20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	AXIS Clinicals Limited 1-121/1, Miyapur Hyderabad- 500 049 India
Name and Address of Bioanalytical Research Site	AXIS Clinicals Limited 1-121/1, Miyapur Hyderabad- 500 049 India
Name and address Statistical Site	AXIS Clinicals Limited 1-121/1, Miyapur Hyderabad- 500 049 India
Corporate address of Organization	AXIS Clinicals Limited 1-121/1, Miyapur Hyderabad- 500 049 India
Contact person	Jaya Chandra Atluri jayachandra.atluri@axisclinicals.com
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**Study no. 017-16,** Tablets 800 mg **Study no. 186-16,** Tablets 100 mg **Study no. 465-16,** Tablets 150 /300 /200 mg **Study no. 404-16,** Tablets 125 mg
Inspection details	
Dates of inspection	18-21 December 2017

Type of inspection	Routine
Introduction	
Summary of the activities	The facility had the capacity to perform bioequivalence / bioavailability studies on both healthy subjects and patients, pharmacokinetic studies, special patient population studies, and phase II-IV trials.
General information about the company and site	AXIS Clinicals, a privately-owned full-service CRO (Contract Research Organization) was established in 2004 with headquarter in Hyderabad, India and global operations in United States, Mexico and India. The CRO offered trial management and monitoring, quality assurance, regulatory submissions, data management and biostatistics.
History	List of inspections was provided. The organization was inspected by various authorities: NABL, ANVISA, US-FDA, UK-MHRA, AFFSSAPS, Turkey MOH, Thai GLP, GCC, MHSD RoK, MCC-South Africa. The organization was last inspected by WHO in March 2015. The current inspection was their second WHO-inspection.
Brief report of inspection activities undertaken	The inspection team covered the following study-related activities under the scope of the inspection: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, study medication accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Analytical operations, the team covered Good Practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was accomplished along with comparison of the source data to study reports
Out of scope	Not applicable

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
HPLC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control

	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

Part 2	**Summary of the findings and comments**

General section

1. Organization and management

The company made a presentation to explain the structure and operations of the organization.

AXIS Clinicals Limited is a contract research organization (CRO), founded in 2004 (Formerly known as Trident Life Sciences Limited) with central headquarters at Hyderabad, India. AXIS provides clinical research services (Clinical trials and Bioequivalence studies) outsourced on a contract basis worldwide with a global reach through its facilities at USA and Mexico.

The company`s structure which occupied an area of 250,000 sq. ft., had the capacity to handle approximately 2000 clinical dosing a month and analyse approximately 35,000 samples per month at Miyapur, Hyderabad, with a bed capacity of 192 arranged in 4 study areas.

The organization had two facilities in India.
Location 1:
Head office
Bioanalytical and Clinical facility
AXIS Clinicals Limited
1-121/1, Survey no.66 & 67, Miyapur, Serilingampally, Hyderabad, Telangana, 500049, India

Location 2:
Clinical facility
Atharva, Opp. Rajpath club, S.G highway, Bodakdev,
Ahmedabad- 380015,
Gujarat- India

The CRO reported that it performed about 100 studies per year, approximately 10 per month. The company had over 90 employees at clinical site and over 100 employees at the bioanalytical site. The regular working hours at the organization was 9:30 am to 6:00 pm. However, it could be extended depending on the running of studies.

The organizational chart included in the CRO master file was reviewed during the inspection.

Recent changes made to the clinical and bioanalytical unit were presented during the opening meeting.

Changes in Clinical Unit:

- Introduced an Online Volunteer Information System [OVIS] to verify the volunteers cross participation in studies. [Effective from 09th July 2016].
- Changes were made for Study Areas and ICU.
- Introduced software for the generation of Vacutainers, Riavials. Individual rooms established in fifth floor for stand by Deep Freezers and for Plasma sample segregation.
- Walk-in chamber was installed in Pharmacy for the storage of Investigational medicinal products.
- Drug Archival facility has been shifted to fifth floor from second floor. The archival facility space in second floor was turned into Pharmacy-2.
- Implemented the procedure for QA witnessing the reconciliation of Investigational Medicinal Products after Drug Administration.
- ECG operation Logs were implemented [Based on WHO observation].
- Introduced New ECG Machines from March 2016 along with operation Logs. Taking the signatures of respective volunteer on print out of ECG from November 2017 [Based on ANVISA observation].
- Implemented the Placing lead (pb) metal letters on the X-ray cassette before exposing for capturing volunteer registration number on X-ray image [Based on WHO observation].
- Placed Emergency Buttons (Nurse Calling System) to each subject bed in all the study areas [Based on WHO observation].
- Clock Monitors were placed in the facility along with Digital clocks [Based on GCC observation].
- Implemented log for the storage and usage of ICU medication [Log book for Issue of Medicines from Emergency Crash Cart] and inclusion of the procedure of review & updating the List of recommended emergency drugs and consumables in ICU [Based on WHO observation].
- Ensuring the proof for date of birth of volunteer. Implementation of procedure for taking signatures of volunteer on all pages of Informed consent Document during Audio and Video recording [Based on WHO observation].

List of changes in Clinical Research laboratory:

- The Laboratory (ACRL) had undergone the NABL Reassessment Audits according to ISO 15189:2012 on May 30th to 31st, 2015 and May 27th to 28th, 2017. The accreditation was granted as per ISO 15189:2012
- Additional instrument Hematology Analyzer was incorporated in to the operations.
- In Serology department EQAS program was changed to CMC Vellore (from RIQAS).
- All ELISA method kits (HIV, HBsAg and HCV) were changed to Bio-Rad (from J. Mitra) and related SOP's were revised.

List of changes in Bioanalytical Unit

- Additional LC-MS/MS instruments (Total 7) were incorporated in to the operations. Subsequently processing equipment was added. Simultaneously, two old LC-MS/MS systems were removed from the operations.
- Computers systems for all LC-MS/MS instruments were replaced with new ones and the operating system was changed to Windows 7 (from Windows XP). Related software was upgraded. Subsequently computer system validation was performed for all systems.
- Software data logger was replaced with new system.
- As part of revision in SOP for Preparation of calibration standards, quality control samples and their acceptance criteria), concentration criteria for MQC and LMQC were revised and procedure for endogenous compounds was incorporated.
- As part of revision in SOP for Bioanalytical Method validation, additional drugs were incorporated in concomitant medication, recovery experiment revised, Matrix effect experiment revised, aqueous stability experiments were revised.
  As part of revision in SOP for Study sample analysis and recording of raw data, processing log were removed for processing equipment like SPE, Evaporators, centrifuges and logbooks were incorporated

2. Computer systems

List of software and computer systems used in the studies were provided.

The IT Manual version 3, effective 1 Nov 2014 was reviewed. The computer system validation procedures were included in the SOP.

User requirements specifications were prepared by the respective unit for any new requirement of instrument or software or customized database/tool. The user requirements were used as guide in evaluation of the requirements for any new instrument or software for the intended purpose.

Monthly data back-ups were provided on tapes, and stored at off-site facilities. Another back-up was also provided which was used to back up data from a source location to a target location on the server. Hence there were two monthly back-ups: One on the tape stored at the off-site archive and the other on the server.

The archival facility used for storage of back-up tape was the Writer information, Agreement was provided dated 9 Oct 2016.

Data integrity check was carried out every six months. Data integrity check was applied to the project-files stored on Local Disk D: Drive. Hence, the stability and endure/withstanding of tapes during the required time of retention could not be verified.

It was noted that they were aware of this issue. The applicable SOP was therefore revised to include a check list for data integrity test. This check list would help to verify different aspects of the data integrity, such as availability of data, details of the records, and the completeness of the data.

Two tapes , from two of studies within the scope of inspection, were retrieved and confirmed for compatibility.

Volunteer Data Base (Bio Secure Lab Chronicle Automation)

It was noted that the CRO was retiring the volunteer registration system and installing a new VMS.

The observations made were addressed adequately.

Analyst software

Analyst® was updated.

The documentation for user requirement specifications for liquid chromatography and mass spectrometer and their application software was approved on 30 June 2016. In this documentation, specifications for Mass spectrometer, for HPLC, for software, pertaining essential features and capability of audit trails were pre-defined.

The IQ, OQ and PQ for analyst software for LC-MS/MS system were reviewed. Date of approval of documentation was recorded as 4 Jan 2017.

OQ validation documentation was reviewed.

The validation documentation was also included:
Appendix A: IQ screen shots
Appendix B: Calibration certificates of digital multimeter
Appendix C: OQ screens
Appendix D: PQ Screen shots

Users were designated to four levels of privileges depending on their roles in the study.

1. Administrator
2. Supervisor
3. Analyst
4. QA

In the recent design, only user role as Supervisor was given right to change the number of smooth.

The Analyst software, pertaining to installed instruments used for the applications in the scope of inspection was challenged for possibilities of modification of folders after completion of the study.

As a part of pre-method validation process, system suitability run was carried out with six reference solutions on 5 Jun 2017. Stock solutions were made on the same day, in 6 different concentrations for each analyte – end time 16:22 hr. Stock solutions were considered as a source for preparation of the reference solutions. Documentation was reviewed and verified.

It was presented that a software system would be launched to establish the e-CRF system, in the end of January 2018.

Issues raised during the inspection were resolved in the company CAPA.

3. Quality management

The quality management system was described in the CRO Master File.

Quality Management System (QMS) was established, documented and implemented in a set of interrelated or interacting elements. The Quality Management System applied to all facilities of AXIS clinicals Ltd in India.

The QMS documentation was structured as follows:

- Policies
- SOPs
- Working instructions
- Conventions, regulatory guideline, records, forms, templates, logs

A QMS management team was responsible to develop and maintain the QMS system. Change controls were documented and SOPs were revised every 3 years. The company maintained hard copies of the SOPs. However, there was a plan to launch an electronic Data Management system from January 2018.

An Excel tracker was in place to provide an overview of the next revision date of the SOPs, which used to be monitored manually. However, the new system acquired can automatically give notification of next revision dates of SOPs to the responsible Heads of Departments.

SOP for Annual internal audit was reviewed. There were also SOPs for audit of different part of studies.

Internal audit schedule was provided for 2016 and 2017, indicating the date of the audit, activity to be inspected, auditee, auditor and remarks, whether performed and when performed. Audit activities started from April each year to the end of November.

The audits carried out for both bioanalytical studies was provided and reviewed:

- In-process audit of bulk spiking, of
- Analytical phase of study,
- Retrospective audit and
- Bioanalytical report audit.

In-process-audits were dated 21 Mar 2017 and 22 Mar 2017 for study 404-16 and 2 Jun 2017 and 6 Jun 2017 for study 465-16.

The audit report of the archiving facility was reviewed. Enterprise's disaster manager was also audited and verified, as well as the data integrity of randomly selected documentation. The last audit report provided was dated 13 May 2015.

List of SOPs reviewed and verified:

- SOP for Management of archival, retrieval and destruction of quality documents effective 27 May 2015.
- SOP for Vendor qualification audits, effective date 20 November 2017 was newly implemented. Hence no audit plan for audit of vendor was in place to be verified.
- SOP for Audit of bioanalytical phase of the study, effective 3 Aug 2015. There were two types of audits as follows:
    - In process audits – executed when the activity was in process, to confirm the compliance to SOPs, study plans, method SOPs, study protocol, WI etc.
    - Retrospective audits – intended to review at least 20 % of the data after completion of the particular activity:
        - Review of the Method development documents
        - Pre method validation doc
        - MV doc
        - Study doc
- SOP for SOP ON SOP, effective 20 Nov 2017.
- SOP for Bioanalytical method development was reviewed, along with the method development documentation.

Concerns raised during the review of the QMS were adequately addressed and CAPAs were provided to address respective issues.

4**. Archive facilities**
The archive facility was located on the third floor.

The facility was accessed by 4 personnel by key-card. Log books were verified.

There was an agreement with an off-site archiving facility located in Hyderabad since 24 Sep 2010, valid until 2020.

The in-house archival facility was equipped with robust rolling racks. The arrangement of documentation was indexed in a book by identifying the racks and rows and rooms. The arrangement was verified, accordingly.

Fire extinguisher canisters and sprinkles (chemical) and smoke detectors were installed in the facility.

Pest control was carried out every week. There was a log provided to verify the presence of the pest control company. The last pest control activity was carried out on 17 Nov 2017.

Humidity (40 ± 10) and temperature log book was reviewed.

A form “Retrieval of documents” from was completed for the documentation requested in relation to the inspection. Information about description and name of documentation, reason for retrieval, data, requested by, authorized by (QA) and archival arrangements were noted.

Later, the description of documentation returned, as well as verification of completeness of documentation would be documented on this form.

The retention period was set for 15 years regardless the agreement with sponsor. This was based on the WHO-agreements.

Bioanalytical samples were retained based on the agreement they had with the sponsor.

Observations made were addressed adequately.

5. Premises During the inspection, a tour of facility was conducted.

Facilities were accessed by individual key cards. Biometric registration was only applied for process of employees’ log in and log out to the building.

Required facilities were equipped with temperature monitoring system. Minimum and maximum temperatures were read and documented in the respective log books, once a day.

Synchronized clocks were located throughout the facility to document the exact time study-activities occurred.

Back-up generators: Diesel Generator and UPS were provided to supply the electricity of the facility in case of emergency. The generator was tested by inspectors and UPS room visited. The daily check log book was verified.

The clinical facility was visited to verify the various steps of screening and inclusion of subjects:

- Registration and Screening of the volunteers
- ECG Facility
- Physician rooms
- Sample collection Room
- ICD process Rooms
- X-Ray Facilities
- Deep Freezer and Centrifugations Room
- Clinical Units divided in 4 wards with a total of 192 bed capacities, with pertaining dosing stations, Phlebotomy area with sample collection stations, Refrigerated Centrifuge, Deep Freezers:-20°C and -70°C, Dining facility :
- Centralized Intensive Care Unit (With four beds)
- Pharmacy

The bioanalytical facility was divided into 4 main areas:

- Freezer room (Sample storage)
- Sample processing Laboratory (I & II)
- 25 x LC - MS / MS Laboratory
- 2 x ICP-OES Laboratory

Screening area

The screening area was divided in female and male sections. The process was followed, starting with providing the introductory information to the individual volunteer, followed by verification of identification documentation and age, measurement of height and weight, calculation of BMI.

Remaining activities were executed according to protocol after signing the ICF. Illiterate volunteers were not accepted.

Clinical Pharmacology Unit

The units were visited without any queries raised.

ICU
The ICU was located on the second floor provided with the required equipment which were calibrated properly. Log books for maintenance and medication used in the ICU were provided. Medications were well-organized.

Bioanalytical lab
The bioanalytical lab was visited to verify the suitability of the facility. For details see section 18 and 20.

Pharmacy
List of people with access right to the Pharmacy and Drug Archival, signed on 1 Dec 2017 was provided. Executive director clinical operations and instrument Engineer also had access to the facilities.

CV for pharmacist, signed on 2 Nov 2017 was provided and reviewed.

JD of the Executive director clinical operations was also provided dated 1 Mar 2017.

Contracts signed with the Sponsors were verified as follows:

For study no. 017-16 and study no. 186-16, agreements were signed 02 May 2016.

For study no. 465-16, agreement was signed 2 Nov 2016 and amended on 27 Feb 2017.

For study no. 404-16, agreement was signed 29 Sep 2016 and amended on 24 Feb 2017.

Concerns raised were addressed in adequate CAPA plan by the CRO:

6. Personnel
Organizational charts were presented to demonstrate the link of the Head of departments.

Training management was achieved by a detailed SOP.

Induction training by each Department Head would be provided for each new employee, followed by a list of SOPs for self-training. Each employee would take an examination to assess his or her understanding of the training. A new electronic system was planned to be launched for management of the training of employees.

In revision of SOPs, a change control was requested based on the revision type prior to completion of the formality of the SOP. As soon as the SOPs were revised, a class room was run to introduce the revised SOP to the required personnel. In case the personnel were not present at the arranged classroom, individual sessions would be organized. Required personnel were invited to attend the class based on the list of employees.

CVs and JDs were selected from the organizational chart and reviewed.

Training matrix was called “Identification of training Needs” which was a part of respective SOP, consisted of the designated groups of employees and applicable training. Employees were categorized into various groups based on their job descriptions. QA was reminded that all employees should be included into these categories and there should not be any inconsistencies between the matrix and the list of employees.

The new electronic Document Management system for generation and management of CVs, JDs, training and lab instruments was presented for the inspectors.

Concerned raised during the inspection were addressed satisfactorily.

Clinical section

7. Clinical phase

A tour of the clinical facility was conducted.

Labelling of study medication, monitoring check, blood sample collection form, verification of vital signs and subjects’ well-being, as well as hygienic condition of the restrooms were inspected.

Inspectors assisted to dosing and blood samples collection activities conducted for the running study 157-17. During the dosing process QA and QC representatives, project coordinator and principal investigator were present and supervised the entire process.

Blood sampling process was verified by QC and QA representatives. The study design was to collect two replicated aliquots of blood.

The clinical phase started with verification of the ICF signature, demographic information, medical history, followed by physical exam based on a pre-populated check list. The volunteer would be sent for ECG after physical exam to verify the pertaining inclusion criteria. If the results failed, the volunteer would be recorded as “no call / repeat / screen failure” depending on the severity of the failure.

After receipt of the sample collection and X-ray result, a new assessment was made to verify the eligibility of the volunteer for participation in the study. HIV test was mandatory for all volunteers.

The process for sample and urine collection was reviewed. The sample containers were labelled by a sticker which was filled out by the custodian prior to the transfer of the samples to the lab, according to the request form.

The boxes (called Sampling Station) provided for the purpose of samples' transfer should be filled with icy-water to ensure cool condition for samples during blood sampling process and transportation to the laboratory.

Performance of ECG was user and password controlled. Patient data including ID, birthdate and gender were entered prior to the measurement process. The process was followed by recording the activity in corresponding log book and stamping the ECG print out. There was no access right allocated to the ECG-operator for making any modification. The data was stored automatically. Nevertheless, no audit trail was available for ECG records.

The ECGs belonging to the following studies were checked and found compliant:

- 503-16
- 586-16
- 453-16 screening and post study
- 404-16

X-ray results were performed every 6 months. If the subjects had a valid X-ray for the last 6 months, no additional X-ray would be performed.
Insurance certificates issued by The New India Assurance Company Ltd were verified:

Study no. 186-16
01/12/2015-30/11/2016

Study no. 017-16
01/12/2015-30/11/2016

Study no. 465-16
01/12/2016-30/11/2017

Study no. 404-16
01/12/2016-30/11/2017

The site had a contract signed with the nearby Hospital for any emergency situations, valid for 3 years starting 14 Jul 2014.

The communications with the Hospital regarding the commencement of the studies was verified. The communication letter was addressed to the Managing Director of Hospital.

According to the SOP for Medical Care in Emergency and Life-Threatening situations, the hospitals should be notified prior to the subjects' enrolment in the respective study. The SOP stated that: "The details of the studies going to be conducted to be informed to anyone of the MOU (Memorandum of Understanding) hospitals before conduct of the study."

Concerns raised during the inspection were addressed in an adequate CAPA plan by the CRO.

8. Clinical laboratory Clinical/Pathology lab

Pathology laboratory was visited and inspected. The samples were received in temperature control box and were registered in registration log book. The bar code was created for every samples and the samples were processed according to the respective SOP/protocol. During the interview, all personnel were competent and well trained.

9. Ethics

The registration certificate Ethics Committees were reviewed and verified.

The following approvals were reviewed:

Study no. 017-16

Protocol V02, dated 17 Feb 2016 and ICF V02 were submitted to the IEC on 14 Mar 2016 and approved on 21 Mar 2016.

Study no. 186-16

Protocol V01, dated 12 May 2016 and ICF V01 were submitted to the IEC on 29 Jul 2016 and approved on 03 Aug 2016.

Study no. 465-16

Submission and approvals of the IEC for the study protocols and ICFs were available as follows:

- Protocol V01, dated 16 Dec 2016 and ICF V01 submitted on 21 Jan 2017 were approved on 25 Jan 2017
- Protocol V02, dated 20 Mar 2017 and ICF V02 submitted and approved on 22 Mar 2017.

Study no. 404-16

Submission and approvals of the IEC for the study protocols and ICFs were available as follows:

- protocol V01, dated 19 Oct 2016 and ICF V01 submitted on 21 Oct 2016 were approved on 26 Oct 2016
- protocol V02, dated 28 Dec 2016 and ICF V02 submitted on 02 Jan 2017 were approved on 05 Jan 2017
- protocol V03, dated 30 Jan 2017and ICF V03 submitted and approved on 31 Jan 2017

Video recording for ICF process was verified for the subjects from the study below:

Study no. 017-16
ACL-55002
ACL-43758
ACL-54464
ACL-54488
ACL-55002

Study no. 186-16
ACL-0122
ACL-2589
ACL-8757
ACL-12742
ACL-19444
ACL-22095

Study no. 404-16
ACL-54762
ACL-17024
ACL-47220
ACL-46808
ACL-59026

Study no. 465-16
ACL-0157
ACL-0312
ACL-41253
ACL-1250
ACL-55403

Observation made were addressed adequately.

10. Monitoring

Study no. 404-16

For Period I of the study: monitoring activities were conducted by two monitors from 10 to 12 Feb 2017. The monitoring visit report was extensively elaborated and had 15 observations and deviations reported. The visit was verified in the visitor's logbook for the visit dates reported.

For Period II of the study: monitoring activities were conducted monitors from 23 to 25 Feb 2017. The monitoring visit report was extensively elaborated and had 16 observations and deviations reported. The visit was verified in the visitor's logbook for the dates reported.

Study no. 017-16

No monitoring reports were provided. However, the follow up letters were available.

Study no. 186-16

For Period I/Group I of the study: monitoring activities were conducted from 19 to 21 Sep 2016.

For Period I/Group II of the study: monitoring activities were conducted from 23 to 24 Sep 2016. The monitoring visit report was very short, missing in detail. The visit was verified in the visitor's logbook for the visit dates reported.

For Period II/Group I of the study: monitoring activities were conducted from 29 to 30 Sep 2016.

For Period II/Group II of the study: monitoring activities were conducted from 03 to 04 Oct 2016.

Study no. 465-16
For Period I/Group I of the study: monitoring activities were conducted from 15 to 16 Apr 2017. The report was consistent, 11 observations and deviations were reported. The visit was verified in the visitor's logbook for the visit dates reported.

For Period I/Group II of the study: monitoring activities were conducted from 04 to 05 May 2017. The report was consistent, 12 observations and deviations were reported. The visit was verified in the visitor's logbook for the visit dates reported.

For period II/Group I of the study: monitoring activities were conducted from 12 to 13 May 2017. The report was consistent, 15 observations and deviations were reported. The visit was verified in the visitor's logbook for the visit dates reported.

For period II/Group II of the study: monitoring activities were conducted from 31 May to 01 Jun 2017. The report was consistent, 11 observations and deviations were made. The visit was verified in the visitor's logbook for the visit dates reported. All observations and deviations reported were verified, among others the CAPA activities performed in compliance report annexure-IV as per SOP.

Concerns raised by the inspection team were addressed adequately.

11. Investigators

Training logs, Delegation log and CVs for the participant investigators were verified and concluded that they were qualified by education, training and experience for BE studies conduct.

12. Receiving, storage and handling of investigational drug products

The pharmacy was well organized and equipped with micro balances calibrated by external service provider once a year. Balances were also calibrated by internal engineer every three months according to SOP.

There was also a humidity chamber for storage of medications.

Upon receipt of medications, the log book would be completed, with date, time and number of unit and specification of storage unit. Data logger was checked and submitted to the sponsor. Forms to be completed were reviewed and verified as follows:

- Check list for receipt of IMP
- Drug receipt form where the drug accountability was monitored

Process for dispensation, preparation of labels and labelling of study medications was described and pertaining documentation was reviewed.

Dispensation of solid oral dosage would be done a day before the scheduled dosing. Liquid oral forms would be dispensed on the same day the dosing was scheduled.

Concerns raised during the inspection was addressed adequately.

13. Case report forms

This was not inspected due to time constraints.

14. Volunteers, recruitment methods

On reporting at Axis, the volunteers were sent to the screening area. Furthermore, volunteers were first enrolled in the in-house database. The nature of the study was explained to the volunteers. If they wished to participate, then the informed consent for screening was provided by the study personnel. Volunteers were handled based on their ability to read. After signing the informed consent form, the volunteers were screened for various tests including their ECG, X-Ray and clinical examination.

As soon as the volunteer was registered into the system, an ID-card was provided and the volunteer was verified in the OVIS system (Intra-CRO volunteer system) to ensure that the volunteer did not participate in any other studies performed by other CROs in the region, within the timeframe banned by the protocol. Volunteers were blocked in the OVIS in the end of period I.

Inclusion – exclusion criteria for selected subjects were verified.

The physician responsible for performing the physical exam was interviewed and the process was observed by the inspection team.

All equipment was labelled with an identification number and calibration date. Drug abuse and alcohol test procedure were verified.

Volunteers were identified by name and labels with barcodes generated in the system for both blood and urine sample processing. A pregnancy test would be provided prior to X-ray for female subjects.

15. Food and fluids

Food and fluids were provided according to the protocols

16. Safety, adverse events, adverse event reporting

AEs of mild and moderate intensity were appropriately reported. No SAEs were recorded for any of the protocols inspected.

Bioanalytical section

The inspection included audit of source documentation and raw data for validation of bioanalytical methods, analysis of subject plasma samples, audit trails for electronic data capture and data handling related to the PK study. Results of calibration standards, quality control samples (QCs), subject plasma samples in analytical runs were inspected along with the chromatograms generated from analytical runs, the preparation of analyte stock solutions, calibration standards, QCs and internal standards, and reagents.

17. Method development, Method validation & Analysis of study samples

Invoices for all working standards were provided and reviewed.

System suitability, Acquisition time, IS area, use of CCs, interspersing of QCs
Chromatograms and pertaining factors across the batches for randomly selected sample analysis were reviewed and verified as noted in the tables below, for respective studies.

The sample arrangement was according to the applicable SOP, with sufficient dispersion of QC samples throughout the batch.

Method development and method validation documentation pertaining to steps taken to demonstrate the reliability of the methods were reviewed and verified as follows:

Study number: 404-16	
Method development	
Literature used in the method development was provided and recorded properly.	Method of detection: LC-MS/MS Extraction: Acidified Acetonitrile Elution Solvent: Acetonitrile: Water 80:20 Mobile phase: Documented Autosampler temperature:10 °C Data generation by Analyst Software Matrix : Human Plasma Anticoagulant: K_2EDTA Smoothing factor used: 4
Method validation	
Two analytes were used in the method validation plan based on the primary requirement from the sponsor. Later due to changes made by the sponsor / regulatory agency, only one of them was determined in the sample analysis. In the bioanalytical notes in the study plan, it was noted that CC and QC samples would be bulk-spiked using spiking dilutions containing both analytes and also the acquisition method in Analyst software would be prepared using the all MRM transition as per method SOP. However, since one of the analytes was not quantified as per the study protocol, only one of the analyte of interest for the current study was tested.	Dilution integrity run was carried out by six individual replicates, done on 17 Dec 2016. Documentation was reviewed and verified.
Precision and Accuracy	Run I: 19 Dec 2016, Run II: 19 Dec 2016; Run III: 20 Dec 2016 Documentation was reviewed and verified.
Stability: Freshly spiked calibration curve and LQC and HQC for comparison	The procedure for stock solution preparation was documented properly.

	Freeze/Thaw Stability experiment details of retrieval of samples were noted on a titled form belonged to the applicable SOP. The required number of freeze thaw cycles was recorded starting from 19 Dec 2016. Cycles were completed on 26 Dec 2016 and samples were processed on the same day. Log book for DF no 2 was reviewed and verified.
	Long term stability of analyte in matrix Sample processing documentation and pertaining analysis run performed on 17 Mar 2017 was reviewed.
Analysis of samples	
<u>Sample receipt & handling:</u> Form for "study samples receipt and storage" dated 22 Mar 2017 was reviewed: Missing samples recorded as 65, temperature at the time of receipt was recorded -71 °C. Log book no for the respective DF was reviewed and verified. For both period I and II, Form for "details of bio-samples transferred from clinical facility to BA facility" dated 22 Mar 2017 was reviewed. The collection of samples was verified: Period I: 11 Feb 2017 Period II: 24 Feb 2017 Availability of samples was also confirmed. CC stock solution prepared on 20 Mar 2017 was verified, together with the pertaining Excel calculation.	Subject sample analytical runs were randomly selected to be reviewed: In general, each batch was a run, containing only samples of one subject.

Preparation of CC working and spiking bulk solutions was documented on 21 Mar 2017. QC preparation was carried out on 21 Mar 2017. The preparation process, as well as the storage documentation on 21 Mar 2017 was reviewed.	
Repeat analysis	Run ID 404_ETH_IDREP_310317, 13, 16, 21, 24(12 hr), 26 was reviewed and verified.
Re-integrated chromatograms	None
ISR	RUN ISR1_310317 start at 16:22 end at 19:45 RUN ISR2_310317 start at 19:47 end at 23:08 RUN ISR3_310317 Start at 23:11 end at 1 Apr at 2:29 Total number of subject samples was recorded as 1807 samples: 923 (period I) + 884 (period II) 182 samples were selected for ISR runs according to the applicable SOP. The result of the reanalysis of incurred samples was reviewed. 99.5 % of results were within the acceptable range. All three runs were conducted one after the other at the same day, although the applicable guidelines required evaluating the accuracy of incurred samples by reanalysis of study samples in separate runs at different days. It was noted that this was taken into consideration in the revised applicable SOP.
Back up calculation	Back up calculation performed for randomly selected subjects.

Study number: 465-16	
Method development	
Literature search was documented. Method development took place between 23 Dec 2016 – 13 Jan 2017, followed by pre-method validation to perform the system suitability, LLOQ check and auto sampler carryover test, the selectivity, finding the best regression factor, performance and calculation of the linearity and precision and accuracy. Three precision and accuracy batch runs by selecting LLOQ, lower (3xLLOQ), middle and higher range QC samples in the calibration Range, were performed to produce the calibration curve. Three calibration curves for each analyte were recorded at each PA running.	Method of detection: LC-MS/MS Sample Extraction Method: Solid Phase Mobile phase: 0.1% Formic acid (pH 2.6 ± 0.3): Methanol, 25:75 (v/v) Data generation: Analyst Matrix: Human Plasma Anticoagulant: K_2EDTA
Method validation	
	<u>Matrix factor</u> Documentation for Matrix factor, dated on 21 Jan 2017, 16:35 with Run ID MV80-01J_ZLN_MF_210117 was reviewed. The preparation of the spiking and solutions and stock solutions, done on 21 Jan 2017 were reviewed. Individual lots used were as follows: 4 plasma matrix from 4 different individuals 2 Haemolysed 2 Lipemic Haemolysed and Lipemic Plasma samples were provided from the Pathological Lab's in Sep 2016.

	Rest of samples were provided by another laboratory, on different days, in Dec 2016 and Jan 2017. Stock weighing form for each analyte and pertaining ISTD was reviewed. The blank matrix usage log was provided and reviewed for each source. The results for matrix effect was provided to be reviewed and compared with the raw data in the software. The plasma samples were also screened for the matrix interference and selectivity, performed on 17 Jan 2017. The raw data and the corresponding run were reviewed. <u>Dilution integrity</u> Samples were run for verification of Dilution integrity together with the P&A test by preparing the DIQC. Preparation of respective spiking solutions from stock solutions was reviewed. The QC and CC stock solutions were independently prepared. The storage of DIQC samples (1-78) was reviewed. Samples were documented to be stored in Deep Freezer at 19:16 on 17 Jan 2017. The log book for respective freezer was reviewed and verified. Receipt and storage of the QC and CC standards samples were documented on the respective template. <u>Carry over</u> Run ASCOT_170117.rdb was performed to ensure the minimization of the carry over effect.

	All results were within acceptable range by using 3 Extracted Blank, 3 ULOQ, 6 Blank, and three LLOQ
Precision and Accuracy	5 Precision & Accuracy runs were performed. One run was rejected due to analyte Retention Time (RT) according to applicable SOPs: SOP for Preparation of calibration curve standards and quality control samples and their acceptance criteria SOP for Investigation of failure in method validation experiments, effective 11 May 2015. Manual re-integration was allowed by supervisor. However, the analyst was not allocated the rights to perform manual re-integration.
Stability: Freshly spiked calibration curve and LQC and HQC for comparison	Long term stability of analyte in matrix MV80-01 LQC and HQC samples from no. 211 to 246, a total of 36 samples of each concentration was stored in cold room CR#1 at 19:10 on 17 Jan 2017 at -20. Corresponding documentation was reviewed. The results were verified, on 31 May 2017. An addendum to the validation report was provided in July 2017 after QA-review.
Analysis of samples	
Sample receipt & handling	Study sample processing for the batch pertaining to Sub no. 58 was reviewed and verified as follows: 1- Study sample batch processing, dated on 21 Jun 2017. Auto-sampler loading time was at 17:36 2- System suitability run dated 21 Jun 2017 for all three analytes and pertaining ISTD 3- LLOQ check for all three analytes and pertaining ISTD 4- Sequence request schedule

	5- Deep Freezer log book for storage and retrieval of one of the subject sample and verified
Analytical run Interspersing of QCs, chromatograms and pertaining factors across the batches were confirmed.	Following subject sample runs were reviewed and verified: Use of calibration standard STD8 was out of acceptable range for subject sample no. 67 and hence it was not used in the analysis' results. Sample ID 67104 was repeated under the code JU, defined as "Value above the truncated calibration range code JU". In the second run, the result was above the ULOQ under code D. The final accepted result was 4182 which was reported. RUN S67PIPII_230617 RUN Investigation_220617.rdb for S52PII (.075 & 1 hr), S55PI (.5 and .75 hr), also identified time-points for two subjects 62 and 58, due to poor chromatography of the original run. An investigation report was made which was available and presented. RUN S58PIPII_220617 RUN S58PIPII_230617 The first run was rejected due to poor chromatographs for two analytes. An investigation batch was reinjected. The number of vials and plate position was checked to verify that the same samples were used. Later the whole batch for subject S58 was re-injected (verified by vial and plate position). The investigation report was reviewed to verify that the matter was reported in the study report.
Repeat analysis	All reported repeat analysis and their respective coding were verified.
Re-integrated chromatograms	None

ISR	466 subject samples were used including the STDs and QCs, starting with reference solution, standard Blank, Standard Zero, STDs and QCs dispersed. Acceptance criteria were met. ISR1_150617 ISR2_150617 ISR6_300617 ISR8_300617 And ISRs 3, 4, 5 and 7 were done respectively on 29, and 30 June 2017 There were two data sets of the ISR1, due to incorrect file-name. Regarding ISR2; one of the STDs (STD3) failed and hence excluded from the data. New concentration was calculated.
Back calculations	Confirmed
Acceptable ranges fulfilled	Confirmed

Concerns raised during the inspection were addressed in an adequate CAPA plan.

18. Sample collection, storage and handling of biological material

The subjects' samples were received from the clinical facility, verified and stored in the deep freezer, recorded in a log book and the "Study samples receipt and storage" form. Samples were sent with a completed form on "Details of bio-samples transferred from clinic facility to BA facility".

Only samples received from other facilities were equipped with data logger. Different colour codes were applied for various replicates and periods. QC was performed in clinical department. A separate form was provided for record of haemolysed samples.

The organization was in ownership of 22 freezers at -70 °C and one at -20 °C.

Samples were labelled with required information, such as protocol and period number, subject and vial ID, as well as the respective time-point, according to the applicable SOP.

CC standards and QC samples were received from the analysts and stored according to the applicable SOP.

Upon request from analyst, the required number of CC standards, QC samples and study samples were retrieved based on processing sample sequence from the deep freezer and documented in the log book.

The Deep freezer and cold room log book for storage and retrieval of LTSP for MV- 80-01 was reviewed and verified.

A reconciliation of pooled plasma for MV-363-00 was requested and provided. The remaining volume available in freezer (Cold room no 1) was calculated 113.3 ml, which was available in the cold room.

Temperature monitoring for DF # 2 was reviewed for the period of January and February. The log showed excursions in temperature on 19 January. The documentation on log book for temperature sensor challenge test was provided to demonstrate that the thermometer was tested on the same date and the excursion was due to the test performed.

19. Data processing and documentation

Electronic raw data and paper raw data, including notebooks and logbooks were reviewed during the assessment of trials' conduct. Documentation regarding all trials selected for inspection was organised and labelled properly and an index including all documentation was available for inspection. Documentation was processed properly. Validated Excel sheet were used for calculation.

Issues raised during the inspection were adequately addressed

20. Good laboratory practices

The bioanalytical facility was visited and observed to be well organized and well maintained.

Weighing room was visited to verify the calibration of the balances. There were three types of balance in the room:

1- Micro balance
2- Analytical balance
3- Top load

Monthly calibration was carried out and documented by the in-house engineer. Documentation for daily calibration was reviewed, for 13 – 20 Dec 2017. An annual calibration was also provided by external service provider.

The SOP for Operation, Calibration and Maintenance of Micropipettes/Multi-pipettes was reviewed.

Micropipettes were calibrated internally every 6 months, once a year externally and every time before study analysis.

The calibration of micropipette ID AP#152 was supervised and verified. According to the SOP the balance calibration should be verified before every pipette calibration.

CAPA provided with regards issues raised in relation with the Good Laboratory practices were acceptable.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The process for providing the randomization list and processing of data from the bioanalytical analysis for pharmacokinetic purposes and statistical calculation, as well as preparation of respective reports were described by designated personnel for Pharmacokinetic and Bio statistic. Data bases used were as follows:

- SAS 9.4
- WINONLIN 5.0.1

QC and QA of the reports were verified.

22. Study report

Bioanalytical reports for studies:

STUDY NO.: 404-16
Version 00 – authorized by Head BA on 21 Apr 2017

STUDY NO.: 465-16
Version 00 – authorized by Head BA 15 Jul 2017

The study reports were cross-examined to ensure the proper contents corresponding the information reviewed during the inspection.

All reports were reviewed by authorized personnel.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The Master File was provided and reviewed. The CRO master file was prepared according to the WHO TRS No. 957, Annex 7.
Annexes attached	Not applicable

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 was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at CRO:

AXIS Clinicals Limited
1-121/1, Miyapur
Hyderabad- 500 049
India

All the non-compliances observed during the inspection that were listed in the complete 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.

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9
   Short name: WHO BE guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report*. World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO multisource guidance
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137)
   Short name: WHO GCP
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5 WHO GDRMP guidance
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

5. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP".
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1
http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1

9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

10. US FDA Code of Federal Regulations Part 11
http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

12. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

13. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf

14. Glove use information leaflet, Patient Safety, Save lives - Clean your hands, WHO, revised August 2009
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

15. WHO Good Clinical Laboratory Practices (GCLP)
http://www.who.int/tdr/publications/documents/gclp-web.pdf