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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA498 (Emtricitabine and Tenofovir Disoproxil fumarate tablets 200mg/300mg) HA535 (Tenofovir Disoproxil fumarate tablets 300mg) HA552 (Emtricitabine and Tenofovir Disoproxil Fumarate tablets [200/300mg] [FC]) **Others seen but not inspected in detail, as covered by USFDA inspections:** HA557 (Lamivudine, Nevirapine and Zidovudine for oral suspension 30/50/60 mg) HA524 (Lamivudine, Nevirapine and Zidovudine tablets 150/200/300mg)
Study number	**Study #:**08-VIN-029 (HA498) **Study** #:07-VIN-150 (HA535) **Study** #:08-VIN-151 (HA552) **Study** #:10-VIN-129 (HA557) – inspected by USFDA **Study** #:08-VIN-047 (HA524) – inspected by USFDA
Title of the study	**HA498:** An open label, balanced, randomized, single-dose, two-treatment, two sequence, two-period, crossover bioequivalence study of Emtricitabine and Tenofovir Disoproxil fumarate tablets 200mg/300mgof Hetero Drugs Ltd, India and Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) tablets, 200mg/300mg of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions. **HA535:** Open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study of Tenofovir Disoproxil fumarate tablets 300mg of Strides Arcolab Limited, India and Reference product Viread® (Tenofovir Disoproxil fumarate) Tablets, 300mg of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions. **HA552:** A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Emtricitabine and Tenofovir

	Disoproxil Fumarate Tablets[200/300mg] [FC] of Strides Arcolab Limited, India and Truvada® (Emtricitabine 200mg and Tenofovir disoproxil fumarate 300mg) Tablets, of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions. **HA557:** An open label, randomized, balanced, two treatment, two period, two sequence, two way crossover, single dose comparative oral bioavailability study of Lamivudine, Nevirapine and Zidovudine Tablets [Dispersible] [30/50/60 mg]of Strides Arcolab Limited, India with EPIVIR® Oral Solution (lamivudine oral solution) 10mg/mL of GlaxoSmithKline, Research Triangle Park, NC 27709, RETROVIR® (Zidovudine) Syrup 50mg/5mL of GlaxoSmithKline, Research Triangle Park, NC 27709 and Viramune® (Nevirapine) Tablets 200mg of Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT 06877 USA in healthy, adult, human subjects under fasting condition. **HA524:** A randomized, open label, two treatment, two sequence, single dose, cross-over, bio-equivalence study of fixed dose combination tablets containing Lamivudine, Nevirapine and Zidovudine (150/200/300mg) of Strides Arcolab Ltd, India and Combivir (Lamivudine/Zidovudine) Tablets 150/300mg of GlaxoSmithKline Research Triangle Park, NC 27709 and Viramune (Nevirapine) 200mg tablets of Boehringer Ingelheim Pharmaceutical Inc, Ridgefield, CT 06877 USA in healthy, adult, human subjects under fasting conditions.
Clinical Part of the study: Name and address of the organization	Veeda Clinical Research Pvt., Limited, Shivalik Plaza A, Near I.I.M. Ambawadi, 380015, Ahmedabad, India
Bio-analytical laboratory: Name and address	Veeda Clinical Research Pvt Limited, Shivalik Plaza A, Near I.I.M. Ambawadi, 380015, Ahmedabad, India Other Facility: Veeda Clinical Research Private Limited (Insignia) Opp. AUDA Garden, SindhuBhavan Road, Bodakdev, Ahmedabad-380059, Gujarat, India
Date of inspection	14 – 18 February 2013

Part 2: Summary

General information about the site(s)

Veeda started their independent CRO operations in April 2005. In July 2005, Veeda acquired a Phase I clinical trials company in Plymouth, UK. In December 2006, Veeda also acquired a data management and statistics unit in Belgium. A new laboratory was started in Ahmedabad, India and was named Insignia, in October 2010. Clinical trial operations were started in April 2011in Kuala Lumpur, Malaysia. A public/private cooperation between Indiana University in the US and Veeda was initiated in December 2012.

There were 3 Veeda facilities in Ahmedabad: Shivalik (clinical, bioanalytical and biostatistics, divided in 2 buildings), Insignia (bioanalytical) and the screening site (Vastrapur, Ahmedabad, about 2 km away from Insignia).

The clinical portion of the studies was conducted at the Shivalik site. There were 17 LC MS/MS machines at the Shivalik site.

Insignia has not yet been inspected as it was being used for recent bioanalytical and QA studies only. Some of the LC MS/MS equipment that it contained had been moved from the Shivalik unit to the Insignia unit.

100 post graduates were described to be working in the bioanalytical units. The capacity was 30,000 samples per month.

The Company stated that 445 studies were done for the USFDA, 139 for the EU and UK MHRA, 33 for Brazil, 24 for Canada, and 19 for Australia.

History of WHO and/or regulatory agency inspections

There have been 7 inspections performed by US FDA (last inspection in 2012), 3 by the WHO (last time in 2009), UK MHRA (1 inspection, the last inspection in 2007) of the Shivalik site. This was the second inspection of the Insignia facility. The first was conducted by ANVISA.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the products HA498 (Study #:08-VIN-029), HA552 (Study #:08-VIN-151) and HA535 (Study #:07-VIN-150). Studies HA557 (Study #:10-VIN-129) and HA524 (Study #:08-VIN-047) were not inspected beyond a verification of corrective actions to the deficiencies raised during 2 inspections performed by the USFDA. The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies. All 3 Veeda facilities in Ahmedabad were covered by this inspection.

Inspected Areas

1. Overview and brief visit of facilities and equipment
2. Management of computerized systems and protection of data
3. Review of source data in electronic and hard copy
4. Reanalyses, repeat analyses, ISR
5. Bio-analytical Method development
6. Bio-analytical Method validation data
7. Plasma selection and pooling
8. Stock solution preparation
9. Stability data
10. Laboratory inspection
11. Physical tour of clinical area
12. Documentation review
13. Pharmacy and investigational products
14. Sample collection, preparation and storage
15. Archives (paper and electronic)
16. Overview of the statistics of the study
17. Recalculation of statistical parameters

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This area was considered to be acceptable overall for the studies that were seen. The observations raised were adequately corrected.

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. These issues were addressed in the submitted CAPAs and found satisfactory.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

The curriculum vitae of the Principle 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.

2.5. RESPONSIBILITIES OF THE SPONSOR

In general, this section was found satisfactory.

2.6. RESPONSIBILITIES OF THE MONITOR

During the inspection, it was found that number of visits by the monitor was not adequate as per the recommended guideline. The sponsor has committed to carry out the required monitoring as per the WHO GCP guideline.

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. The temporary archives for both paper and backup disks were seen at the Shivalik site.

2.9. STATISTICS AND CALCULATIONS

Methods of communicating the information between bioanalytical and the Pharmacokinetics/Biostatistics (PB) department were verified. For studies currently being undertaken at the site, the data is directly transferred through a digital system in LIMS to Winnolin by bioanalytical.

The issue raised during the inspection was addressed adequately and will be verified during the future inspections.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

This area was considered acceptable overall. The issues raised were addressed adequately and will be verified during the future inspections.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The Central Drugs Standards Control Organization (CDSCO) had inspected this site (site inspections are performed, rather than study inspections), when they had applied for the renewal of their licence. Based on the inspection report from CDSCO the DCGI took a decision to approve the site based on their recommendation. 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 considered to be acceptable in the most part. The issues raised pertaining to quality assurance were addressed adequately, the same will be verified during the 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 study ***HA498, HA524, HA535, HA552 and HA557***was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at ***Veeda Chemical Research Pvt Ltd.***

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.