second person of each step.

Dosing was carried out in accordance with SOP for Administration/Dosing of oral investigational Products. The dosing administration was reviewed during the inspection since dosing was scheduled.

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

The documentation related to study in the scope of inspection was thoroughly reviewed to verify the applicable processes for handling investigational products.

13. Case report forms

Randomly selected CRFs were reviewed. The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about COVID test (if applicable), urine alcohol & drug test, clinical examination, inclusion & exclusion criteria, check-in details, meal record, vital signs, pre-dose restriction compliance, drug administration, post-dose restriction compliance, blood sample collection, details of medical event, subject withdrawal, check out details, was recorded in the CRFs for all study periods.

Separate forms were available for recording AE, SAE, and medical events, where the consumption of concomitants was recorded if applicable.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in SOP for Recruitment of volunteers and included a description of the potential methods the CRO used for this purpose. A database was maintained on volunteers 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 right and left thumb fingerprints ensured the identification of volunteers and subjects. The biometric system associated with the volunteer databases was periodically validated.

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 subjects had participated in a previous trial in any CRO registered in the system. Participation data was uploaded to this central repository to prevent over-volunteering. Access to the database was also password controlled.

For drug and alcohol tests, the CRO used the Assuro Tech kit to test the urine samples for six different drugs and alcohol. The respective CoAs were available.

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 and according to the agreement with the catering service.

Timing, duration, and amount of food and fluids consumed were recorded. A dietitian with appropriate qualifications, training, and experience designed standardized meals. Her CV was available and reviewed.

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, in addition to a separate specific form kept with the rest of the study data.

Bioanalytical section

The inspection focused on randomly selected studies, including the associated validation projects. More specifically:

- verification of source documentation and raw data for validation of the bioanalytical methods.
- analysis of subject plasma samples as well as a review of the electronic data.
- review of audit trails and handling electronic data capture related to the BE studies.
- review of results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs, along with the chromatograms generated from the analytical runs.
- verification of analyte stock solutions, calibration standards, QCs, internal standards, and reagents preparation.

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any 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. 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 adequately described and documented, and the usage of IS was justified based on the relevant literature. A copy of the literature was available. After method development, an analytical plan was provided for the method validation. A stable isotope-labeled internal standard was used in the MS methods, and K₂EDTA was applied as an anticoagulant in both studies.

During the method validation as per the applicable SOP, a run was performed to determine the batch with adequate samples of QCs and CCs (so-called Analytical run batch determination) 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 storage period was available before the start of the studies.

The review of the entire method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, whole blood stability, stock solution stability, and reference standard storage stability), hemolytic effect, 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 vendor, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed, and discussed.

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

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

An audit trail generated by the chromatography data management software was reviewed when conducting the studies in the inspection scope.

An observation related to the Method validation was sufficiently handled in the CRO's CAPA plan.

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 took place in accordance with SOP for Insertion/Removal of the venous cannula and collection of blood samples.

Actual sampling times and deviations (as applicable) 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. At the time of inspection, the available secondary aliquots of project were verified.

According to SOP for Discarding of samples, the study samples, QC samples, and pooled matrix were discarded.

19. Data processing and documentation

Integration settings were science-based, justified and consistently applied. 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 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.

20. Good laboratory practices

The facility tours were performed on Day 3 and 4 to verify the facility's suitability for 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 notifications to the custodians responsible for the maintenance of the facility. In addition, the alarms were forwarded to the security station. The automatic alarm system was tested during inspection to verify its proper functionality. Alarms triggered by the monitoring system were captured in the electronic source data and evaluated in logbooks on paper.

For the purposes of qualification verification, the temperature mapping documentation of randomly selected Deep Freezers was reviewed to verify the hotspot and the location of the respective sensor. The temperature mapping process needed to be adequately carried out. Procedures for the maintenance and repair of refrigerators and freezers were available.

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 used in study-related activities. Equipment and its components were labelled with the respective ID number, calibration date, and next calibration date. The equipment usage was adequately documented in the analytical sheets and the respective logbooks for instrument use. The use 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.

Observations related to the Good Laboratory Practices were adequately addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The statistical model underlying the primary BE analysis was stated in the protocol and/or a statistical analysis plan, together with factors which were fixed and factors which were at random in the statistical model.

The statistician's qualification was verified through his CV.

The means of performing pharmacokinetic and statistical calculations (both software and scripts) were specified in the study protocol and the SOP for Preparation of WinNonlin Raw Data Sheet and Pharmacokinetic Analysis for BA/BE Studies. Data analysis conformed with these requirements.

All pharmacokinetic and statistical calculations were made using Phoenix WinNonlin software and SAS application. A second qualified person double-checked data values input in accordance with the respective SOP.

All data was quality controlled by QA-department and receipt of data about timepoint deviations from the respective team was recorded in logbook for Inwards & outwards documentation.

An observation related to the data integrity of statistical calculations was adequately addressed in the respective CAPA plan.

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. Monitoring and audit reports were available before the release of the final study report.

Miscellaneous	
<i>Samples taken</i>	Not applicable
<i>Assessment of the CRO master file</i>	The CRO master (CROMF) file was reviewed.
<i>Annexes attached</i>	Not applicable

Part 3	Inspection conclusion
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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 **Cohance Lifesciences Limited, Clinical Research & Biosciences Division**, located at **Plot No. 26 & 27, TIE, Balanagar, Hyderabad - 500037, Telangana, 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
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- 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>
- 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>
- 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-\(revised-august-2009\)](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://efaidnbnmnibpcjpcglclefindmkaj/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>