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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 | **Ecron Acunova Limited**<br>**(Navitas Life Sciences)**<br>No.52-2, Near Kasturba Hospital OPD Block<br>Manipal 576104<br>India<br><br>The study in the scope of the inspection took place at the former site with the following address:<br>IV floor, Sri Shirdi Sai Baba Cancer Hospital & Research Centre<br>Manipal-576104<br>India |
| Name and Address of Bioanalytical Research Site | **Ecron Acunova Limited**<br>**(Navitas Life Sciences)**<br>No.52-2, Near Kasturba Hospital OPD Block<br>Manipal 576104<br>India<br><br>The study in the scope of inspection took place at the former site with the following address:<br>IV floor, Sri Shirdi Sai Baba Cancer Hospital & Research Centre<br>Manipal-576104<br>India |
| Name and address Statistical Site | **Ecron Acunova Limited**,<br>Mobius Towers, SJR I-Park, EPIP Zone<br>Whitefield<br>Bangalore - 560 066<br>India<br><br>This site was not included in the scope of the inspection. However, a presentation on the procedure related to the statistical part of the studies was provided, and it was discussed in the respective section of this |

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| | report. |
| Corporate address of Organization | **Ecron Acunova Limited; (Formerly known as Manipal Acunova Limited)**<br>Mobius Towers, SJR I-Park, EPIP Zone<br>Whitefield<br>Bangalore - 560 066<br>India<br>Tel: +91-80-4351 5700 |
| WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles | **WHO application no. TB399**<br>Bioequivalence study of Moxifloxacin Dispersible Tablets 100 mg (Dose: 4 ×100 mg) |
| **Inspection details** | |
| Dates of inspection | 18, 20-22 September 2023 |
| Type of inspection | Routine |
| **Introduction** | |
| Summary of the activities | Ecron Acunova is a full-service Contract Research Organization dedicated to providing services in the field of clinical research. The organization specializes in offering its expertise to the generic drug industry.<br><br>Within the Generics vertical, Ecron Acunova operates various sub-domains and departments, which include:<br>- Generics Services:<br>o Clinical Studies (Involving healthy volunteers, patients, and special population studies)<br>o Experience with various dosage forms<br>o Study designs encompassing different levels of complexity<br>- Bioanalytical Services:<br>o Analysis of small molecules<br>o Analysis of macromolecules (proteins/peptides)<br>o Elemental analysis<br>o Pharmacokinetics, Biostatistics, and Data Standardization Services<br>o Medical Writing |

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| | o Clinical Testing Laboratory Services<br>o Project Management<br>o Regulatory Affairs<br>o BA/BE Clinical Data Services<br>o Quality Assurance<br>o Business Development Support |
| General information about the company and site | The CRO operates from four distinct offices situated in Bangalore, Manipal, Mangalore, and Chennai. It holds responsibility for conducting Phase I and bioequivalence studies. Notably, the bioanalytical laboratories are situated within the Manipal and Bangalore facilities.<br><br>The CRO's inception took place with the founding of the company in Manipal in the year 2005. In the subsequent year, 2006, the company embarked on its Bioequivalence (BE) activities and formalized the establishment of the clinical site in Mangalore. Over the course of its development, the organization extended its operations by incorporating a Bioavailability (BA) site in Bangalore and an additional site in Chennai.<br><br>In 2016, a significant development occurred when Ecron Acunova was acquired by TAKE Solutions Limited. Additionally, in 2019, two acquisitions were successfully finalized: KAI Research, now operating under the name Navitas Clinical Research, and Data Ceutics, which is now recognized as Navitas Data Sciences. It is important to emphasize that Ecron Acunova, originally established in 2005, continued to exist as a separate legal entity even after these acquisitions.<br><br>Ecron Acunova's focus and responsibilities are in the area of Bioequivalence (BE) activities. Meanwhile, Navitas Life Sciences, the parent organization under the brand name, oversees all clinical trial activities conducted by the organization. This structure enables them to make contributions to the pharmaceutical and clinical research field. |
| History | The facilities received approval from the Drugs Controller General of India (DCGI) to conduct Bioavailability/Bioequivalence studies. The BA/BE facility situated in Manipal (No. 52-2, opposite Kasturba Hospital OPD) underwent inspection and received approval from DCGI.<br><br>Furthermore, the CRO underwent multiple inspections by international |

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| | regulatory agencies. A comprehensive record of these regulatory inspections was documented in Annexure 02 of the CRO Master File (CRO MF).<br><br>Additionally, the company underwent an inspection by the WHO in July 2012. |
| 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 were reviewed and a tour of the facility was made<br>Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, 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, along with the comparison of the source data to the study reports. |
| **Scope and limitations** | |
| Out of scope | On-site inspection of the statistical site |

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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 |
| | CRF | (electronic) case report form |
| | CRO | contract research organization |
| | CTM | clinical trial manager |
| | CoA | certificate of analysis |
| | CSR | clinical study report |

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| 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 comprehensive presentation was delivered, providing a detailed overview of the organization's activities.

The CRO provided an organizational chart that displayed key positions and the names of responsible individuals. Each section of the organizational chart was properly dated, signed, and authorized, ensuring it stayed current.

Accreditations from the Drugs Controller General of India (DCGI) were obtained for the old facility on 28 Nov 2019, with a capacity of 48 beds, and for the new facility with 150 beds on 26 Apr 2023. This accreditation also covered the bioanalytical facility.

Each employee had a job description outlining their respective responsibilities, and it was randomly verified that these job descriptions were complete, signed, and dated by the relevant staff members.

A list of signatures from authorized personnel involved in the study was available and duly verified. The allocation list was provided in the study plan at the outset of each study.

The principles of Good Laboratory Practices effectively allocated the responsibilities of the test facility management. The CRO management acknowledged that, as the investigator was an employee of the CRO, certain responsibilities typically assigned to the investigator also rested with the CRO management.

The management took measures to ensure that appropriate and technically valid Standard Operating Procedures were implemented and adhered to. A well-organized historical file of all SOPs was maintained. For further details, please refer to section 3.

The standard working hours were officially from 9:00 AM to 5:00 PM, with a second shift during the night. Additionally, the facility operated on the first and third Saturday of the month. However, during clinical trial confinement periods, the facility maintained a 24-hour operational schedule.

## 2. Computer systems

Procedures for Computer System Validation, as specified in the respective SOP, were established to ensure that computerized systems were appropriately validated, operated, and maintained in accordance with the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP), as applicable.

An inventory of computerized systems within the network was readily available, and it was requested to be updated during the inspection. This inventory included a clear identification of systems subject to GxP regulations. Any modifications to the network, including the temporary addition or removal of systems, were meticulously documented.

A sufficient number of computers were in place to facilitate personnel in performing data entry and handling tasks that necessitated calculations and report compilation. These computers were equipped with the necessary capacity and memory to fulfil their intended functions.

Access to software systems housing trial-related data was carefully controlled. The access control method was explicitly outlined, and a meticulously maintained list of individuals with access to the database was kept in compliance with the SOP for System Access Policy and User Credentials. Robust security measures were in place, including the use of secure and distinct individual-specific identifiers and passwords. It is worth noting that during the study within the scope of the inspection, a generic username, i.e., "Administrator" was observed to be in use by the CRO. This practice was subsequently rectified at the time of the inspection.

Software programs utilized for critical processes were mandated to undergo validation suitable for their intended purposes. System release certificates were provided under the user’s oversight to confirm that the software was validated for its intended application and had been developed under control measures consistent with a Quality Assurance (QA) system. The qualification of the selected systems was scrutinized for verification.

A random review of the relevant documentation confirmed that the specific user requirements, regulatory/guideline requirements for Bioequivalence studies, the operating environment in which the system was utilized, and the system’s usage in the studies were considered in the performance qualifications. Quality risk management principles were applied when determining which components required validation. SOPs detailing the usage of each software program employed in BE study activities were available.

Routine updates to critical software programs were conducted as necessary, following a thorough risk assessment to evaluate their potential impact on current data and qualification or validation status. These updates adhered to the guidelines outlined in the applicable SOP. At the time of the inspection, a periodic plan documented in an Excel sheet was in place and discussed. Additionally, the Change request for the revalidation of the chromatography software system associated with the selected LC-MS/MS was available and reviewed.

The network infrastructure, encompassing the complete client/server architecture and interfaces such as laboratory information management systems, underwent design, qualification, management, and control by the IT teams situated in Bangalore and Chennai in collaboration with the Clinical Tech team. The local IT team held responsibility for tasks related to backup, restoration, and resolution of user access issues. Additionally, user management was overseen by the ClinTech Team through request forms and in accordance with the respective SOP, particularly during the initiation and termination of employment.

Data entry procedures, which encompassed data validation methods such as proofreading and double data entry, were appropriately designed. The precise data entry process was explicitly detailed in the SOP. Moreover, following the conclusion of each study, the CRO took steps to relocate the data from the D:Drive on computers associated with LC-MS/MS and securely archived it, aligning with the guidelines outlined in the respective SOP. An archival request form, dated 27 Oct 2022, was made available and thoroughly reviewed. It was further substantiated with the requisite evidence to confirm the complete transfer of data.

Electronic data was backed up at regular intervals in accordance with Site-specific Guidelines on backup procedures. The reliability and completeness of these backups were verified according to the same SOP. Documentation of the last restoration was provided, dated 16 Sep 2023, and verified on 18 Sep 2023.

Access to the server room was controlled through face ID reader device.

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

## 3. Quality management

The CRO had appropriate QA and QC systems with written SOPs to ensure that trials were conducted and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and the applicable regulatory requirements. The CRO used a software system for SOP upload, approval, and authorization. On the first day of the inspection, the relevant SOPs for study activities were provided to the inspection team on a pen drive.

The issuance of templates for sample processing was the responsibility of the QA Unit in accordance with the respective SOP. Additionally, other templates utilized within the bioanalytical laboratory were provided by the QC team, following established control procedures. Nevertheless, it was noted that there was room for improvement in the

process since the sequential numbers on the templates were generated manually and could potentially be altered. Therefore, the CRO has been advised to consider implementing digital methods for the generation of controlled templates.

A Quality manual, dated 31 Aug 2023, was provided. The Quality Manual described the quality policy and quality objectives. The Quality Manual was prepared in compliance with the requirements of ISO 9001:2015 and ISO 27001:2013. It addressed the organization's intent to comply with applicable national and international guidelines required for product/service realization while ensuring customer satisfaction in a regulatory-compliant manner. The intent of this manual was to confirm:

- The products and services provided by the generic business vertical of the organization met customer and applicable statutory and regulatory requirements.
- Facilitated opportunities to enhance customer satisfaction.
- Addressed risks and associated opportunities for mitigation.
- Demonstrated conformity to specified quality management system requirements.

The organization had appointed an independent Quality Assurance Department to oversee compliance with the Quality Management System.

The QA unit had the following responsibilities:

- Ensuring ALCOA-C compliance
- Conducting checklist-based reviews
- Providing CSV support
- Maintaining calibration documentation
- Offering scientific writing and regulatory query support
- Conducting study audits
- Performing system audits
- Managing vendor relationships
- Handling changes control and deviation management
- Overseeing archives
- Managing Document Management System (DMS) and Quality Management System (QMS)
- Coordinating Sponsor and Regulatory inspections
- Providing support for regulatory queries

Both in-process and retrospective QA verifications were carried out, especially in bioanalysis, during the preparation and testing of samples and standards.

The internal audit plan for 2022 and 2023 was provided. The randomly selected audit report was reviewed and discussed.

The company, as outlined in the applicable SOP established guidelines for audit trail reports to be used for the software systems employed for bioanalytical activities. These guidelines detailed the specific data that needed to undergo review. To document the data integrity check, a form was employed, which included relevant questions.

The change request form for the chromatography software system, approved on 9 Aug 2023 was prepared for the transfer of the system to a new facility. The documentation was reviewed and discussed.

Additionally, the audit plan for the period 2022 and 2023 was reviewed.

An observation related to the QMS was adequately addressed in the respective CAPA plan.

## 4. Archive facilities

The CRO maintained a secure storage facility for archiving trial-related documents. This facility was equipped with fireproof measures, humidity control, and pest control to ensure document safety and integrity. Additionally, a third-party facility was utilized for long-term archiving. Both the contract and the respective audit report were reviewed.

Archiving activities were conducted in accordance with the applicable SOP, which outlined the procedures for the archival and retrieval of BA/BE documents. Access to archive storage areas was strictly controlled and limited to authorized personnel. A list of authorized personnel was displayed at the facility's entrance.

Detailed records of document access and return were diligently maintained. The retention period for study documentation, including raw data was defined in the SOP for Disposal of BA/BE documents.

The inspection confirmed the effectiveness of the trial-related documentation archiving procedures by demonstrating successful retrieval and document traceability.

An observation related to the Archiving facility was adequately addressed in the respective CAPA plan.

## 5. Premises

On the second day of the inspection, a facility tour was conducted.

The facility, which spanned 32,000 square feet across four floors, included:

- A 150-bed Clinical Pharmacology Unit.

- A dedicated screening area.
- An integrated Clinical Testing Laboratory.
- Multiple wards designed to accommodate mixed-gender studies.
- An Euglycemic Clamp Facility.
- A state-of-the-art Bioanalytical Laboratory.

The facilities were kept clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

Clinical trials were carried out under conditions that ensured adequate safety for the subjects.

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

Access to the facility was controlled and restricted using key cards/biometric access. To monitor subject exits from clinical facilities, the doors were locked, and subjects were under supervision. Emergency evacuation procedures were in place, and all entries and exits from the facility were meticulously recorded.

The sites hosting clinical activities included a dedicated pharmacy where investigational products were stored under optimal conditions. Access to this pharmacy was strictly controlled, ensuring that only authorized personnel could enter or exit. Detailed records of each visit to the pharmacy were diligently maintained. Within the pharmacy, there was a walk-in stability chamber, access to which was carefully regulated. This chamber was equipped with monitoring technology, including a digital thermometer, to ensure precise temperature control and stability monitoring.

The temperature and humidity of the freezers and refrigerators were monitored using the digital thermometer system. In areas where temperature control was necessary, such as the balance room, measurements of both temperature and humidity were conducted using hygro-thermometers.

The laboratory premises were designed to align with the intended operations. Sufficient space was allocated to prevent potential mix-ups, contamination, or cross-contamination. Furthermore, adequate storage capacity was available for samples, standards, solvents, reagents, and records, ensuring the organized functioning of the laboratory.

Laboratory premises were designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Before conducting tests, staff had access to safety data sheets. Staff received training on using firefighting equipment, such as fire extinguishers. They were also required to wear lab coats and protective gear, including eye protection. For highly toxic chemicals, a safety cabinet was used to prevent exposure. All chemical containers were properly labeled with clear warnings.

Adequate insulation and spark-proofing measures were applied to electrical wiring and equipment, including refrigerators. Safety guidelines for handling compressed gas cylinders were adhered to. The importance of not working alone in the laboratory was recognized by staff. First-aid materials were made available for immediate use.

Containers holding volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were securely sealed. Volatile organic chemicals were managed within certified fume hoods or air extractors, with safety and eye wash stations conveniently accessible in the laboratory.

The premises were equipped with effective systems for waste disposal, fume treatment, and environmental protection in compliance with local and national regulations.

Observations pertaining to the Premises have been adequately addressed in the respective CAPA plan.

## 6. Personnel

An adequate team consisting of medical, paramedical, technical, and clerical staff was on hand to support the trial. The total staff count amounted to 115 employees. Throughout all trial phases, including night-time, personnel were present to uphold the rights, safety, and well-being of the subjects and provide emergency care when necessary. Additionally, contract workers were engaged in specific activities to enhance the team's capabilities.

To ensure the qualifications and training of personnel, we conducted a random review of current curriculum vitae and training records for both full-time and contract workers involved in trial activities.

Observations pertaining to the Personnel were adequately addressed in the respective CAPA plan.

## 7. Clinical phase

The clinical phase of the studies took place within the CRO's premises.

Within the CPU, there were 150 beds available for subjects. Accommodation facilities were equipped with systems that allowed subjects to easily alert CRO staff in case of any need or emergency.

Facilities for changing and storing clothes, as well as for washing and toilet purposes, were maintained in a clean and well-organized manner. They were easily accessible and suitable for the number of users. Additionally, lockable toilets were equipped with alarm systems, and the doors were designed to ensure they could be opened from the outside in case of a medical emergency.

The clinical site consisted of

- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- Subjects' recreation;
- Pharmacy;
- Dosing area;
- Sample processing area;
- Archive facility;
- Dining hall;
- Emergency care room
- Walk-in freezer room
- Nurses counter
- Locker & change room

X-ray tests were conducted at a contracted Hospital in Manipal, as outlined in the respective service agreement. An audit of the facility was carried out on 30 Dec 2021.

Provisions were made to ensure the prompt transportation of subjects to the hospital in case of emergency. However, during the study's inspection, the site was situated within the hospital itself. The hospital was notified one day before the trial's initiation, and they acknowledged the trial's start date.

Access to the randomization list was limited to the pharmacist responsible for the study. These documents were securely transmitted with passwords via email from the

statistician to the pharmacist or stored securely under lock and key in hard copy form. The distribution of these documents was recorded.

All equipment used underwent appropriate calibration at predefined intervals. The proper functioning and performance of emergency-use equipment, such as defibrillators, were regularly verified at suitable intervals.

## 8. Clinical laboratory

An in-house clinical laboratory, specifically Ecron Acunova Limited Clinical Testing Laboratory was established for sample analysis. This laboratory’s accreditation status was valid until 14 Sept 2025.

The laboratory performed haematological tests, urine analyses, and other specified tests in accordance with the study protocol.

To ensure the complete traceability and integrity of samples, a comprehensive process was implemented, encompassing sample labeling, receipt, storage, and chain of custody, all tracked through the applicable software application.

The CRO received information from the laboratory, including details about the analytical methods employed, a dated list of laboratory normal ranges, and the laboratory's accreditation certificate. Furthermore, predefined deviations from normal ranges were outlined in the respective SOP.

The Head of the Clinical Laboratory's curriculum vitae was up to date, signed and was reviewed.

The laboratory created individual reports for each subject and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic or paper formats, depending on their source and the laboratory’s storage capacity.

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

In addition to relocating the BA/BE operations to the new address, the Clinical Testing Laboratory was also moved to its new location (No.52-2, Near Kasturba Hospital OPD Block, Manipal 576104, India). The lab has been fully operational at the new facility since 1 Aug 2023.

## 9. Ethics

The trial was approved by the Independent Ethics Committee (IEC) on 16 Jun 2022, prior to the commencement of any study activities. The independence of this committee from the sponsor, investigator, and CRO was confirmed through an examination of the respective member list. Comprehensive minutes of the IEC meetings were maintained, documenting the discussions, recommendations, and decisions made during these meetings. The IEC was provided with adequate time to thoroughly review protocols, informed consent forms (ICFs), and associated documentation.

Informed consent form

Study information was presented to participants in their vernacular languages, including English and Hindi at a level of complexity tailored to their comprehension. This information was conveyed both verbally and in written form.

Before initiating any trial-related activities, subjects provided informed consent, which was meticulously documented in writing. Additionally, informed consent procedures were recorded through video documentation. The information provided was clear and emphasized that participation was entirely voluntary, and subjects had the right to withdraw from the study at any time without providing a reason. If provided, the reasons for withdrawal were duly recorded in the study records.

Furthermore, participants were provided with information regarding insurance coverage and other compensation or treatment procedures in the event of injury or disability resulting from their participation in the trial. This information was available through an insurance policy.

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

The certificate of translation and back translation for the informed consent documents were subjected to careful review, ensuring the accuracy of the translation process. The translation services were provided by a translation service company, and their certificate of service, attesting to their reliability and competence, was readily available.

## 10. Monitoring

The study was monitored by the sponsor-employed monitor, who had the necessary qualifications to ensure adherence to the protocol, GCP, GLP, and relevant ethical and regulatory standards. This consisted of confirming the proper execution of procedures for completing CRFs and validating the accuracy of collected data.

A pre- and post-study visit and a monitoring visit during the trial were performed. The monitor prepared a written report after each site visit and communicated any issues to the CRO and the sponsor as quickly as possible, even while the study was being conducted, if possible, to enable prompt corrective action. The respective communications and corrective actions were documented.

## 11. Investigators

The principal investigator (PI) was responsible for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee, and signing of the protocol and the final study report. Comprehensive documentation, including the CV, job description, and training logs of the investigators, was available and underwent a thorough review.

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

The information pertaining to the recording of investigational product receipt, storage, handling, and accountability at all trial stages was documented. Additionally, verification was conducted for information concerning the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, and reconciliation of the products. Details of the pharmaceutical product utilized included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through Thermo-lab Humidity chamber.

Randomization was carried out in adherence to the applicable SOP and comprehensive records containing the randomization list and seed were upheld. Access to the randomization list was limited to a dispensing pharmacist and the statistician.

The investigational products (IPs) were appropriately labelled. After printing, a verification process was conducted to ensure compliance with the randomization list before affixing the labels onto the containers. Labels were securely attached to the containers to prevent loss of information when the lid was removed.

To ensure accurate administration, robust procedures for labelling and documenting IP administration were implemented. Tear-off labels were utilized, ensuring that each subject received the correct product. These labels were designed in pairs, with one portion affixed to the container and the second placed on the CRF at the time of dosing.

Empty containers for the test and reference investigational products were separately labelled. They were stored in a secure area, locked and under key control, to prevent any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were carried out in accordance with the specified requirements. Dosing followed the procedures outlined in SOP for Identification and Dispensing of Investigational Products.

The work surface used for product handling underwent cleaning before introducing product bottles into the area. Any product containers, whether full or empty, formulations, labelling materials, contaminants, dirt, and debris were removed from the workspace. Prior to introducing and opening product containers, a second individual verified that the surface area/line was clear and clean. The IMPs were handled using appropriate utensils. Tablets were placed into each container following the randomization list for either the comparator or the test product, as appropriate. It is important to note that the two products, Test and Reference, were handled at separate times, which also applied to the labelled containers. Each step of the process was documented in a sequential and detailed manner. Furthermore, both the work surface used for product handling and its immediate surroundings were cleared and cleaned both before and after initiating the dispensing of subsequent products within the same study.

Investigational product accountability and dispensing records were always maintained. Each activity was documented at the time it was performed, including records of doses administered and returned or destroyed and records of verification by a responsible staff, including QA, QC person, and investigator of each step.

Dosing was carried out in accordance with the SOP for Administration of Investigational Product-(Oral) under the supervision of the investigator and qualified staff member to whom this task was explicitly delegated in writing. The label was checked before dosing and the exact time of dosing was documented on the CRF’s designated page. A mouth check was performed by looking under the tongue, under the lips, in the corners of the mouth, and between gums and cheeks, using a tongue depressor or a spatula and a penlight, in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. Dosing was directly documented in the CRFs.

After dosing, the reconciliation of investigational products was confirmed by a second responsible individual. Samples from the original product containers were retained for potential confirmatory testing. The procedure for sample retention was clearly outlined and described in the respective SOP, with specifics agreed upon in consultation with the

sponsor. Additionally, any dispensed products that were not administered were also retained for documentation.

An observation related to the handling of IMPs was adequately addressed in the respective CAPA plan.

## 13. Case report forms

Randomly selected CRFs from the study underwent a thorough review.

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

Within the CRFs for each subject, copies of clinical laboratory reports and all electrocardiograms (ECGs) were included. Additionally, the CRFs contained comprehensive information regarding vital signs, sample collection, meal intake, water restriction, dosing administration, adverse events (AEs), concomitant medications, and inclusion and exclusion criteria. This comprehensive data was meticulously recorded in the CRFs.

## 14. Volunteers, recruitment

The procedures for recruiting volunteers were clearly outlined in the respective SOPs. These SOPs included a comprehensive description of the various methods employed by the CRO for recruitment purposes.

To manage volunteers effectively and prevent cross-participation, a database known as for volunteer management was maintained. This system specified a minimum timeframe that must elapse between a volunteer's participation in one study and their involvement in the next. Access to this database was strictly controlled via password protection to ensure the confidentiality of information pertaining to volunteers or subjects.

To ensure the accurate identification of volunteers and subjects, a biometric system was used. This biometric system underwent periodic validation. Evidence of device verification, along with the checklist related to 24 Jul 2023, was documented.

Potential volunteers provided informed consent for any screening procedures required to assess their eligibility for participation in the study, in addition to granting consent for their involvement in the research phase of the study. The clinical trial protocol comprehensively detailed the criteria for subject selection, including both inclusion and exclusion criteria, and clearly delineated the necessary screening procedures. To prevent over-volunteering and ensure compliance with participation limits among other CROs, another software system was employed. This system allowed for the verification of

whether any subjects had previously participated in other trials in the area, and participation data was securely uploaded to a central repository for this purpose.

The devices/kits used for alcohol tests and pregnancy were available and verified.

## 15. Food and fluids

Meals were standardized, adequately controlled, and scheduled during the study days. The CRO was able to arrange standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol and according to the agreement with the catering service. The vendor was audited by the CRO. The documentation was available and discussed.

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

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

The study was planned, organized, executed, and monitored to ensure an acceptable safety profile, including the well-being of the volunteers. A qualified medical doctor assumed responsibility for making medical decisions in cases of adverse events, as well as for promptly notifying the relevant health authorities, the sponsor, and, as applicable, the ethics committee, particularly in the event of a serious adverse event.

To address potential emergencies, first-aid equipment, and appropriate rescue medications were readily available in the ICU at the study site. Any treatments administered to a subject were documented and included in both CRF and the corresponding supporting documentation within the ICU.

The CRO maintained adverse event registration and reporting forms, along with a form for documenting the use of concomitant medications as an integral part of the CRF.

**Bioanalytical section**

The following records and activities related specifically to the study related to WHO application Moxifloxacin dispersible tablets were thoroughly inspected:

- Source documentation and raw data for bioanalytical method validation.
- Analysis of subject plasma samples and associated electronic data.
- Audit trails pertaining to electronic data capture and handling in BE studies.

- Results of calibration standards, quality control samples (QCs), and subject plasma samples, including chromatograms from 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. 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.

During the study documentation review, the inspection team received support from knowledgeable and transparent personnel. All necessary chromatography raw data, including the audit trail associated with the study, were made available on a computer within the inspection room.

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

The method development process was described and documented in the designated notebook, adhering to the applicable SOP. The utilization of an Internal Standard (IS) was justified based on relevant literature. A copy of the relevant literature was readily accessible.

At the time of method validation, conducted in May 2014, the whole blood stability had not been verified during the method development phase. In response to new requirements outlined in ICH M10, these guidelines were incorporated into the updated SOP with Edition No. 3, Version No. 2. For the assessment of whole blood stability, the instrument's response to freshly spiked blood served as a reference for comparison with the response obtained from blood that had been spiked and stored for approximately 2 hours. After the method development phase, an initial draft of the Standard Test Procedure (STP) was provided which served as the foundation for the main STP. Following a pre-validation process, a method validation plan was established as the basis for subsequent method validation activities. In the MS methods, a stable isotope-labelled internal standard, Moxifloxacin-D4 HCl, was employed.

The LC-MS/MS method designed for the quantification of Moxifloxacin in human $K_2$EDTA plasma was validated according to the respective bioanalytical method validation plan in alignment with the applicable SOP. As part of the method validation in accordance with the respective SOP, a production run was conducted to replicate the number of samples typically analyzed in a single run, while maintaining acceptable

precision and accuracy standards. This production run consisted of adequate samples, including linearity and quality control (QC) samples (LQC, MQC, and HQC in equal numbers). Mean % nominal concentration and %CV were calculated at each level.

The method validation was conducted in 2014, and the results, which fell within the acceptance limits, were documented in a report issued in May of that year. Subsequently, a gap analysis was conducted to align the already established method with applicable regulatory requirements at the time of study. The outcomes were found to be within the specified limits outlined in the SOP and were reported as Supp-02 to the method validation report.

Sample processing adhered to the established STP and the Sample Analysis Plan was available. This entire process was documented using the corresponding forms. Additionally, an Event Investigation Form was made available to record any unexpected occurrences during sample processing, when they occurred.

Data supporting the stability of the samples under the specified conditions and storage duration were available before the commencement of the study. However, the long-term stability testing was conducted prior to the issuance of the study reports, specifically on 18 Oct 2022.

The method validation review encompassed a range of critical parameters, including precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve assessment, autosampler carry-over evaluation, dilution integrity examination, and various stability tests (including freeze-thaw stability, stock solution stability, and reference standard storage stability). Additionally, the assessment included the evaluation of haemolytic effects, recovery rates, and reinjection reproducibility.

Partial validation was carried out in accordance with the specified requirements. The matrix used for analytical method validation corresponded to the matrix of the actual study samples.

Furthermore, the documentation related to the purchase of plasma from the supplier on 11 Jul 2022 was reviewed, including the receipt, storage, retrieval, preparation, and utilization of the pooled plasma. To effectively manage these plasma lots, the CRO allocated specific numbers to each batch, which were then referenced in the form for bulk spiking schemes during the analysis of study samples for calibration curves (CCs) and quality controls (QCs). The precise consumption of plasma was documented in the blank matrix logbook.

In addition, for the purpose of homogenization, pre-dose samples were drawn and pooled with the plasma acquired from the vendor, with the quantities recorded in the appropriate form for sample transfer and collection. Any excess plasma was securely stored in the freezer after the conclusion of the study and would be documented if eventually discarded.

In each analytical run, there was a simultaneous analysis of calibration curve (CC) standards, quality control (QC) samples distributed evenly throughout the run, and subject samples. The precise sequence for processing was well-defined, documented, and verified. All samples collected from a given subject during all trial periods were analyzed within the same run for consistency.

The acceptance criteria for these analytical runs were established and confirmed through a comprehensive review. This assessment consisted of the evaluation of analytes' retention times, the accuracy of calibration standards and quality control samples, peak integration, and internal standard (IS) peak areas. These criteria were aligned with the applicable SOPs, including SOP for the assessment of chromatogram quality acceptance and SOP for the execution of study sample analysis and the determination of analytical run acceptance criteria.

Prior to initiating each new sequence, a system suitability assessment was carried out. This involved injecting an aqueous equivalent MQC solution of Moxifloxacin alongside the internal standard working stock solution of Moxifloxacin D4. The calculated %CV for retention time (RT) and peak area ratio consistently met the acceptance criteria.

Chromatograms were examined in accordance with the applicable procedures to ensure data integrity and analytical accuracy.

The samples chosen for ISR were selected to include concentrations around $C_{max}$ and within the elimination phase. Acceptance criteria for ISR were outlined in SOP for Incurred Sample Reanalysis.

During the studies within the scope of the inspection, a review of the system audit trail was conducted. Adequate training was provided to the responsible personnel, and this training was well documented. Furthermore, the CRO had a practice of documenting any system errors that were not captured by the chromatography system audit trail. This was achieved through the Windows audit log, specifically, the Application log and System log. It is worth noting that this practice had been recently implemented and had not yet been incorporated into the respective SOPs. As an illustrative example, an incident on 22 Aug 2023, where the application experienced a hang, was captured in both the

application log and system log. This event was duly documented in the corresponding event investigation form.

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

The clinical trial protocol and the information presented to the volunteers clearly specified the details regarding the samples, specifically blood plasma. This encompassed the sampling method, the required volume, and the total number of samples to be collected. To ensure the proper handling of these samples, applicable SOPs were followed. The processes involving the collection, preparation, transport, and storage of the samples were conducted in accordance with SOP for Segregation and Transport of Study Samples from the clinical facility to the bioanalytical laboratory, SOP for Transfer, Processing, and Storage of Bio Samples (from ward to the sample processing room), and SOP which covered the Handling of Biological Samples in the Bioanalytical Laboratory.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were to be considered when calculating the pharmacokinetic parameters.

The labelling of collected samples was carried out to ensure the correct identification and traceability of each sample. This procedure adhered to the SOP which specifically covered labelling in the bioanalytical laboratory. Furthermore, all storage conditions, including freezer temperatures, were controlled, monitored, and consistently recorded throughout the storage period. To facilitate the transfer of samples from the clinical department to the bioanalytical department, the samples (Aliquot 1) were transported on the same floor using dry ice. Although a data logger was not included with the shipment, the precise timing of sample receipt, retrieval, and storage was carefully documented in the respective forms and logbooks to verify the proper transport of samples. Additionally, comprehensive records were maintained to track the storage and retrieval of samples. As a precautionary measure to enhance data redundancy and security, samples were replicated into aliquots, and these duplicates were transferred and stored separately. It is noteworthy that Aliquot 2 was retained within the clinical department and was not transferred to the bioanalytical laboratory throughout the duration of the study.

The management of study samples, QC samples, and pooled matrix was regulated in accordance with the SOP for Handling of Biological Samples in Bioanalytical facility, specifically for Study Sample Management. Subject sample disposal required approval from the sponsor or protocol guidelines. The custodian responsible for sample management must seek approval, typically on a form, from the study director before proceeding with the disposal of biological samples.

## 19. Data processing and documentation

The integration settings were based on scientific principles and were justifiable. A low smoothing factor was maintained to ensure that potential interferences and changes in peak shape were not concealed. Manual integration was not permitted.

The criteria for accepting or excluding CC and QC samples, as well as the overall batch acceptance criteria, were clearly outlined in the relevant SOP.

In all analytical runs, the source data contained comprehensive information about the initial evaluation of runs, which included all calibration samples. This information was retained when repeating the analysis. The calibration range was appropriately truncated, and variations in the internal standard were monitored and factored into the verification process to ensure the validity of the results.

Audit trails were activated on all analytical instruments throughout the method validation and the relevant studies.

For all original analytical raw data, including calculations, chromatograms, and their associated audit trails, adequate documentation practices were observed. This documentation ensured clear traceability, encompassing key details such as the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s) involved. All audit trail files, including results table audit trails, project audit trails, and instrument audit trails, were retained.

Additionally, every data point was traceable to a specific sample, providing information such as the sample number, the time of sample collection, the time of centrifugation, the time when the sample was placed in the freezer, and the time of sample analysis. This level of detail enabled the identification of any potential irregularities in the results that could be attributed to the mishandling of the samples.

## 20. Good laboratory practices

The inspection team conducted facility inspections on Day 2 and Day 3 to assess the facility's suitability, arrangement, and safety.

The deep freezers used for sample storage and the refrigerators employed for storing Reference standards underwent qualification, calibration, and regular maintenance to ensure their reliability and accuracy. To enhance the safety and security of these storage units, an alarm system was integrated with the digital thermometer. This system was designed to trigger call notifications to the facility's security personnel in the event of any temperature deviations. During the inspection, the automatic alarm system was tested to

confirm its proper functionality. Daily monitoring and regular alarm checks were documented to maintain a record of the system's performance. The procedure for defrosting was scheduled to be implemented following the guidelines outlined in the respective SOP.

To confirm the qualification verification, we reviewed the temperature mapping of a selected Deep Freezer, which was conducted on August 10, 2023. This review focused on verifying the hot spot and the sensor's placement within the freezer. The temperature mapping process was executed correctly at the time of inspection.

In the context of maintenance and repair, careful consideration was given to the transfer of samples to equivalent storage units. This was part of ensuring uninterrupted sample storage during any maintenance activities or the relocation of facilities to the new site. During the facility transfer from the old site to the new site, a chart recorder was employed while the digital system was temporarily disconnected.

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, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. Equipment and its components were labelled with the respective ID number, date of calibration, and date of next calibration. The equipment usage was adequately documented in the analytical sheets, as well as the respective logbooks for the instrument usage. The use of columns was recorded in the logbook for the usage of columns.

These activities were verified by random review of the equipment used in study-related activities.

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.

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

**Pharmacokinetic, statistical calculations and reporting section**

## 21. Pharmacokinetic, statistical calculations

On Day 4, a comprehensive presentation was delivered to describe the CRO's procedure for pharmacokinetic and statistical calculations, as well as the generation of a randomization list.

The statistical model that supported the primary bioequivalence analysis was explicitly outlined in the protocol within the section dedicated to the statistical analysis plan.

The qualifications of the statistician were duly confirmed through a review of his CV.

Calculations were executed using the SAS software system. To ensure data accuracy, a second qualified individual cross-checked the input data in accordance with the relevant SOPs as presented in the presentation.

A trial records database was systematically maintained and promptly locked upon the conclusion of the study. This process was accompanied by the gathering of evidence, which was obtained by signing off on QC documentation for time points and concentration data. Subsequently, once the database was locked, the statistical analysis for the study was conducted. The specific dates for locking and conducting the statistical analysis were documented and explicitly mentioned in the study report. This entire process was outlined in a dedicated SOP.

## 22. Study report

The process of study report writing was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report, e.g., SOP for Sample analysis report. No discrepancies were identified between the data in the report and the original (raw) data.

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

| **Miscellaneous** | |
|---|---|
| ***Samples taken*** | NA |
| ***Assessment of the CRO master file*** | The CRO's Master File, version 5 was submitted and reviewed in advance of the inspection. Version No: 05 dated, approved on 28 Aug 2023 was submitted and reviewed. |

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|---|---|
| ***Annexes attached*** | NA |

| **Part 3** | **Conclusion** |
|---|---|

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at ***Ecron Acunova Limited*** located at ***No.52-2, Near Kasturba Hospital OPD Block Manipal 576104; India***.

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR.

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

| **Part 4** | **List of guidelines referenced in the inspection report** |
|---|---|

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 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. 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. 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***

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***