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

| **Part 1** | **General information** |
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| **Organization details** | |
| Company information | |
| Name and Address of Clinical Research Site | **AnaCipher Clinical Research Organization**<br>2nd, 3rd & 4th Floor, Mirrakamshetty Mall<br>Opp. Doordarshan Bhavan, Ramanthapur<br>Medchal – Malkajgiri Dist.<br>Hyderabad – 500 013<br>Telangana<br>INDIA |
| Name and Address of Bioanalytical Research Site | **AnaCipher Clinical Research Organization**<br>2nd, 3rd & 4th Floor, Mirrakamshetty Mall<br>Opp. Doordarshan Bhavan, Ramanthapur<br>Medchal – Malkajgiri Dist.<br>Hyderabad – 500 013<br>Telangana<br>INDIA |
| Name and address Statistical Site | As mentioned above |
| Corporate address of the Organization | As mentioned above |
| GPS coordinates | 17.4147425° N<br>78.4841588° E<br>DUNS No: 65-065-4655 |
| WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles | **WHO application no. NT016**<br>Bioequivalence study of Albendazole chewable tablets 400 mg<br><br>**WHO application no. MA184**<br>Bioequivalence study of fixed-dosed combination of Artemether and Lumefantrine Tablets 80mg/480mg<br><br>**WHO application no. MA181** |

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| | Bioequivalence study of fixed-dosed combination of Artemether and Lumefantrine Dispersible Tablets 20/120 mg<br><br>**WHO application no. TB395**<br>Bioequivalence study of Bedaquiline tablets 100 mg |
| **Inspection details** | |
| Dates of inspection | 11-15 March 2024 |
| Type of inspection | Routine |
| **Introduction** | |
| Summary of the activities | AnaCipher Clinical Research Organization is a privately owned service organization situated in Ramanthapur, Hyderabad, Telangana, India. The company offers its services to national and international sponsors for conducting bioavailability/bioequivalence studies in healthy human volunteers.<br><br>The services provided by the CRO to its sponsors include, but are not limited to:<br>- Regulatory approvals (BENOC, Clinical Trial approval & Import License)<br>- Ethics committee approval<br>- Medical writing (Protocol, ICD, CRF, and Integrated/Clinical Study Report)<br>- Bioavailability/Bioequivalence studies on healthy population<br>- Bioanalytical analysis<br>- Pharmacokinetic and Statistical Services<br>- eCTD<br>- Quality Assurance |
| General information about the company and site | The CRO was initially established as Well Quest Clinical Research in 2001 under the umbrella of PIRAMAL GROUP, which was based in Mumbai. In 2007, it relocated to Hyderabad. Subsequently, the company was renamed Piramal Clinical Research in 2011. Then, in 2015, it was acquired by the AnaCipher division of INDOCO REMEDIES Ltd. and renamed AnaCipher Clinical Research. |
| History | In addition to national approval from CDSCO in Delhi, the AnaCipher site has undergone inspections by various other regulatory agencies, including the US FDA, EMA (Denmark and Finland), and UK MHRA. |

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| | Furthermore, the CRO underwent inspection by the WHO in June 2011, and a desk assessment was conducted on 29 January 2020. |
| Brief report of inspection activities undertaken | The following scope and study-related activities were reviewed:<br><br>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.<br><br>Coverage was provided for the analytical operations to confirm the practices, personnel qualifications, and procedures utilized during the method validations and analytical testing.<br><br>A review of the clinical study data, analytical method validation, and analytical study data was conducted, and the source data was compared to the study reports. |
| **Scope and limitations** | |
| Out of scope | Not applicable |

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| 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 |

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| | GAMP | good automated manufacturing practice |
| | GCP | good clinical practice |
| | GLP | good laboratory practice |
| | GMP | good manufacturing practice |
| | HPLC | high-performance liquid chromatography |
| | 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 |
| | SPE | solid phase extraction |
| | SUSAR | suspected unexpected serious adverse reaction |
| | ULOQ | upper limit of quantification |
| | URS | user requirements specifications |

| **PART 2** | **SUMMARY OF THE FINDINGS AND COMMENTS** |
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## General Section

## 1. Organization and management

A presentation detailing the organization's activities was provided. The opening meeting took place on the 4th floor of the premises.

AnaCipher Clinical Research was approved by the national regulatory authority (CDSCO Delhi) for conducting bioavailability/bioequivalence studies and bioanalytical studies.

The CRO included an organizational chart with key positions and names of persons responsible. The chart was dated, authorized, regularly updated, and included in the CROMF. The organization was managed by the Managing Director, Chief Technical Officer and Associate Vice President (Head of Operations).

Each employee had a job description outlining their responsibilities. Random verification confirmed that the respective staff member signed and dated each job description.

A list of signatures of authorized personnel conducting tasks during each study was available and duly verified.

The Good Laboratory Practices principles outlined the responsibilities of the test facility management. The CRO management understood that since the investigator was a CRO employee, some of the investigator's usual responsibilities also fell under the purview of CRO management.

Management ensured the implementation and adherence to appropriate and technically valid SOPs. Accordingly, a well-organized historical file of all SOPs was maintained.

A list of changes from the last inspection in February 2020 onwards was available.

Working hours at the facility were from 9:30 to 18:30, five days a week.

## 2. Computer systems

An inventory of all computerized systems on the network was available. During the inspection, the list was updated to include all software applications, including those used in the clinical laboratory, along with details on their GxP relevance and validation dates.

Computerized systems were required to be evaluated for their intended use and undergo validation, operation, and maintenance in alignment with the principles of GCP and GLP, as applicable.

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

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

The computerized systems' qualification and/or validation certificates were required to be provided under the user's supervision to ensure that the software underwent validation for its intended purpose and was developed within a controlled environment consistent with a QA system. The qualification of the selected systems was reviewed for verification.

The specific user requirements, regulatory/guideline requirements for bioequivalence studies, the operating environment in which the system was utilized, and the utilization of the system in the studies were all considered during the Performance Qualification. All phases of their life cycle were considered. SOPs for using each software program employed to conduct BE studies were also accessible.

Networks, encompassing the entire client/server architecture and interfaces such as laboratory information management systems, were designed, qualified, managed, and controlled.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.), were devised to prevent errors. The data entry process was delineated in the SOP.

Excel sheets were validated in accordance with the applicable SOP, which was newly implemented on August 4, 2023. During studies in the scope of this inspection, the Excel sheets were not validated but were password-protected. Presently, the CRO utilizes an application for calculations and batch acceptance criteria.

The observations related to the computerized systems were adequately addressed in the respective CAPA plan.

## 3. Quality management

The CRO maintained appropriate QA and QC systems, supported by written SOPs, to ensure that trials were conducted and data generated, documented, and reported in accordance with the protocol, GCP, GLP, GMP, and relevant regulatory requirements.

Additionally, current and relevant SOPs were provided on a pen drive for the inspectors' reference and use throughout the inspection process.

A CRO Master File with version no. 3 was provided. The purpose of the CRO Master File was to:

- Communicate a quality management plan
- Communicate information regarding quality procedures, control, and assurance
- Provide evidence of conformity to the National and International regulatory requirements
- Share knowledge
- Provide evidence of management's commitment to quality

QA personnel conducted audits during the clinical trial process (in-process audits), and these audits did not replace other necessary forms of oversight that might have been required. The QA activities were overseen by the Corporate QA and Corporate Compliance departments, with Site QA reporting directly to the Corporate QA departments.

The main responsibilities of the QA department were (but were not limited to):

- Review of SOPs, validation reports, bioanalytical reports, and clinical study reports.
- Control and distribution of SOPs, validation reports, method SOPs, and study
- Issuance of related forms and overseeing staff training on applicable SOPs. GCP and GLP as applicable.
- Conduct system and facility audits, including in-process and retrospective audits of the clinical, bioanalytical, BSDM, IT, and clinical lab departments.
- Co-ordinate with the sponsor audits and regulatory inspections.
- Providing a compliance report to the sponsors and regulatory authorities. All the study-related operations carried out in the organization were subject to a QA audit.

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

The quality management system encompassed root cause analysis, trend tracking, ensuring data integrity across all aspects, and implementing appropriate corrective and preventive actions (CAPA). The internal audit of vendors, including the qualification and suitability of the plasma supplier, was reviewed and discussed.

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

## 4. Archive facilities

The CRO maintained a secure storage facility on the fourth floor for archiving trial-related documents, equipped with temperature and humidity control, as well as pest control measures. Overall, comprehensive security measures were in place to ensure the safety and integrity of the documentation. Additionally, the CRO had established an offsite archive contract and the facility was periodically audited.

Archiving activities were conducted by the respective SOP. Access to archive storage areas was restricted to authorized personnel, with a list of authorized individuals displayed at the entrance. Records of document access and return were diligently maintained.

The duration for which study documentation, including raw data, should be archived was specified in the SOP and the contract between the sponsor and the CRO, which also covered financing provisions for archiving.

The successful retrieval and traceability of documents during inspections confirmed the effectiveness of the archiving procedures for trial-related documentation.

## 5. Premises

On day 2 of the inspection, a tour of the facility was conducted. A layout of the premises was provided, and critical areas of operation were outlined in the CROMF, along with details.

The facilities were well-maintained, with cleanliness, adequate lighting, ventilation, and environmental control measures. Floors, walls, and working bench surfaces were designed for easy cleaning and decontamination.

Clinical trials were conducted under conditions ensuring subject safety, with appropriate site selection relative to potential risks.

The CRO had adequate space to accommodate personnel and activities necessary for study conduct. The trial site was equipped with suitable facilities, including laboratories and equipment.

Entry to the facility was strictly regulated and monitored through keycards or biometric access. Emergency evacuation procedures were in place, and all entries and exits from the facility were recorded.

Sites hosting clinical activities, such as the pharmacy where investigational products were stored, adhered to access control measures. Entry and exit to the pharmacy were restricted, and comprehensive records of each visit were maintained.

Laboratory premises were designed to suit the operations to be carried out in them, ensuring adequate space to prevent mix-ups, contamination, and cross-contamination. Sufficient storage space was provided for samples, standards, solvents, and reagents.

Safety data sheets were accessible to staff prior to testing, with employees being well-versed in the material safety data sheets relevant to the chemicals and solvents they handled. Fire safety training took place, along with a recent mock drill conducted on April 17, 2023. The training evidence was available and reviewed. Staff was instructed to wear laboratory coats, along with eye protection. To mitigate contamination risks, highly toxic and/or genotoxic samples were managed within safety cabinets. Chemical containers were fully labeled with prominent warnings as necessary.

Electrical wiring and equipment, including refrigerators, were adequately insulated and spark-proofed. Staff was briefed on the importance of avoiding solitary work in the laboratory, and first-aid materials were readily available.

Containers holding volatile organic solvents were sealed appropriately, and volatile organic chemicals were handled under the fume hood. Safety and eye showers were accessible within the laboratory.

For effective waste disposal, systems and measures were in place to treat fumes and safeguard the environment, ensuring compliance with local or national regulations. The system was implemented in accordance with the respective SOP. Waste management services were contracted to a service provider in Hyderabad.

Furthermore, the CRO had a backup generator along with three UPS units in case of interruption in the city electricity supplier, ensuring uninterrupted operations.

## 6. Personnel

A qualified team comprising medical, paramedical, technical, and clerical staff was readily available to support the trial and handle emergencies effectively. At the time of inspection, the clinical unit consisted of 59 staff members out of a total of 120. Throughout all trial phases, including nighttime, trained personnel ensured the protection of subjects' rights, safety, and well-being and provided emergency care. Additionally, contract workers were engaged to enhance the team's capabilities in specific activities.

The curricula vitae and training records of full-time and contract workers involved in trial activities were randomly selected and reviewed for verification.
Phlebotomists/paramedics and/or consultant doctors were contracted as needed and were trained on procedures prior to task assignments. Consultants were also welcome to contribute their technical expertise whenever necessary.

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

**Clinical section**

## 7. Clinical phase

The clinical phase of the studies took place at the CRO premises.

The CPU was equipped with 150 beds and divided into four units. A Care Nurse Calling System was installed in the accommodation facilities to enable subjects to alert CRO staff in case of need.

Facilities for changing and storing clothes and washing and toilet were maintained in a clean, well-organized manner, easily accessible, and suitable for the number of users. Alarmed, lockable toilets were provided, and doors were designed to allow opening from the outside in case of a medical emergency.

The clinical site included a volunteer waiting area, registration area, sample collection area, and ECG rooms,

Provisions were established for the prompt transportation of subjects to the hospital if needed.

Access to the randomization list was limited to the pharmacist responsible for the study. These documents should be password-protected electronically.

All equipment utilized underwent proper calibration at predefined intervals. The functionality and performance of emergency-use equipment, such as defibrillators, were routinely verified at suitable intervals.

## 8. Clinical laboratory

Blood and urine sample analysis related to clinical activities was performed in a designated in-house clinical laboratory. The laboratory was accredited according to ISO 15189 standards and was valid until April 25, 2025.

Throughout the clinical trial, hematological tests, urine analysis, and other specified tests were conducted in accordance with the study protocol.

Stringent procedures were implemented for sample labeling, receipt, storage, and chain of custody to guarantee complete traceability and sample integrity.

The CRO received comprehensive information regarding the laboratory's analytical methods, a current list of laboratory normal ranges, and the laboratory's accreditation certificate.

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

The laboratory generated individual reports for each subject, along with source or raw data for all tests performed, and included them in the Case Report Forms. Paper formats of these reports were archived for studies within the scope of the inspection. Furthermore, the CRO launched a Laboratory Information Management System (LIMS) in April 2023 to enhance data management capabilities and ensure data integrity requirements are met.

## 9. Ethics

The trials were approved by the independent Ethics Committee (IEC) before any study initiation. The respective member list confirmed the committee's independence from the sponsor, investigator, and CRO. The committee's opinions and recommendations were accessible, and the IEC was provided ample time to review protocols, informed consent forms, and associated documentation.

Additionally, the trials were insured with valid policy numbers. Random verification of these policy numbers was conducted during the inspection.

Informed consent form

Information for study participants was provided in Telugu, Hindi, and English languages, tailored to their comprehension levels, both orally and in writing.

Prior to commencing any trial-related activities, subjects provided informed consent, which was documented in writing and recorded via video. The information conveyed was

clear: participation was voluntary, and subjects retained the right to withdraw from the study without providing a reason. The reasons for withdrawal were documented in the study records.

Details regarding insurance coverage and procedures for compensation or treatment in case of injury or disability resulting from trial participation were made available through the insurance policy.

Volunteers were permitted to discuss any concerns regarding potential side effects or reactions from using investigational products with a physician before participating in the trial.

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

## 10. Monitoring

An adequately qualified representative of the respective sponsor monitored the study to ensure compliance with the protocol, GCP, GLP, and relevant ethical and regulatory standards. This involved verifying the proper completion of CRFs and ensuring the accuracy of collected data.

Remote monitoring was conducted for the Albendazole study (NT016), while onsite monitoring was performed for Bedaquiline (TB395), necessitating pre-study visits for the latter. The monitor generated corresponding reports and communicated any identified issues to the CRO. All communication and corrective actions were documented.

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

## 11. Investigators

The principal investigator (PI) was responsible for overseeing the clinical conduct of the study, which encompassed various aspects such as study design, administration of investigational products, liaison with local authorities and the ethics committee, and signing off on the protocol and the final study report.

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

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

Detailed records regarding the receipt, storage, handling, and accountability of investigational products throughout the trial were meticulously maintained. Information pertaining to the shipment, delivery, receipt, description, storage (including specified conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products was verified and documented.

Pharmaceutical products were stored according to the conditions outlined in the official product information provided by the sponsor. These conditions were monitored using a digital temperature and humidity monitoring system. Additionally, information regarding the pharmaceutical products used, including dosage form, strength, lot number, and expiry date, was meticulously recorded.

Randomization procedures were conducted in adherence to the SOP for the generation of the Randomization Schedule, ensuring that records were maintained. This included documentation of the randomization list and seed code. Access to the randomization list was restricted to the individual responsible for its generation, a dispensing pharmacist, and the statistician. A software application was utilized for randomization.

The IPs were correctly labeled. Label compliance with the randomization list was verified after printing and prior to container labeling. Labels were affixed to the containers to prevent information loss upon lid removal.

Effective procedures for labeling and documenting IP administration were implemented to confirm that each subject received the dispensed product. Tear-off portion labels were utilized, with two identical labels provided: one for container affixation and the other for CRF attachment during dosing.

Empty containers for both the test and reference investigational products were labeled individually. They were kept segregated in a secure area under lock and key to prevent potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were executed in compliance with the requirements. Dosing was conducted following the applicable SOP.

The surface where the product was handled underwent thorough cleaning before product bottles were introduced into the area. All product containers, whether full or empty, labeling materials, contaminants, dirt, and debris were removed from the area. A second individual confirmed that the surface/line was clear and clean before introducing and opening product containers. The investigational medicinal products (IMPs) were

managed using suitable utensils. Tablets were dispensed into each container according to the randomization list for the comparator or test product as applicable. Handling of the two products, test and reference, occurred separately, including the labeled containers. Each step was meticulously documented in sequence. The surface and its surroundings were cleared and cleaned both before and after initiating the dispensing of the subsequent product in the same study. The practice was verified during the inspection by observing the accountability of the retained study drug.

Records of investigational product accountability and dispensing were consistently kept. Each activity was documented upon completion, encompassing details such as doses administered, returned, or destroyed. Additionally, verification by a second individual for each step was meticulously recorded.

The inspectors had the opportunity to observe dosing through video records. Dosing occurred under the supervision of the investigator and a qualified staff member specifically delegated in writing for this task. Prior to dosing, the label was verified, and the exact time of dosing was recorded on the designated page of the CRF. A mouth check was conducted, inspecting under the tongue, lips, mouth corners, and between gums and cheeks using a tongue depressor or spatula along with a penlight for solid oral dosage forms to confirm ingestion of the investigational product. Dosing details were directly documented in the CRFs.

After dosing, a second responsible individual verified investigational product reconciliation. Samples from the original container were retained for potential confirmatory testing for a minimum of one year after the expiry date of the latest product. The procedure for sample retention was outlined in the SOP for Retention of Investigational Products and detailed in the contract between the sponsor and the CRO. Additionally, dispensed products that were not administered were also retained.

The administration of tablets during each period for a selected study was verified.

## 13. Case report forms

Randomly selected CRFs from the studies TB395 & NT016 were reviewed.

The trial protocol outlined the specific data to be collected for each volunteer.

Each subject's CRF included copies of clinical laboratory reports and all Electrocardiograms (ECGs). Details regarding dosing administration, sample collection, food intake, physical examinations, and screening activities were documented in the CRF.

## 14. Volunteers, recruitment methods

The procedures for recruiting volunteers and described potential methods utilized by the CRO were outlined in the respective SOP. A database was maintained to prevent cross-participation and specify a minimum interval between a volunteer's participation in consecutive studies. Access to the database was password-controlled to safeguard confidential volunteer information.

Volunteer and subject identification were ensured through a biometric system utilizing fingerprints. The device was validated in 2019.

Informed consent was obtained from potential subjects for any screening procedures necessary to assess eligibility for the study, as well as for participation in the research segment. The clinical trial protocol detailed subject selection criteria (including inclusion and exclusion criteria) and screening procedures. The software system OVIS was utilized to check if any subjects had previously participated in a trial, also by the CROs registered in the system, with participation data uploaded to prevent over-volunteering.

For urine drug testing, a Rapid Chromatographic Immunoassay kit was used. Due to COVID restrictions, urine alcohol tests were conducted using a kit. It was noted that the CRO was employing a different device during the inspection.

## 15. Food and fluids

Meals were standardized and controlled, following a schedule during the study days. The CRO coordinated the provision of standardized meals, snacks, and beverages for study subjects in accordance with the clinical trial protocol and the agreement with the catering service, BLR Enterprises.

The timing, duration, and quantity of food and fluids consumed were documented. Before sample collection, ambulatory subjects were queried about their food and beverage intake. A dietitian with suitable qualifications, training, and experience designed standardized meals.

## 16. Safety, adverse events, adverse event reporting

The study was planned, organized, conducted, and monitored to ensure an acceptable safety profile, including for the volunteers. A medical doctor was delegated to make medical decisions in the event of adverse events and was responsible for notifying the relevant health authorities, the sponsor, and, when necessary, the ethics committee, particularly in the case of serious adverse events.

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

The CRO maintained adverse event registration and reporting forms as part of the CRF, along with records of concomitant medication.

**Bioanalytical section**

The inspection primarily targeted studies NT016 (Albendazole and Albendazole sulfoxide with the respective Internal Standards) and TB395 (Bedaquiline), along with their associated validation projects. Spot checks were also considered for other studies. The investigation specifically scrutinized the following records and activities:

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

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were verified. The reason for the study sample repeat analyses and all instrument failures was reviewed, when applicable. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions when applicable.

During the review of study documentation, the inspection team received adequate support from knowledgeable and transparent personnel. Access to the Chromatography software application and raw data was granted during the inspection, facilitating thorough examination.

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

The method development process was described and documented. The use of Internal Standards (IS) was justified based on pertinent literature, a copy of which was available. Following method development, an analytical plan (Method SOP) was provided as a foundation for method validation. Stable isotope-labeled internal standards were employed

in the Mass Spectrometry (MS) methods, and appropriate anticoagulants were applied, ensuring method accuracy and reliability.

During the method validation according to the applicable SOP, a run was conducted to assess the batch with sufficient samples of QCs and CCs, known as Analytical Run Size Evaluation. These batches were designed to be comparable in length to those anticipated for routine analysis.

The sample processing was documented in the respective forms. Additionally, an Investigation Report Form was available to record any unexpected activities encountered during sample processing, as needed.

Data to substantiate the stability of the samples under the specified conditions and storage duration was accessible prior to the commencement of the studies, except for long-term stability, which was conducted prior to the issuance of the study reports.

The method validation review included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), hemolytic effect, recovery, and reinjection reproducibility. Partial validation was conducted in accordance with the applicable requirements.

Furthermore, during the inspection, it was verified that for study NT016's bioanalytical method validation, freshly spiked calibration standards were used for at least one Precision and Accuracy run, while frozen calibration standards were used for the others. For the analysis of study samples on the respective instrument, a carry-over assessment, should have been conducted alongside one run of accuracy and precision during the partial method validation. An addendum addressing this issue was provided and reported.

The matrix used for analytical method validation was consistent with the matrix of the study samples, including anticoagulants. Plasma for pooled plasma preparation was obtained either internally or from a supplier. The external supplier was particularly used for lipemic and hemolyzed plasma. Documentation related to purchase and preparation, such as screening reports, purchase orders, receipts, storage, retrieval, and utilization of pooled plasma, was thoroughly reviewed and discussed. The procedures for receipt and handling of the Blank Biological Matrix were described in the respective SOP.

Each analytical run included calibration curve (CC) standards, Quality Control (QC) samples interspersed throughout the run, and subject samples, all processed simultaneously. The precise sequence of processing was defined and documented. All

samples collected from a particular subject across all trial periods were analyzed within the same run. Acceptance criteria for analytical runs were verified through a comprehensive review of various parameters, including analytes' retention time, accuracy of calibration standards and QC samples, peak integration, and Internal Standard (IS) and analyte peak areas, in accordance with applicable SOPs such as SOP for Preparation of calibration curve standards, QC samples, and analytical run acceptance criteria, as well as evaluation of internal standard variation during the study. System suitability and stabilization tests were conducted prior to the initiation of runs each day, except when there was no time gap between consecutive runs.

Incurred sample reanalysis (ISR) was conducted both during and after the completion of the respective study. A minimum of 10% of samples for the first 1000 samples and 5% from the remaining samples exceeding 1000 were selected, covering all subjects and periods. These samples were chosen with concentrations around $C_{max}$ and in the elimination phase. The acceptance criteria for ISR were outlined in the SOP for Incurred Samples Reanalysis. The results of the tests on Bedaquiline were thoroughly reviewed and discussed.

The system audit trail review was conducted by the project manager during the studies within the scope of the inspection after the completion of the study. It was noted that the practice was revised to be performed by the Laboratory's Quality Control (QC) Team.

The observations related to this section were adequately addressed in the respective CAPA plan.

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

The specification of samples (blood plasma), sampling method, volume, and number of samples were outlined in the clinical trial protocol and the information provided to the volunteers. Collection, preparation, and storage of samples adhered to the respective SOP. The most recent SOP, effective from 19 Oct 2023, introduced a new practice of storing different aliquots separately; previously, aliquots were stored together. Samples were collected, centrifuged, and divided into aliquots in the CPUs before being transferred to freezers in the Deep Freezer room, which clinicians accessed. The number and specifications of biological samples were documented in each deep freezer’s logbook, along with the applicable templates for sample transfer.

Actual sampling times and any deviations from the prespecified sampling times were meticulously recorded, and these deviations were taken into account when calculating the pharmacokinetic parameters.

Clear labeling of collected samples ensured accurate identification and traceability of each sample. Storage conditions, including freezer temperature, were controlled, monitored, and documented throughout both storage periods. Comprehensive records of sample storage and retrieval were consistently maintained.

As per an SOP, study samples, QC samples, and pooled matrices were appropriately disposed of. Samples provided for clinical laboratory testing were discarded following the applicable SOP. Random verification of evidence was conducted for study NT016.

The utilization of RS and pooled plasma in preparing stock solutions and spiked samples, along with the consumption of QC and CC aliquots, was thoroughly examined and discussed. The CRO was advised to take into account spillage of IS and pooled plasma when documenting these materials.

During the studies within the scope of the inspection, the sample room custodian issued retrieval/storage requests for biological samples using sequential numbers. These forms were not issued under QA supervision and were not reconciled post-study to verify that only necessary forms were issued. It was noted that this practice has been revised, and request forms are now issued under QA department supervision, with reconciliation conducted after study completion.

## 19. Data processing and documentation

The integration settings were based on scientific principles and were justified. The smoothing factor was maintained at a low level to prevent the masking of potential interferences and changes in peak geometry.

The relevant SOP outlined the acceptance and exclusion criteria for CC standards and QC samples, as well as batch acceptance. Chromatograms were acquired and processed using the peak area ratio method with Chromatography software.

The concentration of unknown samples was calculated using regression analysis of spiked standards, with the reciprocal of the square of the ratio of drug concentration to internal standard concentration as a weighting factor.

The source data for all analytical runs incorporated information from the original first evaluation, including all calibration samples, even in cases of repeated analyses. Calibration range adjustments were appropriately made, and variations in internal standards were monitored and incorporated into result validity assessments.

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

Original analytical raw data, such as calculations and chromatograms, along with their associated audit trails, were documented to ensure traceability regarding sample number, equipment used, date and time of analysis, and technician name(s). All audit trail files, including results table audit trail, project audit trail, and instrument audit trail, were saved.

Each data point was directly linked to a specific sample, including sample number, collection time, centrifugation time, freezer placement time, and analysis time, facilitating the identification of any abnormal results potentially caused by sample mishandling.

## 20. Good laboratory practices

On Day 3, a facility tour was conducted to assess its layout and safety standards.

Adherence to the general principles of Good Laboratory Practices was ensured during the bioanalytical phase of BE studies, supported by a QA system.

Deep freezers utilized for sample storage and refrigerators for reference standard storage underwent thorough qualification, calibration, and maintenance as per the SOP. An alarm system linked to the digital thermometer was in place to notify custodians via SMS and calls. During inspection, the automatic alarm system was tested to confirm its functionality, with daily monitoring and alarm checks being duly documented.

For qualification verification, the temperature mapping of a selected Deep Freezer was assessed to confirm the measurement of hot spots and the sensor placement. The mapping procedure was conducted correctly during the inspection. Transferring samples to comparable storage units was duly considered for maintenance and repair purposes.

Balances, along with other measuring devices and equipment used during trials, underwent periodic calibration and verification prior to usage to ensure suitability for their intended purposes.

The operation, use, calibration, checks, and preventive maintenance procedures of the equipment were outlined in the corresponding SOPs. Records were meticulously maintained to meet the requirements. These activities were verified through random inspections of equipment utilized in study-related tasks.

The equipment and its components were properly labeled with their respective ID numbers, calibration dates, and upcoming calibration dates. Equipment utilization was documented in analytical sheets and corresponding instrument logbooks. Moreover, column usage was logged in the designated column usage logbook.

Chemicals, reference substances, reagents, solvents, and solutions were labeled to indicate their identity, purity, concentration (if applicable), expiry date, and specific storage instructions.

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

**Pharmacokinetic, statistical calculations and reporting section**

## 21. Pharmacokinetic, statistical calculations

On Day 5, the biostatistician delivered a presentation concerning the generation of randomization, the transfer of study data between the Biostatistical Clinical and bioanalytical Departments, and the statistical and pharmacokinetic calculations.

Concentration data management followed the respective SOP guidelines. Pharmacokinetic calculations were performed using dedicated software. Study data was securely stored in designated folders with restricted access, and QA verified the results following established procedures. A data flowchart for CSR & Data Listing Preparation was presented during the session.

Upon dispatch of the study report to the sponsor, the study data was archived accordingly.

## 22. Study report

The process of writing the study report was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies were identified between the results stated in the report and the original (raw) data during the inspection.

The study report included a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and a report on its validation. The Principal Investigator approved the clinical study reports before data transfer to the statistical department. The responsible staff and management also approved the bioanalytical reports. Monitoring and audit reports were available before the release of the final study report.

| **Miscellaneous** | |
|---|---|
| ***Samples taken*** | Not applicable |
| ***Assessment of the CRO master file*** | The CROMF with version number 03, effective from 10 May 2023, was submitted and reviewed. |
| ***Annexes attached*** | Not applicable |

| **Part** | **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, 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 at ***AnaCipher Clinical Research Organization***, located at ***2nd, 3rd & 4th Floor, Mirrakamshetty Mall, Opp. Doordarshan Bhavan, Ramanthapur, Medchal – Malkajgiri Dist., Hyderabad – 500 013, 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. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   ***Short name: WHO BE guidance*** or ***TRS996 Annex 9***

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

3. 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***

4. 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***

5. 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***

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. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   ***Short name: WHO GCP***

8. 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***

9. 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***

10. 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***

11. 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***

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

13. 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***

14. 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***

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Frothiest report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
***Short name: WHO No. 937, Annex 4***