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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Macleods Pharmaceuticals Ltd, Bioequivalence Department, R&D III Plot No. 18, Street no. 9 MIDC, Andheri - (East), Maharashtra India Macleods Pharmaceuticals Ltd, Bioequivalence Department, R&D II Plot no. 95, Road no. 16, Opp. Suncity Hotel MIDC, Andheri (East) Mumbai, Maharashtra, 400 093, India
Name and Address of Bioanalytical Research Site	Macleods Pharmaceuticals Ltd (Bioequivalence Department), R&D III Plot No. 18, Street no. 9 MIDC, Andheri - (East), Maharashtra India
Name and address Statistical Site	Macleods Pharmaceuticals Ltd (Bioequivalence Department), R&D III Plot No. 18, Street no. 9 MIDC, Andheri - (East), Maharashtra India
Corporate address of Organization	**Head Office** Atlanta Arcade, Church Road, Near Leela Hotel Andheri-Kurla Road Andheri E, Mumbai – 400059, India Tel +91-22-66762800 Website: www.macleodspharma.com
GPS coordinates	R&D-II: 72.87°E 19.12°1'4 27°N R&D-III: 72.87°E 19.12°N 23°N
WHO product numbers covered by the inspection/ Product names/	**WHO application no. HA 769** Bioequivalence study of Flucytosine Tablets 500 mg **WHO application no: TB 390** Bioequivalence Study of Bedaquiline Tablets 100 mg.

Study numbers/ Study titles	**WHO application no: TB 391** Bioequivalence Study of Linezolid Dispersible Tablets 150 mg **WHO application no: TB 398** Bioequivalence study of Rifapentine Tablets 300 mg **WHO application no: TB 397** Bioequivalence Study of Pretomanid Tablets 200 mg
Inspection details	
Dates of inspection	Site R&D III: 6 Feb – 10 Feb 2023 Site R&D II: 13 Feb – 15 Feb 2023
Type of inspection	Routine
Introduction	
Summary of the activities	The CRO had the capacity to run bioavailability/bioequivalence studies under fasting and fed conditions, steady state studies, inhalation studies, in-vitro studies (Invitro release test, (IVRT), Invitro permeation test studies (IVPT) and invitro binding studies), vasoconstriction studies and impurity analysis of API and finished product.
General information about the company and site	Macleods Pharmaceutical Bioequivalence Department is the in-house department of Macleods Pharmaceutical Limited. The company was incorporated in the year 1986. The Bioequivalence Department started being operational at R&D-I in September 2005. The organization supplies medicinal products to the Indian market, USA, Europe, Canada, CIS, South-East Asia, Africa, Latin America, and the Middle East. Macleod is an R&D-driven company that develops formulations across various therapies in multiple dosage forms. It operates within seven Department of Scientific and Industrial Research-approved R&D centers for a range of development activities, including: - API - Formulation's research - Analytical development - Bioequivalence study centre The Bioequivalence Department consisted of R&D II, III (in Mumbai), and IV (in Ahmedabad) units. R&D-I was recently shifted to R&D-III, hence; R&D I was no longer operating as a bioequivalence unit.

History	The facilities and the systems were inspected by the US FDA, MHRA, MCC-South Africa, Ministry of Health-United Arab Emirates, Ministry of Health- Malaysia, ANVISA and Ministry of Public Health-Thailand. R&D-I & II underwent an onsite inspection by WHO in July 2017. A desk assessment review was carried out in September 2020.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Not applicable

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioanalytical
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis

CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
LC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
ISF	investigator study file
ISR	incurred sample reanalysis
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OOS	out of specification
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 INSPECTION AND COMMENTS

General section

1. Organization and management

An opening meeting took place at the R&D II – Suncity site as a joint opening meeting with the US FDA inspector. A presentation was provided explaining the activities of the organization in detail. The inspection continued physically at R&D-III site from 6 to 10 February and at R&D-II site from 13 to 15 February.

The CRO had an organizational chart depicting key positions and the names of responsible persons.

There was a job description for each employee, including their responsibilities. It was randomly verified that every job description was signed and dated by the staff member to whom it applied.

A list of signatures of the authorized personnel performing tasks during each study was available. The protocol training forms, and delegation of duties related to WHO application HA769 were verified.

The CRO management was aware that as the investigator was an employee of the CRO, some of the duties usually assigned to the investigator would, similarly, reside with the CRO management.

It was ensured by the management that appropriate and technically valid SOPs were implemented and followed. Maintenance of a historical file of all SOPs was adequately organized. A digital copy of SOPs related to analytical, clinical, QA, statistical, IT, and general activities was provided at the inspection team's disposal.

2. Computer systems

A list of software and computerized systems was provided for the study activities. During the inspection, an inventory log for the software systems related to the pathology laboratory was also prepared.

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and were validated, operated, and maintained in accordance with the principles of GCP and GLP, as appropriate.

A periodic review of the GxP computerized system was planned to ensure that systems were compliant and that all documentation was complete, accurate, and in line with the current business process. The periodic review was applicable for all the applications that support GxP processes at the Bioequivalence Department of Macleods Pharmaceuticals Ltd. The inspectors emphasized that the CRO should consider the data integrity and challenge the options available in the system, which could lead to any data integrity issue during the revalidation.

There were enough 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 accessing the database was maintained. Secure and unique, individual-specific identifiers and passwords were used.

Randomly selected software programs used to perform key activities were inspected to verify their suitability and validation for the intended use. The respective qualification documentation was reviewed.

The qualification and/or validation certificates were provided under the user's supervision.

The specific user requirements, regulatory/guideline requirements for BE studies, the operating environment in which the chromatography software system was used, and the usage of the system in the studies were considered during the qualification of the respective systems.

Quality risk management was defined in the respective SOP when deciding which functionality needed to be validated. All phases of the systems' life cycle were considered. SOPs for usage of each software program used to perform activities of a BE study was available. SOP for User Rights Management for Analyst Software was reviewed and discussed.

Regular updates to key software programs were planned in the Periodic Review Planner - 2023, following an assessment of the potential impact it could have on current data and qualification or validation status.

The specification of CD/DVD tapes, storage of data, and the procedure for backup archiving of all relevant electronic data was specified in SOP for the backup and retrieval procedure for electronic data effective 30 Jan 2023, including frequency of backup. The previous backups were not overwritten during automated incremental daily, fortnightly, and monthly backups. The disaster management of data was also described in the SOP. Installation of antivirus application was documented. The fortnightly backup tape was sent to a remote location for disaster management. The monthly backup tape was in the custody of the QA department.

Networks, including the entire client/server architecture and interfaces such as laboratory information management systems, were appropriately illustrated in the applicable flowchart.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.) were designed to prevent errors.

The relevant Unit completed a form for backup retrieval, i.e., 'Requisition for data restoration'. Upon receipt of the approved form (approved by QA), the IT-authorized trained person restored data from the CD/DVD tapes. The backup tape of instrument data was challenged once a year to ensure that the backup process was authentic, accurate, reliable, and usable. The last restoration protocol for Qualification of backup and restoration process of BE department was available. The report concluded that the back and restoration were sufficient, using the monthly backup tape dated 12 Oct 2022. The requisition form was prepared and approved on 26 Apr 2022.

The performance of backup for Biochemistry analyser on the CD-room device was discussed.

Observations related 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.

A Quality manual with version no. 16, effective 11 Apr 2022, was provided.

The quality assurance unit was an independent body and reported to the management. The QA unit had its own SOPs to ensure that studies were performed, and data were generated, documented (recorded), and reported in compliance with the protocol, GCP, GLP, and the applicable regulatory requirements.

Both in-process and retrospective QA verifications were executed correctly.

The quality management system recently included root cause analysis and tracking for trends in their practice. An annual master schedule for trend analysis year 2023 was available, covering the temperature & humidity of different facilities, SOP deviations, change control, CAPA, and equipment malfunctions. The implementation of appropriate corrective and preventive action (CAPA) was adequately addressed in the company's response.

A list of vendors and the respective audit plan for 2023 was available and reviewed.

The company defined the audit trail review process, the applicable checklists, the audit trail queries and reports to be used for different systems and different purposes in the respective SOP. It was specified which data was required to be reviewed and how the data and any possible modifications were presented in the audit trail.

The SOP for Change control was discussed in relation to the change request raised for shifting the BA facility from the facility I to III. The respective form was provided for which a different version of SOP was applicable. Before implementing the change request, the CRO did not produce a comprehensive overview of all the changes that might impact the CRO's quality management system. It was noted that the practice was amended in the recent SOP.

A new software was internally developed (a link was provided to the QA department) to automatically generate a specific number for the templates used in the clinical and bioanalytical activities. The software was validated following the current SOP for validation of the computerized systems. However, during the study, the CRO issued a template for "Summary of clinical raw data" and recorded it in a logbook. This template served as a logbook to issue the templates used for study-specific forms with sequential numbers. A reconciliation was performed at the end of each study, and both used and unused templates were kept with the rest of the source documents.

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

4. Archive facilities

The CRO had secure storage space. The facility was equipped with hygro-thermometer to monitor the temperature and humidity, rat traps, a fire extinguisher, and a flood sensor.

The archiving activities were managed following SOP Archiving and Retrieval of Documents.

Access to archive storage areas was controlled and restricted to authorized personnel. A list of authorized personnel was displayed at the entrance of the facility.

Records of document access and return were maintained. The length of time for which study documentation, including raw data, should be kept in the archive was defined in the applicable quality document.

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

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

5. Premises

During the inspection, a tour of the facilities was conducted.

The R&D II facility consisted of CPU units, including a sample processing and storage area and an area for check-in activities. Clinical facilities were located on the ground, second, and third floors. The check-in activities, including the ICF presentation and recruitment of subjects, were also performed on the ground floor.

R&D III consisted of a clinical facility, i.e., CPU, a pathology laboratory on the ground floor, and a bioanalytical section on the first floor. The second floor consisted of a change room, sample processing laboratory, washing area, balance room, sample storeroom (analytical), and staff canteen.

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.

Entry to the facility was restricted and controlled through key cards / biometric access. Alarm systems to detect the exit of subjects from clinical facilities were installed, and the doors were locked. The Emergency evacuation was ensured. Any entry to and exit from the facility were recorded via digital systems.

The Sites where clinical activities took place included a dispensing area where investigational products were stored under appropriate conditions, with entry and exit restricted by access control. Appropriate entry/exit records of each visit to the dispensing area were maintained.

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

Laboratory premises were designed to provide protection to 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.

Safety data sheets were available to staff before testing was carried out. Staff working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff was trained to use the firefighting equipment, including fire extinguishers, fire blankets. Staff was instructed to wear laboratory coats or other protective clothing, including eye protection. Toxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison”, “flammable,” or “radioactive”) whenever appropriate.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Staff was aware of the need to avoid working alone in the laboratory. First-aid materials were provided, and the staff was instructed in first-aid techniques, emergency care, and antidotes.

Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were closed with an appropriate seal. Volatile organic chemicals

were handled under certified fume hoods or air extractors, and safety and eye showers were available in the laboratory.

Premises had suitable systems to dispose of waste, treat fumes, and protect the environment in conformance with local or national regulations.

Diesel Generators and UPS systems were available to supply the electricity in case of city-supply interruption. The details were provided in a table presented during the opening meeting: The facilities, including the ambulance were visited and the respective maintenance records were reviewed.

Observation related to the Premises was adequately addressed in the respective CAPA plan.

6. Personnel

There was enough medical, paramedical, technical, and clerical staff with the appropriate qualifications, training, and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies. The number of staff members counted to 210 + 15 (Pathology lab) at the time of inspection.

At all trial stages, including at night, there were qualified and trained personnel to ensure that the subject's rights, safety, and well-being were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities.

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

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO.

The CPUs in R&D II (96 beds) and III (36 beds) were equipped with 132 beds. Systems were in place in the accommodation facilities so subjects could alert CRO staff in case of need.

Facilities for changing and storing clothes and for washing and toilet purposes were clean, well-ordered, easily accessible, and appropriate for the number of users. Lockable toilets were alarmed, and doors were designed to ensure they could be opened from the outside should a medical emergency occur.

The clinical site consisted of

- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy
- CPU
- Pharmacy
- Room for the administration of the investigational products and sample collection
- Sample processing (e.g., plasma separation) and storage (freezer)
- Archive facility
- Preparation of standardized meals and a dining hall
- subjects' recreation
- ICU
- X-ray (at R&D III)
  The Atomic Energy Regulatory Board, Radiological safety division issued an accreditation certificate from the radiation safety viewpoint on 8 May 2019 that was valid until 8 May 2024. The certificate applied to the measured maximum radiation levels (MR/hr) at different locations, including outside the patient entrance door.

Provisions were made for the urgent transportation of subjects to the hospital, and the email receipt was confirmed. A simulation was successfully carried out. The report, checklist for simulation activity, and participant list were available and reviewed.

Alcohol and drug tests were done at the check-in and screening area by the trained staff. Drugs of abuse Test kits underwent a quality control test before use by batch. The activity was documented on a form for a Quality control test for drugs of abuse kit. The respective certification of analysis was also provided by the vendor. The CoA for one kit was reviewed.

Access to the randomization list was restricted to the pharmacist in charge of the study. The randomization list was provided in a sealed envelope before submission to the pharmacist, and it was kept in a locked cabinet under the pharmacist's supervision.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment were verified at appropriate intervals.

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

8. Clinical laboratory

An in-house clinical laboratory located at R&D III, Ground floor, was used for analyzing samples. The laboratory was accredited by NABL in accordance with ISO 15189:2012. The certificate was valid for the period of the studies. In addition, the laboratory participated in proficiency testing schemes and interlaboratory testing programs.

Hematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol.

Sample labeling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

The CRO kept the information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges, and the accreditation certificate of the laboratory.

The current and signed curricula vitae of the Head of the Clinical Laboratory were 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 using the Laboratory Information system in electronic and paper formats.

Data integrity requirements were ensured for all tests related to the study by limiting the access rights to the software systems used for sample analysis.

If the result of the analysis were OOS, the analysis was repeated. If the second analysis was also outside the specification defined in the SOP, then a third analysis was conducted to determine whether the first or second result should be transferred to LIS.

9. Ethics

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

Informed consent form

Information for study participants was given to them in vernacular language, i.e., Hindi and & Marathi, and at a level of complexity appropriate to their understanding, both orally and in writing.

Informed consent was given by the subject and documented in writing before starting any trial-related activities. The information was clear: participation was voluntary, and the subject had the right to withdraw from the study on their initiative at any time without giving a reason. The reasons for withdrawal from the study were included in the study records.

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through the 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 certificates of translation and back translation of the applicable version of informed consent were reviewed.

10. Monitoring

The studies were monitored by monitors employed by the CRO. The monitors were appropriately qualified to ensure that the study was conducted in accordance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. This included verifying the use of correct procedures for completing CRFs and verifying the accuracy of data obtained.

A 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 conducted (when applicable), to enable prompt corrective action. The randomly selected respective communications and corrective actions were reviewed.

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.

12. Receiving, storage and handling of investigational drug products

The information concerning the receipt, storage (including storage conditions), handling, and accountability of investigational products at every trial stage was recorded. The information about the shipment, delivery, description, dispensing, administration, return, and/or destruction of any remaining pharmaceutical products was also verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions in stability and humidity chambers, as specified in the official product information provided by the sponsor. The conditions were monitored through software application designed to monitor the temperature.

Randomization was performed in accordance with the Generation of randomization, and records were maintained, including the randomization list and seed. The randomization list was accessible only to the PI, a dispensing pharmacist, and the statistician.

The IPs were properly labelled. Compliance of all labels with the randomization list was verified once they were printed and before the labelling of the containers. Labels were pasted onto the container to ensure the information was not lost once the lid was removed.

Adequate routines for labelling and documenting the administration of the IP were established to verify that each subject did receive the product dispensed for them by using labels with a tear-off portion. Labels were designed to have two identical labels to have one portion to be pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The empty containers were labelled separately for the test and the reference investigational products. They remained segregated in a secure area to avoid the risk of any potential mix-ups until the dispensing stage.

Dispensing and dosing were performed in accordance with the requirements specified in SOP for Dispensing of IP & SOP for Administration of IP.

The surface on which the product was handled was thoroughly cleaned before bringing bottles of the product into the area. A second person from the QA department verified that the surface area/line was clear and clean before bringing in and opening product containers. The IMPs were handled with appropriate utensils. Tablets were distributed into each container in accordance with the randomization list for the comparator or the test product as appropriate. The two products, i.e., Test & Reference, were handled at different times. This also applied to the labelled containers. Every step was sequentially recorded in detail. The surface upon which the product was handled, and its surroundings were cleared and cleaned immediately before and after initiating the dispensing of the following product, also in the same study.

Investigational product accountability and dispensing records were always maintained. Each activity was documented when performed, including records of doses administered and returned or destroyed and records of verification by a second person of each step.

Dosing was carried out in accordance with applicable SOP 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.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for possible confirmatory testing for at least five years after approval of the product or in agreement with the authorities' requirements. The retained samples of selected studies were verified during the inspection. The retention period of Investigational Products was defined in SOP for Archiving, Retrieval, and disposition of unused investigational products, i.e.,

- As per the agreement between the sponsor and the bioequivalence department of Macleods Pharmaceuticals Ltd.
- As per regulatory requirement
- Each reserve sample should be retained for at least five years following the date on which the application or supplemental application was approved, or, if such application or supplemental application was not approved, at least five years following the date of completion of the bioequivalence/bioavailability study.

Observations related to the Handling of IMPs were adequately addressed in the respective CAPA plan.

13. Case report forms

Randomly selected CRFs, including screening documentation and the data registered in the volunteer database, were reviewed. The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about volunteer registration number, subject number, date of ICF presentation, screening activities, demographics, inclusion/exclusion criteria, medical history, laboratory parameters acceptable range, X-ray result, IMP administration record, blood collection record, vital & subject questionnaire, clinical case record at the time of check-out, post-study safety assessment, including AE events (if applicable) and subject withdrawal/dropout record, was recorded in or kept with the CRFs.

The CRFs records were cross verified with the respective logbooks for check-in / check-out visits, ECG & X-ray logbooks, Screening visitor logbooks, Volunteer Data Base (VDB), randomization list, HR records, sample transfer sheets & timepoint sheets.

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

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the applicable SOP and included a description of the potential methods the CRO used for this purpose, such as taking advantage of word of mouth. After a few years of operation, the CRO now had a pool of volunteers who could be contacted to be available for screening and recruitment. A Volunteer Database System was maintained on volunteers to avoid cross-participation and specify a minimum time that should elapse between a volunteer's participation in one study and the next. Access to the database was password controlled to secure confidential information on volunteers or subjects.

A biometric system using a thumb fingerprint ensured the identification of volunteers and subjects. The biometric system was periodically validated. The documentation was available.

The informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study. The clinical trial protocol described criteria for subject selection (inclusion and exclusion criteria) and screening procedures.

A software system, i.e., the OVIS application, was used to determine whether any subjects had participated in a previous trial conducted by any CRO registered in the application. Participation data was uploaded to this central repository to prevent over-volunteering.

15. Food and fluids

Meals were standardized and adequately controlled and scheduled during the study days. The CRO was able to arrange standardized meals, snacks, and drinks for the study subjects, using their in-house kitchen, as described in the clinical trial protocol according to a meal plan prepared by the nutritionist. The kitchen was visited during the inspection and found clean and appropriate.

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 when required by the protocol.

16. Safety, adverse events, adverse event reporting

A post-study safety assessment was arranged to investigate each volunteer's laboratory parameters and ECG results. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities and, when applicable, the ethics committee, specifically in the case of a serious adverse event, in accordance with the applicable SOP.

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

The CRO had adverse event registration and reporting forms as part of the CRF.

An observation related to the Safety and AE reporting was adequately addressed in the respective CAPA plan.

Bioanalytical section

The inspection of bioanalytical activities, with focus on selected studies included:

- Verification of the abilities of the validation methods
- Review of method development process
- Audit of source documentation and raw data for validation of the bioanalytical methods.
- Investigation of analysis of subject plasma samples as well as a review of the electronic data.
- Inspection of Audit trails for electronic data capture and handling related to the BE studies.
- Review of results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs, along with the chromatograms generated from the analytical runs.
- Review of 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 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.

For review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. A copy of the raw data on the chromatography software system was provided to be reviewed by the inspection team.

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

The method development process was adequately described and documented, and the usage of IS was justified based on the relevant literature. A copy of the literature was available. After method development, a method validation protocol was provided as a basis for the method validation. A stable isotope-labeled internal standard was always used in the MS methods, and appropriate anticoagulants were deployed in plasma samples.

During the method validation as per the applicable SOP for Bioanalytical Method Validation, as well as other applicable SOPs, a run (Production batch) was performed to determine the batch with adequate blank samples of QCs and CCs comparable in length to those expected to be used for analysis.

The sample processing was documented in the respective forms. A note to file was also provided to record any unexpected activity during sample processing, when applicable.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the studies, except for the long-term stability, which was performed before the submission of the study reports.

The review of the entire method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability) and hemolytic effect, recovery, and reinjection reproducibility. Partial validation was performed according to the requirements. The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. The documentation of the plasma collected at the site, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed, and discussed.

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

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

The system audit trail review was not carried out at the time of the studies in the scope of the inspection. However, the practice was recently implemented, and adequate training was planned to be provided to the responsible personnel.

Observations related to the Method validation and Sample analysis 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 the number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport, or shipping and storage of samples took place in accordance with the applicable SOPs, e.g., SOP for Blood collection during study, transfer of biological samples and discard of biological samples.

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.

Labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots; one was shipped to the BA unit, and the other was stored at the clinical unit. They were kept separately during sample processing at the clinical unit.

As per SOP for Discard of Stored Biological Samples, the study samples, QC samples, and sample aliquots were discarded when applicable.

Observations related to the Sample collection and handling of biological samples were sufficiently addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based and entirely justified. The smoothing factor was kept low enough not to mask possible interferences and changes in peak geometry.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in their SOPs. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. The calibration range was adequately truncated. Internal standard variations were trended and used as part of the verifications of result validity.

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

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented in a manner that ensured traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). All audit trail files were retained (e.g., results table audit trail, project audit trail, and instrument audit trail).

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, the time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

20. Good laboratory practices

A tour of the facility at the BA unit, i.e., R&D-III, was performed on days 3 & 4 to verify the facility's suitability in terms of arrangement and safety.

The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE studies, with an established appropriate QA system.

Deep freezers for storage of the samples and refrigerators for storage of the Reference Standards were adequately qualified, calibrated, and maintained. An alarm system was associated with the digital thermometer to trigger notifications at the security level and convey the message to the sample custodians. The automatic alarm system was tested during inspection to verify its proper functionality.

For qualification verification, the temperature mapping of a randomly selected Deep Freezer was reviewed to verify the hotspot and the location of the respective sensor. The hotspot was identified in the freezer, and the sensors were placed correctly in different spots, including the hotspot in the freezer. The sensor was appropriately protected to avoid the environment's influence on the temperature. Hence, it was concluded the temperature mapping process was adequately carried out at the time of inspection. Transfer of samples to equivalent storage units was appropriately considered under maintenance and repair.

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

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. These activities were verified by random review of the equipment used in study-related activities. Equipment and its components were labelled with the respective

ID number, calibration date, and next calibration date. The equipment usage was adequately documented in the analytical sheets and the respective logbooks for instrument usage. The use of columns was recorded in the logbook for the usage of columns.

Randomly selected qualification and calibration documentation of was reviewed to be verified. The activity was performed in accordance with the applicable SOP.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA.

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

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The applicable statistical model underlying the primary BE analysis was stated in the protocol. The respective study protocol specified the means of performing pharmacokinetic and statistical calculations.

Calculations were made using SAS application for both randomization list generation and PK analysis. A second qualified person from QA double-checked the data values input in accordance with the applicable SOPs related to Pharmacokinetics and statistics following SOP for Conducting audits of the pharmacokinetic and statistical phase. The inspectors emphasized that the adequacy of QA verification should be evaluated to ensure that the study activities were performed in accordance with the applicable protocol and SOPs.

After rectification of QA observations, project-wise backup for all study data and audit trail(s) along with PDF copies of chromatograms, batch files, result tables, calibration curve, standard plots, audit trails of result table, and other related data were taken on CD/DVD by IT authorized trained person. After backup, the respective department, i.e., bioanalytical, or clinical, verified the content of the CD/DVD for accurate data. Upon confirmation of accurate data in the CD/DVD, the IT person locked the respective project/study folder. After that, the folder was accessible only to the IT administrator. The project CD/DVD was sent to QA for archival.

The statisticians' qualification was verified through their CVs.

22. Study report

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

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

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CRO master (CROMF) file, authorized 29 Aug 2020 was submitted and reviewed.
Annexes attached	Not applicable

Part 3	**Inspection 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 guidelines at ***Macleods Pharmaceuticals Ltd, Bioequivalence Department***, located at the following addresses:

R&D II
Plot no. 95, Road no. 16, Opp Suncity Hotel
MIDC, Andheri (East)
Mumbai, Maharashtra,
400 093, India

R&D III
Plot No. 18, Street no. 9
MIDC, Andheri - (East), Maharashtra
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. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***
   https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y

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
   https://apps.who.int/iris/handle/10665/44092

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
   https://www.who.int/publications/i/item/9241208503

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
   Short name: WHO Ethics Committee Guidance
   https://www.who.int/publications/i/item/9789241502948

6. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
   Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
   https://www.who.int/publications/i/item/WHO_TRS_957

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***
https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y

8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
Short name: Glove use information leaflet
https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009)

9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf

10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://apps.who.int/iris/handle/10665/331814

11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS 1033, Annex 4
https://apps.who.int/iris/handle/10665/340323

12. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).
Short name: Declaration of Helsinki
https://apps.who.int/iris/handle/10665/268312

13. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
Short name: ICH M10
https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf

14. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs-1019---annex-3-good-manufacturing-practices-guidelines-on-validation

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4
https://apps.who.int/iris/handle/10665/43443