



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB239 Prothionamide 250 mg capsules (Other products studies briefly inspected included MA82 Artesunate/Amodiaquine tablets 100 mg/270 mg tablets, TB242 Ethionamide 250 mg tablets and TB223 ethambutol/isoniazid/pyrazinamide/rifampicin 275/75/400/150 mg tablets)
Study number	ARL/10/320 (Other studies briefly inspected included ARL/09/935, ARL/11/021 and ARL/09/439)
Title of the study	<u>Principal study inspected:</u> A randomized, open label, balanced, two-sequence, two-treatment, two-period, single dose, crossover bioequivalence study of prothionamide tablets 250 mg manufactured by Micro Labs Ltd., with PETEHA [®] (Prothionamide Tablets 250 mg) manufactured by Fatol Arzneimittel, Germany, in normal, healthy, adult male human subjects under fasting condition Dates of study : - Clinical phase: 23 July 2010 to 25 July 2010 (Period I) and 1 August 2010 to 3 August 2010 (Period II) - Bioanalytical phase: 5 April 2011- 27 April 2011 (Subject analysis). Long term stability testing performed on 4 February 2012.
Clinical Part of the study: Name and address of the organization	Accutest Research Laboratories Pvt Ltd A-31, M.I.D.C., TTC Industrial Area, Khairane, Navi Mumbai 400 709 India
Bio-analytical laboratory: Name and address	Mr. Atul Solankar, Vice-President, Corporate Quality Assurance & Regulatory Affairs, atul.solankar@accutestindia.com
Date of inspection	15-18 May 2012

Part 2: Summary

General information about the site(s)

The company had 4 sites, 2 in Ahmedabad , 1 in Baroda and 1 in Mumbai. The Navi Mumbai site has 2 CPU units, 1 pathology lab and 2 bioanalytical laboratories.

History of WHO and/or regulatory agency inspections

The WHO Prequalification of Medicines Programme has conducted about 8 inspections of the different Accutest sites. The Navi Mumbai site was recently inspected on 28 and 29 May 2009 and in September 2011.

Accutest had one site in Navi Mumbai and separate offsite Archive. The main building (A-31) included 4 floors where activities were conducted as per the following:

- Ground floor - clinical unit I and II, sample collection, dosing, pharmacy and ICU (Intensive care unit)
- Basement - pathological and X rays laboratories
- 1st floor - onsite archive, Quality Assurance (QA) department and cafeterias,
- 2nd floor - analytical laboratory, statistics department, onsite storage of samples.

The offsite archive was located approximately 6 km away from the CRO. The principal bioanalytical laboratory (A-91) was located 1 block away from the main building.

Both bioanalytical laboratories (A-31 and A-91) were covered by this inspection. There were 10 HPLC-MS/MS instruments in A-31 and 6 in A-91.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product TB239 Prothionamide 250 mg tablets (Study code ARL 10 320). The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Other studies which were briefly inspected (spot checks on selected data) included:

	Products reference and name	Sponsor	Study code
1	TB223:ethambutol/isoniazid/pyrazinamide/rifampicin 275/75/400/150 mg Tablets	Microlabs	ARL/09/439
2	MA82: amodiaquine/artesunate 270/100 mg Tablets	Maphar Casablanca for Sanofi Aventis	ARL/09/035
3	TB242: ethionamide 250 mg Tablets	Micro Labs	ARL/11/021
4	HA482: Lamivudine/Nevirapine/Stavudine 150/200/30mg Tablets	Varichem	SA//07/010

Data for the following was available for inspection but was not reviewed in view of no major concerns identified in the inspected studies:

1	HA420: Lamivudine 300mg tablets	Mylan	US/07/042
2	HA456: Abacavir/Lamivudine 60/30mg tablets	Mylan	US/AHD/07/040 (Bio-analytical only)
4	HA489: Lamivudine/Tenofovir 300/300mg tablets	Cipla Ltd	ARL/09/296
5	HA500: Efavirenz/Emtricitabine/Tenofovir 600/200/300 mg Tablets	Cipla Ltd	BBRC/US/08/001 (Bio-analytical only)

Inspected Areas

On day 1, after the CRO presentation, inspectors proceeded to a tour of the clinical facilities and of the archives located at A-31.

During this tour, inspectors visited the CPUs 1 and 2, screening rooms and the ICU. The CTMS database for subject registration, screening and study participation, was consulted. Digital fingerprint recognition was verified to function appropriately through a positive and negative identification of randomly picked persons present during the inspection. Subjects were verified to have complied with the 3 month wash-out period requirement in between studies at the site (the only limitations of this system being that a subject could still have participated in another study at another CRO without having declared it to Accutest). Inspectors also examined the ECG equipment. A computerized system was in use which allowed storage of ECGs, however the format in which they were stored and controls in place were verified to adequately protect data authenticity.

On day 2, inspectors focussed on a review of the following documents for Study ARL/10/320

- Qualifications of the investigator
- Composition of the independent ethics committee
- List of documents sent to the IEC
- Translation of the informed consent form
- List of side effects of the study drug (translated and original version in Hindi)

The pharmacy activities were reviewed and reserve samples of the investigational products were inspected. Reconciliation was verified.

The day was ended by a short visit and preliminary inspection of the bioanalytical data for subjects 3, 5, 26, 28, 38, 39, 52, 54 of study ARL/10/320.

On day 3, inspectors focussed on the review of bioanalytical data for the analysis of subject samples from the ARL/10/320 study which included:

- A review of sample handling storage and preparations records
- Transfer of plasma samples to freezer MI/01/003/00016 at A-31 and their removal and transfer to A-91.
- Processing of QCs, CCs, QCs and samples for subjects 1 to 6, 26, 28, 37 and 52.
- Long term stability preparations
- Records of destruction of analytical aliquots

The day was ended by re-performing pharmacokinetic parameter calculations and statistical analyses for ARL/10/320 using SAS software with the help of a biostatistician on the 4th floor.

On day 4, inspectors reviewed selected portions of the other studies, namely:

-ARL/09/035: Electronic bioanalytical verifications included the original data for subject No. 62, the reanalysis results, comparing the integration performed and their adequacy as well as mass spectrometry parameters. Failing QCs records were verified. For subject No 8, the batch was rejected because 3 out of 4 QCs had failed.

Recalculations using SAS yielded:

LAUC inf 98.7635, 110.562, p 0.20

LAUCt 99.4518, 111.2331, p 0.14

LCmax 93.3757, 121.6239, p 0.43

-SA/07/010: Bioanalytical data was reviewed electronically on Analyst software.

The integrations for subjects No 1, No 2 were verified in detail and were found to be adequate. The individual time point values were verified for stavudine, subjects 1 and 2 and for lamivudine for subject No. 38. Subject No. 43 and 44 were also selected based on a low AUCt ratio of 86.68.

Verifications were performed on Subject 17 of Study ARL/10/320 using Excel.

Inspectors performed the statistical analyses for ARL/10/320 using SAS software with the help of a biostatistician on the 4th floor.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

For Study ARL/10/320: Justification for the trial, respect of ethical principles were found to be adequate in general.

2.2. THE PROTOCOL

For Study ARL/10/320: Version 1 of the protocol was verified to match the information which had been submitted to the WHO for assessment. It was sent and received by the IEC on 14 July 2010.

2.3. PROTECTION OF TRIAL SUBJECTS

For Study ARL/10/320: Subjects were covered by insurance according to a study-specific contract. Protection of the subjects and ethical considerations were considered to be adequate in general.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

For Study ARL/10/320: The responsibilities of the investigator were found to be fulfilled in the most part.

2.5. RESPONSIBILITIES OF THE SPONSOR

For Study ARL/10/320: Responsibilities of the sponsor were described in the master service agreement as well as in the clinical trial protocol and were considered to be adequately fulfilled in the most part.

2.6. RESPONSIBILITIES OF THE MONITOR

This area was not inspected in detail due to time constraints.

2.7. MONITORING OF SAFETY

For Study ARL/10/320: The handling and reporting of adverse events was found to be adequate in general.

2.8. RECORD-KEEPING AND HANDLING OF DATA

For Study ARL/10/320: CRF, ICFs and blood collection timepoint records and randomization were verified for all subjects and were considered to be acceptable in general.

2.9. STATISTICS AND CALCULATIONS

For Study ARL/10/320: Calculations of pharmacokinetic parameters and statistics were performed using SAS. The data input and sheets were re-entered into SAS in and their accuracy and completeness were verified by inspectors. The SAS commands

were verified and the results were compared to those found in the report in order to confirm that the pharmacokinetic parameter statistics were correct and confirmed bioequivalence.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

For Study ARL/10/320: Copies of the labels for investigational products A and B were made and retained. Minor issues noted with regards to records of segregation and labelling of containers were addressed in the company's corrective actions.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The study ARL/10/320 had been approved by the DCGI.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

This aspect was found to be adequate in general.

Part 3: Conclusion

1. 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, the study ARL/10/320 entitled *A randomized, open label, balanced, two-sequence, two-treatment, two-period, single dose, crossover bioequivalence study of prothionamide tablets 250 mg manufactured by Micro Labs Ltd., with PETEHA[®] (Prothionamide Tablets 250 mg) manufactured by Fatol Arzneimittel, Germany, in normal, healthy, adult male human subjects under fasting condition* was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Accutest Research Laboratories Pvt Ltd A-31 & A-91, M.I.D.C., TTC Industrial Area, Khairane, Navi Mumbai 400 709 India.
2. Although not inspected in detail, the spot-checks performed on data related to the following studies did not reveal anything to indicate that they were conducted not in compliance with GCP and GLP.
 - a) TB223: ethambutol/isoniazid/pyrazinamide/rifampicin 275/75/400/150mg Tablet (ARL/09/439)
 - b) MA82: amodiaquine/artesunate 270 /100 mg Tablets (ARL/09/035)
 - c) TB242: ethionamide 250 mg Tablets (ARL/11/021)
 - d) HA482: Lamivudine/Nevirapine/Stavudine 150/200/30mg Tablets (SA/07/010)
3. Data for the following was available for inspection but was not reviewed in view of no major concerns identified in the inspected studies. There was nothing noted to suggest that they were conducted not in compliance with GCP and/or GLP:

- a) Data for the following was available for inspection but was not reviewed in view of no major concerns identified in the inspected studies:
- b) HA420: Lamivudine 300mg tablets (US/07/042)
- c) HA456: Abacavir/Lamivudine 60/30mg tablets [US/AHD/07/040 (Bio-analytical only)]
- d) HA489: Lamivudine/Tenofovir 300/300mg tablets (ARL/09/296)
- e) HA500: Efavirenz/Emtricitabine/Tenofovir 600/200/300 mg Tablets [BBRC/US/08/001 (Bio-analytical only)]

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.