

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

<b>Part 1</b>	<b>General information</b>
<b>Organization details</b>	
Company information	
Name and Address of Clinical Research Site	<b>Lupin Bioresearch Center (LBC)</b> Sai Trinity A Wing, Unit 1, 2, 3, 4, 5 & 6 Survey No. 146/2/1B Pashan Pune, 411021 India
Name and Address of Bioanalytical Research Site	<b>Lupin Bioresearch Center</b> Sai Trinity A Wing, Unit 1, 2, 3, 4, 5 & 6 Survey No. 146/2/1B Pashan Pune, 411021 India
Name and address Statistical Site	<b>Lupin Bioresearch Center</b> Sai Trinity A Wing, Unit 1, 2, 3, 4, 5 & 6 Survey No. 146/2/1B Pashan Pune, 411021 India
Corporate address of Organization	<b>Lupin Ltd.</b> 3rd Floor, Kalpataru Inspire off. Western Expressway highway Santacruz East, Mumbai Maharashtra 400055 India
WHO product numbers covered by the inspection/ Product names/ Study	<b>TB375 (only BA part)</b> Bioequivalence Study of Isoniazid Tablets 300 mg  <b>TB385</b> Bioequivalence Study of Cycloserine Capsules 250mg  <b>RH091(only Clinical part)</b>

*Lupin Bioresearch Center, Pune India-CRO*

*11-14 April 2022*

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numbers/ Study titles	Bioequivalence Study of Levonorgestrel and Ethinyl Estradiol Tablets 0.15 mg/0.03 mg  <b>HA737 (Only Pharmacokinetics &amp; Statistical Analysis)</b> Bioequivalence Study of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50 mg/300mg/300mg
<b>Inspection details</b>	
Dates of inspection	11-14 April 2022
Type of inspection	Initial
<b>Introduction</b>	
Summary of the activities	Lupin Bioresearch Center was established in Pune in 2009 to conduct developmental bioavailability and/or bioequivalence studies and regulatory biostudies on healthy human volunteers for new formulation products of oral, inhalational, topicals, injectables, etc., developed by Lupin R&D units.
General information about the company and site	Lupin Bioresearch Center is an integral part of the Medical Research Division of Lupin Limited, a transnational pharmaceutical company.  The company has 15 manufacturing plants with seven R&D facilities located in Pune & Aurangabad, India, and the US (New Jersey and Florida) with infrastructure for developing innovative technologies and creating knowledge-based in chemical synthesis and drug delivery systems. Lupin has facilities for manufacturing of generic formulations, and versatile products mix including antibiotics, antidiabetic, antiviral, antidepressants, antifungals, cardiovascular, macrolides, oral contraceptives, ophthalmic suspensions, Injectable formulations, respiratory products, controlled substance programs, etc. Lupin Limited exports drugs to all developed and other major countries of the world.
History	LBC was inspected by various authorities, i.e., DCGL, US FDA, ANSM-France, EMA, and UK MHRA. A summary of Regulatory Inspections was available. The CRO was not previously inspected by WHO.
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.

	<p>Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.</p> <p>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.</p> <p>The company’s procedures and activities for processing of data, report writing, and statistical analysis were also inspected.</p>
<b>Scope and limitations</b>	

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	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
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

<b>Part 2</b>	<b>Summary of the findings and comments</b>
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<b>General section</b>
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### 1. Organization and management

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

LBC was a company registered with the registrar of companies under the companies act, 1956, issued by Registrar of Companies, Maharashtra, Mumbai. Additionally, the bioanalytical facility was approved by CDSCO (Central Drugs Standard Control Organization) on 7 Apr 2020 under the provisions of New Drugs and Clinical Trial Rules.

An organization chart depicting key positions and the names of responsible persons for each department was available. The organization chart was dated and authorized on 8 Feb 2022.

There were job descriptions for personnel, including a description of their responsibilities. Randomly selected job descriptions, CVs, and training records were verified to be signed and dated by the staff member to whom it applied.

The number of staff counted to 147, including contract workers at the time of inspection. The organization was managed by Dr Dhananjay Bakhle (EVP Medical Research) and Dr Ravi Kasibhatta (Senior Vice President). The Company had working hours from 8:30 am to 5:30 pm.

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

For the bioanalytical part of the trial, the Good Laboratory Practices were clearly established and followed.

For the clinical part of the trial, the Principal Investigator was an employee of the CRO, hence some of the responsibilities usually assigned to the Investigator resided in a similar way to the CRO management. The CRO management ensured that the principles of GCP and GLP were in compliance with the applicable requirements, within the CRO.

Observation made in relation to Organization and management was adequately addressed.

## **2. Computer systems**

A List of software and computerized systems used in the studies was provided. However, a more complete inventory index and periodic review schedule of GxP computerized software systems were available with information about the equipment number, software system name, and version no. GAMP category, client identification number, ER/ES applicability, initial validation, last validation date, periodic review frequency, next periodic review date, system status, actual review date, and any applicable remarks. The document was approved on 5 Apr 2022. MassLynx chromatography software system was used for the studies in the scope of the inspection.

Data validation methodology was specified in writing and performed accordingly. Changes to data entered in the database were made by authorized persons only and they were specified and documented.

The validation documentation of the selected software systems was reviewed to verify that the computerized systems were adequately qualified and validated. The qualification included planning, execution, and record of tests on equipment and systems, to demonstrate that the system performed as intended. Quality risk management was applied to SDMS software system to choose which components needed to be validated.

Validation documentation of the wireless digital thermometer software system was available. The system was released on 9 November 2017 with respective qualification documentation, i.e., IQ, OQ, and PQ.

The company had a license for the operation of chromatography software systems on standalone computers. There were a sufficient number of computers to enable personnel to perform data entry and data handling, perform required calculations, and compilation of reports, with sufficient capacity and memory for the intended use.

There was access control to the trial-related information entered and stored in computers. The method of access control was specified and a list of people who had access to the database was maintained. Secure and unique, individual-specific identifiers and passwords were used.

SOP for the usage of each software program, used for BE activities was provided in the respective SOPs.

There was a system in place for the implementation of regular updates to the key software programs, whenever required. A risk assessment on the potential impact that it could have on the current data and on qualification or validation status was also carried out.

Electronic data was backed up at regular intervals. The reliability and completeness of these backups were verified. SOP for backup, restoration, and archival of computerized systems, effective 15 December 2021 was provided. The backup was performed in accordance with a schedule defined in the procedure with a predefined frequency. The backup was carried out via backup tools. For standalone computers, the data was first stored on the C: Drive. A utility was used to back up the data on the server. Later, the data was transferred to the backup media, which was a magnetic tape, through the server. The backup data on the Media tape was retained for 36 months, from the first day of backup. The number of media tapes depended on the tape capacity.

The data generated on the chromatography software system was stored on the C: Drive and was manually uploaded into the SDMS database for data review, by printing the data/reports into the system.

There was a schedule for data restoration to check the data for retrievability, readability, and accuracy. The activity was recorded in the restoration log, The schedule for data verification of applications was available on a form. The restoration ID number was generated through a ticketing application, i.e., an application operated by the Head Office which was demonstrated during the inspection.

Observations made in relation to Computerized systems were adequately addressed in the respective CAPA.

### **3. Quality management**

The CRO had appropriate QA and QC systems with written SOPs to ensure that the trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, and the applicable regulatory requirements. It was ensured that appropriate and technically valid SOPs were established and followed, and all SOPs were approved and regularly updated. Maintenance of a historical file of all SOPs was confirmed. A Quality manual was designed to ensure organizational quality and compliance procedures.

QA personnel were independent of the work they were quality assuring.

A document for the governance of risk management and compliance guidelines was available to protect the study data integrity. There was also a guideline for human error control to create awareness and guide the employees to reduce, control, and prevent human errors. There was an annexure to list the probable errors that might be encountered during the study at the BA department. The process was implemented, and a monthly report was sent to the management. A quality monthly report was provided to the management.

Both in-process and retrospective QA verifications (e.g., in bioanalysis), during samples, and standards preparation and testing were carried out.

The quality management system included root cause analysis, tracking trends, ensuring all aspects of data integrity, and implementing appropriate corrective and preventive action (CAPA).

Observations made about the QMS were adequately addressed.

### **4. Archive facilities**

The CRO had sufficient and appropriately secure storage space which was fireproof, relative humidity-controlled, and pest-controlled, for archiving the trial-related documentation. Archives were also protected from flooding. The in-house archive facility was used to temporarily store the study documentation and long-term depot of another type of documentation.

An agreement with a remote archive facility was signed for long-term storage of the study documentation.

Archiving and retrieving documentation were in accordance with SOP for The archival of documents. Access to archive storage areas was controlled and restricted to authorized personnel. The list of authorized personnel was displayed at the entrance of the archive facility. Maintenance of records of document access and return was verified during the inspection. The length of time for the study documentation, including raw data, was kept in the archive facilities as defined in the respective SOP. Due to their enduring research value, it was specified as 5 to 15 years. All data, including paper and electronic versions, were easily retrievable and traceable upon inspection request.

Observations made in relation to the Archive facility were sufficiently addressed.

## **5. Premises**

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

LBC was located with easy access to premier hospitals in case of any emergency/ safety needs. LBC had six occupied floors with an area of approximately 22,240 sq. feet situated on the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, and 6<sup>th</sup> floors. Floor Layouts were available.

The LBC was comprised of the following Departments:

- Clinical Research;
- Bioanalytical Research;
- Biopharmaceutics Department;
- Quality Control;
- Quality Assurance.

The facilities were 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.

Entry to the facility was restricted and controlled by digital key cards. There were alarm systems to detect the exit of subjects from clinical facilities, and the doors were locked, except for the emergency exits in case of emergency. Any entry to and exit from the restricted facilities were recorded.

The site where clinical activities took place included a pharmacy 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 pharmacy were maintained. The dispensing procedure was verified to be carried out according to the applicable procedures.



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

Laboratory premises were designed to provide adequate protection to all employees by ensuring safety measures such as safety shower, eyewash stations, goggles, safety cabinets, and first kit box, etc., while handling or working in the presence of chemicals and biological samples. The premises were equipped with fire alarm systems, including a fire extinguisher and gas masks.

Highly potent or volatile substances were adequately handled. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison”, “flammable”) whenever appropriate.

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

Observation made in relation to the Premises, was adequately addressed.

## **6. Personnel**

There were a sufficient number of 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. They received the study-specific information and training required for their work performance.

Contract workers were also employed to perform certain activities in accordance with their respective contracts.

Current curricula vitae and training records were kept for full-time and contract workers who were randomly verified during the inspection. Records of training and assessment of knowledge of GCP, GLP, and any other relevant area and/or technical activity were maintained.

Environment, health, and safety measures were defined and described in the respective Manual. The organization had plans to test the measures by different means, such as training and mock drills based on the applicable plan.

## Clinical section

### 7. Clinical phase

There was sufficient space to accommodate the study subjects. Beds were available for the subjects. Overnight stays were required for the night prior to dosing to ensure adequately controlled conditions and that there was no intake of food or medication within the number of hours that was specified in the trial protocol.

The accommodation facilities were equipped with alarm systems 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 emergency alarm buttons, and doors were designed to ensure they could be opened from the outside should a medical emergency occur.

Provisions were made for the urgent transportation of subjects to the contracted Hospital. An ambulance was available for the ready transport of subjects to the hospital during their accommodation in case of emergency.

Access to key documents, such as randomization lists, was restricted to specific personnel, such as the pharmacist in charge of the study. These documents were locked in a secured cabinet, and their distribution was documented.

Adequate function and performance of emergency-use equipment (e.g., defibrillators) in the ICU were verified at appropriate intervals.

The Clinical site had rooms and areas, as appropriate, for the following:

- subjects' registration and screening;
- obtaining informed consent of individual subjects without compromising privacy;
- subjects' housing;
- subjects' recreation;
- pharmacy;
- 2 x CPU with 56 bed capacity, including 14 bunk beds. It was noted that the top bunk was not in use. This could be verified by the number of subjects recruited for each study;
- sample processing (e.g. plasma separation) and freezer room;
- dining area
- ICU

- archive facility
- clinical pathology laboratory

X-ray activities were outsourced through a service agreement. There were other agreements at the time of the studies in the scope of this inspection.

The calibration of randomly selected equipment was verified. The equipment was appropriately calibrated at predefined intervals.

- 8. Clinical laboratory** A suitable clinical laboratory on the first floor was used to analyze samples. The Laboratory accreditation and a CV of the Head of the Laboratory were verified.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol. Sample labelling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

The clinical department received information about the analytical methods used in the laboratory, together with a dated list of laboratory normal ranges, as per the SOPs such as STP for Estimation of the complete blood count on ABX Pentra.

Individual reports were generated by the respective software system for each subject And were included in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic and paper formats. The laboratory instruments used for the sample testing were equipped with an audit trail.

The observation made in relation to the Clinical Laboratory was adequately addressed.

**9. Ethics**

Trials were approved by Independent Ethics Committees (IEC), before any trial activities were conducted. These Committees were independent of the sponsor, the investigator, and the CRO. Detailed minutes of the discussions, recommendations, and decisions of the IEC meetings were kept.

The IEC was given sufficient time to review protocols, Informed consent forms (ICFs), and related documentation.

Concerning Informed consent, information for study participants was given to them in three languages 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 that participation was voluntary and that the subject had the right to withdraw from the study on their initiative at any time, without giving a reason.

Adequate insurance and other procedures for compensation or treatment were provided to the subjects in case of any incidence of injury or disability resulting from participating in the trial or during the screening. The insurance policies for the studies in the scope of inspection were verified.

## **10. Monitoring**

The monitors of the studies were appropriately qualified. The main responsibility of the monitor for a BE study was 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 completion of the CRFs and confirming the accuracy of data obtained.

The procedures for the selection of monitors and the respective process were described in the SOP for Monitoring of clinical research studies. The monitors were employees of Lupin. The presence of monitors was verified.

Observation made in relation to the Monitoring was adequately addressed.

## **11. Investigators**

The Principal Investigator (PI) was responsible for the clinical conduct of the study, including clinical aspects of the 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.

The investigators had appropriate qualifications, and they were suitably trained and had experience in the conduct of BE studies. The investigators were permanent employees of the company.

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

All the information concerning the receipt, storage, handling, and accountability of investigational products at every stage of the trial was handled and documented by a qualified pharmacist, including records of information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining pharmaceutical products. Details

of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions with restricted access as specified in the official product information provided by the sponsor.

If the clinical part of the study took place at Lupin, the randomization was performed in accordance with SOP for Generation of randomization schedule for BE studies, and the records were maintained, including the randomization list and the seed number. The randomization list was stored in a locked cabinet in the pharmacy under the supervision of the pharmacist.

Compliance of all labels with the randomization list was verified once they had been printed and prior to labelling of the containers. Labels were designed to have an identical tear-off part pasted onto the container and CRF to avoid mix-ups.

Dispensing and packaging were performed according to the requirements.

Dosing was performed in accordance with the SOP for the administration of IMP under the supervision of an investigator and qualified staff members to whom this task had been explicitly delegated in writing.

The dosing was directly documented in the CRF with information about the exact time of dosing and verification of the mouth check. The inspector observed the administration of dosing of one ongoing trial at the time of inspection. Investigational product reconciliation after dosing was verified by a second responsible person.

Observations made in relation to the Handling of IPs, were adequately addressed.

### **13. Case report forms**

Randomly selected CRFs were reviewed for study-related activities and information, together with lab reports, ECG results, and X-ray reports. The information was cross-checked with the respective ICFs, randomization list, enrolment list, screening logbook, and subject visit log.

### **14. Volunteers, recruitment methods**

Prospective volunteers reported to the Clinical housing area through word of mouth and a local database of subjects. New volunteers were registered in the applicable database.

Volunteers were received at the gate security, where they were registered upon their arrival in a logbook for screening or study logbook, respectively.

Initially, volunteers underwent registration by documenting the volunteer details and confirming adequate literacy skills in the volunteer registration form after receiving the volunteer consent for registration in Lupin's database. Volunteers' details were updated in the volunteer database, a unique five-digit volunteer registration number was allotted to each volunteer, and a volunteer photo identity card was generated. Subsequent visits of volunteers to the CRO facility for any purpose would be identified by a unique registration number in the registration database. The registration database was used only to verify the eligibility of the volunteers already registered in the database through biometric devices (left and right thumb, index finger, and photo). Screening validity (21 days window prior to the check-in period) and project eligibility to avoid double participation were checked by the staff responsible for registration. The OVIS database was used to prevent cross-participation in clinical studies across CROs.

Volunteers underwent the screening process after giving the informed consent for screening as prescribed in SOP for Procedure of screening and selection of volunteers. During the screening, the volunteer's medical information was verified and documented in respective forms as defined in relevant SOPs. Volunteers' data was maintained in a database with restricted access to only the concerned staff. The associated audit trail could only be reviewed by the registration manager.

During screening activities, volunteers undertook study-specific procedures, if required, such as x-ray, ECG, protocol-specific physical exam, haematology, biochemistry, serology, and urine tests up to 21 days prior to the check-in process.

Volunteers selected in the screening and reporting for the study participation underwent the study informed consent process. Informed consent presentation was given in groups in vernacular language by the designated study personnel, followed by a One-on-One presentation with the Clinical Research Physician and/or CRA to resolve medical/general study-related queries. Volunteers could proceed with the study-specific activities only after having obtained their informed consent for the study participation. Ample time was given to the volunteers to decide on their study participation. The Informed consent process (One-on-one) was audio recorded for HIV and Leprosy drug studies. Concerned study personnel obtained consent for study participation from volunteers.

Sample size per protocol was defined in accordance with SOP for Sample size determination for Clinical Studies, and through the SAS software system by the statistician. The result was communicated to the protocol writing group.

Observations made in relation to the Recruitment were adequately addressed.

### **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, by contracting the food preparation to the catering service provider, i.e., Ansh Caterers in accordance with the respective service agreement.

The records of food intake were maintained by the mean of timing, duration, and amount of food and fluids consumed. Prior to samples being obtained from ambulatory subjects, they were asked about their food and drink consumption, and if the protocol contained specific requirements. The fasting periods before dosing were ensured to be in accordance with the respective protocol.

Standardized meals were designed by a dietitian with appropriate qualifications, training, and experience.

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

The studies' planning appropriately included adequate evaluation of risk to the subjects. The studies were planned, organized, performed, and monitored so that the safety profile was acceptable.

First-aid equipment and appropriate rescue medication were available and ready for emergency use at the ICU department to properly care for subjects who required emergency or other medical treatment. The usage of drugs in emergency cases was verified in the respective logbooks. Any treatment given to a subject was documented and included in the CRF and the supporting documentation, as necessary.

A medical doctor was responsible for medical decisions in the case of adverse events and for notifying the relevant health authorities, the management, and, when applicable, the ethics committee, without delay, in the case of serious adverse events. Appropriate timelines were respected in accordance with the national regulations. The ICU's staff was adequately trained to execute medical care in an emergency.

The CRO had appropriate adverse event registration and reporting forms, which were part of the CRF.

**Bioanalytical section**

The inspection included the audit of source documentation and raw data for validation of the bioanalytical methods, analysis of subject plasma samples as well as a review of the electronic data, audit trails for electronic data capture, and handling related to the BE studies. Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs were inspected along with the chromatograms generated from the analytical runs. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited.

Chromatograms and their integration, absence of signals in the blank samples, and 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 the personnel who were well-informed and transparent.

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

The process of method development was adequately described and documented and the usage of IS was justified based on the applicable literature. A copy of the literature was available. After method development, a DAP (Draft analytical procedure) was provided as a basis for the method validation, in which the integration parameters were also defined. A stable isotope-labelled internal standard was always used in the MS methods, and K<sub>2</sub>EDTA was applied as an anticoagulant.

During the method validation as per applicable SOP a run was performed to determine the batch with 120 samples of QCs and CCs (so-called Analytical run batch determination) that was comparable in length to those that were expected to be used for analysis. However, during the study LBC-19-141 (WHO application TB385), each analytical run contained between 124 to 132 samples. It was explained that each run consisted of two sample processing batches by using 4 sets of QCs spread throughout the run. The analytical run and the analytical batch were separately defined in the respective SOP.

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 prior to the issuance of the study reports.

The review of the full 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 as per the applicable 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, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma was reviewed and discussed.

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 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 stabilization test were done prior to the start of runs on each day.

Of the first 1500 samples, 10% were used to run Incurred Sample Reanalysis (ISR), and of the subsequent samples, 15.38% were used for ISR. The samples were selected with concentrations around  $C_{max}$  and in the elimination phase. The acceptance criteria were clearly defined in the applicable SOP.

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 implemented, at the time of inspection. The respective records were documented in the logbook for the usage of the instruments and the respective checklist.

Observations made in relation to the method validation and sample analysis, were adequately addressed.

## **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 followed the applicable SOP.

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 aliquot I & II, shipped, and stored separately.

As per SOP for Study sample management in the Bioanalytical research department, the study samples, QC samples, and pooled matrix were discarded after one month from the date of QA authentication of the analytical report or after two months from the date of completion of the study whichever earlier. Samples belonging to the Cycloserine study were disposed based on the form for Study samples disposal, together with the bulk spiked QC samples. The respective logbooks were verified.

Observations made in relation to the method of Subjects' sample handling, were adequately addressed.

## **19. Data processing and documentation**

Integration settings were science-based and fully justifiable. 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 the batch acceptance, were clearly defined in the applicable SOP. When the analysis was repeated, the source data for all the analytical runs contained all information about the original first evaluation of runs (collecting all calibration samples). 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 with respect to 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 was performed to verify the suitability of the facility 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. There was an alarm system associated with the digital thermometer to trigger SMS and call notifications to the custodians responsible for the maintenance of the facility. The automatic alarm system was tested during inspection to verify its proper functionality. The daily monitoring and all the alarm checks were documented.

For the purposes of qualification verification, the temperature mapping of the Deep Freezer was reviewed to verify the Hot spot and the location of the respective sensor. It was noted that the practice was amended in July 2021. The process of temperature mapping was properly 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, 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 a 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 usage of equipment was adequately documented in the analytical sheets, as well as the respective logbooks for the usage of the instrument. The usage of columns was recorded in the logbook for the usage of columns, as well as in the logbook for the usage of LC-MS/MS. The records were cross 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, either on the label or on the CoA.

Observations made in relation to the Good Laboratory Practice, were properly addressed.

## **Pharmacokinetic, statistical calculations and reporting section**

### **21. Pharmacokinetic, statistical calculations**

At the time of the inspection, the company had outsourced the pharmacokinetic and statistical activities to SynergenBio, CRO in Pune on a project-based service agreement where the summary of services was defined.

The statistical part of the studies in the scope of the inspection was completed by Lupin's Biopharmaceutics department, including the preparation of the statistics as stated in the protocol or the statistical analysis plan. Lupin was also a part of the protocol writing for the determination of an appropriate sample size. Results from a pilot study were generally considered to verify the studies' sample sizing. The statistician was one of the protocols.

Statistical calculations were made using validated software at the time of the studies in the scope of the inspection. A software system was also used for the generation of the seed number and the respective randomization list.

Data values from the clinical part of the study were transferred to the statistician from the data management group, using a software system for the generation of data lists used for pharmacokinetic calculation purposes. Once the transfer of data from the CRFs was completed, all access to the project folder would be revoked upon a request from the team to the IT department. Transfer of data was quality controlled by the QC team and verified by the QA team, before data lock.

However, data values in the studies related to WHO applications RH091 and TB385 were not transferred through the respective software system. The data was provided by an associate scientist in PDF format and sent to the QA team to be verified before the transfer of data to the statistician. After the completion of the study, a zip folder was provided

containing the study data, incl. CRFs on a share point to the Report-writing group. The share point was equipped with an audit trail. During the inspection, the data on the list of sample collection and time deviation was randomly cross-checked with the respective CRFs to verify the integrity of the list for the dose administration time deviation at the time of statistical analysis.

Observations made in relation to the Statistical analysis, were adequately addressed.

## 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 of the validation of this method. The Principal Investigator approved the clinical study reports before the transfer of data to the statistical department. The bioanalytical reports were also verified by the responsible staff and management. Monitoring and audit reports were available before the release of the final study report.

<b>Miscellaneous</b>	
<b><i>Samples taken</i></b>	Not applicable
<b><i>Assessment of the CRO master file</i></b>	<p>A CRO master (CROMF) file was provided with the respective CAPA plan.</p> <p>A CRO master file should provide introductory information of the organization and cover all information required by the guidelines for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7).</p> <p>According to the abovementioned guideline, the CRO master file should be a document prepared by the CRO containing specific and factual information about the CRO and the conduct of clinical studies, as well as the analyses of samples and related operations carried out at the named site. It was expected that a CROMF provided information on the policies, approach and general activities of a CRO. It should serve as general information by regulatory inspectors in addition to the trial-specific data and information submitted</p>

	for assessment. It should also provide an overview of the organization’s approach to GCP, GLP and other guidelines pertaining to its activities.
<i>Annexes attached</i>	Not applicable

<b>Part 3</b>	<b>Initial conclusion – inspection outcome</b>
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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 ***Lupin Bioresearch Center (LBC), Sai Trinity A Wing, Unit 1, 2, 3, 4, 5 & 6 Survey No. 146/2/1B, Pashan, Pune, 411021, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.

<b>Part 4</b>	<b>List of guidelines referenced in the inspection report</b>
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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**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex09.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf)
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://www.who.int/tdr/publications/documents/gclp-web.pdf>
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 Annex 3**  
[https://apps.who.int/iris/bitstream/handle/10665/37340/WHO\\_TRS\\_850.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1)

4. WHO good practices for pharmaceutical quality control laboratories, 2010 (WHO Technical Report Series, No. 957), Annex 1.

**Short name: WHO GPPQCL Annex 1**

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/GoodpracticesPharmaceuticalQualityControlLaboratoriesTRS957Annex1.pdf](https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodpracticesPharmaceuticalQualityControlLaboratoriesTRS957Annex1.pdf)

5. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.

**Short name: WHO TRS 1010, Annex 9**

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/TRS1010annex9.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1)

6. 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>

7. 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/ethics/publications/9789241502948/en/>

8. 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;jsessionid=B7F180F317E8BE2DB4289C7BF9A561FF?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf;jsessionid=B7F180F317E8BE2DB4289C7BF9A561FF?sequence=1)

9. 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/medicines/areas/quality\\_safety/quality\\_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf?ua=1)

10. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).

**Short name: Glove use information leaflet**

[http://www.who.int/gpsc/5may/Glove\\_Use\\_Information\\_Leaflet.pdf](http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf)

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 No. 1033, Annex 4**

<https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations>

12. 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 Technical Report Series, No. 1003, 2017, Annex 6

**Short name: WHO multisource guidance**

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/trs1003\\_annex6.pdf](https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf)

13. 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 1025, Annex 4**

<https://www.who.int/publications-detail/978-92-4-000182-4>

14. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. WHO Technical Report Series, No.961, 2011, Annex 9.

**Short name: WHO TRS No. 961, Annex 9**

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1)

15. Ethical principles for medical research involving human subjects, 52<sup>nd</sup> WMA General assembly, Edinburgh Scotland, October 2000.

**Short name: Declaration of Helsinki**

[https://www.who.int/bulletin/archives/79\(4\)373.pdf](https://www.who.int/bulletin/archives/79(4)373.pdf)

16. Good manufacturing practices: guidelines on validation, WHO Technical Report Series, No. 1019, 2019

**Short name: WHO TRS No. 1019, Annex 3**

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/WHO\\_TRS\\_1019\\_Annex3.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1)