



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	Levonorgestrel Tablets 1.5mg (RH31) Levonorgestrel Tablets 0.75mg (RH32)
Study number	207-11 (Levonorgestrel 1.5mg tablet, RH31) PLNB 09280 (Levonorgestrel 0.75mg tablet, RH32)
Title of the study	1. Single dose Fasting BE study of Levonorgestrel Tablets (0.75mg, Sponsor, Mylan) and Plan B Tablets (0.75mg, Duramed) in healthy female volunteers. 2. An open label, balanced, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of Levonorgestrel 1.5mg tablet of Famy Care Ltd, India with that of Norlevo (Levonorgestrel) tablet 1.5mg of HRA Pharma in healthy, adult, human female subjects under fasting conditions.
Clinical Part of the study: Name and address of the organization	Lambda Therapeutic Research Ltd. Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, <u>Ahmedabad-380 061</u>, Gujarat, India. Tel. No. 079-40202020 Fax. No. 079-40202021 Lambda Therapeutic Research Ltd., 7th Floor, The Great Eastern Summit -A, Plot No. 56, Sector 15, CBD Belapur, <u>Navi Mumbai – 400614</u>, Maharashtra, India. Tel. No.: +91-22-2756 2220 / 2224 Fax No.: +91-22-2756 231
Bio-analytical laboratory: Name and address	Lambda Therapeutic Research Ltd. Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, <u>Ahmedabad-380 061</u>, Gujarat, India. Tel. No. 079-40202020 Fax. No. 079-40202021

Date of inspection	15 to 16 October 2012 (Ahmedabad) 17 to 18 October 2012 (Navi Mumbai)
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Part 2: Summary

General information about the site(s)

1. According to the Site Master File (SMF) and presentation, **Lambda Therapeutic Research Ltd, Ahmedabad** has been providing contract clinical research services since 1999. The company is head quartered at Ahmedabad, India; Lambda has a global presence in London, Canada and Poland. Lambda Therapeutic Research Ltd, Ahmedabad occupies currently a space of 2,50,000sq.ft. in a four-storey building with a 360 bed capacity to house healthy volunteers for clinical studies (Bio-analytical (BA) /Bioequivalence (BE) studies). It has four clinical wards (90 beds in each ward) for conducting bioequivalence studies and has a dedicated 16 bedded phase-I unit exclusively for conducting First-In-Man studies.
2. According to the SMF and presentation, **Lambda's Navi Mumbai facility** is located on second, seventh and eighth floors of 'A' wing of The Great Eastern Summit building. It consists of approx. 15,000 sq. ft. floor area and has various sections to carry out clinical study related activities. The clinical facility is spread over in an area of 6000 sq. ft.

Second floor: Part of this floor is occupied by Lambda. This floor has screening area for volunteers. This consists of waiting and screening consent areas, Clinical Examination Room, Electrocardiography (ECG) Room, phlebotomy section and wash rooms (Bathroom, toilet and urinals).

Seventh floor: This floor is fully occupied by Lambda. There is a Clinical facility (CPU) of 42 beds (21 sets of bunk beds) along with two single bedded dedicated Intensive Care Unit (ICU) unit, Informed Consent presentation room, Change room for study subjects, Housing and recreation area for study subjects, phlebotomy area (having 8 phlebotomy stations), Freezer room for storage of bio-waste generated during studies and pantry to serve meals (breakfast, lunch, dinner and snacks) to subjects during studies. There are five bathrooms & toilets (Attached) in the clinical facility. Each bed is provided with a call bell device to be used by subjects in case of emergency. Similar call bells are also installed in bathroom/toilets for subjects' safety. There are separate meeting rooms, server room, reception area and wash rooms for staff and visitors on the same floor.

Eighth floor: This floor is also fully occupied by Lambda. This consists of Samples centrifugation, separation and an interim storage room for plasma/blood samples, Pharmacy to store and dispense Investigational Medicinal Products, Documentation room, Archives and staff office (Quality Assurance (QA), Quality Control (QC)- Clinical and Clinical Trials Management office) and staff canteen.

History of WHO and/or regulatory agency inspections

1. The last WHO inspection was performed at the Ahmedabad facility in July 2004. According to the Site Master File (SMF), **Lambda Ahmedabad** had received various regulatory inspections, namely from USFDA, AFSSAPS France, MHRA UK, WHO Geneva, OGYI Hungary and Turkey- MOH. In addition to the above, Lambda has been accredited by ANVISA Brazil, and MoH Thailand (Thai FDA) for its systems and compliance to GCP & GLP. Lambda's Clinical Laboratory has been accredited by College of American Pathologists (CAP) and National Accreditation Board for Testing and Calibration Laboratories (NABL).
2. This was the first WHO inspection at **Lambda Navi Mumbai** facility. From the opening meeting presentation, it was noted that none of the regulatory agency appeared to have inspected the Navi Mumbai facility. It later advised that Lambda Navi Mumbai had been inspected thrice by the USFDA (2007, 2010 and 2012), once each by the OGYI Hungary (2009) and ANVISA Brazil (2005) authorities.

Focus of the inspection

The inspection focused on the clinical (RH31 and RH32) and bio-analytical portion (RH31) of the bio-equivalence study conducted for the product Levonorgestrel 0.75mg (RH32) and 1.5mg (RH31) tablet conducted at Lambda Ahmedabad and Navi Mumbai facilities. The inspection covered various sections of the WHO Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Note: The bio-analytical portion of RH32 was conducted by Matrix Labs Ltd. (Now Mylan) Clinical research Centre, Hyderabad, India. Based on the previous GCP inspection compliance history, this portion of the RH32 study was not inspected.

Inspected Areas

Day 1 (Ahmedabad) 15th October 2012

After the introduction and opening meeting, the following documents were reviewed:

- Contract between the sponsor and Lambda
- Insurance
- Independent Ethics Committee (IEC) meeting records and approval of the protocol and associated documents for the studies for RH31
- Informed consent forms
- Composition of the ethics committees and minutes of meeting
- Case report forms

Day 2 (Ahmedabad) 16th October 2012

Inspectors gave feedback and then continued with their review of study documentation.

- The inspectors performed a tour of the facilities which included the registration, screening, subject change rooms, CPU, ICU, Pharmacy (which included a verification of reconciliation of both Investigational Products and the documentation of line clearance).
- Inspectors also reviewed analytical data relating to study 207-11 directly on the HPLC MS/MS system which was used at the time of the study.

Day 3 (Navi Mumbai) 17th October 2012

After introduction and opening meeting, following documents were reviewed:

- Project contract between the sponsor/Famy Care and Lambda Navi Mumbai
- Insurance
- IEC Aditya meeting records and the approval of protocol and associated documents for the studies for RH32
- Informed consent forms and subject information sheet
- CV of Principal Investigator and Co-investigator
- Composition of the ethics committees and minutes of meeting
- Case report forms
- Facility tour (screening, clinical and QA & Archive)

Day 4 (Navi Mumbai) 18th October 2012

The inspection team reviewed the following documents:

- Dosing versus randomization
- SOP for blood sample management
- Labels for blood samples
- Sample storage conditions
- Logbooks for storage, retrieval and shipping of samples

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This part of the trials was found to be satisfactory overall for the studies examined and for the facilities.

2.2. THE PROTOCOL

The protocols for RH 31 and RH 32 were reviewed and found generally satisfactory.

2.3. PROTECTION OF TRIAL SUBJECTS

In general, this area of GCP was found acceptable with the exception of illiterate subjects and their signature for acknowledging the consent. The response submitted was found to be acceptable and will be verified during future inspections.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

In general, this area met the GCP requirement. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.5. RESPONSIBILITIES OF THE SPONSOR

There were some issues noted regarding this section which were adequately addressed. The corrective action and preventive actions will be verified during future inspections.

2.6. RESPONSIBILITIES OF THE MONITOR

For the mentioned studies, there were no monitoring reports available. The CRO has submitted the response that in consultation with sponsor, monitoring will be done for the future studies. This will be verified during future inspections.

2.7. MONITORING OF SAFETY

In general, the monitoring of the safety of the subjects was found acceptable. More attention is required to ensure subjects with adequate haemoglobin level (within normal range) are enrolled in the study. This aspect will be verified during future inspections.

2.8. RECORD-KEEPING AND HANDLING OF DATA

There were number of issues noted on the poor handling of data, the Clinical Research Organization (CRO) is committed to address all these deficiencies in a timely manner. This aspect will be verified during future inspections.

2.9. STATISTICS AND CALCULATIONS

In general, this area was found acceptable.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

It has been noted that the reference product was purchased from a non-legally authorised sources. It is mandatory for the sponsor to ensure the authenticity of the sources before using such products in their BE studies. This aspect will be verified during future inspections.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Not applicable

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

In general, the QA was found to be acceptable in Ahmedabad site. There were some deficiencies observed in Navi Mumbai site. The CRO is committed to address the weaknesses identified, and the same will be verified during future inspections.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the **Clinical Part of RH32 and Clinical & Bio-analytical Part of RH31** were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Lambda Therapeutic Limited, Ahmedabad and Lambda Therapeutic Limited, Navi Mumbai.

All the non-compliances observed during the inspection that were listed in the full 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.

Note: The bio-analytical portion of RH32 was conducted by Matrix Laboratories Ltd. Hyderabad, India and was not inspected.