



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA549 and MA099
Study number	# S-12-324 (HA549) and # CPL-12-427 (MA099)
Title of the study	<u>HA549</u>: A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover bioequivalence study of fixed dose combination of Efavirenz 600mg + Lamivudine 300mg + Tenofovir Disoproxil Fumarate 300mg Tablets and SUSTIVA® (efavirenz) 600mg tablets of Bristol-Myers Squibb Company, Princeton, NJ 08543 USA, Viread® (tenofovir disoproxil fumarate) 300mg Tablets, of Gilead Sciences, Inc. Foster City, CA 94404, USA and EPIVIR® (lamivudine) 300mg tablets of GlaxoSmithKline Research Triangle Park, NC 27709 in healthy human adult subjects, under fasting conditions. <u>MA099</u>: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, oral bioequivalence study of Artemether and Lumefantrine 20/120mg tablets and Coartem® (Artemether/Lumefantrine) tablets 20mg/120mg of Novartis Pharmaceuticals Corp. Suffern, New York 10901 in healthy human adult subjects, under fed conditions.
Clinical Part of the study: Name and address of the organization	Semler Research Center Private Limited P A Arcade, No 21, 22, 23 Kodigehalli Main Road Sahakarnagar Bangalore-560092 Tel 080-43027100
Bio-analytical laboratory: Name and address	Semler Research Center Pvt. Ltd. 75A, 15th cross, I Phase, JP Nagar, Bangalore-560078 Telephone: 080-42627200, Fax: 080-26640683
Date of inspection	25 to 28 March 2013

Part 2: Summary

General information about the site(s)

Semler Research Center (SRC) is part of US based Arnold A Semler Inc, in business since 1946. SRC was founded in 2006, is a privately owned pharmaceutical services company with its business offices in Los Angeles, CA and Bangalore, India. SRC provides wide services primarily in the areas of pharmaceutical development, bioavailability and bioequivalence studies, early and late phase clinical development, regulatory services and medical & scientific writing. SRC employs 190 people.

The corporate office is located at J.P. Nagar, Bangalore, Karnataka where opening meeting took place. The bioanalytical facility is located at 2nd floor of the corporate office and is spread over about 7000 sq. ft. The facility has demarked to support the smooth flow of activities such as, access controlled sample storage area, sample processing room, balance room, washing room and Instrumentation room.

Bangalore clinical facility is located at Kodigehalli, Bangalore, Karnataka. The facility is about 20,000 sq. Ft area spread over 3 storey building. Clinical facility is 72 bedded (24+24+24) for BA/BE divided into 3 different wards along with the well-equipped intensive care units (2 beds divided into 2 units). The clinical research centre is clearly demarked as per the activities such as volunteer screening area, counselling area, in-house clinical testing laboratory, volunteer housing area along with the wash rooms, Investigational Products (IPs) administration area, phlebotomy (sample collection and processing area), access controlled pharmacy, recreation area and dining rooms for the study volunteers.

History of WHO and/or regulatory agency inspections

- Drug Controller General of India (DCGI) approval in 2011
- WHO Geneva inspection in 2010 and 2011
- USFDA inspected in May and September 2012

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the products, Artemether + Lumefantrine 20/200mg tablets (MA099) and Efavirenz 600mg + Lamivudine 300mg + Tenofovir Disoproxil Fumarate 300mg Tablets (HA549). The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

A. BIOANALYTICAL PART

1. Overview and brief visit of facilities and equipment
2. Management of computerized systems and protection of data (verification of documentation vs. practice)
3. Review of source data in electronic and hard copy (Sample analysis for Period I and Period II)
 - Back calculations
 - Acceptability of runs
 - Review of source data (Preparation of matrix, stock, QCs and stability (weighing, calculations, and chromatograms, method development and validation)
4. Reanalyses, repeat analyses, ISR
5. Bio-analytical Method development
6. Bio-analytical Method validation data
 - SOP
 - Protocol and report
 - Precision, accuracy etc.
7. Plasma selection and pooling
8. Stock solution preparation
 - QCs
9. Stability data (stock solution and samples)
 - Short term
 - Long term
 - Freeze thaw
 - In injector/Autosampler
10. Laboratory inspection
 - Instruments and equipment
 - Pipettes
 - Sample management
 - Deep freezers
 - Reference standards
 - Fridges

B. CLINICAL PART

1. Overview of clinical part presentation
2. Physical tour of clinical area including:
 - Registration (this will include an examination of the databases in use and means of retaining information on subjects)
 - Screening (instruments used)
 - subject change rooms
 - CPU
 - ICU
 - Pathology laboratory

- Pharmacy
- 3. Documentation review
 - Contract between Sponsor and investigator
 - Review of Sponsor responsibilities
 - Review of CRO responsibilities
 - Principle Investigator and staff involved in the study
 - Review of Ethics Committee composition, responsibilities, SOPs, detailed minutes of meetings discussing the study under review
 - Review of Protocol, volunteers, ICF, Screening and CRFs
 - Verification of Source data
 - QA Audit reports
 - Monitor reports
 - Randomization
- 4. Pharmacy and investigational products
 - Site inspection. CPU
 - Dosing
 - Storage
 - Reconciliation of IPs
 - Line clearance procedures and documentation.
- 5. Sample collection, preparation and storage
 - Visit of applicable areas and of refrigerators, deep freezers and ultra-deep freezers in use
 - Qualification and performance verification of equipment.
- 6. Archives (paper and electronic)
 - Access control
 - Document traceability
 - Protection of documentation and
 - Statistical analysis

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. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.2.THE PROTOCOL

For the studies that were seen, protocols were considered to be acceptable overall.

2.3. PROTECTION OF TRIAL SUBJECTS

Although most of the elements were fulfilled, some issues of concern were found during the inspection which had been addressed adequately. This will be verified during the next inspection.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

The curriculum vitae of the principal investigator and co-investigator confirmed their adequate qualification and competency in Good Clinical Practices. The assigned investigator was responsible for the recruiting of suitable subjects based on the inclusion and exclusion criteria. The information given in the protocol was communicated to subjects before the start of the BE studies.

The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.5. RESPONSIBILITIES OF THE SPONSOR

The observations raised pertaining to the inadequate responsibility of the sponsor had been adequately addressed, and the same shall be verified during the next inspection.

2.6. RESPONSIBILITIES OF THE MONITOR

The observations raised pertaining to the inadequate monitoring had been adequately addressed, and the same shall be verified during the next inspection.

2.7. MONITORING OF SAFETY

The subjects were assessed before the entry of subjects into study as per the selection and withdrawal criteria stated in the protocol. The vital signs and clinical examination were conducted as per the protocol. Also, the protocol required handling and reporting of adverse events and serious adverse events. In general, this area was found satisfactory.

2.8. RECORD-KEEPING AND HANDLING OF DATA

The archives and electronic records were found to be acceptable overall.

2.9. STATISTICS AND CALCULATIONS

Methods of communicating the information between bioanalytical and the Pharmacokinetics/Biostatistics (PB) department were verified briefly. Statistics and calculations were performed by a biostatistician located at the J.P. Nagar in Bangalore. In general, this area was found satisfactory.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The test and reference quantities were verified and found to be satisfactory. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The facility had been approved by the Central Drugs Standard Control Organization (CDSCO). An observer from the CDSCO was present and observed the WHO inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

This area was generally satisfactory. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

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 study *HA549* and *MA099* was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Semler Research Centre (SRC) at JP Nagar (bioanalytical) and PA Arcade, Sahakarnagar (clinical), Bangalore, India.

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.