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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Lambda Therapeutic Research Ltd.** Lambda House, Plot No.38, Survey No. 388, S.G. Highway, Gota Ahmedabad - 382 481 Gujarat INDIA
Name and Address of Bioanalytical Research Site	**Lambda Therapeutic Research Ltd.** Lambda House, Plot No.38, Survey No. 388, S.G. Highway, Gota Ahmedabad - 382 481 Gujarat INDIA
Name and address Statistical Site	**Lambda Therapeutic Research Ltd.** Lambda House, Plot No.38, S.G. Survey No. 388, Highway, Gota Ahmedabad - 382 481 Gujarat INDIA
Corporate address of Organization	Same as above
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no: RH093** Bioequivalence study of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg sugar coated Tablets **WHO application no: NT014** Bioequivalence study of Albendazole 400 mg chewable tablets **WHO application no: CV018** Bioequivalence study of Nirmatrelvir tablets & Ritonavir tablets, co-packaged for oral use 150 mg (2 × 150 mg (total dose 300 mg)) + 100 mg

	WHO application no: HA761 Bioequivalence study of Lopinavir and Ritonavir tablets USP 200 mg/50 mg (2 tablets x 200 mg / 50 mg, i.e. 400 mg / 100 mg dose) **WHO application no. HP012** Bioequivalence study of Daclatasvir Tablets 60 mg **WHO application no. HA719** Bioequivalence study of fixed dose combination of Darunavir and Ritonavir tablet 400/50 mg (2 tablets) **WHO application no. HP022** Bioequivalence study of Daclatasvir Tablets 60 mg **WHO application no. NT005** Bioequivalence study of Albendazole Tablets 400 mg
Inspection details	
Dates of inspection	5-9 June 2023
Type of inspection	Routine
Introduction	
Summary of the activities	Lambda conducts clinical studies, including Phase I trials, for both generic pharmaceutical and biological products. These studies are conducted with the purpose of preparing applications for submission to regulatory authorities worldwide, such as the USFDA, ANVISA, EMA, Health Canada, and WHO. Additionally, Lambda carries out research on new chemical entities and new formulations. Furthermore, Lambda also conducts studies on nutraceuticals and cosmetic products to provide support for the claims made by the sponsor during the marketing of these products.
General information about the company and site	Lambda Therapeutic Research is a full-service Global Clinical Research Organization (CRO) headquartered in Ahmedabad, India, with facilities and operations in Mehsana (India), Pittsburgh (USA), Las Vegas (USA), London (UK), Toronto (Canada), and Warsaw (Poland). Lambda provides comprehensive end-to-end clinical research services to the global innovator, biotech, and generic pharmaceutical industries. In North America, Lambda operates under the unified brand of Novum Pharmaceutical Research Services, a 50-year-old CRO and fully owned subsidiary of Lambda.

	Lambda delivers a full spectrum of clinical research solutions, covering Early Phase (First-in-Man studies, PK/PD Studies), Phase II-IV Clinical Trial Management, Bioanalytical and Large Molecules, Biosimilars Development, Medical Imaging Analysis, Biostatistics and Data Management, Drug Safety and Pharmacovigilance, Central Clinical Lab Services, as well as Medical Writing Support, globally.
History	Lambda has undergone regulatory inspections conducted by various regulatory bodies. These included the DCGI, regulatory authorities in Portugal, the PHSS in the Netherlands, AGES in Austria, BfARM in Germany, the Standards Council of Canada (SCC), USFDA, ANSM in France, AEMPS in Spain, MHRA in the UK, OGYEI in Hungary, and the Ministry of Health in Thailand. Lambda was previously inspected by the World Health Organization (WHO) in December 2017.
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, computerized system controls and qualification, and a tour of the facility. Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with 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
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management

	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

PART 2	SUMMARY OF THE FINDINGS AND COMMENTS

General section

1. Organization and management

A presentation was provided explaining the activities of the organization in detail.

Lambda Therapeutic Research Ltd., located at Lambda House, Plot No. 38, Survey No. 388, Ahmedabad, Gujarat, India, is a registered clinical research organization. It holds a valid registration certificate in Form CT-09 by CDSCO (HQ), Delhi, under the New Drugs and Clinical Trial Rules, 2019. The certificate allows Lambda Therapeutic Research Ltd. to operate as a Bioavailability/Bioequivalence study center with a clinical facility comprising 360 beds and a Bioanalytical facility. Furthermore, on 14th September 2020, CDSCO approved the firm's request to increase the bed capacity from 360 to 376.

The CRO maintained up-to-date organizational charts that listed key positions and responsible individuals. These charts were authorized by the managing director, and regularly reviewed.

The CRO had a Master Service Agreement in place with sponsors. The agreement with the sponsor was provided and reviewed. Within the agreement, specific provisions and timelines were defined for the retention of investigational medical products (IMP), documentation, and biological samples.

Each employee had a job description outlining their responsibilities. Random verification confirmed that the job descriptions were signed and dated by the respective staff members.

A list of signatures of the authorized personnel performing tasks during each study was available and randomly verified.

Management made sure that appropriate and technically valid Standard Operating Procedures (SOPs) were implemented and followed. They also ensured that a well-organized historical file of all SOPs was maintained.

The CRO's official working hours were from 9:30 AM to 6:20 PM, six days a week, apart from every second Saturday, which was designated as a non-working day.

2. Computer systems

A list of software and computer systems used in the studies was submitted.

The CRO maintained a software inventory for GxP computerized systems, following the guidelines outlined in the Computer System Validation SOP. Generally, the systems in use were validated, and any changes made to these validated systems underwent a thorough review process that assessed associated risks and impacts. For handling changes in systems, processes, infrastructure, and IT systems, the activities were defined in SOP for Change Control. All change requests were reviewed and approved by the QA team or other designees, as applicable. The validation team was responsible for conducting validation activities. In case of any identified gaps during periodic assessment, hardware upgrades, or other changes that could affect the software's validated state, revalidation of the software was performed. Periodic Review of computerized system was carried as per the applicable SOP.

The organization utilized multiple servers of different makes and models for their storage area network. These servers had an adequate storage capacity, allowing them to handle large volumes of data. The servers were integrated to manage data generated by various applications.

Regular backups of all generated data were scheduled according to the frequency and process outlined in SOP for Backup and Restoration of Electronic Data. An annual restoration process was conducted, and the last restoration documentation from 2022 was requested and reviewed. A yearly restoration plan was provided, and once finalized, the process was initiated. Documentation for verifying the content of folders was available and reviewed. Random checks were performed by the respective departments to ensure the content was intact and readable.

Lambda had a procedure in place for data archival after project completion. A flowchart was provided to illustrate the backup architecture and data archival routes. According to the archival diagram, the data was transferred to the respective storage appliance that was automatically synchronized with the cloud. Once stored in the cloud, the archivist responsible for the procedure notified the IT department to delete the source data on the

respective workstations, instruments, or applications. A Data Verification RG Team was assigned to verify the data before deletion. The respective application was implemented around June 2022. The cloud system was provided by a service provider. A generic service agreement was available from the service provider, and the purchaser was required to agree to the terms upon purchase.

Access to software systems containing trial-related information was regulated in compliance with SOP for User Access Management. The SOP defined the method of access control, ensuring that only authorized individuals had access to the database. A maintained list documented the people granted access. To enhance security, unique and individual-specific identifiers and passwords were utilized for authentication purposes.

The software programs utilized for essential tasks were mandated to undergo validation to ensure their suitability for the intended purpose. Qualification and/or validation certificates were obtained under the user's supervision. Randomly selected systems' qualification/validation documentation was reviewed.

The Performance qualification considered the user requirements, regulatory/guideline requirements for BE studies, the system's operating environment, and its usage in the studies. Functional quality risk assessment guided the selection of components for validation. Standard Operating Procedures were available for each software program used in the BE study activities. A few randomly selected SOPs were reviewed.

Networks, including the full client/server architecture and interfaces such as laboratory information management systems, were designed, qualified, managed, and controlled. A basic diagram was provided and approved on 21 Sep 2022.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.) were generally designed to prevent errors. The data entry process was specified in the applicable procedures.

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

3. Quality management

Lambda had established manuals, policies, and master quality documents to implement their quality system. They utilized an electronic SOP Management System. The SOPs were collaboratively authored by department representatives, reviewed by department leads/designees and Quality Assurance, and authorized by a designated Management Representative.

Lambda aligned their SOPs and systems with sponsor requirements to ensure the collaboration, especially when project sponsors mandated specific SOPs or systems. The electronic SOP Management System served as a storage facility for SOPs, but the overview of SOPs, including revision schedules and reviews, was managed outside of the system. Once the review process was completed, the initiator uploaded the SOP into the system for approval and signatures. After approval, the responsible person downloaded the new SOP into the training folder, and another responsible person handled the upload into the e-Training system. The e-training matrix enabled the applicable staff to access the approved SOP, read and understand it, and electronically sign it within the system. A presentation was provided to demonstrate the QMS software system during the inspection.

Lambda provided a Quality Manual. The Quality Manual outlined Lambda's Quality Policy, organizational structure, and advocated quality systems for their daily operations. It offered an overview of Lambda's objectives, business areas, and served as a guide for quality management of processes and systems within the organization.

QA personnel were not directly involved in trial-related activities. Both in process and retrospective verification of study data was done and recorded in the respective QA-statement for each study.

Management of Deviations and CAPA was performed in accordance with applicable procedures such as procedure for conducting of Quality Review Board meeting, including root cause analysis, tracking for trends, ensuring all aspects of data integrity and the implementation of appropriate corrective and preventive action (CAPA).

An in-house audit was conducted following the respective SOP. The inspection team requested the audit report for March 2023, but the CRO declined to share it due to internal procedures. However, communication evidence related to the audit was available and reviewed.

The company implemented audit trail reviews as per specific SOPs. Additionally, the SOP for Good Documentation Practice provided general instructions for performing an audit trail review. Each SOP provided guidance on which data should be reviewed, how the audit trail should present data and any modifications, and which changes were considered acceptable in routine system use. The respective checklists accompanied the SOPs to document the audit trail review process and its outcomes. Adequate training on the SOPs was provided to the relevant personnel.

4. Archive facilities

The facility was inspected during the previous inspection and found adequate.

Document access and return records were maintained, following the specified time period outlined in the respective SOP and the contract between the sponsor and the CRO. The contract also included provisions for financing the archiving process. The trial-related documentation was successfully retrieved and traced during the inspection, verifying the effectiveness of the archiving procedures.

5. Premises

During the inspection, a tour of the clinical facility was conducted on Day 3.

The premises consisted of:
Basement

- Pantry
- Bio-waste management area
- Store
- Reception

Ground Floor

- Screening & Check-in area
- Clinical Pharmacy (with 3 dispensing rooms)
- President Office
- Human Resources Development
- Finance & Purchase
- Library
- Archives

First Floor

- Clinical facility - divided in two wings (Wing 1A & 1B) of 90 beds each.
- ICU
- Sample Separation
- Quality Assurance-Early Phase
- Business Development & Project Management
- Clinical Data Management
- Report Group (Report compilation)
- Biostatistics & Programming
- Regulatory Affairs

- Engineering Services
- Management Representative Office
- Directors' office

Second Floor
- Clinical Facility - divided into two wings (Wing 2A & 2B) of 90 beds each.
- ICU
- Sample Separation
- Pathology Laboratory
- Bioanalytical-Protein Biosimilars.
- Information Technology
- Information and technology Quality Assurance-(IT-QA)
- Protocol Writing
- Medical Imaging
- Service, Calibration and Validation
- Regulatory and Compliance

Third Floor
- Bioanalytical Laboratory
- Bioanalytical-Protein Biosimilars
- Clinical facility (Phase-I)
- Training hall
- Archives
- Regulatory and Compliance

Fourth Floor
- Clinical Trial Management Operations
- Clinical Trial Management (Medical Services)
- Quality Assurance-Late Phase
- Medical Imaging
- Report Group (Report writing)
- Training Hall

The facilities were kept clean and had adequate lighting, ventilation, and environmental control at the time of inspection. 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 site selected was appropriate to the potential risk involved. The

departmental divisions within the facility were designed to facilitate smooth and one-way movement of people and materials. To control personnel access, magnetic locking mechanisms were installed at the entrance doors of different sections or departments. Employees were provided with Access/I-Card based on their specific requirements, ensuring that only authorized individuals could enter or exit the departments (through an electronic access control system). Emergency evacuation measures were implemented, and all entries and exits from the facility were recorded for documentation purposes for critical areas such as the pharmacy and freezer room.

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.

Laboratory premises were designed to suit the operations that were 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, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Safety data sheets were available in an electronic folder 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. Selective Staff (25 of them) was trained to use the firefighting equipment, including fire extinguishers. Staff was instructed to wear laboratory coats or other protective clothing, including eye protection. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings whenever appropriate.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Rules on the safe handling of cylinders of compressed gases were observed, and the staff was familiar with the relevant colour identification codes. 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, and emergency care.

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

Premises had suitable systems in place to dispose waste, treat fumes and protect the environment in conformance with local or national regulations. Backup generator and UPS room were well maintained.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. The number of members of staff counted to about 800 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. In specific activities, contract workers were employed to complement the team's capabilities.

Training records at Lambda were kept in both hard copy and electronic formats using a software. The specific guidelines for training were outlined in SOP for Training and SOP for Contractual Staff Training, specifying the details and frequency of training. The training sessions were conducted by department heads within their own departments, across departments, or with the help of external experts.

To ensure accuracy, random samples of current curricula vitae and training records were reviewed for both full-time employees and contract workers involved in trial activities.

Clinical section

7. Clinical phase

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

Lambda Therapeutic Research Ltd, located in Ahmedabad, occupied a spacious four-story building. The facility included a 360-bed capacity to accommodate healthy volunteers participating in clinical studies, specifically BA/BE studies. It consisted of four clinical wards, with each ward having 90 beds, dedicated to conducting bioequivalence studies. Additionally, there was a separate Phase-I unit with 16 beds exclusively for First-In-Human studies, along with two designated ICUs equipped with four beds.

Systems were in place in the accommodation facilities so that 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 equipped with alarm bells, and doors were designed to ensure they could be opened from the outside should a medical emergency occur. A separate area was designated for female volunteers.

The clinical site consisted of
- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- CPU;
- Subjects' recreation;
- Pharmacy;
- Room for the administration of the investigational products and sample collection;
- Sample processing (e.g., plasma separation) and storage (freezer);
- Archive facility;
- A dining hall;
- ICU;
- X-ray facility.

A radiologist consultant was contracted since 1 Aug 2017, to review and assess X-ray records performed at the in-house X-ray facility in the screening area. The government of India's Atomic Energy Regulatory Board issued a registration certificate for the operation of medical diagnostic X-ray equipment on 13 Aug 2020, which was valid until August 2025.

Provisions were made for the urgent transportation of subjects to the hospital.

The equipment used was calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified at appropriate intervals.

8. Clinical laboratory

An inhouse accredited internal clinical laboratory was utilized to analyze samples during the clinical trial. The laboratory's accreditation certificates, including those from bodies like NABL and CAP, were available in the respective Trial Master File (TMF). The TMF also contained the laboratory's normal ranges for various tests.

As specified in the study protocol, the laboratory conducted hematological tests, urine analysis, and other specified tests. To ensure traceability and sample integrity, sample

labeling, receipt, storage, and chain of custody processes were implemented using the laboratory's LIMS system.

The TMF contained the list of analytical methods employed by the laboratory, along with the dated laboratory normal ranges and accreditation certificates. The current and signed curricula vitae of the Head of the Clinical Laboratory was also reviewed.

Individual reports for each subject were generated by the laboratory and included in the eCRFs. The laboratory archived the source or raw data for all performed tests in electronic or paper formats.

To ensure data integrity, the laboratory employed adequately validated systems for sample analysis. In most cases, the results were transferred to the LIMS system automatically.

9. Ethics

Trials underwent approval by an independent ethics committee (IEC) prior to commencing any study. The committee's independence from the sponsor, investigator, and CRO was verified through the member list. The approval letter contained detailed discussions, recommendations, and decisions from the IEC meetings. Adequate time was given to the IEC for reviewing protocols, informed consent forms (ICFs), and related documentation.

An insurance policy, covering the study period of RH093, was reviewed and available.

When applicable, the TMF contained the license to import the drug issued by the local authority (CDSCO).

Informed consent form

Information for study participants was given to them in vernacular language, i.e., Gujarati 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 their concerns regarding potential side effects or reactions from using the investigational products before participating in the trial with a physician.

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

10. Monitoring

The studies were monitored by monitors who were either employed or represented by the sponsor. The monitors ensured that the study adhered to the protocol, GCP, GLP, and relevant ethical and regulatory requirements. They verified the correct completion of Case Report Forms (CRFs) and the accuracy of collected data.

A monitoring visit log was included in the Trial Master File (TMF), documenting the recommendations and observations shared with the site in a timely manner. The monitors covered specific periods as determined by the sponsor.

Pre-study, post-study, and regular monitoring visits were conducted according to the sponsor's schedule. After each site visit, the monitor prepared a written report and communicated any issues to the CRO and sponsor to enable corrective action in timely manner, if possible, even during the ongoing study. These communications and any corrective actions taken were documented.

A monitoring-related observation was adequately addressed in the respective CAPA plan.

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 CRO utilized an application to manage Investigational Medicinal Products (IMPs) in clinical studies. This specialized software organized various aspects related to handling, tracking, dispensing, administration, and documentation of IMPs. It ensured compliance with regulatory requirements and facilitated the management of these products throughout the clinical trial process.

Information regarding the receipt, storage, handling, and accountability of investigational products at each stage of the trial was recorded in the IMP Track application or on relevant templates as needed. For studies RH093 and CV018, random verifications were conducted on the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products. Essential details about the pharmaceutical product, such as dosage form, strength, lot number, and expiry date, were included in the records.

The pharmacy had separate storage rooms for IMPs and retained samples in stability chambers or refrigerators (if applicable). The dispensing areas were completely isolated from the rest of the pharmacy, following hygienic provisions. This was achieved by implementing a changing area and a separator before entering the facility, which was equipped with a LAF (Laminar Air Flow) bench. Pharmaceutical products were stored in accordance with the specified conditions mentioned in the official product information provided by the sponsor. The monitoring of these storage conditions was conducted using the a digital temperature monitoring system, which was installed in 2021. The data from this monitoring period was successfully retrieved and reviewed.

The shipment was monitored throughout the transportation process. The shipment documentation and communication between the CRO and sponsor were reviewed specifically for study RH093.

Randomization was carried out following the SOP for Randomization schedule management. This SOP governed the generation, review, and release of all randomization schedules used to allocate treatments to subjects in clinical studies conducted by Lambda, whether internally or externally. The same SOP also applied to the random selection of subject chromatograms for submission purposes. Records pertaining to randomization, including the randomization list and seed, were duly maintained.

Labels were generated using the respective software system. The IPs were appropriately labelled. The compliance of all labels with the randomization list was verified after printing and before labelling the containers. The barcoded labels were securely attached to the containers to prevent information loss when the lids were removed.

Dispensing and packaging procedures were performed in accordance with the SOP for Handling of IMPs.

The surface on which the product was handled was thoroughly cleaned before bringing bottles of the product into the area. Any product containers (full or empty, labelling

materials, contaminants, dirt, and debris) were removed from the area. A second person verified that the surface area/line was clear and clean before bringing in and opening containers of the product. The IMPs were handled with appropriate utensils. Tablets were distributed into each container in accordance with the randomization list for the reference 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 recorded sequentially in detail in the software system. 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.

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

Investigational product accountability and dispensing records were maintained using a software system. However, during the fourth period of study CV018, paper records were used for dispensing due to a software system downtime. Each activity was documented at the time of performance, including the recording of administered doses, returned, or destroyed doses, and verification by a second person for each step.

The documentation for the destruction IMPs related to study RH093 was available. It included communication with the sponsor and confirmation from the service provider, dated 20 Aug 2021, following the expiry of products as per the agreement with the sponsor.

Dosing was conducted following SOP for administering the IMP to participants. The investigator and a qualified staff member, specifically assigned in writing, supervised the dosing process. Prior to dosing, the barcode on the volunteers' ID card and the IMP container were checked against the label. The exact time of dosing was then documented on the designated page of eCRF using the time register software system. To ensure the intake of the IP, a mouth check was performed. This involved examining under the tongue, under the lips, in the corners of the mouth, and between the gums and cheeks. The software system provided an alert for this activity. Immediately after dosing, the actual time of administration and any other required information for each participant were automatically recorded. These details were captured in the respective individual eCRF or as deemed appropriate.

After dosing, the pharmacist and another designated person verified the reconciliation of the investigational product. The records of this verification were maintained in the TMF. Samples of the product in its original container were retained for a minimum of one year

after the expiry date of the most recent product. This retention period was defined and explained in the respective SOP and was outlined in the contract between the sponsor and the CRO. Additionally, any dispensed products that were not administered were also kept for further reference.

13. Case report forms

The e-CRFs were created within the software system, following the protocol and relevant SOPs. These e-CRFs were then submitted for appropriate review, which might include sponsor review if necessary. Once finalized, the e-CRFs were made live in the system to collect data from the volunteers participating in the specific protocol or study. The development and general guidelines for designing the e-CRFs were outlined in an SOP, which focused on clinical data management involvement for in-house studies.

As part of the inspection process, a random selection of e-CRFs from the study was reviewed. For this review, e-CRFs were selected from two specific studies, namely Study RH093 and Study CV018. All instances of protocol deviations and discontinued subjects, along with their AEs and subsequent follow-ups, were included in the review.

The CRO has introduced a new procedure for establishing a predetermined range of acceptable laboratory values, considering various factors such as population and regional differences. This list has been incorporated into the protocol and investigators were now using these values to assess the laboratory results of volunteers. However, this practice did not apply to the studies conducted before 2019. Therefore, the values for study RH093 were assessed at the discretion of the investigators and a note was included in the TMF on 16 May 2018. This note explained the approach taken in evaluating the laboratory reports for volunteers enrolled in WHO submission studies, prior to the initiation of the study.

At the time of study RH093, there was no logbook available to document the usage of the ECG instrument. However, a new procedure has been introduced to address this issue and now includes the recording of ECG machine usage.

In study RH093, a binder was used to compile the medical screen record. This included the ICFs, screening ECG records, and X-ray reports (if applicable). Other source data related to the study protocol was directly entered into the eCRF. This included information such as inclusion and exclusion criteria, laboratory reports, vital signs, meal intake, dose administration, IMP handling, blood collection, biological sample processing, screening and post-study physical examinations, adverse events, and concomitant medication.

To ensure accuracy, the information regarding adverse events and concomitant medication was randomly cross verified with the logbook that recorded medication usage in the ICU. The results of drug and alcohol tests, obtained through devices, were also directly recorded in the eCRF. The system automatically generated the date and time of reporting for these results.

The eCRF was designed to include the scheduled time for blood collection and dosing administration, with the ability to populate the actual time in the system. Any deviations from the study protocol were documented in the respective system.

14. Volunteers, recruitment methods

The procedures for recruiting volunteers were outlined in the applicable SOP. This document provided details on the various methods employed by the CRO for recruiting volunteers. To ensure proper management, a dedicated module in the application was utilized. This software served the purpose of preventing cross-participation and enforcing a minimum time gap between a volunteer's participation in one study and their involvement in the next. To safeguard the confidentiality of volunteers' information, access to the software was strictly controlled through password protection. This measure aimed to secure any sensitive or private details associated with the volunteers or subjects involved in the studies. Volunteers were identified using a retina-reader system, which was validated along with the entire software system.

Potential subjects were required to provide informed consent not only for their participation in the research portion of the study but also for any screening procedures necessary to determine their eligibility. The clinical trial protocol outlined specific criteria for subject selection, including both inclusion and exclusion criteria, as well as the screening procedures to be followed.

To prevent individuals from participating in multiple trials, a software system called OVIS was utilized. This system served as a central repository for study participation data, allowing researchers to check if potential subjects had previously participated in other trials. Access to the database was password controlled to ensure security and confidentiality. It was observed that volunteers often came from distant cities or locations. To protect the subject’s safety, it's essential to prevent their participation in multiple studies. Implementing robust measures for the reliability of the OVIS software system is therefore vital for achieving these goals. This would help in accurately identifying individuals who may have already participated in other trials and prevent them from 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 as described in the clinical trial protocol and according to the agreement with the catering service. The invoice for study RH093 with the catering service was available.

Timing, duration, and amount of food and fluids consumed were recorded in the eCRF. Before samples were obtained from ambulatory subjects, they were asked about their food and drink consumption. An inhouse dietitian with appropriate qualifications, training, and experience designed standardized meals.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of a serious adverse event.

First-aid equipment and appropriate rescue medication were available in the ICU and ready for emergency use at the study site. 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 sections, as well as consumption of concomitant medication as part of the eCRF.

Bioanalytical section

The inspection primarily focused on two studies, namely, RH093 and CV018, along with their associated validation projects. Additionally, spot checks were conducted for study NT014. The following records and activities were investigated during the inspection:

- Source documentation and raw data pertaining to the validation of bioanalytical methods.
- Analysis of subject plasma samples, as well as the corresponding electronic data.
- Audit trails associated with electronic data capture and handling specifically related to the bioequivalence (BE) studies.
- Examination of results from calibration standards (CCs), quality control samples (QCs), and subject plasma samples in analytical runs. This included a review of chromatograms generated during these analytical runs.
- Assessment of the preparation process for analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

These aspects were thoroughly examined to ensure compliance and reliability in the respective studies and validation projects.

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.

For a review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The inspectors had access to electronic copies of electronic raw data associated with the inspected studies and method validations.

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 the development of the method, a draft method SOP was provided as the basis for the method validation. A stable isotope-labelled internal standard was consistently employed, and K_2EDTA was utilized as an anticoagulant for studies RH093 and CV018.

As part of the method validation following the respective SOP, a run was conducted to determine the batch size for analysis. For study RH093, a batch of 150 QCs along with the respective CCs was used. Similarly, for study CV018, a batch of 190 QCs and CCs was employed. This batch size was selected to be comparable in length to the batches expected to be used for actual 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 issuance 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 reference standard storage stability), haemolytic 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 purchase documentation of the plasma from volunteers recruited by the in-house clinic, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed, and discussed. Haemolytic plasma was performed according to an inhouse protocol and by spiking the whole blood into plasma. Lipemic plasma was obtained from volunteers after consumption of a high fat meal.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, were all processed simultaneously. The exact sequence of processing was defined and documented. All samples collected from a given subject during all trial periods were analysed 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 a stabilization test were done prior to the start of runs on each day.

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

The system audit trail review was carried out at the time of the studies in the scope of the inspection, and adequate training was provided to the responsible personnel.

18. Sample collection, storage and handling of biological material

The clinical trial protocol and the information provided to the volunteers outlined the specification of samples (blood plasma), the sampling method, volume, and number of samples. Collection, preparation, transport, and storage of the samples were performed in accordance with the established SOPs.

To ensure precise calculation of pharmacokinetic parameters, the eCRF automatically captured the actual sampling times and noted any deviations from the planned schedule. These deviations were considered during the analysis process. Additionally, the eCRF effortlessly transferred the list of timepoints to the PK software for further analysis.

To ensure accurate identification and traceability, the labels for collected samples were systematically generated using the respective software system. This automated process helped eliminate the possibility of human errors, thus improving the accuracy of sample

labelling. The standardized sample management workflow facilitated by the software system also ensured consistency throughout the process.

Throughout the storage period and transportation, all storage conditions, including freezer temperature, were controlled, monitored, and recorded. Digital temperature monitoring systems were utilized for this purpose.

A software system was used in creating and maintaining detailed records for each sample. These records contained important information such as sample ID numbers, storage locations, timestamps for storage and retrieval, and relevant metadata. Such comprehensive records provided an overview of the sample inventory, simplifying the tracking of necessary information. When samples were stored, the software system diligently recorded key details like the storage location, date, and time. This thorough documentation created a complete audit trail, enabling precise tracking of sample movement and storage history. The recorded details were essential for maintaining sample integrity, complying with regulations, and supporting quality control procedures. To prevent any compromise, samples were duplicated in aliquots, shipped, and stored separately.

As per SOP for Storage of biological samples and solutions in the freezer/refrigerator, the study samples, QC samples, and pooled matrix were discarded.

19. Data processing and documentation

Integration settings were science-based and could be 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 the applicable SOP. 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, 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 was performed on Day 2 to verify the suitability of the facility in terms of arrangement and safety.

Within the Bioanalytical department on the 3rd floor, the following dedicated sections were established to conduct various laboratory activities

- Instrumentation room
- Sample processing laboratories
- Freezer rooms
- Balance rooms
- Chemical store
- General store
- Wash area
- Documentation room
- Wet/Dry ice storage room
- Utility room
- Office area

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

The storage of samples in deep freezers and reference standards in refrigerators within the Bioanalytical department was well-managed. These storage units were appropriately qualified, calibrated, and maintained. An alarm system was integrated with the digital thermometer. The temperature monitoring system had the capability to send SMS and email notifications to the designated custodians responsible for facility maintenance. To ensure its reliability, the automatic alarm system underwent testing during the inspection to verify its proper functionality. The daily monitoring and alarm checks were diligently documented.

To ensure qualification verification, the temperature mapping of randomly selected Deep Freezers was reviewed. This review aimed to verify the hotspot and the placement of the respective sensors. The temperature mapping process was carried out accurately during

the inspection. Proper consideration was given to the transfer of samples to equivalent storage units during maintenance and repair activities.

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. 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, 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.

The qualification of the randomly selected instruments was verified.

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.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

During the inspection, a comprehensive presentation was delivered, covering activities related to pharmacokinetic and statistical calculations, as well as the transfer of data across departments.

The respective software systems processed the study data and generated an Excel file that could be utilized in PK database for pharmacokinetic (PK) analysis. This streamlined process avoided manual data handling and enhanced the efficiency.

The statistical model for the primary bioequivalence (BE) analysis was outlined in the protocol, with input from the biostatistician. The methods used for conducting pharmacokinetic and statistical calculations, including the software and scripts utilized, were specified in the study protocol.

Observations regarding PK and statistical calculations and reporting were adequately addressed in the respective CAPA plan.

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	N/A
Assessment of the CRO master file	CRO Master File was submitted and reviewed.
Annexes attached	N/A

Part 3	**Conclusion – outcome of inspection**

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at ***Lambda Therapeutic Research Ltd.***, located at ***Lambda House, Plot No.38, ,*** Survey No. 388, ***S.G. Highway, Gota, Ahmedabad - 382 481, Gujarat; 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***

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, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
    Short name: WHO No. 937, Annex 4