



Prequalification of Medicines Programme

WHO PUBLIC INSPECTION REPORT

Bioequivalence Study

Part 1: General information

WHO product numbers covered by the inspection	HA477: Atazanavir 300mg caps
Study number	ATA/2009/421
Title of the study	Open Label, Randomized, Two-treatment, Two-Sequence, Four-period, Single-dose, Replicate Crossover Oral Bioequivalence Study of Atazanavir Sulfate 300 mg Capsule of [REDACTED] and Reyataz [®] 300mg Capsule of Bristol-Myers Squibb Company, Princeton, NJ 08543 USA, in Healthy, Adult, Human Subjects under Fed Conditions
Clinical Part of the study: Name and address of the organization	Synchron Research Services (Pvt) Ltd, 2nd Floor, Swagat Plaza II, Iscon - Bopal Road, Ambli, Ahmedabad 380 056, India
Name and email address of contact person (Clinical part)	Mr Moorthy R Aripaka
Date of inspection	17 May 2010

Part 2: Summary

The purpose of the inspection was to inspect the clinical part of the bioequivalence study performed at Synchron Research Services (Pvt) Ltd, (hereafter referred to as Synchron), including the examination of related source data and to evaluate whether the study was conducted in compliance with the protocol, Good Clinical Practices (GCP) and related WHO standards as applicable.

General information about the site

Synchron, located in Ahmedabad was inspected on the above-mentioned date. The company was established in 1998, and had a presence in India and Thailand. The facilities were located in Ahmedabad, Bangalore and Bangkok. It was now a partner of Parexel Int. and employed about 140 people in total.

About 97 people were employed in Ahmedabad. 18 people were listed as employed in the clinical department, 3 in the pharmacy and 9 in QA. The CRO used contract physicians, radiologist and phlebotomists. It also had a database of over 6000 volunteers. The clinical laboratory was outsourced. Periodic audits were performed. The CRO had an in-house X-ray facility.

The facilities included:

- Chambers, SG Highway (Corporate office in Ahmedabad)
 - 2nd floor - Dispensing and logistics pharmacy
 - 3rd floor - data management and QA, BD and finance
 - 6th floor - archives

- Swagat Plaza, Bopal Rd (Visited in the afternoon)
 - 2nd floor Clinical BE/BA and CPUs with 32, 14 and 30 beds

Synchron archived data off site as well as on site. Most of the archives were explained to be kept on site.

History of WHO and/or regulatory agency inspections

This was the first inspection of this site conducted by WHO.

The site had been previously inspected by the following agencies:

- 2005 - Afssaps
- 2007 - MHRA
- 2009 - Afssaps (France) and BFarm (Germany)
- 2009 - US FDA
- 2010 - US FDA

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product HA477: Atazanavir 300mg capsules. The inspection covered the relevant sections of the WHO GCP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

After arrival, the inspectors were taken to the boardroom at Synchron (corporate offices) where they were introduced to representatives of the CRO. These included Mr Moorthy R Aripaka - Director: Quality Assurance. This unit was responsible for e.g. SOPs, archives, audits and other quality systems. Dr Nirav Shah was the responsible clinical investigator for the inspected study.

The CRO presented a brief history of events which included. According to the CRO, it performed 4 to 5 pivotal studies per month. About 60 - 60% of studies are for sponsors from EU. Data management tools included:

- SAS
- Kinetika
- WinNonlin (Thailand)
- MedDRA
- WHO Drug reference list

The initial documentation review took place after the opening meeting - at the corporate office which was about 4km away from the clinical unit where the study inspected, was conducted. For the abovementioned study on Atazanavir 300mg capsules, study number ATA/2009/421 - 99 volunteers were screened and 48 enrolled for the study.

Study details included:

- Period I: 29 Jan 2009 (47 dosed) [excluding dosing for Subject 26]*
- Period II: 6 Feb 2009 (43 dosed) [S2, S26, S34, S45 & S48]*
- Period III: 14 Feb 2009 (43 dosed) [S2, S26, S34, S45 & S48]*
- Period IV: 22 Feb 2009 (42 dosed) [S2, S26, S34, S36, S45 & S48]*

* Reasons for subjects who were not dosed

S2 lost to follow-up after period 1 dosing

S26 withdrawn before period 1 dosing

S34 lost to follow-up after period 1

S36 withdrawn from period 4 dosing

S45 withdrew after period 1

S48 withdrew after period 1

There were 76 samples per subject - 3307 samples in total, and no missing samples were reported. Samples were shipped on 4 March 2009 (first aliquot) to the sponsor, and the second aliquot was destroyed after confirmation for this was obtained from the sponsor.

The proposed plan was presented to the organization and agreed upon.

The following documents were reviewed and / or the activity was explained:

- Form T12 of the India Drugs and cosmetics Act
- Independent ethics committee review procedures
- Notification to ethics committee
- Ethics committee notice of the meeting
- Ethics committee functioning SOP
- Recruitment of volunteers
- List of subjects for the screening
- Identification numbers allocation SOP for volunteers
- Insurance
- Contract between sponsor and Synchron
- Sponsors site audit before the site was contracted for studies
- Monitoring report
- Screening, and study consent forms
- Source data and results
- Documentation relating to study drugs accountability and dispensing records, and study drug labels
- Randomization schedule and dosing sheets for all subjects
- Chest X-ray films
- Enrolment of subjects
- Lists of signatures of staff present during the study
- Training records, job descriptions and organization chart
- Case report forms (CRF)
- Compensation list
- Letter of shipment of the products
- Receiving of the products
- Line clearance
- SOP for biological sample shipment from CRO to the bio analytical laboratory
- Records of shipment of samples outside Synchron
- SOP on training
- Log book for retention samples
- Registry to enter/exit the dispensing room
- Reconciliation of reference and study products
- Archives
- Archiving and retrieval register
- Temperature log for deep freezer
- Sample transfer records
- Data logger records
- SOP on deviations and deviation records

- Screening area
- Volunteer Data base (VPMS - old and new version, and OVIS)
- Area where informed consent was obtained
- Medical examination area
- Dosing area
- Blood sample withdrawal area
- Clinical unit
- Dining and recreation area
- Sample preparation room
- Centrifuge calibration records
- Intensive care unit (ICU) / emergency room
- ICU medication usage record
- Pharmacy
- Dispensing room
- Dispensing documentation

RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator were defined, selection of subjects were done in accordance with defined procedures. Subjects were properly informed, ICFs were signed by the volunteers. Local drug authority was accordingly informed about the study. The study protocol was reviewed and approved by the ethics committee. Adverse reactions were recorded. The Monitor performed a site audit during the trial period I.

Pharmaceutical products were handled appropriately. The trial site had adequate premises.

MONITORING OF SAFETY

Subject safety was monitored, adverse events were reported and subjects received necessary treatment.

RECORD-KEEPING AND HANDLING OF DATA

Handling of data was generally considered acceptable. Some findings were made regarding appropriateness of the archiving activities.

HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply of products and storage of products as well as labeling and packaging were found in general to be acceptable. Dispensing was done in accordance with GMP principles. There was evidence and records that the dispensing had been done under conditions avoiding possible mix up.

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, the clinical part of study ATA/2009/421; performed at Synchron, Ahmadabad; India was considered to have been conducted at an acceptable level of compliance with WHO GCP.

Areas that needed to be addressed included the handling of deviations, sample management, training of personnel and archiving of records.

Part 4: Reference documents

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Expert Committee on the Use of Essential Drugs. Sixth Report. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf
2. OECD Principles of Good Laboratory Practice (GLP). [C(97)186/Final], 1997
http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
3. Additional guidance for organizations performing in vivo bioequivalence studies. WHO Technical Report Series, No. 937, 2006, Annex 9
www.who.int/prequal