World Health Organization

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WHO Prequalification Unit (PQT) – Inspection Services Team (INS)
WHO PUBLIC INSPECTION REPORT
WHOPIR
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	ADVITY Research Private Limited 3rd & 4th Floors, Archies Continental P. No. 2A, 3, S. No. 1094 & 1095 Adj: Kukatpally Metro station Kukatpally Hyderabad 500 072 Telangana, India
Name and Address of Bioanalytical Research Site	ADVITY Research Private Limited 3rd & 4th Floors, Archies Continental P. No. 2A, 3, S. No. 1094 & 1095 Adj: Kukatpally Metro station Kukatpally Hyderabad 500 072 Telangana, India
Name and address Statistical Site	ADVITY Research Private Limited 3rd & 4th Floors, Archies Continental P. No. 2A, 3, S. No. 1094 & 1095 Adj: Kukatpally Metro station Kukatpally Hyderabad 500 072 Telangana, India
Corporate address of Organization	ADVITY Research Private Limited Archies Continental Adj: Kukatpally Metro Station Kukatpally, Hyderabad - 500 072 Telangana, INDIA
WHO product number covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA800** bioequivalence study of Tenofovir Disoproxil Fumarate, Lamivudine & Dolutegravir Tablets 300mg/300mg/50mg

Inspection details	
Dates of inspection	From 7 to 11 April 2025
Type of inspection	Initial
Introduction	
Summary of the activities	ADVITY Research Private Limited, hereinafter referred to as ADVITY, is a Contract Research Organization providing clinical research services in the areas of Bioavailability/Bioequivalence studies, clinical trials, and pharmacovigilance. ADVITY offers its services to the pharmaceutical industry globally.
General information about the company and site	ADVITY Research Private Limited (ADVITY) is a Hyderabad-based organizatioin established in September 2021. The organization specializes in Bioavailability/Bioequivalence studies, clinical trials, and pharmacovigilance services, offering comprehensive support to the global pharmaceutical industry. ADVITY operates from state-of-the-art leased facilities, with dedicated infrastructure for BA/BE and PV activities. The company holds regulatory approvals from CDSCO and maintains certifications in line with national and international standards.
History	The US FDA and ANVISA have inspected the CRO. This was the first WHO PQ inspection.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed during the inspection: The company's background, conduct of clinical studies, informed consent procedures, ethics committee approvals, and related correspondence, test article accountability, dispensation and storage practices, as well as the processing and handling of biological (plasma) samples collected during the study. Additional focus was placed on equipment calibration, employee training, computerized systems, and a facility tour. With regard to analytical operations, the inspection covered the firm's practices, personnel qualifications, and procedures applied during method validations and analytical testing. A thorough review was conducted of the clinical study data, analytical method validation, and associated analytical study data, including a comparison of the source data with the final study reports.

	Additionally, the CRO arranged for the use of an electronic portal to facilitate the upload of requested documentation, including SOPs, during the inspection. This allowed for efficient and secure access to relevant documents by the inspection team.
Scope and limitations	
Out of scope	Not applicable

Abbreviations

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

The CRO maintained an organizational chart that depicted key positions along with the names of the responsible individuals. The organizational chart, updated in March 2025, was duly authorized and regularly maintained. The CRO was granted a Registration of Bioavailability or Bioequivalence Study Centre by CDSCO in May 2022, with a validity period of five years.

A Master Service Agreement (MSA) with the sponsor was available and reviewed. In addition, a project-specific contract was also presented. The MSA was executed on 17 May 2023. The agreement included provisions related to the retention of study records for a minimum of 15 years, and the retention of biological samples (specifically, the second lot of study samples from pivotal studies intended for regulatory submission, to be retained for a period of six months). Intellectual property rights were also addressed within the agreement.

Job descriptions were available for all employees, clearly outlining their respective responsibilities. A random verification confirmed that each job description was duly

signed and dated by the respective staff member. Study personnel had received protocol-specific training, with attendance documented. Individual training was also provided, tailored to each staff member's assigned role and level of involvement. GCP certificates for the Clinical Investigators were available and reviewed.

A list of signatures of authorized personnel involved in the conduct of the study was available and verified. The co-investigator was granted permission to delegate duties to other staff, as recorded on the form for Study Activities and Duty Delegation for the clinical portion, with reference to the respective SOP. However, the co-investigator's authority to delegate specific duties related to on-call responsibilities in the absence of the Principal Investigator was not clearly defined in the SOP or reflected in the delegation list. The SOP was therefore revised during the inspection to address this issue.

In general, the principles of Good Laboratory Practice defined the responsibilities of the test facility management. The CRO management acknowledged that since the investigator was an employee of the CRO, certain responsibilities typically assigned to the investigator would, by extension, reside with the CRO management.

The management ensured that appropriate and technically valid SOPs were implemented and adhered to. The maintenance of a historical file of all SOPs was adequately organized and documented.

Confidentiality agreements and code of conduct documents were available to ensure the protection of confidential data and to address potential conflicts of interest.

The standard working hours were from 09:00 to 18:00, with operations conducted in shifts. The second and fourth Saturdays of each month were considered holidays.

Observations related to Organization and management were adequately addressed in the respective CAPA plan.

2. Computer systems

The Validation Master Plan, Amendment No. 03, classified as a major amendment with a defined review period of three years, was established to ensure that computerized systems were suitable for their intended purpose. The plan outlined that such systems were to be validated, operated, and maintained in compliance with the applicable principles of GCP and GLP. Regular updates to key software programs, when required, could be performed in accordance with the Periodic Review Schedule of Validated Computerized Systems/Software, as outlined in the VMP. The VMP also described the management, monitoring, and control of the network. The physical location of the servers was identified.

An inventory of all computerized systems connected to the network was available, with clear identification of those subject to GxP regulations. Any changes to the network, including the temporary addition or removal of systems, were documented. A sufficient number of computers were available to enable personnel to perform data entry, data handling, required calculations, and report compilation. The computers were equipped with adequate capacity and memory for their intended use.

Access to software systems containing trial-related information was controlled in accordance with the SOP for User Account Creation for Computer Systems. Access rights were granted to new users based on requests initiated by the Human Resources department. In the event of employment termination, an Exit Form was issued to ensure proper deactivation of access. The method of access control was defined, and a list of authorized personnel with access to the database was maintained. Secure, unique, and individual-specific user identifiers and passwords were employed.

Software programs used to perform study-related activities were required to be suitable and validated for their intended use. Qualification and/or validation certificates and reports were available and had been provided under the supervision of the system users to ensure that the software was validated appropriately and developed in a controlled manner, in alignment with a Quality Assurance system. The qualification of the selected system was reviewed for verification.

During the inspection, it was explained that the Interactive Web Response System (IWRS) was not utilized for the bioequivalence study but was used exclusively for patient-based studies. The Data Management System was employed by QA and QC personnel for review purposes of chromatography data. A cross-participation database, shared with other CROs, primarily located in the southern region of India, was deployed.

SOPs governing the use of each software program employed in the conduct of the bioequivalence study were available. It was ensured that access rights granted to investigator site staff were aligned with their delegated responsibilities and respective tasks, when applicable.

Electronic data was backed up in accordance with SOP for Data Backup and Restoration, effective from 25 April 2024. Departmental drive data stored on the file server was backed up to both the main server and cloud storage, with a valid license. Backup procedures, firewall configurations, antivirus authentication protocols, security patching, system monitoring, and penetration testing were implemented in accordance with the applicable SOPs

A flowchart illustrating the network architecture, including the complete client/server structure and all relevant interfaces, was available for review. The flowchart incorporated the following key elements:

- A Network Overview, depicting the overall network layout, including local area networks (LANs) and wide area networks (WANs), where applicable.
- A Client/Server Architecture section, identifying client devices (e.g., workstations, terminals) and servers, along with their respective connections. Data flow between clients and servers was clearly illustrated.
- Security Elements, such as firewalls and access control points, were also indicated within the flowchart.

The reliability and completeness of backups were verified at six-month intervals. Evidence of this verification was available and reviewed.

3. Quality management

The CRO had established appropriate Quality Assurance and Quality Control systems, supported by written Standard Operating Procedures, to ensure that clinical trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, and applicable regulatory requirements. These procedures were in accordance with SOP for Document Control and Management, effective from 4 January 2025. SOPs were prepared and approved using an Adobe e-signature system, subsequently printed and distributed according to a predefined distribution list. Obsolete SOPs were formally withdrawn and archived in a designated folder.

Forms and templates were issued in accordance with SOP for Preparation of SOP, effective from 27 December 2024. The CRO distinguished between forms and templates. Forms were prepared in a controlled manner under the supervision of the QA department and were considered controlled documents. In contrast, templates were not classified as controlled documents and were made available to users in a dedicated folder to facilitate documentation of respective activities. A list of forms and templates used for various activities was available. Documents were labeled accordingly: 'FM' for forms and 'TP' for templates. Templates were primarily used for in-process and retrospective audits of studies and, as such, were not subject to document control procedures.

A Quality Manual (Version No. 01) was provided for review. The purpose of the Quality Manual was to define quality as the extent to which services meet customer needs and comply with applicable regulatory requirements. The manual outlined the scope and structure of the Quality Management System, aiming to ensure quality across work processes, data generation, and service delivery.

QA personnel were not directly involved in trial-related activities. In-process audits conducted by QA personnel did not substitute for the oversight responsibilities assigned to other designated individuals.

The QA unit was responsible for overseeing the study to ensure compliance with applicable quality standards and regulatory requirements. Responsibilities included verifying study-related activities, maintaining and updating the Quality Management System, ensuring that protocols and SOPs were available and adhered to, and confirming the reliability and traceability of study data. The QA unit conducted regular internal audits, monitored contract facilities for compliance with GCP and GLP, ensured that the trial report accurately reflected the conduct and outcomes of the study, and promptly reported audit findings to the relevant stakeholders.

Both in-process and retrospective QA verifications—such as those conducted during bioanalytical activities while samples and standards were being prepared and tested—were performed in accordance with SOP for Bioequivalence Study Audits, effective from 18 January 2022 and applicable at the time of the study. The QA unit maintained annual plans for internal audits, and the audit plans for the years 2024 and 2025 were available for review.

The company defined audit trail review procedures in SOP (Computerized System Audits), effective from 18 January 2025. The SOP specified the types of data subject to review. Audit trail reviews and their outcomes were documented in the respective logbook.

The observation related to Data integrity and QMS has been adequately addressed in the respective CAPA plan.

4. Archive facilities

The CRO maintained a secure storage facility for the archiving of trial-related documents. The archive was equipped with humidity control (monitored using a hygrothermometer). The pest control measures were also implemented. In general, the CRO implemented comprehensive security measures to ensure the safety and integrity of archived documentation.

Archiving activities were conducted in accordance with the applicable SOP. Access to the archive storage areas was controlled and restricted to authorized personnel, with a list of authorized individuals displayed at the facility entrance. Records of document access and return were maintained. The retention period for study documentation, including raw data, was defined in the SOP and also specified in the contractual agreement between the sponsor and the CRO.

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

The observation related to the Archive facility has been addressed in the respective CAPA plan.

5. Premises

During the inspection, a facility tour was conducted on Day 2, focusing on the clinical areas.

The facilities were maintained in a clean condition and were equipped with adequate lighting, ventilation, and environmental controls. Floors, walls, and workbench surfaces were constructed of materials that were easy to clean and decontaminate, supporting proper hygiene and contamination control.

Clinical trials were conducted under conditions that ensured the safety of study subjects. The selected site was appropriate concerning the potential risks involved. Documentation of a fire mock drill, including evidence of the temporary disabling of access-controlled doors designated as emergency exits, was available and reviewed. The drill was conducted on 17 August 2024 and documented following the applicable SOP. The attendance sheet for the drill was also available for review.

The CRO had sufficient space to accommodate the personnel and conduct the activities required for the performance of the studies. The trial site was equipped with adequate facilities, including appropriately maintained laboratories and essential equipment, to support the conduct of clinical trials.

Access to the facility was restricted and controlled through keycard entry systems. Alarm systems were installed to detect any unauthorized exit of subjects from clinical areas, and/or the doors were secured. Provisions for emergency evacuation were in place. Entries to and exits from the facility were recorded to ensure traceability and security.

Clinical activities included a pharmacy. IMPs were stored under appropriate conditions. Access to the pharmacy was restricted and controlled, with entry and exit records maintained for each visit. The pharmacy was equipped with a humidity chamber and a cold chamber, and IMPs were stored in accordance with their specified storage requirements. Temperature and relative humidity data were downloaded and retained in line with the procedures outlined in the relevant SOP. The primary temperature and humidity control of the stability chamber was managed using the monitoring systems. A hygrothermometer was also installed and visible within the pharmacy. A selected alarm log for the humidity chamber was reviewed. No temperature excursions were noted;

however, minor humidity fluctuations occurred due to electricity interruptions. These fluctuations were adequately addressed and monitored by the responsible pharmacist.

The laboratory premises were appropriately designed to support the operations conducted within them. Sufficient space was provided to prevent mix-ups, contamination, and cross-contamination. Adequate storage facilities were available for the secure and organized storage of samples, standards, solvents, reagents, and records. The premises were structured to ensure adequate protection for all employees and authorized external personnel, including inspectors and auditors. Safety measures were in place to protect individuals handling or working in proximity to chemicals and biological samples.

Safety Data Sheets were made available to staff. During the inspection, the laboratory was recommended to include an index for the corresponding binder. Staff were trained in the use of firefighting equipment and instructed to wear appropriate protective clothing, including laboratory coats and eye protection. All chemical containers were clearly labeled, with prominent hazard warnings displayed where applicable.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators, to ensure safety in the laboratory environment. Staff were aware of the importance of avoiding working alone in the laboratory. First-aid materials were readily available, and personnel were instructed in basic first-aid techniques.

Containers holding volatile organic solvents, such as mobile phases or solvents used in liquid-liquid extraction, were sealed appropriately to prevent evaporation and exposure. Volatile organic chemicals were handled under certified fume hoods systems. Safety showers and eye wash stations were accessible within the laboratory.

The premises were equipped with appropriate systems for waste disposal and fume treatment. ADVITY was registered with the Biomedical Waste Management program, authorized by the Telangana State Pollution Control Board (TSPCB) for the disposal of biowaste. SOP for Handling of Biowaste and Chemical Waste and SOP for Handling of Biological Samples and Mercury Spillage were reviewed and found to be acceptable.

SOP for Maintenance of Power Backup Contingency Equipment, effective from 18 June 2022, was reviewed along with the Business Continuity Test report dated 31 March 2025. These documents were assessed to verify, among others, the adequacy of the CRO's power backup measures in the event of an electricity interruption.

6. Personnel

A sufficient and qualified team comprising medical, paramedical, technical, and clerical staff was available to support the conduct of the trial and to respond effectively to foreseeable emergencies. The total number of staff members was 185 at the time of inspection. At all stages of the trial, including nighttime operations, qualified and trained personnel were present to safeguard the rights, safety, and well-being of the subjects and to provide care in case of emergencies. Contract workers were engaged for specific activities to complement 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.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted on the premises of the CRO. The ADVITY clinical facility had a total capacity of 94 beds, distributed across four clinics located on the 3rd floor of the building. Systems were in place within the accommodation areas to enable subjects to alert CRO staff in case of need.

Facilities for changing and storing clothes, as well as for washing and toilet purposes, were clean, well-maintained, easily accessible, and appropriate for the number of users. Lockable toilets were equipped with alarm systems to ensure subject safety.

The clinical facility included designated areas for volunteer registration, screening, medical examinations, and sample collection. Dedicated rooms were available for ECG, X-ray, drug and alcohol testing, and special care. Separate washrooms were provided for volunteers and staff. The facility also included clinical units for volunteer accommodation, an audio-visual consent area, and appropriate storage facilities. These provisions ensured efficient operations and the availability of necessary clinical accessories to support the conduct of the studies.

The Special Care Unit, located on the 3rd floor, was equipped for intensive care management and comprised five beds with appropriate emergency equipment. Provisions were in place for the urgent transportation of subjects to a designated hospital. A notification was sent to the hospital on the day of initiation of Period 1 of the study in the scope of the inspection (4 April), and a response was received on 12 April. It was noted that, following this instance, the CRO amended its practice to ensure that feedback from the hospital is obtained on the same day of notification moving forward.

Access to the randomization list was restricted to the pharmacist responsible for the study. The document was securely stored under lock and key. The list was printed using a password-protected printer and provided to the pharmacist as a hard copy enclosed in an

envelope. However, it was noted during the inspection that the procedure did not clearly specify whether the envelope was required to be sealed. This point was discussed, and the relevant SOP was subsequently updated to include the requirement for the envelope to be sealed, signed, and dated.

All equipment used was calibrated at predefined intervals to ensure accuracy and reliability. The functionality and performance of emergency-use equipment, such as defibrillators, were also verified at appropriate intervals to confirm their readiness for use.

The observation related to the Clinical phase was adequately addressed in the respective CAPA plan.

8. Clinical laboratory

A clinical laboratory was engaged for the analysis of study samples. The laboratory was accredited in accordance with ISO 15189:2012. The accreditation certificate, available in the Trial Master File was valid until 4 January 2026, including the time of the study under inspection.

All samples, including screening and post-study safety samples, were collected in appropriate vacutainers by designated phlebotomists as per the study requirements. The samples were transferred to the outsourced clinical laboratory using a sample transfer box equipped with coolants to maintain sample integrity. Temperature conditions within the transfer box were monitored using a data logger to ensure that sample quality was preserved during transport.

Hematological tests, urine analysis, and other protocol-specified assessments were performed during the clinical trial. Procedures for sample labeling, receipt, storage, and chain of custody were in place to ensure full traceability and the integrity of the samples. The CRO received relevant documentation from the clinical laboratory, including a dated list of laboratory normal reference ranges, and a copy of the laboratory's accreditation certificate. The applicable and signed curriculum vitae of the Head of the Clinical Laboratory, dated 8 September 2023, was reviewed during the inspection.

The laboratory generated individual reports for each subject and provided printed copies for inclusion in the Case Report Forms. Additionally, the CRO had access to a secure portal where the Laboratory uploaded the laboratory results. A random selection of lab reports was accessed and reviewed on this portal during the inspection.

The Laboratory was subject to regular audits by the CRO, with the most recent vendor audit conducted on 7 March 2024. The corresponding audit report was available and reviewed. It was verified that the laboratory utilized a validated Laboratory Information System (LIS) to manage and document laboratory data.

9. Ethics

The trial was approved by the Independent Ethics Committee prior to the initiation of any study-related activities. The Committee's independence from the sponsor, investigator, and CRO was verified through the review of the IEC 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 the study protocols, informed consent forms, and other related documentation.

Informed consent form

Information for study participants was provided in vernacular languages—English, Telugu, and Hindi—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 procedures. Additionally, the informed consent process was recorded via group video. The information conveyed that participation was voluntary and that subjects had the right to withdraw from the study at any time, without providing a reason. Reasons for subject withdrawal, when provided, 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 participation in the trial was available through the insurance policy. The policy was issued by the insurance company. It was confirmed that the insurance coverage applied to the first 50 trials conducted under this policy, as specified in the limitations section of the policy document. This information was verified during the inspection through email communication with the Business Manager of the insurance company, dated 8 April 2025.

Volunteers were given the opportunity to discuss any concerns regarding potential side effects or reactions associated with the use of investigational products with a physician prior to their participation in the trial.

Certificates of translation for the informed consent forms were reviewed. Back-translation was conducted only when specifically required by the sponsor or when staff fluency in the respective language was deemed insufficient. In other cases, the accuracy of the translation was evaluated by the staff through a thorough review of the translated documents.

10. Monitoring

The study was monitored by monitors employed by the CRO and/or sponsor. The monitors were appropriately qualified to ensure that the study was conducted in compliance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. Their responsibilities included verifying the use of correct procedures for completing CRFs and ensuring the accuracy of the data collected.

The CRO was audited by the sponsor on 28 and 29 June 2022. An audit closure report was available and reviewed. Monitoring visits were conducted during both periods of the trial, and a written monitoring report was prepared by the monitor for each period.

Additionally, a summary form containing key trial information—such as the housing of study subjects, the number of subjects who completed each period, details of any withdrawals, medical events, post-dose adverse events, missing samples, and dosing station information—was prepared by ADVITY and submitted to the sponsor.

11. Investigators

The Principal Investigator was responsible for the clinical conduct of the study, including oversight of clinical aspects of the study design, administration of the investigational products, liaison with local authorities and the ethics committee, and signing of the study protocol and final study report. The Confidentiality Statement and Investigator Declaration were available in Version 1, dated 29 November 2023.

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

Comprehensive records were maintained for the receipt, storage, handling, and accountability of investigational products at all stages of the trial. Information regarding shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, and the return of any remaining investigational products was verified. Details of the pharmaceutical products used, including dosage form, strength, lot number, and expiry date, were documented and reviewed.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The stability chambers were used for storage purposes, monitored by the digital temperature and humidity monitoring system, ensuring compliance with required environmental conditions.

Randomization was performed in accordance with the SOP for Request for Randomization Schedule Generation. Relevant records, including the randomization list and seed, were maintained. Access to the randomization list was restricted to the biostatistician who generated it, the dispensing pharmacist, and the statistician, ensuring confidentiality and compliance with study blinding requirements.

Investigational Products were labeled in accordance with study requirements. Compliance of all labels with the randomization list was verified after printing and before their application on the containers. Labels were affixed in a manner that ensured critical information remained intact and visible even after the container lid was removed.

Adequate procedures for labeling and documenting the administration of Investigational Products were established to ensure that each subject received the product specifically dispensed for them. Labels were designed with a tear-off portion, consisting of two identical sections—one affixed to the IMP container and the other affixed to the CRF at the time of dosing—to maintain traceability and verification of proper administration.

Empty containers for the test and reference investigational products were labeled separately and stored in a secure, locked area. Segregation was maintained throughout storage to prevent any risk of mix-ups before the dispensing stage. Dispensing and packaging procedures were carried out in accordance with the applicable requirements and SOP.

The surface used for handling investigational products was thoroughly cleaned prior to introducing product bottles into the area. All product containers (full or empty), dosage formulations, labeling materials, contaminants, dirt, and debris were removed. A second person verified that the surface area or dispensing line was clear and clean before the containers were brought in and opened. Appropriate utensils were available, and during the inspection, the relevance of using a spatula for handling retained samples was reiterated.

Tablets were dispensed into individual containers in accordance with the randomization list, specific to either the test or comparator product. The test and reference products were handled at separate times, in line with the procedure outlined in the form, which was issued in a controlled manner. This procedure was also applied to labeled containers. All steps were recorded in sequential detail. The surface and surrounding area were cleaned both immediately before and after the dispensing of each product, including subsequent batches within the same study.

Investigational product accountability and dispensing records were maintained in accordance with applicable requirements. Each activity was documented at the time it was performed, including records of doses administered and returned. Verification of each step by a second person was recorded to ensure accuracy and compliance with established procedures.

Dosing was conducted in accordance with SOP for Administration of Investigational Products to Study Subjects, effective from 12 February 2025. The procedure was carried out under the supervision of the investigator and a qualified staff member who had been explicitly delegated this task in writing. Labels were 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, inspecting under the tongue, under the lips, in the corners of the mouth, and between the gums and cheeks to confirm that the subject had swallowed the investigational product. Dosing activities were directly documented in the CRFs.

Investigational product reconciliation following dosing was verified by a second responsible person. Retention samples of the product in its original container were maintained for potential confirmatory testing, with a retention period of at least one year beyond the expiry date of the most recently used product. This requirement was specified in the contract between the sponsor and the CRO. Additionally, any dispensed but non-administered investigational products were retained in accordance with applicable procedures.

13. Case report forms

Body Mass Index and height measurements were taken manually using calibrated weighing and measuring equipment prior to screening and subsequently transferred to the software system used for screening activities. Upon verification of eligibility, a unique volunteer identification number was automatically assigned by the system. This number remained associated with the volunteer for all future study participations. Eligibility was defined as the absence of participation in any clinical study during a predefined period. Only verified eligible individuals were permitted to proceed to the screening phase.

Randomly selected CRFs from the study were reviewed during the inspection. The data collected for each volunteer was in accordance with the specifications outlined in the trial protocol.

The results of screening activities were recorded in the software system, printed, and filed in the respective subject binders. Laboratory reports were also printed and maintained alongside other relevant documentation. A photograph of the urine test results for alcohol and drug screening (kit) was included in the subject files. All ECG recordings were included for each subject. Information related to inclusion and exclusion criteria, physical examinations—including pre-enrolment checks—and compliance with study restrictions was recorded in the CRFs.

ECG results were printed on controlled paper using the ECG device, in addition to being stored both on the server and within the device's internal physical memory. The device had a storage capacity for 200 records, which were cleared by the QC personnel after verifying the completeness of the records. This activity was appropriately documented. ECG data were also transferred via LAN to the central server for storage and retention in accordance with applicable requirements. Furthermore, the records were uploaded into the respective software system to facilitate preliminary evaluation by the study physician and subsequent review by an external cardiologist with system access. The ECG audit trail for the study period was made available and reviewed during the inspection.

An X-ray room and equipment were available for conducting radiographic examinations. The room was equipped with a steel lead-lined door, as confirmed by the invoice dated 28 January 2022. A qualified technician was responsible for operating the equipment. Following imaging, the cassette was processed, and the image was uploaded into the database, which was interfaced with the respective software system. This integration allowed for direct evaluation of the X-ray images by a contracted radiologist. X-ray results were considered valid for a period of six months.

The time interval between blood collection and storage in the deep freezer at the clinical department, including the centrifugation process, was randomly selected and verified during the inspection.

Pre-study drug and alcohol testing was performed using kits manufactured by Assure Tech. The relevant certificates for the kits were available for review. Usage of the kits was documented on the 'Kit Usage Record' form , in accordance with the respective SOP.

14. Volunteers, recruitment methods

Procedures for the selection of volunteers were outlined in applicable SOPs, such as SOP related to Study/Research Feasibility Assessment and Volunteer Registration. These procedures included descriptions of the methods employed by the CRO for volunteer identification and screening. A dedicated database was maintained to track volunteer participation and prevent cross-participation. The system also enforced a minimum washout period between a volunteer's participation in successive studies. Access to the database was password-protected to safeguard the confidentiality of volunteer and subject information.

Identification of volunteers and subjects was ensured through the use of a biometric system. In addition, subjects were identified using their national Aadhar cards, providing a dual method of verification to ensure accurate identification throughout the study.

Informed consent was obtained from potential subjects for screening procedures required to determine eligibility, in addition to separate informed consent for participation in the research portion of the study. The clinical trial protocol outlined the criteria for subject selection, including inclusion and exclusion criteria, as well as the required screening procedures.

A software system, i.e., Clinical Trial Volunteer Registration, was used to determine whether subjects had participated in previous trials. Participation data were uploaded to this central repository following the administration of the first dose, as a measure to prevent over-volunteering. Access to the database was restricted. The designated individual responsible for registration received the relevant information and documentation from the CPU once dosing had been completed.

The screening facility, including rooms designated for ECG, X-ray, blood sample collection, and physical examinations, was visited during the inspection and found to be acceptable for the intended activities.

15. Food and fluids

Meals provided during the study were standardized, controlled, and scheduled in accordance with the clinical trial protocol. The CRO arranged standardized meals, snacks, and beverages for study subjects through an agreement with the catering service provider.

The timing, duration, and quantity of food and fluids consumed were documented. A qualified dietitian was responsible for designing the standardized meals, and the meal menus were prepared and provided accordingly.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, conducted, and monitored to ensure an acceptable safety profile for all participants, including volunteers. A medical doctor was responsible for making medical decisions in the event of adverse events and for notifying relevant health authorities, the sponsor, and, where applicable, the ethics committee, in accordance with SOP for Adverse/Serious Adverse Events Monitoring, Recording, and Reporting.

Fifteen forms were issued for the purpose of documenting the 'Management of Adverse Events.' However, none were utilized, as no adverse events occurred during the study. Additionally, there was no recorded use of medication in the ICU medicine usage logbook.

First-aid equipment and appropriate rescue medications were available in the ICU and readily accessible for emergency use at the study site. Any treatment administered to a subject was documented in both the CRF and the ICU logbook for Accountability of Emergency Medicines. The CRO maintained adverse event registration and reporting forms as an integral part of the CRF.

Bioanalytical section

The study data and associated validation activities were inspected in detail. The following records and procedures were reviewed:

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

Chromatograms and their integration were reviewed, with particular attention to the absence of signals in blank samples and any unexplained interruptions in the injected sequences. Repeat analyses of study samples were examined in accordance with SOP for Repeat Analysis. Records of instrument failures were also reviewed.

The provisions for incurred sample reanalysis and the related documentation were verified. Justifications and documentation for the reinjection of analytical runs were reviewed and compared with the applicable provisions.

The inspection team received adequate support from knowledgeable and transparent personnel throughout the review of the study documentation. During the inspection, full access was granted to the Chromatography software system and the respective study chromatography data.

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

A copy of the relevant literature was available for reference. Stable isotope-labelled internal standards were consistently used in the mass spectrometry methods. K_2EDTA was employed as the anticoagulant, consistent with that used for the collection of subject samples.

Method validation was conducted in accordance with the respective SOP. One validation report was used for the estimation of Tenofovir and Lamivudine, and another validation report for the estimation of Dolutegravir.

As part of the validation process, an analytical run was performed to determine the suitable batch configuration, incorporating a representative number of QCs and CCs. This batch configuration was designed to mirror the expected length and structure of those planned for routine sample analysis.

Sample processing activities were documented using the respective forms. When applicable, a Note to File was prepared to record any unexpected events or deviations observed during sample processing.

Data supporting the stability of the samples under the specified storage conditions and duration were available before the sample analysis, and during method validation. Long-term stability data were generated and reviewed prior to the issuance of the final study reports.
The method validation review encompassed all critical parameters, including precision and accuracy (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, and various stability assessments—such as freeze-thaw stability, stock solution stability, and reference standard storage stability. Additional evaluations included haemolytic effect, recovery, and reinjection reproducibility. Partial validation was conducted in accordance with applicable requirements.

The matrix used for analytical method validation matched that of the study samples, including the same anticoagulants and additives. Documentation related to the purchase of plasma from the supplier covering receipt, storage, retrieval, preparation, and consumption of pooled plasma, which covered receipt, storage, and consumption of pooled plasma, was reviewed and discussed during the inspection. It was noted that the triglyceride content for the lipemic blank plasma was not available at the time of the study. However, the CRO has since amended its practice, and the relevant documentation is now available for recent studies.

This study was conducted using two methods, in accordance with the approved study protocol. All sample analysis activities were performed in accordance with SOP for Project Sample Analysis, Data Checkup and Batch Acceptance and SOP for Chromatogram Acceptance Criteria.

All study samples were analyzed within the established linearity ranges.

Each analytical run included calibration curve standards, quality control samples interspersed throughout the run, and subject samples, all of which were processed simultaneously. The exact processing sequence was predefined and documented. All samples collected from an individual subject across all trial periods were analyzed within the same analytical run to ensure consistency.

Acceptance criteria for the analytical runs were confirmed through the review of multiple parameters, including analyte retention times, accuracy of calibration standards and QC samples, peak integration, and internal standard peak areas, in accordance with the applicable SOPs. System suitability tests were performed prior to initiating each day's runs or following any run interruption. System suitability was assessed by injecting six consecutive injections of the aqueous standard (AQ STD). A run was also conducted for the stabilization of the system before the analysis. The systems demonstrated adequate sensitivity and reproducibility during project sample analysis. Carry-over was evaluated by injecting the reconstitution solution immediately after the highest calibration standard (AQ ULOQ), as well as a blank sample following the ULOQ standard. In addition, both aqueous and extracted Lower Limit of Quantification (LLOQ) samples were injected before initiating the sample analysis. No carry-over was observed for the analyte or the internal standard (ISTD) in either aqueous or extracted samples.

For the first 1,000 samples, 10% were selected for Incurred Sample Reanalysis (ISR), while 5% of the subsequent samples were subjected to ISR. Samples were selected around the Cmax and during the elimination phase to ensure meaningful assessment. The acceptance criteria for ISR were clearly defined in the SOP for Incurred Sample Reanalysis.

System audit trail reviews were conducted at the time of the studies included in the scope of this inspection. Documentation confirmed that responsible personnel had received adequate training on these procedures.

The observations related to method validation were adequately addressed in the respective CAPA plan.

18. Sample collection, storage, and handling of biological material (Both)

The specifications of the samples (blood plasma), including the sampling method, volume, and number of samples, were defined in the clinical trial protocol and communicated to the volunteers. The collection, preparation, transfer, and storage of samples were carried out in accordance with applicable SOPs, including SOP for Transfer of Pharmacokinetic Samples to Bioanalytical Laboratory and SOP for Receipt and Management of Biological Samples.

Actual sampling times and any deviations from the pre-specified sampling schedule were recorded, and such deviations were taken into account during the calculation of pharmacokinetic parameters.

Collected samples were clearly labeled to ensure accurate identification and full traceability, in accordance with the applicable SOP. All storage conditions, including freezer temperature, were continuously monitored and recorded using the digital temperature and humidity monitoring system throughout the storage period and during transportation. Records of sample storage and retrieval were maintained accordingly.

Samples were aliquoted in duplicate, and aliquots I and II were stored separately. The remaining QC and CC samples were still available, and the respective reconciliation was verified during the inspection.

19. Data processing and documentation

Integration settings used during chromatographic analysis were science-based and fully justifiable. The smoothing factor was set at a level low enough to avoid masking potential interferences or alterations in peak geometry.

The criteria for the acceptance or exclusion of CC and QC samples, as well as for overall batch acceptance, were clearly defined in the applicable SOP. Source data for all analytical runs included comprehensive information from the original first evaluation of runs, including all calibration samples, particularly in cases where analyses were repeated. The calibration range was appropriately truncated. Variations in internal standard responses were trended and utilized as part of the verification process to support the validity of the analytical results.

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, 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.

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to minimize the risk of errors. These procedures were defined in the applicable SOPs, including SOP for Bioanalytical Data Transfer.

20. Good laboratory practices

A tour of the laboratory was conducted on Day 4 of the inspection to assess its suitability in terms of layout, operational arrangements, and safety measures. The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE studies, with an established appropriate QA system.

Deep freezers used for sample storage and refrigerators used for the storage of reference standards were qualified, calibrated, and maintained in accordance with applicable requirements. An alarm system, integrated with a digital thermometer, was in place to alert security personnel in the event of temperature excursions. The functionality of the automatic alarm system was tested during the inspection and found to be operational. Daily monitoring activities, along with all alarm checks, were documented appropriately. For the purposes of qualification verification, the temperature mapping of the Deep Freezer was reviewed to verify the Hot spot and the location of the respective sensor. The temperature mapping process was properly carried out at the time of inspection.

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

The operation, use, calibration, routine checks, and preventive maintenance of equipment were described in the respective SOPs. Records of these activities were maintained in accordance with applicable requirements. Compliance was verified through a random review of equipment used in study-related activities. Each piece of equipment and its components were labeled with a unique identification number, the date of the last calibration, and the date of the next scheduled calibration. Equipment usage was documented in the analytical worksheets as well as in the corresponding instrument usage logbooks. The use of chromatographic columns was recorded in a dedicated logbook, in accordance with SOP for Receipt and Maintenance of Analytical 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.

The observation related to Good Laboratory Practices was adequately addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations, and reporting section

21. Pharmacokinetic, statistical calculations

A presentation was provided by the biostatistician during the inspection, detailing the procedures for statistical and pharmacokinetic (PK) calculations. The presentation outlined the processes for data handling, PK analysis, statistical evaluation, and reporting, and included references to the applicable SOPs governing these activities.

Pharmacokinetic analysis was conducted in accordance with EC-approved protocols using SAS®. The data used for PK analysis were stored in a study-specific folder and included treatment codes, randomization sequences, sampling time point deviations, values below the limit of quantification (BLQ, recorded as "zero"), and missing values. Rearranged datasets were submitted to Quality Assurance via email for review and clearance before analysis.

PK analysis was performed in a blinded manner for the study, with unblinding occurring only after the initial PK computations were completed. Following the PK analysis, statistical evaluation, applying ANOVA models as per protocol and regulatory requirements, was also performed using SAS®. Programs and outputs were saved in the respective study folder, and results were shared with the Principal Investigator, Head – Clinical, and QA.

Final results were routed through Project Management to the sponsor and shared with Medical Writing for inclusion in the Clinical Study Report. In the event of re-analysis, data unlocking required prior approval from the Principal Investigator and Head QA.

Outlier testing was conducted based on protocol-defined criteria or specific regulatory/sponsor requests. Confirmations of outliers involved the Principal Investigator and Bioanalytical Investigator.

The following SOPs governed these activities:

- Randomization Schedule Generation
- Estimation of Pharmacokinetic Parameters
- Statistical Analysis using Pharmacokinetic Data

The observation related to the Data lock was adequately addressed in the respective CAPA plan.

22. Study report

The process of clinical study report preparation was verified during the inspection. No discrepancies were identified between the results presented in the study report and the original raw data during the random review of study data.

The study report included a section on the bioanalytical component of the trial, detailing the bioanalytical method used and a summary of its validation. The Principal Investigator reviewed and approved the clinical study report prior to data transfer to the statistical department. The bioanalytical report was similarly reviewed and approved by the responsible staff and management. Monitoring and audit reports were available and reviewed before the release of the final study report.

Miscellaneous	
Samples taken	***Not applicable***
Assessment of the CRO master file	The CRO master (CROMF) file was submitted before the inspection and it was reviewed.
Annexes attached	***Not applicable***

Part 3	**Conclusion – inspection outcome**

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines of ***ADVITY Research Private Limited***, located at ***3rd & 4th Floors, Archies Continental, P. No. 2A, 3, S. No. 1094 & 1095, Adj: Kukatpally Metro station, Kukatpally, Hyderabad 500 072, 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, before the publication of the WHOPIR.

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

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***

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