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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Aizant Drug Research Solutions Pvt Ltd Clinical Development Division Survey No 172/173, Apparel Park Road Dulapally Village, Dundigal-Gandimaisamma Mandal Medchal-Malkhajgiri District Hyderabad – 500 100, Telangana India
Name and Address of Bioanalytical Research Site	Aizant Drug Research Solutions Pvt Ltd Clinical Development Division Survey No 172/173, Apparel Park Road Dulapally Village, Dundigal-Gandimaisamma Mandal Medchal-Malkhajgiri District Hyderabad – 500 100, Telangana India
Name and address Statistical Site	Aizant Drug Research Solutions Pvt Ltd Clinical Development Division Survey No 172/173, Apparel Park Road Dulapally Village, Dundigal-Gandimaisamma Mandal Medchal-Malkhajgiri District Hyderabad – 500 100, Telangana India
Corporate address of Organization	Same as above Phone No.: + 91 40 2379 2190/91/92 Fax No.: + 91 40 2379 2223 D-U-N-S Number 650372951 FEI Number 3008243902
GPS coordinates	CP-I: Latitude: 17.551778° Longitude: 78.460985°

WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA796** Bioequivalence study of Emtricitabine/Tenofovir Alafenamide tablets 200mg/25mg **WHO application no. HA804** Bioequivalence study of Emtricitabine, Tenofovir Disoproxil Fumarate, Levonorgestrel and Ethinyl Estradiol Tablets 200 mg/ 300 mg/0.15 mg/0.03 mg **WHO application no. TB416** Bioequivalence study of Cycloserine Capsules USP/Intl.Ph 250 mg **WHO application no. TB417** Bioequivalence study of Linezolid Dispersible tablets 150 mg (4 × 150 mg tablets) **WHO application no. TB408** Bioequivalence study of Bedaquiline Tablets 100 mg
Inspection details	
Dates of inspection	16-20 June 2025
Type of inspection	Routine
Introduction	
Summary of the activities	The facility provided services in bioavailability, bioequivalence, bioanalysis, pharmacokinetics, biostatistics, and clinical diagnostics. BA/BE studies are conducted on various dosage forms, including tablets, capsules, extended-release preparations, powders for oral suspension, suspensions, and IV injections. These studies are conducted for pharmaceutical companies, both in India and abroad, using various biological matrices, including plasma, serum, and whole blood.
General information about the company and site	Aizant was established in 2006. The main facility was spread over approximately 4 acres, with a built-up area of about 40,000 sq. ft. dedicated to clinical development division activities. As part of its business expansion, another clinical facility—the Clinical Pharmacology Unit-II (CPU-II)—was established in 2017 at St. Theresa's Hospital, 2nd Floor, Premises. However, the facility was closed by the end of June 2022 due to administrative reasons. This facility was not used for any of the studies within the scope of the inspection.

	Following this, the CPU-II unit was relocated to the first and second floors of Maitrivihar Commercial Complex. This site had also not been used for any of the studies within the scope of the inspection.
History	The CRO had previously been inspected by WHO in October 2011, March 2015, July 2017, and March 2022, as well as by various national regulatory authorities. A list of these inspections was provided.
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 a 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 outlining the organization's activities in detail, including a layout of the premises.

The CRO was approved and the renewal process was underway, and the laboratory had been inspected by the CDSCO on 17 March 2025.

The CRO maintained an organizational chart that depicted key positions and the names of the responsible persons. The organizational chart was dated 10 June 2025, approved, and kept up to date. A list of key personnel, including their qualifications, experience, and responsibilities, was provided in Annexure 4 of the CROMF. The Chairman and Managing Director (CMD) served as the head of the organization, with each department head within the clinical development division ultimately reporting to the CMD. Other departments—such as Human Resources, Business Development, Finance/Accounts, Purchasing, Information Technology, and Engineering—supported the clinical development division in fulfilling its operational requirements.

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 Exclusive Services Agreement between the CRO and the sponsor was amended on 27 October 2022. The main agreement included provisions regarding the retention of records and biological samples.

The management ensured that appropriate and technically valid SOPs were implemented and followed. The maintenance of a historical file for all SOPs was adequately organized. The SOPs had been uploaded to an e-portal made available to the inspection team during the inspection.

2. Computer systems

A list of software and computer systems used for the study-related activities was provided. The CRO maintained a documented record of the computerized systems used for study activities. This record included details such as the department, computer ID, instrument ID, operating system, software version, and any remarks, when applicable. Systems were utilized across various departments, including Bioanalytical, Clinical Pharmacology, and Diagnostics, and it was maintained in accordance with the organization's SOP to ensure traceability and compliance in the use of computerized systems in clinical research activities.

Procedures for computer system validation, as outlined in the respective SOP, had been 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.

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

The software programs used to perform key steps were suitable and had been validated for their intended use. A certification had been issued under the supervision of the Quality Assurance unit. Selected systems were reviewed for verification.

The performance qualification took into account specific user requirements, applicable regulatory and guideline requirements for BE studies, as well as the operating environment, including system compatibility, update requirements, user skill level, business continuity, and upgrade needs. The usage of each system within the context of the studies was also considered. SOPs governing the use of each software program employed in conducting the BE study activities were available. It was ensured that access rights assigned to site personnel were consistent with documented delegations and aligned with their respective responsibilities.

Regular updates to key software programs were implemented as required, following a risk assessment to evaluate the potential impact on existing data and the qualification or validation status. These activities were conducted in accordance with SOP for Verification of Computerized Systems, effective from 13 June 2025. The IT Department was responsible for managing the periodic review of computerized systems, which was scheduled to occur annually, with a permissible variation of ±1 month, in line with

Attachment 5, "Schedule for Periodic Review of Computerized Systems". In the event that discrepancies were identified during the review, a CAPA was required to be initiated.

Department-specific schedules had been established, and a periodic review checklist for computerized systems was completed for each system to confirm compliance with the defined requirements. The completed checklist for a computer and the respective instruments, dated 16 September 2024, was available and reviewed.

SOP for Backup and Restore Management defined the procedures for backing up and restoring electronic data at Aizant. It covered both automatic and manual backups, backup schedules, retention policies, and data restoration processes. Responsibilities were assigned to the IT Department, user departments, and QA, including provisions for periodic verification and disaster recovery protocols. The SOP also included forms and templates to ensure consistent implementation.

A detailed flowchart was included in the applicable SOP, during the inspection, in accordance with respective change control request, to illustrate the network architecture, including the complete client/server structure and all relevant interfaces. The diagram depicted the layout of the network, covering both local and wide area networks, and indicated key security features such as firewalls.

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

3. Quality management

This section had been previously inspected adequately. Therefore, during the current inspection, the focus was placed on the critical and ongoing processes and elements of the QMS. The CRO uploaded the SOPs and all requested documentation to an e-portal for the inspection team's perusal.

The Internal Audit Plan for 2024 was reviewed. Audits were conducted biannually and covered the following departments: Bioanalytical, Clinical Pharmacology, Diagnostics, Pharmacokinetics and Biostatistics, Human Resources and Administration, Purchase, Information Technology, Project Management, Archives, and Quality Assurance. The status of all 2024 CAPAs was verified. Vendors were audited every two years, and the Vendor Audit Plan for 2024 was also discussed.

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

site used electronic document management, electronic training management application, and electronic QMS applications.

A Quality Manual, effective 11 December 2022, was provided. Both in-process and retrospective QA verifications were performed, including verifications during bioanalysis while samples and standards were being prepared and tested. The quality management system incorporated root cause analysis, assurance of data integrity, and the implementation of appropriate CAPA.

The company had defined, in the applicable SOPs—such as SOP for Daily Monitoring of Audit Trails for Mass Spectrometers and the respective software system SOPs—the audit trail queries or reports to be used for different systems and purposes, supported by system-specific checklists. A logbook was maintained for documenting the audit trail review of ongoing projects. SOP for the LIS software system was also reviewed to confirm the practice of audit trail review.

The process for the issuance of controlled templates was amended and defined in SOP for the electronic document management system. This procedure outlined the management of documents from creation to retirement within the system. All forms issued by the QA Document Controller, whether through the application or manually, were required to be printed on light green-colored paper to facilitate easy identification and differentiation from other documents. Reference copies, including forms and documents, were issued on white-colored paper. For pages issued via the system, each page was required to indicate that it was QA-issued and to bear the “ISSUED BY QA” flat stamp. Manual distribution remained applicable in specified cases, as defined in the procedure.

4. Archive facilities

The facility located on the G-floor had been adequately inspected during the previous inspection.

The CRO maintained a secure archive for trial-related documents, equipped with fireproof measures, humidity control, and pest control. Access to the archive storage areas was controlled and restricted to authorized personnel, with a list of authorized individuals displayed at the facility entrance.

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

5. Premises

During the inspection, a brief tour of the facility was conducted on Day 4, as the facility had been sufficiently covered during the previous inspection.

The facilities were generally well maintained, with adequate cleanliness, lighting, ventilation, and environmental control. Floors, walls, and workbench surfaces were designed to be easily cleanable and decontaminated.

Entry to the facility was restricted and controlled through keycard access. Alarm systems were installed to detect unauthorized exit of subjects from the clinical facilities, and/or the doors were locked. Emergency evacuation measures were in place. All entries to and exits from the facility were recorded. The emergency exit at the CPU was secured, with the key kept in a designated and secured location next to the emergency exit door.

Sites where clinical activities took place included a pharmacy for the storage of investigational products under appropriate conditions. Entry and exit to the pharmacy were restricted through access control, and proper records of each visit were maintained.

Temperature and humidity of the facilities were monitored using a digital monitoring system and/or Hygrothermometers, depending on the criticality and requirements of the facility. Alarm logs from facilities monitored by the digital thermometer were randomly selected and reviewed during the inspection. The CRO followed a practice of weekly monitoring of alarm logs based on a predefined plan, in accordance with the applicable SOP. Each review was assessed with corresponding remarks, indicating that any excursions were evaluated where applicable. Hygrothermometers were used in areas considered less vulnerable to temperature excursions. Additionally, temperature logs were printed daily, reviewed, and stored as part of the study documentation.

Safety Data Sheets were available to staff prior to the commencement of testing. Laboratory personnel were familiar with and knowledgeable about the Material Safety Data Sheets relevant to the chemicals and solvents in use. Staff had been trained in the use of firefighting equipment, including fire extinguishers. First-aid materials were provided, and staff were instructed in first-aid techniques and emergency care procedures. Containers holding volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were appropriately sealed to prevent exposure and contamination.

Observations related to the Premises were addressed in the respective CAPA plan.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and respond effectively to foreseeable emergencies.

At all stages of the trial, including night hours, qualified and trained personnel were present to ensure the rights, safety, and well-being of subjects and to provide emergency care as needed. Contract workers were engaged to perform specific activities that complemented the capabilities of the core team.

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

Personnel participated in the training program in accordance with SOP for Training of Personnel and SOP for Training Management System.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted on the premises of the CRO, CPU-I. The facility comprised a total of 80 beds, divided between two clinics—Clinic-1 and Clinic-2—each equipped with 40 beds and an additional 2-bed ICU.

Topics that had been satisfactorily covered during the previous inspection were not the focus of the current inspection, if no changes were applied.

In case of emergency, a hospital was designated and contracted to receive and treat study participants. A valid agreement was in place, effective from April 2017, with the latest amendment covering the period from April 2022 to April 2027. Mock emergency runs were conducted annually, and quarterly emergency training was provided to the relevant personnel. Training records dated 15 June 2025 and the last emergency mock run conducted in February 2025 were reviewed. The mock run included scenarios from the restroom to the patient ward, the patient ward to the ICU, the ICU to the ambulance (via both lift and ramp), and transfer to the referral hospital's ICU. All steps were executed successfully in accordance with the procedures outlined in the appliable guidelines.

Access to the randomization list was restricted to the pharmacist in charge of the study and QA. The documents were either password-protected if maintained electronically or securely stored under lock and key if in hard copy. Requests for the randomization list were documented. The distribution of the printed randomization list was recorded in the

Document Distribution Record. Afterward, the documents were sealed in envelopes and custodied by QA and the pharmacist.

The Master Calibration Plan for 2024 was reviewed. Equipment used in study-related activities was appropriately calibrated at predefined intervals. The functionality and performance of emergency-use equipment, such as defibrillators, were verified at suitable intervals.

8. Clinical laboratory

A clinical laboratory was located and accredited at the CP-I facility for the analysis of samples. Haematological and clinical chemistry tests, urine analysis, and other protocol-specified tests were performed during the clinical trial. In addition to its in-house laboratory, the CRO had used an external laboratory for certain studies within the scope of the inspection, as specified in the respective protocols. Laboratory normal ranges and accreditation certificates were available and reviewed.

The pathology laboratory ensured full traceability and sample integrity through proper labeling, receipt, storage, and chain of custody procedures—from sample collection to reception at the external laboratory. Samples were shipped along with cool pads to maintain appropriate conditions. Although continuous temperature monitoring during shipment was not in place, temperature and time were verified and documented both prior to shipment and upon receipt in the applicable test requisition forms.

It was noted that the labeling of samples collected for safety assessment purposes during the screening and post-study phases was performed manually. Each sample was identified by handwriting the relevant details, rather than using pre-printed barcodes or automated labeling systems. The corresponding information—including subject ID, sample type, collection date and time, and other relevant identifiers—was documented on a standardized sample collection and transfer template (Requisition Form). This form accompanied the samples and served as the primary record for ensuring proper identification and traceability. Upon completion, the requisition form and associated samples were distributed to the appropriate department within the pathology laboratory for further processing.

Although the respective CVs for the Laboratory Director were not filed in the ISF, vendor qualification and requalification documentation for the external laboratory were reviewed, dated November 2023 and April 2025, respectively. The qualification process included audits conducted by Aizant personnel as part of the vendor evaluation.

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

Data integrity requirements for all study-related tests were ensured through the use of adequately validated systems for sample analysis. Specifically, the Haematology Analyzer and its interface with the LIS were reviewed and discussed with regard to data modification, reference range updates, and corresponding entries in the software audit trail. The calibration certificate for the equipment was verified and found to be valid until 10 January 2026. It was confirmed that the incorporated software application of the Haematology Analyzer did not allow data editing.

9. Ethics

Trials were approved by the Independent Ethics Committee prior to initiation. The Committee's independence from the sponsor, investigator, and CRO was verified through the review of the member list. Detailed minutes of the meetings documented the discussions, recommendations, and decisions of the IEC. The IEC was provided with sufficient time to review study protocols, informed consent forms, and related documentation.

Informed consent form

Information for study participants was provided in vernacular languages (Telugu, Hindi, and Tamil) and communicated at a level of complexity appropriate to their understanding, both orally and in writing.

Informed consent was obtained from each subject and documented in writing prior to the initiation of any trial-related activities. Additionally, the informed consent process was recorded on video, with the recordings maintained for a period of one year. The information provided to subjects was clear, emphasizing that participation was voluntary and that subjects had the right to withdraw from the study at any time, on their own initiative and without providing a reason. Reasons for withdrawal, when available, were documented in the study records.

Information regarding insurance coverage and procedures for compensation or treatment in the event a subject was injured or disabled during trial participation was available through the applicable insurance policy. The policy covered the period from 4 June 2023 to 3 June 2024.

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.

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

10. Monitoring

The studies were monitored by personnel employed by the CRO/sponsor.

For study related to the WHO application HA804, a pre-study visit was conducted on 1 April 2024, followed by interim monitoring visits on 2 April 2024, 5 April 2024, and 20 April 2024, and a closeout visit on 7 August 2024. The monitor prepared a written report after each site visit and communicated any issues to the CRO and the sponsor, including during the conduct of the study, to facilitate timely corrective actions. The respective communications and corrective actions were documented and available.

11. Investigators

The Principal Investigator was responsible for the clinical conduct of the study, including the clinical aspects of study design, administration of the investigational products, liaison with local authorities and the ethics committee, and the signing of both the protocol and the final study report.

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

Information concerning the receipt, storage, handling, and accountability of investigational products at each stage of the trial was properly recorded. Documentation related to the shipment, delivery, receipt, description, storage (including conditions), dispensing, administration, reconciliation, return, and/or destruction of remaining pharmaceutical products was verified. Details of the pharmaceutical products used—such as dosage form and strength, lot number, and expiry date—were also documented. Temperature excursions were noted during the transit of the test product, when applicable. Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through the digital temperature monitoring system.

Randomization was performed in accordance with the applicable SOP, and all relevant records, including the randomization list and randomization seed, were maintained. Access to the randomization list was restricted to the statistician who generated it, the dispensing pharmacist, and QA.

The investigational products were properly labelled, and label samples were verified. Compliance of all labels with the randomization list was confirmed upon printing and prior to labelling of the containers. Labels were affixed directly onto the containers in a manner that ensured the information remained intact even after the lid was removed.

Through a random selection of IMPs, the processes related to drug accountability and the storage of IMPs in the pharmacy were verified.

Investigational product accountability and dispensing records were maintained. Each activity was documented in real time, including records of doses administered, returned, or destroyed, along with verification of each step by a second person.

Dosing was conducted in accordance with SOP for the oral administration of solid dosage forms, under the supervision of the investigator and a qualified staff member explicitly delegated for this task in writing. The label was verified prior to dosing, and the exact time of administration was documented on the designated page of the CRF. For solid oral dosage forms, a mouth check was performed using a tongue depressor or spatula and a penlight to inspect under the tongue, lips, corners of the mouth, and between gums and cheeks to confirm that the subject had swallowed the investigational product. The dosing solution and quantity administered were also recorded. Dosing was directly documented in the CRFs.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for possible confirmatory testing for at least one year after the expiry date of the most recently received batch. Sample retention procedures were defined in the respective SOP and specified in the contract between the sponsor and the CRO. Dispensed but non-administered products were also retained.

For study related to the WHO application no. HA804, remaining tablets from period R1 were verified against the accountability records.

13. Case report forms + reconciliation forms

The identification of source data was defined in the study protocol.

For study related to WHO application no. HA804, spot-checks were conducted on randomly selected CRFs.

The data to be collected for each volunteer were specified in the trial protocol. Copies of urine pregnancy tests, clinical laboratory reports, X-ray reports, and all ECGs were

included in the CRFs for each subject. The CRFs also documented information on informed consent documentation obtention, compliance with inclusion and exclusion criteria, adherence to protocol-defined restrictions, adverse events, alcohol and drug screening results, medical examinations, meal and fluid intake details, vital signs, modified patient health questionnaire, and dosing details, including investigational product labels.

Discontinuations and withdrawals from studies within the scope of the inspection were also randomly checked.

14. Volunteers, recruitment methods

Screening procedures were conducted in accordance with the respective SOP, which covered the informed consent process and participant interview procedures.

Procedures for recruiting and registering volunteers were defined in an SOP and included a description of the methods employed by the CRO for this purpose. A volunteer management system database was maintained to prevent cross-participation and to enforce the minimum required interval between a volunteer's participation in successive studies. Access to the database was password-controlled to ensure the confidentiality of volunteer and subject information.

Identification of volunteers and subjects required verification of valid proof of identity and address. Proper identification was further ensured through a biometric system using fingerprint recognition, as defined in the SOP. The validation of the biometric feature of the system was completed in May 2023. The system was used from the date of upgradation until September 2024 for electronically recording screening visit information, including demographics, compliance with restrictions, vital signs, personal and past history, physical examination, and clinical assessment. As per the applicable Change Control notification, from September 2024 until the full implementation of the software enhancements, the CRO discontinued generating screening records within the system. Instead, templates were printed via the system's respective module, and documentation of screening records was completed on paper.

An audit trail review of the system during screening activities was conducted, and no concerns were identified. The implementation of the volunteer system's enhancements had not been finalized at the time of the inspection.

Informed consent was obtained from potential subjects prior to conducting any screening procedures required to determine eligibility for the study, in addition to the informed consent for participation in the clinical trial. The clinical trial protocol detailed the subject

selection criteria, including inclusion and exclusion criteria, as well as the screening procedures.

A software system was utilized to verify whether any subject had previously participated in a clinical trial. Participation data were uploaded to a central repository to prevent over-volunteering. Access to the database was controlled to ensure confidentiality.

The volunteer management system also functioned as a repository for X-ray reports and ECGs, and was used to document participant enrolment, assignment of participant numbers, replacement by standby volunteers, early release of volunteers before dosing, dosing assignment, and sample collection plan assignment.

15. Food and fluids

Meals were standardized, adequately controlled, and scheduled during the study days. Standardized meals, snacks, and drinks for study subjects were prepared within the CRO facilities, as specified in the clinical trial protocol. Records related to meal orders, accountability, compliance, and verification for Periods I and II were reviewed.

The timing, duration, and quantity of food and fluid intake were recorded. Prior to sample collection from ambulatory subjects, they were questioned regarding their recent food and drink consumption. A qualified and appropriately trained dietitian was responsible for designing the standardized meals.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, conducted, and monitored to ensure that the safety profile remained acceptable, including for the volunteers. A medical doctor was responsible for making medical decisions in the event of adverse events and for notifying the relevant health authorities, the sponsor, and, where applicable, the ethics committee, particularly 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. It was recommended that all emergency equipment remain readily accessible and that any obstacles to its use be removed. Any treatment administered to a subject was documented in the CRF and supported by corresponding records maintained in the ICU.

The CRO maintained adverse event registration and reporting forms as part of the CRF. For study related to the WHO application HA804, adverse event reporting forms, event descriptions, and follow-up forms were reviewed and verified.

Bioanalytical section

For the inspection of the bioanalytical portion, focus was placed on studies related to applications WHO application no. TB417 and WHO application no. TB408, including the associated validation projects. More specifically, the following records and activities were reviewed and investigated:

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

Furthermore, chromatograms and their integration were reviewed, including the absence of signals in blank samples and any unexplained interruptions in the injected sequences. The reasons for the study sample repeat analyses and all instrument failures were examined. The provisions and documentation of the incurred sample reanalysis were confirmed. Justification and documentation for the reinjection of analytical runs were verified and assessed against established provisions—for example, ISR02 for the Linezolid study, where the last few samples were reinjected due to HPLC leakage and poor chromatography for a QC sample.

For the review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The complete study data processed using the Analyst software application were uploaded into the available system for review and investigation.

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

The method development process was described and documented in accordance with SOP for Bioanalytical Method Development, Pre-Method Validation, and Method SOP Preparation. The use of internal standards was justified based on relevant literature, and a copy of the referenced literature was available. Following method development—such as Linezolid study dated 27 October 2022—a pre-method validation was conducted. Subsequently, a method SOP was prepared to serve as the basis for method validation. A stable isotope-labelled internal standard, such as Linezolid D8, was consistently used in MS methods, and K_2EDTA was applied as an anticoagulant.

During method validation, in accordance with the applicable SOP, a run was conducted to determine the appropriate batch size using an adequate number of QCs and CCs. This run, called "Size Determination run," was designed to reflect the length and structure of the analytical runs expected to be used during the analysis of study samples.

An investigation of events could be conducted in cases defined and required completion of a checklist for investigation of events, in accordance with the respective SOP. This process was verified through the review of the investigation report related to the specific analytical run.

Data supporting the stability of the samples under the specified storage conditions and duration were available prior to the initiation of the studies, in accordance with SOP for Bioanalytical Method Validation (Stabilities).

The review of the complete method validation included assessments of precision and accuracy (P&A), sensitivity, selectivity, matrix effect (including haemolytic and lipemic effects), calibration curve performance, autosampler carry-over, dilution integrity, various stability parameters (e.g., freeze-thaw stability, stock solution stability), recovery, and reinjection reproducibility. Partial validation was conducted as per applicable requirements.

The matrix used for analytical method validation matched the matrix of the study samples, including the use of anticoagulants (K_2EDTA in calibration curve samples and K_3EDTA in QCs for Linezolid). The interference of the anticoagulants was tested during the method validation. Documentation related to the purchase of plasma from the provider—including receipt, storage, retrieval, preparation, and consumption of pooled plasma—was reviewed along with the respective logbooks.

The CRO implemented a new practice following the Linezolid study (May 2024) to conduct onsite audits of plasma suppliers. As a result, blood plasma is currently procured from a new supplier. Proof of the onsite audit, dated 26 July 2024, was presented and reviewed during the inspection. This new practice, however, did not apply to the studies in the scope of this inspection.

Additionally, it was noted that blank matrices supplied by the vendor were to be used for method development, method validation, and sample analysis for a period of three years when stored below –15°C, in accordance with SOP for Receipt, Identification, Labeling, Storage, Handling, Usage, and Disposal of Biological Matrices.

Pooled plasma preparation records were reviewed, along with the screening results of plasma lots to confirm that they met the required interference criteria.

Each analytical run included calibration curve standards, QC samples interspersed throughout the run, and subject samples, all of which were processed simultaneously. The exact sequence of processing was predefined and documented. All samples collected from a given subject across all trial periods were analyzed within the same run.

Acceptance criteria for analytical runs were confirmed through the review of analyte retention times, calibration standard, and QC sample accuracy, peak integration, and internal standard peak areas, in accordance with applicable SOPs, including SOP for Analysis, Repeat Analysis, Batch Acceptance, and Data Transfer of Study Samples. A daily system suitability and stabilization test was performed prior to the injection of any experiment, in accordance with the respective SOP.

For Incurred Sample Reanalysis, samples were selected at concentrations around Cmax and during the elimination phase. The procedure and acceptance criteria were defined in the applicable SOP. Randomly selected ISR samples and any associated repetitions were identified, reviewed, and discussed, along with supporting evidence of any related instrument errors.

The system audit trail review was conducted at the time of the studies within the scope of the inspection. Adequate training was provided to the responsible personnel in accordance with applicable SOPs and relevant learning materials. Training activities were documented in a training logbook. Notably, a training session titled Audit Trail from an FDA Investigation's Perspective, dated 5 September 2024, was conducted and recorded.

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

The specifications of the samples (blood plasma), including the sampling method, volume, and number of samples, were defined in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport, shipping, and storage of samples were carried out in accordance with SOP for Study Sample Management.

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, ensuring accurate identification and full traceability of each sample. Storage conditions, including freezer temperatures, were controlled, continuously monitored, and recorded throughout the storage period and during

transportation. Records of sample storage and retrieval were maintained. Samples were aliquoted, with duplicates shipped and stored separately to safeguard sample integrity.

The usage and potential disposal of study samples, QC samples, and pooled matrices were conducted according to SOP for Study Sample Management.

19. Data processing and documentation

Integration settings were science-based and fully justifiable. The smoothing factor was maintained at a sufficiently low level to avoid masking potential interferences or alterations in peak geometry.

The criteria for accepting and excluding CC standards and QC samples, as well as overall batch acceptance, were clearly defined in the applicable SOP. Source data for all analytical runs included complete information from the original evaluation of the runs—containing all calibration samples—even when analyses were repeated. The calibration range was appropriately truncated. Variations in internal standards were trended and used as part of the result validity verification process.

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

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented in a manner that ensured traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). 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 the sample number, time of sample collection, time of centrifugation, time the sample was placed in the freezer, and time of sample analysis, allowing for the determination of whether any aberrant results might have been caused by sample mishandling.

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to prevent errors. The data entry process was defined in the SOP for Management of Clinical Study Report.

20. Good laboratory practices

Tours of the facility were conducted on Days 2 and 4 to verify its suitability in terms of layout and safety, with particular focus on the established areas that had not been covered during the previous inspection.

The general principles of Good Laboratory Practice were followed during the bioanalytical phase of the BE studies, supported by an established and appropriate QA system.

Deep freezers used for sample storage and refrigerators used for storing reference standards were qualified, calibrated, and properly maintained. An alarm system integrated with digital thermometers was in place to notify designated custodians in case of temperature excursions. Daily monitoring activities and all alarm checks were documented accordingly.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs, and records were maintained in accordance with applicable requirements. These activities were verified through a random review of equipment used in study-related activities. All equipment and components were labelled with their respective ID numbers, calibration dates, and next calibration due dates. Equipment usage was properly documented in the analytical sheets and corresponding instrument usage logbooks.

Columns were stored under the supervision of the designated custodian in the Deep Freezer room, secured in a locked drawer, and labelled with the brand and capacity. Usage details, number of injections, and post-project washing activities were documented using controlled templates and logbooks.

Reference standards were stored in two separate refrigerators within the DF room—one designated for expired RS and the other for non-expired RS. Records of RS consumption were maintained on a controlled template. A random verification was performed to confirm the documented usage of Bedaquiline and Bedaquiline D6 for the preparation of QC and CC samples, as well as analyte stock solutions to be used for system suitability and stabilization.

The business continuity plan test exercise conducted in May 2025 was reviewed, along with the records of cybersecurity training provided in June 2025.

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

21. Pharmacokinetic, statistical calculations

On Day 5 of the inspection, the Head of Biostatistics delivered a structured presentation outlining the laboratory's biostatistical activities. The session included an overview of the applied methodologies and the relevant SOPs governing statistical evaluations and data handling practices:

- Randomization Schedule Generation and Distribution Process

The process for generating and distributing the randomization schedule was governed by internal procedures to ensure controlled, traceable, and compliant management throughout clinical trial execution. The sequence of activities is outlined below:

- ✓ Request Initiation

The randomization schedule request was initiated by the Pharmacist, who prepared the formal request. This request was reviewed by Quality Assurance for completeness and compliance, and then submitted to the designated Statistician for further action.

- ✓ Randomization Schedule Creation

Upon receipt of the request, the Statistician generated the randomization schedule using SAS software, following the procedure defined in SOP for Generation of Randomization Schedule for Clinical Studies. The generated programs and associated files were stored in a secure, access-controlled server folder, accessible only to the Pharmacokinetics (PK) and Statistics departments.

- ✓ Schedule Sealing

The randomization schedule was printed within the PK department, signed by authorized personnel, and sealed. It was then formally handed over to QA in a sealed envelope to ensure confidentiality and integrity.

- ✓ Distribution and Access Control

QA verified the randomization schedule and stamped it as "Verified by QA." Reference copies were distributed to the Pharmacist and Clinical QA, and the distribution was documented. Master and reference copies were securely stored under lock and key, with access limited to authorized personnel.

- Pharmacokinetic and Statistical Analysis Process

Concentration data and clinical updates were securely shared and compiled into individual tables. QA reviewed and approved the data, authorizing analysis. The Statistician conducted pharmacokinetic and statistical analyses per SOPs using validated software. Results were compiled into Tables, Listings, and Figures, which were then incorporated into the Clinical Study Report by the medical writer and returned for review by the PK/Stats team.

SOP for Database Lock and Unlock was available and provided a detailed description of the process. It ensured completion of data entry, query resolution, coding, and reconciliation prior to database lock. Authorization from relevant stakeholders and a final backup were required. Unlocking was permitted only for justified critical corrections, with re-locking steps repeated. Strict access controls and documentation were maintained throughout.

22. Study report

The study report was randomly compared with the raw data to verify that discrepancies between the results stated in the report and the actual original (raw) data did not occur.

Miscellaneous	
Assessment of the CRO master file	The CRO master (CROMF) file, effective as of November 29, 2024, was reviewed.

Part 3	**Conclusion – inspection**

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, ***Aizant Drug Research Solutions Pvt Ltd, Clinical Development Division***, located at ***Survey No 172/173, Apparel Park Road, Dulapally Village, Dundigal-Gandimaisamma Mandal, Medchal-Malkhajgiri District, Hyderabad – 500 100, Telangana; India*** was considered to be operating at an acceptable level of compliance with the applicable WHO Guidelines.

The deficiencies observed during the inspection that were listed in the full report were addressed by the CRO to a satisfactory level, before the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

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

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

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

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***

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

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

7. 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***

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

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

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

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

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

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

14. Guideline for Good Clinical Practice, E6 (R3), ICH Harmonised Guideline, Adopted 6 January 2025
    Short name: ICH GCP E6 (R3)

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

16. 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