



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB 236 (Cycloserine 250 mg Capsules)
Study number	Project No BA10508106 01
Title of the study	An Open Label, Randomized, Two-Period, Two-Treatment, Two-Sequence, Crossover, Balanced, Single Dose, Evaluation Of Relative Oral Bioavailability Of Cycloserine Capsules 250 mg Of Dong-A Pharmaceutical Co. Limited, Korea With That Of 'SEROMYCIN®' (Cycloserine) 250 mg Capsules Of The Chao Center for Industrial Pharmacy & Contract Manufacturing, USA In Healthy Adult Male Subjects Under Fasting Condition
Clinical Part of the study: Name and address of the organization	Cliantha (previously named BA Research India Ltd.), Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India, Tel# +91-79-66135601, Fax# +91-79-66135602.
Bio-analytical laboratory: Name and address	Cliantha (previously named BA Research India Ltd.), BA Research House, Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380 054, Gujarat, India, Tel# +91-79-2685 3088-92, Fax# +91-79-2685 3093.
Date of inspection	19 to 20 June 2012 (Clinical) 21 to 22 June 2012 (Bio-analytical)

Part 2: Summary

General information about the site(s)

Clantha Research (formerly known as BA research India Ltd and renamed in October 2011) has 3 sites, one in Vadodara and two in Ahmedabad (one site at sigma corporate and one at Ahmedabad head office, Bodakdev). The company was originally founded in 2004. The bio-analytical laboratory was upgraded to 18 LC MS/MS in 2010 and is located at Head Office (HO) in Ahmedabad.

- Clinical Facility, HO, Ahmedabad: 2 Clinics with total 96 beds, 2 ICUs, Check in area, 2 Freezers at -20°C and 3 Freezers at -70°C. The bio-analytical laboratory at Headquarters has 3 API 5500s, 11 API 4000s, 4 API 3000s and 1 ICP-OES for interim analyses, 1 walk-in freezer.
- Clinical Facility, Sigma, Ahmedabad: 3 Clinics with total 100 beds, 3 ICUs, Check in area, Diagnostic lab, 1 walk in chamber at -20°C, 3 Freezers at -20°C and 3 Freezers at -70°C, PK calculation, Statistical analysis, Central Training Department and QA department. Pharmacokinetics and biostatistics are located on Statistical Analysis System (SAS) and are enabled with WinNonlin and SAS software.
- The clinical site in Vadodara has 4 clinics with a total of 200 beds and 4 independent ICUs but it was not inspected for this study

History of WHO and/or regulatory agency inspections

The last WHO inspection was performed in October 2010. Since the last inspection, the site has been inspected by the USFDA, AEMPS and AGES. Line clearance was added, as well as 2 LC/MS-MS and 13 new SOPs were set into place as well as 7 new work instructions. In November 2011, a new archival facility was established at the Sigma site.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product TB236 Cycloserine 250 mg capsules. 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

Day 1

Three informed consents were given (general, screening and study specific). The Declaration of Helsinki was displayed in the informed consent room but was too small for ease of reading. It was recommended to put up a bigger and clearer

Declaration of Helsinki in this area preferably in English and with a translation into local language(s).

Registration of subjects was done by putting information input into the On-line Volunteer Information System (OVIS). It was noted about 30 000 subjects were registered in the database at this time. Right hand index finger reading is used to retrieve subjects. A positive identification test was done. Initials are obtained from the OVIS system and based on this, the subject name and characteristics were retrieved. X-rays are taken every 6 months for all subjects. For rejected subjects due to abnormal laboratory values, for instance, the information is placed in the database.

Initial general physical examination includes verification of the different systems, verification of history and allergies, family history. Vitals are taken. The physician stated that it takes 5 to 10 minutes for the full physical examination which appeared to be much shorter than that normally found during inspections of this activity.

The ECGs are taken using Smart ECG Viewer software. ID, initials, date of birth are entered in the system. The ECGs are scanned and deleted once the pdf file is created. It was noted that there was no written procedure describing this practice. (See section on observation). There was no procedure available at the point of use of the ECGs. A similar issue was noted at the registration computers. The reason for that is that the procedures are available electronically on the computers as claimed, however controlled hard copies of the procedures were not readily available during the inspection.

Oxygen cylinders, defibrillators and emergency medicines were inspected and found satisfactory.

In the afternoon, inspectors visited the following areas:

- The pharmacy, which included verification of reconciliation and of storage conditions of the Investigational products.
- Training room
- Archives

Day 2

Inspectors focused on the review of clinical documentation and included:

- Master signature log
- Master services agreement between Dong A Pharmaceutical Co. Ltd. and BA Research India Limited.
- Confidentiality agreement between BA Research India Ltd and Dong-A Pharmaceutical Co. Ltd.
- Project specific contract for study BA10508106-01

- Administration of investigational products to subjects procedure SOP CRLCL035.000, dated July 10, 2009. It was noted that mouth check was not explained in detail.
- BA Research India Ltd., sample storage notification form.
- Sample storage notification form, where Dong-A Pharmaceuticals Co. Ltd., where Dong A agreed to the destruction of the samples on June 21, 2011 for 1232 aliquot I and 1232 Aliquot II samples (actual date of disposal was June 23, 2011).
- Quality assurance unit (clinic) SOP CRLQ002.000, dated 1 July 2009.
- There was insufficient documentation of the exact step in the process where randomization of the test and reference products was verified. (See section on observation).
- Contract with Oriental Insurance Company Ltd. Policy 141400/48/2010/2100 from the period of 18/01/2010 to 17/01/2011. An issue was raised during the last WHO inspection regarding the exclusion of claims arising from hepatitis or any syndrome thereof.
- QA Audit Plan form and schedule for 2012. Note: vendor qualification SOP was requested since it was not included in this QA audit plan and schedule.
- SOP on Submission of documents to the independent ethics committee, SOP CRLCL023.000 3 July 2009.
- Statistical analysis was redone in front of inspectors.

Day 3

The following lists of activities/areas were inspected on day 3:

- QA checks: SOP for QA in –process audits. SOP entitled « Quality Assurance Unit (Laboratory) », SOP CRLQ001.001. It was noted that there was no mention of in process audits other than a mention that they will be done at least once for each study hence no procedure for in-process audits as such. It is noted that a form was available but it did not show the extent of the checks that would be performed.
- Event identification management and resolution form: this was not a controlled document (there was no version number) and there was no SOP for investigations at this time, just a form to be filled. (See section on observation).
- An example of an investigation was shown and was thorough, except that copies of the analytical results were not present with the form but the level of documentation and explanations were sufficiently detailed.
- Project meeting records were maintained, with names and signatures of the analysts, operators, sample handlers as well as the sample receipt dates, study initiation dates, number of subjects in each run, bulk spiking dates, validation dates, study completion and repeat analysis.
- Pipette calibration is done every 3 months.
- Training
- Performance verification of balance was seen.

- Laboratory logbooks on 19 September 2010, equilibration of system for MS12, 146.MV.001, Run 1 samples injected with system suitability samples. On September 20, Run 2 samples injected with system suitability samples. Calibration of instrument performed on September 3, 2010. Peerless Basic C18 column 110208730603 was used.
- Blank human plasma
- Spiking
- Technician validation was performed by extracting 6 set of QCs and 1 set of CCs (except for LLOQs and ULOQs. At the time of sample analysis, long-term freezer stability had not been tested.

Day 4

Following list of activities/areas were inspected on Day 4:

- Description of Administrator Console for Analyst Software, Document ID AAC-01 v2.0 was seen. Different access rights were defined for the system administrator, project manager, operator, in house engineer, and vendor/engineer. Manual integration: is allowed for the operator.
- Modify processing algorithm is allowed for the operator and not for all. Runs for subject 1 and 2, 8, 15, 16. Repeats,
- ISRs were performed on 5 October and on 27 September. ISR samples are selected at between HQC and LQC, 5 to 10% of total number of subject samples present. One at CMax and one after CMax.
- Long term at 112 days, freeze thaw (28 August 2010). 4 and 6 cycles on 6 sets of LQC and 6 sets of HQC. All of them were extracted with 1 set of fresh standards and 1 set of fresh Qcs.
- 1.19, 1.27 RT for freeze thaw. The first 4 freeze thaw cycles thaw for 2 hours. 6 sets of 0.6 mL volumes each were done. Blank plasma 180810.
- Freezer logbook was consulted for FWI-01, No. 064.
- 3700, 3704, 3767, 3760, 3771, 3964, 3965, 3966, 3967, 3968, 3969 blank plasma lots were used for cc standards. Pooled to get 955 mL volume on August 18. 210 mL volume of pooled kept separately for study. ID BA10508106 01 pooled plasma Cycloserine for the study. Same for validation 175 mL on August 18
- For QCs: 288 mL on 17 August 2010, 3700, 3704, 3760, 3766
- Calibration and temperature records were seen for the -70°C deep freezers, although not in use for the study under inspection.
- Qualification report dated 16/09/2010 for the -20 +/- 10°C walk-in-freezer FWI-01.
- Method development was started on July 5th 2010.
- Study on interference with concomitant medication was reviewed. Volumes of stock solution were shown. The same extraction method of processing was used for validation as for subject analysis.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

For Study BA10508106 01: Justification for the trial, respect of ethical principles were found to be adequate in general.

2.2.THE PROTOCOL

The Protocol was found in general to be acceptable.

2.3. PROTECTION OF TRIAL SUBJECTS

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

The responsibilities of the investigator were found to be fulfilled in the most part.

2.5. RESPONSIBILITIES OF THE SPONSOR

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

Case report forms were appropriate.

2.7. MONITORING OF SAFETY

Subject safety was monitored. There were no adverse events during this study.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable.

2.9. STATISTICS AND CALCULATIONS

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

Supply of products and storage of products as well as labelling and packaging were found in general to be acceptable.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Not applicable.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and acceptable.

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 Project No BA10508106-01 was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *Cliantha (previously named BA Research India Ltd.), Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India and at Cliantha Research Limited, Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380 054, Gujarat, 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.