

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

<b>Part 1</b>	<b>General information</b>
<b>Organization details</b>	
Company information	
Name and Address of Clinical Research Site	Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, 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, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382 481, Gujarat, India
Name and address Statistical Site	Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382 481, Gujarat, India
Corporate address of Organization	Lambda Therapeutic Research Ltd., Plot No. 38, Survey No. 388, Near Silver Oak Club, S.G.Highway, Gota, Ahmedabad-382 481, Gujarat, India
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Study no: 319-12 Tablets 450 mg  Study no: 555-12 Tablets 600 mg / 300 mg  Study no: 821-15 Tablets 600 mg  Study no: 327-14 (Only Clinical part) Tablets 800 mg/160 mg  Study no: 746-15 Tablets 60 mg  Study no: 551-15 (Only Clinical part) Injectable suspension 150 mg/mL  Study no: 072-16 Dispersible Tablets 100 mg

<b>Inspection details</b>	
Dates of inspection	11-15 December 2017
Type of inspection	Routine
<b>Introduction</b>	
Brief summary of the activities	The facility has the capacity to perform bioequivalence and bioavailability studies in healthy subjects / patients, in addition to a dedicated unit for conducting Phase I (First in-human) clinical studies.
General information about the company and site	<p>Lambda CRO started as early as 1999 in Ahmedabad, India to provide clinical research services to Pharmaceutical, Biotechnological and Medical device companies. Head office was located in Ahmedabad, India.</p> <p>Lambda was expanded by opening a new clinical facility in Mehsana in 2017, in addition to Navi Mumbai in 2003, as well as other sites in India. The CRO also acquired additional CRO organisations in Poland and Canada – thereby expanding their service delivery.</p>
History	<p>A list of inspections previously performed by a number of national medicines regulatory authorities was provided which included inspections from the authorities of Brazil, France, Thailand, Hungary, India, Turkey, EMA, USFDA, UK, Canada, Germany and Netherlands.</p> <p>Lambda was last inspected by WHO in October 2012.</p>
Brief report of inspection activities undertaken	<p>The inspection team covered the following company and study-related activities: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, product dispensing 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> <p>The inspection covered the following analytical operations: quality management 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 accomplished along with comparisons of the source data to study reports.</p>
Out of scope	Not applicable

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
	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
	(IEC	(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>Brief summary of the findings and comments</b>
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<b>General section</b>
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## 1. Organization and management

Lambda Therapeutic Research Ltd, a global CRO, with Ahmedabad, India as the Headquarter of the organization was established in 1999. The CRO was built up to provide end to end services, from Phase I to pharmacovigilance, with over 500 employees. The CRO had other offices in India: bases in Navi Mumbai, New Delhi, Hyderabad and Mehsana. The company was also globally represented, in London, Toronto and Poland. Lambda Therapeutic Research Ltd, Ahmedabad occupied currently a space of 250,000 sq.ft. in a four-story building with a 360 beds capacity to house healthy volunteers for clinical studies, as well as BA/BE studies. There were four clinical wards (90 beds in each ward) for conducting bioequivalence studies. In addition there was a dedicated 16 bedded phase-I unit exclusively for conducting First-In-Man studies.

A business development manager represented the company in Turkey, in addition Lambda provides technical support to clinical and BA facilities in Bangkok, Thailand.

The CRO has its own pathological laboratory accredited by CAP and NABL.

Organization charts were provided depicting key positions and the names of responsible persons, in addition to organograms for each department. The CRO Master file was also available. Designated teams in Biostatistics and programming, design of the protocol, Clinical data management were examples that were reviewed during the inspection. A list of employees is kept by HR department.

The company completed around 300 studies per year. Since 1999, more than 6000 studies were finalized. Approximately 8-10 new methods are under development monthly.

Working hours starts 7 am with 24 hours open.

### **Major changes since the previous WHO inspection (2012) include the following:**

- New IECs were engaged in approval of the studies.
- The CRO acquired LC MS/MS, FTIR, and LHS instruments.
- New software systems with different operations were in use.

## 2. Computer systems

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

An arrangement was in place to take an incremental daily back-up of the data generated on the software linked to the LC-MS/MS. A full back up was provided on a weekly basis and transferred to an offsite archiving facility, 10 km away from the Headquarter. The archiving facility was also a property of the Corporate Lambda.

For daily back up, a raid level I system was used to create two identical disks installed in the system. Disk I was replicated to provide an identical disk II.

Once the study was completed, data is transferred to two DVDs, one for in-house archiving and the second one to be stored at the offsite archiving facility.

For the data system used in management of clinical trial data, a daily incremental back-up as well as a weekly full back-up was provided. Back-up tapes were transferred to the offsite archiving facility on a weekly basis.

The final data generated from software was stored in DVDs with required quality to ensure the accuracy and quality of the data during the required retention period. Annual data restoration was performed to verify the quality of the data over the time.

Data restoration report for year 2016 was reviewed, confirming that 15 project-related DVDs since 2004 were retrieved from the LTR and off-site archiving facility by IT. The study data was restored on a secured network drive and made available to the end-user for verification. It was later confirmed by end-users that the files were opening in proper format and were readable. The documentation was signed 28 Dec 2016 confirming that the data restoration was successfully monitored.

A plan for data restoration of 2017 was in process. The plan was reviewed.

Data restoration confirmation was performed every December each year.

### Validation plan for selected computer systems:

Computer validation documentation for the software vs. Computer validation SOP was reviewed. IT department performed the Installation Qualification (IQ) with Operational (OQ) and Performance Qualification (PQ) carried out by the user department; follow by preparation of the respective report. The user specification was prepared by the user department, in conjunction with the vendor.

In the OQ documentation of the system validation, it was demonstrated that as soon as PI or any other medical reviewer approved the inclusion of the volunteer, no further changes could be made. Furthermore, users allocated with PI role in the system, as well as the role of the QC people who had the access right to issue the Declaration of Clarification Form (DCF) were checked. The current practice was demonstrated.

#### Data base used for analytical runs

In order to check the functionality of software the following instruments were visited:

- Instrument no 02
- Instrument no 17

The system was explicitly reviewed to confirm that software was provided in Full Security mode and in that mode, the software applied checksums to all data and metadata files to ensure that the files created in software could not be modified or renamed except through security-controlled and audit logged actions.

SOP for Checking data security in computers attached with LC-MS/MS systems was applicable to all computers which generated and stored source files of LC systems installed in BA department.

In the case an analyst or designated person should try to delete any files, the Security Check.txt will issue an error message “Cannot delete Security check: Access is denied” or “You need permission to perform this action”. This was verified on the log book for tracking of data security on D: Drive of Computer attached with LC MS/MS.

#### Database used for management of clinical trial data

Computer validation of selected software used for Clinical Trial Management, including User Requirements, effective date 15 Oct 2015 was reviewed.

There was a newer version, only applicable to the Subject Screening with the corresponding PQ script.

The step regarding MSR Review and eligibility declaration was tested in this version. The whole process was demonstrated and verified by using the applicable user profiles. PI verified the inclusion of the volunteer in the system. Later the QC-reviewer made changes and created a DCF. DCF was notified to the screening coordinator and PI. PI implemented the alteration. Once the PI made the respective alteration, the screening coordinator was not able to make any further modifications.

The observations made in relation with computer systems were addressed adequately.

### 3. Quality management

The CRO's quality management was described exclusively in the Quality manual and CRO Master File and was organized as follows:

- Manuals (Quality Manual)
- Policies (HR and Technical Policies)
- Standard Operating Procedures (SOPs – system and method SOPs)
- Protocols and Plans

According to the SOP; Standard Operating Procedure for Standard Operating procedure, all SOPs should be reviewed every 2nd year. A master list of SOPs, maintained by QA was provided. The respective department was notified six month in advance. An electronic Data Management System (DMS) for SOPs was under development.

There were two types of SOPs: Local specific to India and Global SOPs applicable for the global system.

Standard Operation Procedures were selected and reviewed as follows:

- SOP for Procurement and handling of Emergency medicines in clinical facility.
- SOP Guideline for method development of analytes from biological matrix
- SOP User access management
- SOP In-house Audits. The SOP described the in-process study specific audit and also the system audit. The system audit was planned per calendar year, prepared by January each year, indicating which area should be audited and when.  
The audit plan for 2016 and 2017 was provided.  
The audit report for November 2017 was present, including the system audit status and the time of audit, the name of auditor and the area audited. It was confirmed that the audit report was sent.
- SOP Vendor evaluation system  
The process was reviewed: The assessment was made by QA, jointly with operation team. A log of approved vendors was kept. A continuous assessment of vendors was carried out every two year.  
An annual audit plan of vendors was provided. The audit plan for 2017 was verified. The software for management of clinical trial service provider was audited on 20-21 February 2017.  
The agenda, inspection report and response from the auditee were reviewed.  
CV and JD of the auditor were confirmed signed on 8 Jan 2017.
- SOP for Operation and maintenance of LC-MS/MS effective 8 Jun 2011.

The list of vendors, providing service to Lambda was provided.

Training documentation generated in e-learning system was present.

#### **4. Archive facilities**

The archiving facility was located on the Ground floor and was equipped with fire proof door, smoke detectors and powder based sprinkles, fire extinguisher canisters and mouse traps. All paper documentation was preserved in boxes, marked with document type, project number, binder ID and the content.

A pest control activity was outsourced to inspect the facility for different type of pests. The execution of the pest control was verified.

The facility was secured from unauthorized access by providing access only under supervision of the authorized personnel. The list of authorized personnel with access to the archiving facility was provided.

There was a SOP for Archive Management which was followed. A request would be issued, mentioning the reason for retrieval of the documentation, and authorized by the respective Head of department. The process was handled according to the SOP.

Since February 2017, a new software was in use for archiving purposes, with the software applicable to the projects completed in 2017.

Regarding the retention time of the documentation, based on the agreement between the CRO and the client, and depending on the applicable requirements, Lambda kept track of retention time and transfer outdated documentation to the client. The client decides whether documentation should be discarded, returned or archived.

DVDs from study 821-15 were retrieved from archive, both from in-house and off-site facility. It was verified that the data was still retrievable.

#### **5. Premises**

During the inspection, a tour of facility was provided. Lambda had 360 beds for conducting BA/BE studies and 16 dedicated beds for conducting first in man studies.

The premises were consisted of two wings with 4 floors housing Clinical and BE facilities:

##### Ground Floor:

- Main reception
- Archive facility
- Screening
- Pharmacy



#### 1<sup>st</sup> Floor:

- Clinical Data Management
- Biostatistics and Programming
- QA
- Clinic wards 1A and 1B

#### 2<sup>nd</sup> Floor

- Clinical Trial Management
- Medical Imaging
- Clinical laboratory
- Clinic wards 2A and 2B

#### 3<sup>rd</sup> Floor

- Bioanalytical
- Phase 1

Access was restricted only to the authorized personnel by use of card keys to different operational areas. The list of personnel authorized to the archiving facility, Pharmacy and CPU was provided and reviewed.

Temperature and humidity of facilities including freezers was monitored by digital thermometer. Additionally, a Cobalt wireless monitoring system was also used for freezers through transmitters. The system was examined every 6 months.

The temperature log for selected freezers for the period of 12 Jun – 20 Jul 2017 was reviewed and verified.

The following SOPs were applicable to monitoring of temperature:

- SOP for Temperature recording of freezer and refrigerator
- SOP for operation, maintenance and calibration of Eurotherm graphic recorder
- SOP for operation, maintenance and calibration of Cobalt wireless data logger system

The SOP Temperature Recording of freezers and refrigerator was verified.

The alarm was tested for two freezers: (-55° C to -75° C) and (-17° C to -27° C), and was found to operate at an acceptable level. Alarms were received by the responsible person. Acknowledgment of receipt of the alarms triggered was provided to the Inspector.

Records for 3 alarms triggered were verified as follows:

- 17/11/2017 Logger ID at 04:11:00 with duration of 30 min
- 19/11/2017 Logger ID at 05:27:00 with duration of 15 min
- 14/11/2017 Logger ID at 21:30:00 with duration of 60 min.

Diesel generators with capacity of 500 KVA (2 units) were available on site and all the electric equipment were connected to the generators. 8 UPS units with individual capacity of 60 KVA were also available. The generators were checked daily as per the corresponding logbook. The functionality of the generators, in case of a power failure, was verified.

Synchronized clocks were located throughout the facility to document the exact time study activities occurred. Clocks were wire-connected to a master clock which was operated by internet and server monitored.

#### Screening area

The screening area was visited.

#### Clinical Pharmacology Unit (CPU)

There were 4 wards located in two floors with 360 beds. It was observed that within the first 4 hours following dosing, Volunteers have no access to the rest area where the rest rooms were located.

Volunteers were identified and segregated by uniform colour code as well as a barcodes on their ID-cards generated by software applicable to the study.

#### ICU

The ICU was visited. ICU housed 4 beds, a vital sign machine, ECG machine, BP measurement device, Oxygen cylinder etc. All physicians were additionally trained by external trainer to perform paramedics in emergency situations to be kept up-to-date.

A logbook was kept for recording the use of emergency medicines. An inventory log was also provided.

Medication required to be kept cool were stored at room temperature (25 °C) which was compliant with local requirements, as long as the room temperature was kept below 25 °C. Maximum and minimum room temperature was verified to be within the acceptable range at the time of inspection. Additionally, the temperature log for the period of 1 – 8 Dec 2017 was reviewed and verified.

Adverse events were not recorded in the respective logbook.

### Bioanalytical lab

The Bioanalytical department on the 3<sup>rd</sup> floor was spread over 27,800 sq. ft. area and the following sections were visited to verify the execution of various laboratory activities:

- Instrumentation rooms
- Sample processing laboratories
- Freezer rooms
- Balance rooms
- Wash area

The unit operations were segregated in sections. The department was equipped with different instruments. There were weighing balances in the balance room. The daily routine calibration of the balances was verified.

The refrigerators for storage of solutions and freezers for storage of samples (-65 °C) and blank samples for method development processes (-20 °C) were inspected.

An excel sheet was provided to keep the overview of all working standards with expiration date. The list would be flagged as soon as there was one month left to the expiration date.

### Pharmacy

The pharmacy area, with restricted access limited to the authorized personnel (pharmacist), was utilized for receipt, storage, dispensation and archival retention of study medications.

The pharmacy had three sections:

- 1- Receiving area. Courier parcels are checked for number of containers, damage and availability of the data-logger - including any temperature excursions.
- 2- Storage area of study medications, which includes freezers and refrigerators.
- 3- Dispensing area.

It was observed that medicines were stored according to appropriate storage conditions in cabinets, humidity chambers and refrigerators and monitored by digital thermometers.

The observations made in relation to the inspected areas were addressed adequately.

## **6. Personnel**

Key personnel for selected departments were interviewed and their CV, Job Descriptions and training records were reviewed and verified. Employees were trained as per their job responsibilities.

There was a software system used to record the presence (log in and log out) of employees at the office.

There was an e-learning system to maintain the training records electronically. Job codes were implemented in the system to define the training matrix, classified in different levels. Each job code was linked to the list of SOPs and manuals as per the job responsibilities in the respective department. Job codes were operated by the moderator of that department who was responsible for training of the respective staffs.

As soon as an SOP was revised, the moderator would upload the information into the system and the system would generate a notification for scheduling the training. If required, the moderator made a schedule to train the required staff, manually. Once the SOP was uploaded, the respective employees would receive a notification, 5-10 days prior to the effective date as a training reminder. The moderator was also responsible to ensure that all required employees received the training within the timeline. A deviation report, with pertaining CAPA would be generated if the timeline was not kept.

The role allocation documentation for study 746-15 was reviewed. 10 analysts were involved in the study. Their CV and JDs were provided and reviewed.

## Clinical section

### 7. Clinical phase

A tour of the clinical facility was performed.

Labelling of study medication, monitoring check, blood sample collection form, verification of vital signs and subjects' well-being, as well as hygienic condition of the restrooms were inspected.

The SOP for Phlebotomy in Clinical Studies was verified.

Inspectors supervised the dosing and blood samples collection activities conducted for study 0719-17 and to blood samples collection for study 0110-17. During the dosing process QA and QC representatives, the project coordinator and the principal investigator were present and supervised the entire process.

Barcoded blood samples were scanned through the software. Hence, the scheduled time was automatically calculated based on the dosing time. Actual time of blood sample collection was recorded automatically when the aliquot barcode was scanned. Blood sampling process was verified by QC and QA representatives.

No observations were raised by the Inspectors for dosing and blood samples collection processes.

The SOP for Usage and Maintenance of Oxygen Cylinder in Clinical Studies was verified.

According to the SOP, the water in the Wolff bottle (Humidifier) for oxygen cylinders was changed once a week. The site provided medical references based on which the SOP was created, however since the activities indicated in the SOP were performed under different conditions (such as no permanent oxygen flow at ICU versus permanent oxygen flow indicated by the medical references provided), it was advised that the process could be improved. The site agreed to amend the current practise and to fill the humidifier with water just before utilisation.

The site had contracts signed with two Hospitals and an ambulance in case of an emergency.

In accordance with applicable SOP, Lambda would inform the responsible person at the hospital of any study initiation visits. The communication with Hospitals and acknowledgment of receipt regarding the study initiation were verified and found acceptable.

In recruitment of the volunteers, it was identified that the number of volunteers with insignificant abnormal lab values was very high. A presentation was provided by the site regarding the outside normal ranges values and the reason why there were so many deviations from the normal range.

Reference range for safety parameters was an important criterion for ascertaining the eligibility for enrolment and the safety assessment of volunteers. Since the reference range used in the laboratories in India, was the Western population, there was a need to modify the reference range to adjust it to the Indian population, with regards to variation in genetics, lifestyle, environmental and inherent characters of population of the region.

Therefore, the CRO had performed a retrospective data analysis to obtain data from laboratory results of healthy volunteer from 2012 - 2016. Health status of the volunteers was determined during screening of which the clinical examination included BMI, medical history, vitals, general and systemic physical examination.

A presentation was provided to demonstrate the rationale behind the regional adjustment of the normal range reference in details. Kit literature and applicable guidelines used in modification of the laboratory reference range was presented. It was shown that each Lab should investigate the transferability of the expected values to its own patient population.

Volunteers with lab results outside the proposed normal reference range would be excluded from a specific study. A list of subjects with a new reference range was provided for inspection team's review.

Observations made during the inspection was addressed adequately.

## **8. Clinical laboratory**

The Clinical/Pathology laboratory premises used were generally spacious and adequate for their use.

## **9. Ethics**

Protocol and ICF for the following studies were reviewed:

- Study no: 319-12
- Study no: 555-12
- Study no: 821-15
- Study no: 327-14
- Study no: 551-15
- Study no. 072-16

The inspection identified that a member of the Independent Ethic Committee belonged to the same hospital which had a financial agreement with Lambda Therapeutic Research Ltd. for any emergencies.

- Study no: 746-15

## **10. Monitoring**

### **Study no: 319-12**

Monitoring was not done on site.

### **Study no: 555-12**

Monitoring was not done on site.

### **Study no: 821-15**

The visitors' logbooks were verified for all monitoring visit dates with the following monitoring activities identified:

- On 11 May 2016, the site initiation was monitored, on behalf of sponsor.
- On 12 May 2016, the check-in related activities as well as dosing related activities on 13 May 2016 for the Phase-I of the study were monitored on behalf of The Government Pharmaceutical Organization, Thailand;
- On 09 Jun 2016, the check-in related activities for the Phase-II of the study were monitored on behalf of The Government Pharmaceutical Organization, Thailand;
- On 10 Jun 2016, the dosing related activities for the Phase-II of the study were monitored on behalf of The Government Pharmaceutical Organization, Thailand;
- On 12 July 2016 & 13 July 2016, the bio-analytical phase of the study was monitored on behalf of The Government Pharmaceutical Organization, Thailand;

- On 10 August 2016, the close-out visit of the study was monitored on behalf of The Government Pharmaceutical Organization, Thailand.

**Study no: 327-14**

Representative from sponsor visited the facility for the site initiation on 16 September 2016, for the interim monitoring on 19-20 September 2016/ Period-I and on 27-28 September 2016/ Period-II.

The visitors' logbook was verified for all monitoring visits reported.

**Study no: 746-15**

Representative from sponsor monitored the clinical phase of the study for Period-I on 27 and 28 May 2017 and for Period-II on 04 and 05 June 2017.

The visitors' logbook was verified for all monitoring visits reported.

However, the Inspector noted that there was only one monitoring visit report completed for all visits and signed on 13 Jun 2016. The report was elaborate and activities conducted detailed properly.

**Study no: 551-15**

Sponsor's representatives on behalf of sponsor, India monitored the clinical phase of the study. Various study related activities like refilling, weighing of syringes and dosing were monitored. A review of the ICF, Trial Master File, e-CRF and Medical Screening Records of the subjects as well as other study related documents was completed. Details are as follows:

The visitors' logbook was verified for all monitoring visits conducted.

The Inspector noted inconsistencies in the time of entry and exit for two monitors reported on 02 Jul 2016 into/from the facility, however another record was present in the logbook to confirm the visit records.

**Study no: 072-16**

The monitoring visits reported:

- Representative from sponsor, India monitored the clinical phase of the study for Period-I from 03 to 05 October 2016;
- Representative from sponsor, India monitored the clinical phase of the study for Period-II from 11 to 13 October 2016.

The visitors' logbook was verified for all monitoring visits conducted.

Observations made in relation with this section were all addressed adequately.

## **11. Investigators**

Investigators had appropriate qualifications, training and sufficient experience in the conduct of BE studies, as supported by their CVs.

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

A software program was used to record the study medication receipt, and all pertaining information. The Shipment records received on 7 Dec 2017 was reviewed.

At the time of start of the conducting the clinical part of the study, a randomization list was provided by the designated staff, verified by the project coordinator and submitted to the pharmacist in a hard copy.

In the clinical management software, a form was completed by the pharmacist to generate the labels pertaining to the particular randomization list with barcode. Test drug containers were prepared prior to the reference drug container. The randomization sequence was uploaded by statistic personnel into the system which was verified against the hard copy received by the pharmacist. “Requisition of IMP and label verification” form was received and verified.

As soon as the dispensation of study medication was complete, no modification of labels would be possible.

The refrigerators were linked to the digital temperature monitors to keep the temperature between 2-8 °C. A list of the refrigerators’ contents was provided by keeping a log of the medications stored in the respective refrigerator.

Issues raised in this context were sufficiently corrected.

## **13. Case report forms**

This section was not inspected due to time constraints.

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

### Recruitment

On reporting at Lambda, the volunteers were directed towards the screening area located on the ground floor, after collection of their cell phones. Furthermore, volunteers were first enrolled in the in-house databank. The volunteers were explained about the studies with the help of the volunteer information sheet. If they wished to participate, then the informed consent for screening was provided by the study personnel. Volunteers were handled based on their ability to read. Illiterate subjects would be accompanied with an impartial witness. ICF was verified by subject’s



fingerprint and witness' signature. Impartial witness received a lump sum for transport fee and snacks expenses (300 INR). This was verified for the present witness during the inspection. The ICF was kept in a folder. After signing the informed consent form, the volunteers were screened for various tests including their ECG, X-Ray and clinical examination.

The audit trail check was only possible field to field and not by subjects or period of time.

As soon as the volunteer was registered into the system, an ID-card was provided and the volunteer was verified in the OVIS system (Intra-CRO volunteer system) to ensure that the volunteer did not participate in any other studies performed by other CROs in the region, within the timeframe banned by the protocol. Volunteers were blocked in the OVIS as soon as they were enrolled in the study.

Biometrics from iris was also registered in the system.

Inclusion – exclusion criteria for selected subjects were verified. No remarks were made.

The physician performing the physical exam was interviewed and the process was observed. All results were recorded in the electronic system contemporaneously.

All equipment was labelled with an identification number and calibration date. Drug abuse and alcohol test procedure were verified. No observation was raised.

Two types of ECG machines were used prior to February 2016. ECG machines were replaced on 02 Feb 2016 with new device type.

ECG records were stored on server and audit trail was available. The respective audit trail data could be retrieved by providing the date or volunteer ID. The server based ECG was started to be used from 25 Feb 2017.

Volunteer was identified by name and labels with barcodes generated in the system for both blood and urine sample processing. A pregnancy test would be provided prior to X-ray for female subjects.

Observations identified in relation to this section was addressed satisfactorily.

## **15. Food and fluids**

The dining area was visited.

Food and fluids were provided according to the protocol requirements.

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

No SAEs were reported for any of the studies inspected.

### **Bioanalytical section**

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

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

The Certificate of Analysis (COA) and the shipment documentation for the analyte used in the Study no: 746-15 and the pertaining IS, were reviewed, confirming that the standard remained stable at the temperature kept during the shipment. It was shipped from the company addressed in Mumbai to Lambda Ahmedabad:

The log book for receipt of working standards was reviewed.

COA for IS was also reviewed and verified.

System suitability, Acquisition time, IS area, use of CCs, interspersing of QCs  
Chromatograms and pertaining factors across the batches for randomly selected sample analysis were reviewed.

The sample arrangement was as follows:

STD Blank, STD zero, spread QCs and STDs and subjects arrange as xperiodIsample-sequence and xperiodIIsample-sequence, followed by yperiodIsample-sequence and yperiodIIsample-sequence

Method development and method validation documentation pertaining to steps taken to demonstrate the reliability of the methods were reviewed and verified as follows:

<b><u>Study number: 746-15</u></b>	
<b>Method development</b>	
<p>The literature survey was collected in a specific folder including: Literature survey of the drug, chromatography of drug and/or active metabolites, internal standard and effect of minor changes of chromatography conditions.</p>	<p>Method of detection: LC-MS/MS Extraction was documented. Elution Solvent Methanol in 2mM Ammonium formate buffer pH 5.0 Mobile phase: Ammonium formate buffer (pH 5) Auto-sampler temperature: 6.0 Matrix: Human plasma Anticoagulant: K2EDTA Smoothing factor 3 for smooth iteration and 2 for Smooth width.</p> <p>The method development was done according to the corresponding SOP. No manual re-integration was allowed.</p>
<b>Method validation MV(I)-261-17</b>	
<p>The Method validation period was mainly between 8 Jun and 18 Jun 2017. However, the long term plasma stability was performed later on 19 Jul 2017 and 20 Jul 2017 as Add I. the bioanalytical report was issued on Sep 2017.</p> <p>The preparation of QC and CC stock solution, done on 08 Jun 2017 independently was reviewed. Also another separate QC and CC stock solutions for long term stability analysis purposes were prepared.</p> <p>The pertaining spiking solutions for both sets were provided and the documentation was reviewed.</p> <p>A validated Excel sheet was used to provide the calculated concentration for preparation of</p>	<p><b>Dilution integrity</b> Preparation of stock solution for DQC 8 Jun 2017, preparation of matrix spiking 12 Jun 2017, dilution of QC 13 Jun 2017 (PA-I), 13 Jun 2017 (PA-II) and 14 Jun 2017 (PA-III) was reviewed.</p> <p><b>Precision and Accuracy</b> The analyst involved in this analysis (P&amp;A 13 and 14 Jun 2017) was confirmed to be present at the office from 9:30 am to 6:50 pm</p> <p>PA II was performed on inst. 12 on 13 Jun 2017 started at 18:17. Dilution factor used: 5.00 PA I&amp;III was performed on inst. 16 PA I was performed on 13 Jun 2017 PA III was performed on 14 Jun 2017</p>

<p>the solutions. The weighing documentation was present.</p> <p>For analysis purposes, a schedule was prepared. Sample sequences were originally organized in a provided software system, which was linked to clinical trial management software. After preparation, the first sequence was imported into the instrument. The basic information was already incorporated in the system, which was implemented in the sequence list and obtained by analyst. Samples were requested by the analyst from the custodian.</p>	<p>QC samples were not freshly prepared, but they were frozen in the freezer and treated the same way as for the analysis of study samples.</p> <p>6 QC samples (anticipated LLOQ, less than 3 times the LLOQ, mid, high and anticipated ULOQ) were used to assess Accuracy, Precision, Dilution integrity, as well as Recovery factor. Freezer ID was verified.</p>
<p><b>Precision and Accuracy</b></p>	<p>It was done in the same run as the above mentioned Dilution integrity analysis.</p>
<p><b>Stability:</b></p>	<p>Freshly spiked calibration standards and LQC and HQC for comparison were used in this run.</p> <p><u>Stock solution preparation:</u> Short time stability:</p> <p>Three CC (A, B and C) were aliquoted from the stock solution which was prepared on 8 Jun 2017 and stored in the refrigerator, retrieved on 14 Jun 2017 at 12:45 (documentation provided) and kept on the Bench from 12:48 until 22:10 Fresh solution was also retrieved from the same refrigerator.</p> <p>Preparation of dilution from the abovementioned solutions was documented. Pipettes ID used were also recorded on the form for Short term stock solution stability.</p> <p><u>Freeze/Thaw</u> The process was verified for FT plasma matrix:</p>

	<p>4 cycles were organized from 13 Jun 2017 to 15 Jun 2017. Main bulk spiking was prepared on 12 Jun 2017. FT preparation was verified.</p> <p><u>Bench Top</u> The Process was verified for BT stability of plasma matrix</p>
<p>Blank plasma samples used for preparation of CC and QC samples were collected according to the protocol.</p> <p>The documentation for each individual sample was provided with the complete information of date of collection, ICF signed, initials, batch number for the plasma provided, quantity and so on.</p> <p>Altogether, plasma samples from 12 individuals, 2 haemolysed, 2 lipemic and 1 blood sample were provided. Plasma samples were pooled as pooled matrix with individual batch numbers.</p> <p>Pooled plasma was used to prepare the aliquots of CC and QC samples. CCs and QCs aliquot preparation documentation was reviewed and verified. The reconciliation of the pooled plasma was discussed with the CRO.</p> <p>Issues raised were addressed adequately.</p>	

<b>Study number: 555-12</b>	
<b>Method development</b>	
	<p>Extraction was documented in the SOP Mobile phase Acetonitrile in 2 mM Ammonium formate buffer (pH 4.5) in ratio of 65% / 35% Auto-sampler temperature: 4.0 Matrix: Human plasma Anticoagulant: K2EDTA Three LC-MS/MS Instruments were used for full validation and for Long time stability test.</p>
<b>Method validation</b>	
Stability:	<p>Long term stability of analyte in matrix</p> <p>A form called Long term stability of analyte in matrix was completed for MV-525-12 on 28 Dec 2012</p> <p>QCs used in the run:</p>

	<p>QC solutions were spiked on 22 Oct 2012 and stored at -65 in freezer. They were divided in 6 replicates for analysis purposes from A to F.</p> <p>The freezer logbook for this method validation was also reviewed and verified.</p> <p>Stability was established for 66 Days: Freshly spiked CCs were provided as Pagination no 494, dated 28 Dec 2012.</p> <p>The pooled matrix used in preparation of CCs was also checked, pooled on 22 Oct 2012.</p> <p>Microbalance used for preparation of stock solution of CC on 18 Oct 2012 was verified.</p> <p>Preparation of CC stock solution which was the source of freshly made CC spiking samples was reviewed.</p> <p>The QCs for stability test (number of aliquots provided were 48 of each) were prepared and stored on 22 Oct 2012 at 17:20. The QC samples were stored in the freezer for 66 days.</p> <p>Sample batch processing form for retrieval of the QC batches and making 6 replicates of each aliquot was reviewed. The sample analysis started at 12.44 was reviewed and verified, along with calculation of the acceptable range.</p>
<b>Analysis of samples</b>	
	<p>Randomly selected sample analytical runs were reviewed and all samples and respective sample processing form were verified.</p> <p>Check runs were required to be recorded in log sheet for check runs injected on a day for the applicable instrument.</p> <p>Issues raised during the inspection were addressed adequately.</p>
Repeat analysis	<p>There were two reanalyses. No re-integration</p> <p>According to the current practice implemented in SOP for Study conduct in bioanalytical, if the instrument used in the pivotal study sample</p>

	<p>analysis, was not validated in the Method Validation process, at least one P and A data should be available using the respective instrument.</p> <p>At time of the study, the practice was to perform the system suitability test and auto-sampler carry-over. If the Mass chromatography parameters were not the same, two P and A would be performed prior to the initiation of the analysis.</p> <p>It was verified that the system suitability test was done on instrument with 6 injections of ULOQ and two LLOQ.</p> <p>The repeated run was reviewed to investigate the reason for the repeat of pertaining sample. The reason was documented as lab accident and the documentation explained that there was 10 min gap between this sample and next sample and the result was lost due to bug in the system. The issue was defined in the applicable SOP as laboratory accident.</p>
Re-integrated chromatograms	None
ISR	<p>Number of sample used to run ISR analysis was a total of 162 for each Test drug.</p> <p>Acceptance criteria were defined in SOP Incurred sample reproducibility.</p> <p>The retrieval of the samples on the freezer log for this study was recorded 8 Nov 2012.</p>
Back calculations	Back calculation performed for randomly selected subjects was verified.

<b><u>Study number: 821-15</u></b>	
<b>Method development</b>	
	<p>Method of detection LC-MS/MS</p> <p>Extraction was documented</p> <p>Matrix: Human plasma</p> <p>Anticoagulant: K2EDTA</p>
<b>Method validation</b>	<p>MV(I)-186-16</p> <p>Also addendum I for the LTPS</p>
	<p>Matrix effect:</p> <p>For preparation of samples to carry out the Matrix effect run on 13 Feb 2016, ten lots were used.</p>

	<p>P &amp; A II analysis was processed on 13 Feb 2016, followed by Recovery run. Matrix effect was processed as the consecutive second run.</p> <p>LC-MS/MS Instrument used was verified.</p>
<p>Precision and Accuracy</p>	<p>P &amp; A II Recovery was addressed, in the order as follows</p> <ul style="list-style-type: none"> <li>• P&amp;A samples</li> <li>• Recovery samples</li> <li>• Matrix effect</li> </ul> <p>Arranged in 5 different folders.</p> <p>Run PAII ME (Matrix effect) was verified.</p> <p>The Recovery of ISTD with regard to the Area response of ISTD and the determination of the pertaining Accuracy was also confirmed.</p>
<p>Analysis of samples was performed on two instruments For pre-study validation of the instrument per current practice, the superseded SOP was applicable. At the time of study, only pre-validation of the instrument was carried out according to the applicable SOP.</p>	
<p>Analytical run</p>	<p>One analytical run was reviewed.</p> <p>The process was verified.</p> <p>Sample request was confirmed through software system.</p>
<p>ISR</p>	<p>Number of sample used and acceptance criteria were verified.</p>



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

A software system was established for handling of blood samples since 2013.

The storage and all the activities pertaining to the storage of the samples, such as verification of samples, retrieval for analysis, requested by analyst would be scanned through the sample barcode into the database system.

Samples data was recorded in the system at the clinical site by the time the samples were collected, and an email was submitted to BA-site. The samples were transferred to the BA-site freezer room in a box containing dry ice. A data logger would be used in case the samples were transferred from other clinical sites. Upon the receipt of the samples at the BA-site, the box and information was confirmed in the system. Within 7 days after receipt of the samples, the samples would be retrieved from the freezer and verified one by one.

The sample request control was reviewed in the system and verified.

All the samples were labelled with a barcode with all sample information in the system.

Once the analyst provided the sample sequence schedule, the custodian would provide the samples according that, scanning them into the system. In case, the sequence missing any sample or incorrect sample was scanned, the custodian would receive a notification and system would prevent the completion of retrieval of samples. No further QC of samples would be done by analyst as the process was implemented in the system. The electronic system performed the e-QC check which was considered to be secured enough.

Regarding applications performed before 2013, such as Study 555-12, the collection of the blood samples was conducted in a different way:

A form called study sample transfer detail captured the details such as name of drug, period number, anticoagulant, total number of subjects, total number of time points and total number of storage box.

Detailed of haemolysed samples and details of missing samples were recorded on a different form, for each lot separately.

A total of 1644 samples were received for both periods for Study 555-12. The receipt of samples were verified and QC-ed.

Request form for discarding the biological samples for MV(I)-238-16 for CC/QC both for first period and for LTPS was reviewed and verified. No remarks were made.

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

The organization was processing data both electronically and in paper form, based on the type of documentation and systems available.

e-CRFs were generated in software system, used for clinical data. Another software system was used for processing of bioanalytical part of data.

The systems were validated according to their procedures. However, the validation documentation was not thoroughly inspected due to the time constraints.

Documentation in paper form, such as forms used in processing of bioanalytical activities was recorded and archived properly according to their procedures.

## **20. Good laboratory practices**

List of equipment and instruments used in the studies was provided.

The process for calibration of the micropipette on higher and lower position was observed to ensure proper calibration procedure.

Observations made in connection with calibration of micropipettes were addressed sufficiently.

Pipette calibrations were performed every three months by designated personnel, and once a year by outsourced service provider.

Calibration certificates for microbalance used in 555-12 was reviewed. The service was provided by an external service provider. A new service provider was contracted.

All together the CRO had 60 freezers at -65.

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

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

#### Randomization

SAS software was used to create the randomization list. The request was received from the project coordinator by email based on the protocol requirements for scheduling the randomization.

Randomization list was printed out and signed and QC-ed by the designated personnel.

The schedule was uploaded by biostatistician into the trial management software, to which the pharmacist had access.

The Biostatistician team was divided to two groups:

- Pharmacokinetic team
- Statistic team

Sealed list would be provided for blinded studies to be handed over to the pharmacy custodian.

Sample size is determined based on the molecule and past studies also the literature available.

PK analysis was performed using software system Phoenix.

Clinical data was uploaded into the bioanalytical management software by clinical department and an email was sent to the pharmacokinetic team. Only after the QC review and verification of the data in software, the data would be available to the statistician.

Interviews were performed within the biostatistician team.

- Biostatistics and programming personnel responsible for writing the statistical methodology sections of protocols and statistical analysis plans of clinical studies (SAP)
- Personnel responsible for providing scientific inputs in study designs and performing population pharmacokinetic analysis

Issues raised in relation to this section were corrected satisfactorily.

## **22. Study report**

The team leader for clinical report writing was interviewed on 14 Dec 2017. The team was divided to three groups under his supervision:

- Statistic
- Clinical
- Bioanalytical

The clinical report was provided using the data available in (eCRF), extracted in Excel sheets and uploaded to the software. A hard copy binder was also maintained by BA team for the Bioanalytical part of the study. The report was QC-ed prior to the submission of the report to the compilation team who was responsible for finalization of the report, as well as the preparation of the dossier. The dossier would be audited and approved by QA prior to the submission to the sponsor.

Miscellaneous	
<i>Samples taken</i>	Not applicable
<i>Assessment of the CRO master file</i>	CRO master file was provided and reviewed.
<i>Annexes attached</i>	Not applicable

Part 3	Conclusion
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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 study was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at **CRO Lambda Therapeutic Research Ltd.; Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of guidelines referenced in the inspection report
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- 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**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex09.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf)
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report.* World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390  
**Short name: WHO multisource guidance**  
[http://apps.who.int/prequal/info\\_general/documents/TRS937/WHO\\_TRS\\_937\\_\\_annex7\\_eng.pdf](http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.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**  
<http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html>
4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5  
**Short name: WHO TRS No. 996, Annex 5 WHO GDRMP guidance**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex05.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf)
5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM (98)17. 26. Jan 1998.  
**Short name: WHO GLP**  
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.  
<http://www.ispe.org/gamp-5>
7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.\* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2011/08/WC500109686.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf)
8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1  
<http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1>
9. Good Practices for Computerised Systems in Regulated “GXP” Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.  
[http://www.picscheme.org/pdf/27\\_pi-011-3-recommendation-on-computerised-systems.pdf](http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf)
10. US FDA Code of Federal Regulations Part 11  
<http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1>
11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems  
[http://ec.europa.eu/health/files/eudralex/vol-4/annex11\\_01-2011\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf)

12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as “GLP”.  
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
  
13. 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 TRS No. 961, Annex 9**  
[http://apps.who.int/prequal/info\\_general/documents/TRS961/TRS961\\_Annex9.pdf](http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf)
  
14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7  
**Short name: WHO TRS No. 957, Annex 7**  
[http://www.who.int/medicines/publications/TRS957\\_2010.pdf](http://www.who.int/medicines/publications/TRS957_2010.pdf)
  
15. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009  
[http://www.who.int/gpsc/5may/Glove\\_Use\\_Information\\_Leaflet.pdf](http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf)
  
16. WHO Good Clinical Laboratory Practices (GCLP)  
<http://www.who.int/tdr/publications/documents/gclp-web.pdf>