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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Micro Therapeutic Research Labs Private Limited, Plot No. 46 (Part), Rengasamy Street, Chrompet Chennai – 600044 Tamil Nadu India
Name and Address of Bioanalytical Research Site	Micro Therapeutic Research Labs Private Limited, Plot No. 46 (Part), Rengasamy Street, Chrompet Chennai – 600044 Tamil Nadu India
Name and address Statistical Site	Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram Chennai – 600 059 Tamil Nadu India
Corporate address of Organization	Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram Chennai – 600 059 Tamil Nadu India
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Study no: LAMI-2733-15 Bioequivalence study of tablets 150 mg/ 200 mg/ 300 mg
Sponsor	Shanghai Desano Biopharmaceuticals Co Ltd, China

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Inspection details	
Dates of inspection	20 - 24 November 2017
Type of inspection	Routine
Introduction	
Brief summary of the activities	The facility had the capacity to perform bioequivalence / bioavailability and in-vitro studies in healthy subjects / patients. The site housed a clinical and bioanalytical department.
General information about the company and site	The company was established in 2005 and located in two addresses: Building one was located at Chrompet, Chennai and spread over 21 000 square feet area, consisted of CPU, ICU and the bioanalytical laboratory. Building two spread over 40 000 square feet and was located in Selaiyur, Chennai, housing the CPU and bioanalytical laboratory equipped with LC-MS/MS instruments.
History	The company was audited by different authorities and regulation bodies since 2016, among others US FDA x11, DCGI x7, AGES x2, ANVISA x5, AFSSAP x2 Inspection report from AGES was provided and reviewed.
Brief report of inspection activities undertaken	
Scope of inspection	The inspection covered the clinical and analytical sections of the aforementioned study. The scope of the inspection included: Inspection history and company's organization, clinical study performance, including 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. In terms of the Analytical operations, the inspection covered clinical practices, qualifications of personnel, and adherence to the CROs quality system utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data were accomplished along with comparisons of the source data to the reported data.

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
	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	**Brief summary of the findings and comments**

General section

1. Organization and management

A presentation was provided by the President of Micro Therapeutic Research Labs (MTR) to explain the activities of the organization and the application under the scope of the inspection. The CRO consisted of two sites located in Chennai and was managed by the Managing Director Dr M. Ganesan, with managers of 12 different groups reporting directly to him. The CRO provided services in Bioavailability/Bioequivalence studies.

MTR had approximately 220 employees led by Heads of departments. The CRO developed more than 260 molecules.

The master Agreement between the CRO and a Sponsor was reviewed. Retention time for documentation was agreed as 5 years for WHO submissions and other retention time as per applicable requirement. Subject samples were available at the site.

A list of contracts with vendors, dated 2 Nov 2017, providing different services was inspected.

Changes since the previous inspection performed by the USA-FDA, 2017 were as follows:

<u>Clinical:</u>

1. Sampling of investigational product from all the shipment for dosing and retention purpose
2. Communication to sponsor in case of any protocol deviation or addendum report generated for the study
3. Impact assessment for the stored PK samples in case of any power outage occurs before the analysis
4. Improved the documentation practices for recording the case history during clinical study

Bioanalytical

1. Complete resolution of the interfering peaks from analyte peak of interest for quantification of drugs/metabolites during bio analysis
2. Inclusion of all the precision and accuracy batches for global % cv and % nominal calculation.
3. Inclusion of usage log book for clinical freezers
4. Inclusion of additional calibration parameters for ECG equipment
5. Removal of malfunctioned instrument from the work place
6. Changes made in the PK/SAS SOP's to meet the ANVISA requirement
7. Inclusion of procedure for matrix effect experiment in the presence of concomitant medication
8. Maintaining the record for volunteers excluded from the study
9. Vendor agreement for oxygen cylinder supplier is included in the system
10. Recording the routine cleaning maintenance activities in the cold room log book
11. Changes made in the training system and SOP
12. Improved documentation procedure for recording the date/time errors

2. Computer systems

Master list of Software at Chrompet site, MTR-ML-001, last updated 2 Nov 2017 was provided.

Databases investigated during the inspection included the following:

- Volunteer Management System (VMS) – in-house database for registration of volunteers
- OVIS used to check cross participation of volunteers between registered CROs in India
- SAS 9.4
- Winonlin 6.4
- MassLynx 4.1

The IT network structure was presented. The sites were equipped with a separate IT infrastructure, using VPN connectivity.

Back-ups were provided as tape drives, project CD back-up and online server back-up. The server room was located in a secure access-controlled room.

Three periodic back-ups were provided:

- Daily back-up which was incremental back up on the server in the IT room
- Weekly back-up as full back up
- Monthly back-up as full back up

All the generated data were stored on the server from which different type of back-ups were provided on tapes.

There was also another back up called CD-back up applied to the instrument (LC-MS/MS) which was requested by QC- and QA-team, as well as the BE-supervisor. A CD back up was hence provided after the completion of the study.

Weekly and monthly back up were taken on a magnetic tape which was stored off site. Compatibility of tapes was checked every three months by requesting the CD and tape from the archive to ensure that the data was still retrievable. The source data was also verified by comparing it to the archival folder on the server.

In case any employees left the company, a form should be completed. Each and every department should meet the respective employee to give approval forms (no-due form) before their departure.

Different versions of Windows were in use, such as XP, Windows 7, Windows 8.1 and Windows 10.

Windows XP was still in use to operate workstations controlling HPLC MS/MS systems.

Master validation plan was present with the date of last validation and next validation if applicable. The plan was developed based on a risk assessment report carried out by the system administrator and the user requirements.

Volunteer Management System (VMS) – in-house database for registration of volunteers

The VMS was tested by mock registration of a new volunteer. A total number of 28623 subjects were registered in the VMS.

The OVIS was also tested. No match was found in the OVIS database.

Investigators were using the generic username as “Investigator”.

Modifications were made to the mocked registration to check the audit trail.

MassLynx 4.1:

Waters carried out the validation of the system and the documentation was provided and reviewed.

It was verified that MassLynx used full security mode by checking the properties.

6 user levels were used in MassLynx: Administrator, Method Developers, Analysts, Operator, Reviewers and Maintenance (for instrument engineers). The Analyst access rights were verified against the list of users' privileges in MassLynx software. Access rights for various designated groups were also confirmed.

SOP for validation of laboratory computerized systems and software was reviewed.

The Qualification Protocol and Report for one of the Waters LC-MS/MS instruments with application software – MassLynx Version 4.1 was provided and reviewed with effective date 2 Sep 2017.

Alteration of date and time on the computer for one of the LC-MS/MS instruments, with access as administrator was verified and found not to be possible to be executed. It could be done, by stopping the server and changing the date and time. However, the MassLynx could not be accessed after alteration of date and time, since the computer would hang and the software could be corrupted if proceeds to access the system.

Qualification protocol and report for Waters LC-MS/MS instruments Application software-MassLynx version 4.1 was reviewed.

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

3. Quality management

MTR had established a Quality Management System with the structure presented in a pyramid of three levels:

1. Policy (Quality Manual) where the system was described in detail.
2. Procedures (SOPs) and Operational documentation, divided in 6 categories.
3. Quality reports

The QMS was operated independently by Quality Assurance (QA). Quality control applied to all activities relating to clinical and BA part.

A description of the Quality Management System was presented in the Quality Manual.

SOPs and pertaining operational documentation would be revised every two years. However, the revision frequency for bioanalytical SOPs were every 3 years. A change control procedure for revision was in place. Log books to record day to day activities were in place.

A SOP tracking-system, in Excel format, accessed by QA was in place. The list was reviewed once a week. In case any SOP was due for revision, a reminder would be sent to the execution team. The Execution team would request for the change control form, and carry out the revision according to

the procedure. As soon as all concerned staffs were trained in the revised SOP, the SOP would become effective.

The following SOPs were reviewed and verified:

- SOP for Training and development, effective 10 Nov 2017.
- SOP for Audits and issuance of audit reports. Annexure for audit plan was implemented.
- SOP for Facility and system audits.
  Both facility audit and system audit were defined and the frequency of the audits was predefined. A 3 monthly or 6 monthly audit-plan is available depending on the type of the audit. In addition, an in-process auditing is conducted with any analytical activity of any Bioanalytical study verified in the presence of QA representative.
- SOP for Clinical sample analysis.
- SOP for Quality control functions in clinical/bioanalytical department.
- SOP for Acceptance and rejection of chromatography and analytical batches and their reporting.
  It was verified that for regulatory submissions, the smooth factor less than 5 would be used throughout the method validation and clinical study sample analysis. Manual integration was not accepted.
- SOP for Reintegration of chromatograms.
  It was emphasized that the same integration parameters for calibration curve, quality control and clinical sample analysis would be used. However the integration parameters could vary from batch to batch.
- SOP for System and data security. Training was provided for those who were working in IT department.
- SOP for Clinical Sample Analysis.

The training records of the following QA staffs were selected and found to be compliant:

- RA-QA – Training was documented prior to the SOP effectiveness
- Technical officer QA – Training was documented prior to the SOP effectiveness

System Audit plans were reviewed. Area of focus, date of event planned, and assigned auditor were noted on the plan, which would be signed on the date the audit was conduct.

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

4. Archive facilities

The onsite archiving facility was located at the Selaiyur site, protected from fire by fire proof door, inert gas filler and fire extinguisher. Electronic devices and raw data were stored in data safety cabinets. According to their procedure, pest control was required to be carried out twice in a month.

The process for retrieving of documentation from the archiving facility was investigated. The request form for the study documentation necessary for the inspection was received and approved by QA. The approval was kept by the archivist and documentation was verified to be delivered to the requester.

Archiving requisition form for monthly back-up for the period of study: 1 Feb 2016, 29 Feb 2016 and 28 Mar 2016 were provided. They were identified by MTR-MBT (Monthly back up Tape)-Month-Year and contained the data generated on the server for the period of the study.

The offsite archival facility used for storage of documentation was located in Oragadam, in Chennai. The address was recorded in the Quality Manual.

Access to archives was granted to two archivists.

5. Premises

During the inspection, the inspection team visited the Chrompet facility with its different units, the pathology lab and the archival facility at Selaiyur site.

The Chrompet facility consisted of clinical and bioanalytical laboratory units:

1. Clinical Unit consisted of:
    a. Volunteers' Waiting area
    b. Counselling area
    c. Registration area
    d. Screening area
    e. Phlebotomy station – sample collection
    f. ECG room
    g. Examination room
    h. X-ray room
    i. Ultra-Sonogram room
    j. Volunteers' check-in area
    k. ICU
    l. 2 Housing area
    m. Phlebotomy area
    n. Sample separation area
    o. Pharmacy at second floor

2. Bioanalytical Unit consisted of:
    a. Instrumentation room
    b. Sample processing room
    c. Balance room
    d. Freezer room and cold room

Temperature in the different units was monitored by installed digital thermo hygrometers.

Access to units was restricted by key cards. The only unit with biometric access was the security office.

IT issued key card for new employees upon receipt of request from the respective team leader.

IT and QA maintained the record for access rights. On the employment of an employee, QA request for access rights to restricted area, based on the pertaining designation. A form would be filled out by the QA to be submitted to IT-department. IT would issue the access card. The system used to provide the record of access rights was called Honeywell which was a Door-Access database, provided by Accel-infotech. An unofficial Excel sheet with the name and roles of employees with access right was presented by IT.

Premises were equipped by Power back-up facility through the UPS installed in the facility with adequate capacity. There was also a secondary back-up provided supported by a diesel generator.

An uncontrolled list for sample storage and pharmacy Chrompet was provided.

6. Personnel

Organizational charts, valid at the time of the inspection were provided and reviewed. The documentation was included in the Quality Manual. The company listed 50 staffs employed at the Chrompete site.

Each employee had to undergo a specific training program including:

- Induction training
- Orientation training
- Aspect of Quality system related to the assigned task
- Job specific training

According to the respective SOP, a new employee would be evaluated within a week after completion of the required training. Ongoing training was provided as a continuous education program when new technology / system was introduced, followed by evaluation of the training. The evaluation would be quarterly, or/and monthly.

A training matrix plan was provided, organized by roles, departments and the respective SOP to be trained on.

The list of study personnel for related activities was provided which included the name of staff involved and the study specific training documentation. The list was signed off by staff and the trainer. Personnel received training relating to their designated roles in the study.

The following training documentation, CV and JD were reviewed:

- Team Leader pharmacokinetics, the PK analyst for the study
- VRM; Clinical, date of joining 19 Jul 2017
- CRA, Clinical, date of joining 7 Oct 2017
- Training documentation for A K B who was responsible for chromatograms reading, check of raw data sheet and reconciliation of data. Training records was found acceptable.
- Manager BA
- Head Diagnostics
- Sr. Manager
- Clinical Sr. Phlebotomist

Observations made in relation to this section were adequately addressed in the company's CAPA.

Clinical section

7. Clinical phase

The contract and Master Agreement between the Sponsor and the CRO was reviewed and verified.

The clinical facility was visited during the dosing process. Labelling of study medication, monitoring check list and blood sample collection, verification of vital signs and subjects' well-being, hygienic condition of restrooms were verified.

Delegation log for study site personnel was verified. It was noted that all site personnel listed on the log were authorised to conduct the "Inform Consent" process, regardless the experience or the role assigned in the study.

The collection of blood sample was documented on the record page of the CRF, including anticoagulant used, dosing time-point, scheduled time of the sample collection, actual time of sample collection and initials /date of phlebotomist / sample collection.

After blood samples were collected at each time point, in pre-labelled tubes, they were sent to the sample processing room for centrifuging and freezer-storage. Samples were centrifuged according to the time, speed and temperature established in the respective protocol. Freezers' temperature was monitored by digital thermometer which could trigger buzzer alarm in the facility and the security through automated phone call.

If any sample was haemolysed, the sample would be identified by respective chart, coded from A to D, and samples were recorded under in the form. The missing samples were also documented, accordingly.

The ICU was strictly accessed by key card. The facility was visited to ensure the suitability of the facility.

The calibration certifications of defibrillator, vital sign machine and nebulizer for the period of study and the most current ones were reviewed and verified.

The following SOPs were verified:

- SOP for Operation, maintenance and calibration of electro cardiogram recording machine
- SOP for Operation, maintenance and calibration of alcohol breathe analyser
- SOP for Operation, maintenance and calibration of defibrillator cum cardiac monitor
- SOP for Operation, maintenance and calibration of ICU and its equipment
- SOP for Handling an emergency

Issues identified during the visit of the facility was addressed satisfactory by the CRO.

8. Clinical laboratory

The site was a NABL accredited central diagnostic laboratory with the following devices:

- Fully automated Biochemistry analyzer
- Fully automated Immunoassay analyzer
- Fully Automated Hematology Cell counter
- Fully Automated ESR analyzer
- Urometer (Automated)
- Refrigerated Centrifuge

9. Ethics

Chennai Ethics Committee approved the study protocol V02 dated 24 Jul 2015 with 7 EC members signing for study approval on 28 Sep 2015. The protocol amendment was approved on 19 Nov 2015.

There was no board member list of EC members who voted for amendment, since only the members' secretary signed the approval letter.

Submission letters to EC were verified as follows:

- On 13 Oct 2015 submission of Clinical investigator CV's.
- On 25 Sep 2015 submission Inform Consent Document (ICD) of Tamil and Telugu version.
- On 19 Nov 2015 submission of amendment 1, Additional Inform Consent document.

All signed ICFs were verified as follows:

- Main ICF, Amended ICF, screening ICF and ICF for Registration.

The protocol was approved on 12 Nov 2015 by Directorate General of Health Services Central Drugs Control Organization Drugs Controller General India No. 12-09/2015/BE EXP/MTR-75/DC.

An insurance certificate was issued and found to be valid (04 Apr 2015 - 03 Apr 2016) issued by The New India Assurance Co. LTD Company. The insurance policy was verified on the Insurance Company's website.

10. Monitoring

The monitors visit report was verified. The Responsible monitor had 30 years' experience in Pharmaceuticals according to her CV. The monitor was present during the dosing for both period I and II.

The visitor's logbook was verified for the monitor's visits. The monitor was present at period I on 01 Dec 2015 from 07:45 till 14:56, and in period II on 22 Dec 2015 from 07:55 till 14:40.

11. Investigators

Training logs, Delegation & Authorisation log and CVs for the investigators involved in the study, were verified.

12. Receiving, storage and handling of investigational drug products

The pharmacy area, with restricted access limited to the Pharmacists, was utilized for receipt, storage, dispensing and archival retention of study medications.

Medications were stored, in cabinets, humidity chambers and refrigerator, depending on their storage condition, all monitored by digital thermometers.

All entries and exits to and from pharmacy should be logged in a logbook. However, the study related activities could be recorded in different documentation, including entries and exit of pharmacy.

Receipt, randomization, dispensation, handling and storage, and subject dosing, also the retention of study medication was inspected and verified to be according to the applicable SOPs.

Documentation for retention of study medication for study number LAMI-2733-15 with the date of retention 23 Dec 2015, including the details of study medication and batch number, for both Test and Reference, number of units and quantity was reviewed and verified. The medication was stored in sealed boxes on a assigned shelf.

The sponsor invoice of the study medication dated 13 Nov 2015 was verified. IMP delivery was outsourced to DHL courier from the sponsor to the site facility. The temperature log T301, ID 2622520872 was verified.

Issues identified in relation with this section were all addressed sufficiently.

13. Case report forms

Case report form was not verified due to time constraints.

14. Volunteers, recruitment methods

VMS (volunteer management systems) was used for registration of subject recruitment. VMS was licensed for 2 devices and 6 users.

Every subject was registered in the registration logbook upon their arrival. The subjects were informed about the study before signing of the pertaining ICF. The screening procedures were performed as per protocol requirements. The drug abuse and alcohol tests were performed. After the tests results were negative, the Physical examination and ECG process were carried out.

15. Food and fluids

Food and fluid were provided according to the protocol requirements.

16. Safety, adverse events, adverse event reporting

The CRO had a contract with the Hospital "Hindu Mission Hospital" and ambulance services for emergency situations valid from 02 Apr 2015 until 01 Apr 2016.

The communication with the Hospital prior to the study initiation was verified. For period I communication was done on 28 Nov 2015 and for period II on 21 Dec 2015. The hospital was located 7 km from the facility.

No SAE was reported during the studies.

Bioanalytical section

17. Method development

SOP for Bioanalytical method development was reviewed and compared with the method development plan for one of the analytes.

Manual re-integration was not allowed at the CRO.

Preparation of method development was properly documented and according to the applicable SOP. Preparation of solution was documented and included the weighing printouts. The information on the literature used for method development for the properties of the compounds was provided.

The method development documentation contained raw data, AQSCCQC, Specificity/Selectivity data, IS normalized matrix factor, ASCOT, PA (Precision and Accuracy), Weighing factor and recovery.

The invoice details for purchase of working standard from Clearsynth were provided with order date 23 Nov 2015.

A pre-method validation was also performed to verify the system suitability and carry over, specificity and selectivity and IS normalized matrix factor, to set the LLOQ and ULOQ etc.

8 Calibration standards, as well as 6 replicates of 5 different levels of QC were provided for each compound. Smoothing iterations and smooth width used in the method development in MassLynx 4.1 were documented.

18. Method validation

The method validation performed for two of analytes was started on 17 Dec 2015 and ended 27 Dec 2015 with respective validation report dated 8 Jul 2016 version 03.

The method validation performed for the other analyte was started on 1 Jan 2016 and ended 7 Jan 2016 with respective validation report dated 8 Jul 2016 version 03.

During the inspection, source documentation and raw data for validation of bioanalytical method and analysis of subject plasma samples, as well as audit of the electronic data, audit trails for electronic data capture and handling of data related to the PK study were reviewed. The preparation and results from calibration standards (CC), quality control samples (QC), internal standards pertaining to solutions and reagents and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from analytical runs, including their respective parameters.

The following method validation documentation pertaining to steps taken to demonstrate the reliability of the method was reviewed and verified:

- SOP for Bioanalytical Method Validation.
- Preparation of washing solution for two analytes; MV-390-15-01; 5 % Acetone-M in water. The expiration was set up for four days from the day of preparation. Documentation of 4 consecutive preparations was provided, dated: 16, 19, 22 and 26 Dec 2015
- Preparation of Diluent – Acetone – M: Water (50:50) for analyte used in MV-392-15-01. The expiration was set up for four days from the day of preparation. Documentation of three consecutive preparations was present, dated: 1, 4 and 7 Jan 2016.
- Preparation of weak wash solution Acetonitrile: water 70:30; for analyte. Documentation of 5 preparations was provided.
- Preparation of Internal standard solution used for method validation purposes. Two batches were prepared: 31 Dec 2015 and 7 Jan 2016
- Preparation of Stock solution for CCs and QCs, 2 Jan 2016, including calculation, Identification numbers, 6 lots of Plasma, and LQC, HQCs stored for FT and LTPS, respectively in -30 and -70 °C. Stock solutions for QCs and CCs were prepared separately.
- Within-Precision-Run with RUN ID: PA-01, executed on 3 Jan 2016. Due to bad chromatograms, it was re-injected according to their SOP on the same day in the afternoon. The RUN ID PA-01-01-R was also checked and verified.
- Between-Precision-Runs were as follows:
    - RUN ID: PA-02; repeated due to erroneous peak area for both analyte and IS, and the repeated run failed in precision on 3 Jan 2016
    - RUN ID PA-03 passed on 4 Jan 2016
    - RUN ID PA-04, was performed due to PA-02 failure – Passed the precision on 4 Jan 2016
- No chromatogram re-integration was performed through the study.
- Carry-over Run was executed 3 Jan 2016, using the samples from Precision and Accuracy tests.
- Matrix Effect RUN ID: Matrix effect was executed 6 Jan 2016. Preparation of Fresh CCs and QCs were also reviewed. The plasma samples from individuals were checked and verified.

- Preparation of stocks for Short time and Long-time Stock solution stability test for two analytes was reviewed, together with the storage documentation and was verified.
- Long-time matrix solution stability for two analytes was done outside the method validation and reported in version 3 of the report.
  However, an interim long time matrix solution was performed for 17 days. The subject concentration analysis for both analytes was performed between 6 and 24 Jan 2016 which was 18 days.

Issues identified were addressed adequately.

19. Sample collection, storage and handling of biological material

Receipt of samples was reviewed by interviewing the custodian at the deep freezer storage area. The sample issuance and re-storage at BA facility was reviewed for study EZET-3380-17, date of request 21 Nov 2017. The sample issuance was requested by Analyst, approved by BA/Head or Designee and authorized by Clinical Head or Designee.

The deep freezer room (sample storage room) was visited to investigate and verify the procedure for receipt and handling of the samples from the clinical unit. There were two -70 °C freezers for the storage of blood samples from volunteers.

The freezer thermometer was tested. It took 10 minutes before the alarm went off, however no notification call was made by the security or any other designated personnel. A root cause investigation took place. Data logger for this thermometer was provided which demonstrated increasing temperature.

The log books for both freezers were reviewed.

Temperature log for two Freezers at -70 was verified for the period of study.

A freezer at -20 °C was used to store the blank matrix samples.

The CRO was carrying out a forcible temperature check every three months. The documentation for the last check on 15 Nov 2017 was verified. A malfunction observed during the audit was the forcible alarm check that was carried out. Maintenance was requested. The CRO stated that the temperature record of all storage areas is QA-reviewed on a daily basis and it would be captured in the next check.

A specific form was competed documenting the number of samples sent to the BE site, along with the number and identification of the missing and haemolysed samples. The data was checked and verified by the custodian on the form “for List of missing, haemolysed and sample shipment”. Number of samples was verified.

Time-points for sample storage, storage condition prior to the shipment, length of shipment time and shipment condition was verified.

Samples received from clinical unit were not stored separately. Both main and replicate aliquots, also samples from different periods were kept in the same freezers in different boxes, which did not prevent the samples not being mixed up.

9 plasma lots were used in method validation of analyte from 9 different sources, all collected in-house. 6 plasma samples, 1 haemolyzed, 1 Lipemic and one heparinized lot were provided according to their SOP for selectivity/specificity/blank screening. Date, volunteer ID and tests performed were verified. The anticoagulant used, with exception to the heparinized sample, was K3EDTA. The heparinized sample was used to verify the interference of heparin used in collection of samples.

The Deep freezer log book for receipt and storage of samples in the study was reviewed and verified that two aliquots were received on 31st Dec 2015 for both period I and II. Aliquot I for period I and II was stored in the Deep Freezer in two different racks and Aliquot II was stored in another Deep Freezer. Documentation for storage and transfer of study samples were verified.

Issues raised during the inspection were adequately addressed

20. Analysis of study samples

Analysis of study samples was performed according to the applicable SOP for Clinical sample analysis. The SOP required preparing, printing sample schedule/sequence and obtaining the required samples per sample-schedule from custodian / designated personnel. The withdrawal of samples was documented in the logbook. The sample list report, logbooks for different freezers for storage of CC and QC working solutions sets and storage of samples were reviewed.

The sample schedule/sequence was prepared as per analytical batch organization mentioned in the section 6.3 of the abovementioned SOP. QC samples were dispersed approximately at equal interval of clinical samples. In order to calculate the batch acceptance criteria, 2 sets of QC: LQC, MQC and HQC, were used in the sample analysis. All samples from a subject were analysed in the same batch if not sample re-analysis. 137 samples would be present in a complete batch in the study in the scope of the inspection.

At the time of sample analysis, the “Sample Issuance and re-storage at bioanalytical form” was completed to be handed over to the sample custodian as requested for withdrawal of biological samples, after approval from concern team leader.

There was a Sample List form prepared by MassLynx 4.1 consisting of all samples required for the Run. Custodian delivered the samples according to this list to the Analyst and both had signed and dated the form.

The following sample analysis runs were randomly selected and compared with the data generated in the report for further verification of results of calibration standards and respective calibration curve, QC, IS RT, back calculation using respective slope and intercept, preparation of CC and QC and sample processing record:

- ID no: 21-Jan-16_S52_S53.
  Smoothing factor: 3
  Smoothing width: 2 (used for sample analysis for analytes L and N)
  S53 PII 3.50 was a repeat due to Code K:
  If peak area of IS in samples varied by more than ±60% of the average peak area of IS of accepted calibration curve standards (CCs) and quality control samples (QCs) in a batch, the samples would be repeated in replicates according to sample volume and the repeated value would be accepted for pharmacokinetic and statistical calculation. Also, these samples would be included in the calculation of repeat percentage for total repeats.
- There were 2 Repeat sample Runs:
  ID RUN 25-Jan-16_Rep.qld: Concerned analyte L run failures
  ID RUN 25-Jan-1_Repeat-02.qld: Concerned analyte N run failures
  The repeat 2 was performed since the interference in STD Blank at analyte RT, in the first repetition was more than 20 %. Hence another repeat was done only for analyte N. The first repeat run could not be accepted for the analyte failure runs.
  Reported results were verified.
- S04-S05:
  Repeat: ID no: 23_Jan_16_S04_S05
  Repeated due to Code A – Verified
  IS Area verified to be within the acceptable range 60 %, according to their SOP.
- S07 PI 00.33 – First concentration was above ULOQ – A dilution was prepared and sample was re-analysed. The results were still above ULOQ. Documentation and presence of QC verification available.
- S12 PI 00:75
  Original Run ID 8 Jan 2016_S06_S07
  Repeat ID RUN 25-Jan-1_Repeat-02.qld
- S10 & S11
  Run ID: 23 Jan 16_S10_S11(repeat), also the original run and the run with excluded STD B was reviewed.
  This batch had a STD B with CV% above 15 % and when the STB was excluded, STD C was also above 15 % and due to Code A, it was required to repeat the whole batch.
- S12 Code E repeat. The dilution was checked
  Run ID: 12 Jan 16 S12_S13
  Run ID 25-Jan-1_Repeat-02.qld
- Run ID: 22_Jan_16_S20_S21; failed and the whole batch was repeated. Date of run: 21 Jan 2016 at 23:08 – due to the interruption in the instrument: An investigation was made and the interruption was due to gas fluctuation. Hence the whole batch was repeated with Run ID: 27 Jan 16 S20_S21
  In this batch, two samples in period I and II, were above the ULOQ.

These two samples were repeated under RUN ID: 28 Jan 16_Repeats_01 for analyte Z
There was still one sample above ULOQ which was reported.

- RUN ID 25 Jan 16 S39_S40 – 3 samples were originally above ULOQ
  Repeated under Run ID RUN ID: 28 Jan 16_Repeats_01
  Instrument no. 12 was used.
- The verification of result data by the BA department (including QC) and QA review procedure was also verified.
- The smoothing factor used for analyte Z for MV was 3x3 (Instrument no. A) and 4x4 (Instrument no. B)
- ISR runs for analyte Z:
  26 Jan 16 ISR-01 (Error -01)
  26 Jan 16 ISR-01 (Error-02)
  27 Jan 16 ISR 02
  CCs were freshly made. The repeat was due to Nitrogen gas failure. The ISR was run the first time at 9:14 hr. The samples analysis stopped due to instrument failure at 9:31 hr. Affected samples were re-injected after 10:55 hr. These samples were indicated by R as Re-injected. The process was stopped again after 11:28 hr and re-injected at 12:08 hr. Samples 105-114 were also stopped at 13:24 hr and re-injected at 16:53 hr. Error was due to the Nitrogen flow. Documentation was verified.

  Issues raised during inspection were addressed adequately

21. Data processing and documentation

Electronic raw data and paper raw data, including notebooks and logbooks were reviewed during the assessment of the conduct of the trial. Documentation selected for the inspection was organised and labelled properly and an index including all documentation was available.

336 ECGS from 6 different studies were reviewed: BUPR-1K-507-12, BUPR-1K-508-12, FEXO-2223-14, FENO-2845-15, LAMI-2733-15 and ABE-2311-14
No identical ECGs were detected.

Validated Excel sheet were used for calculation.

22. Good laboratory practices

The laboratory facility consisted of activity rooms, instrument room and a weighing room with appropriate balances.

The process for calibration of the micropipette was observed to ensure proper calibration procedure. Pipette calibration record was reviewed. The documentation was recorded according to the SOP for Operation, calibration and cleaning procedure for pipettes. The weighing

documentation was also recorded. Pipette calibration record was reviewed and verified for a period of three months.

Calibration certificates for two freezers for a period of one year were provided and reviewed. The calibration was performed according to SOP for operation, maintenance and calibration of freezers.

One of the LC-MS/MS instruments inspected, was under service and the reporting of equipment malfunction was completed on 5 Oct 2017. The maintenance log for the instrument for the period of study was checked. It was verified that there was no restoration activity during the said period.

Water qualification certificate provided by Pharma analytical lab was provided for the period of the study, 14 Dec 2015 - 1 Feb 2016.

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

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

The randomisation list was verified versus IP labels for all subjects and both periods, without any remarks.

The PK part of the study was carried out at the Selaiyur site. The statistician left the company in 2016 after completion of the study. The PK facility was transferred to the Chrompet site. Responsible personnel at Chrompet was interviewed.

Randomization design was described in the protocol. The randomization schedule was requested by the pharmacist and approved by the investigator. A request dated 23 Nov 2017 for a randomly selected study was followed up during the inspection. Log book for randomization schedule was reviewed. The randomization list was printed out via a secured printer which was operational by a statistician specific password and handed over to the pharmacist, and recorded in a log book. If electronically provided, a password is generated to access the randomization list. The procedure was described and demonstrated according to the SOPs.

- SOP for Statistical analysis using statistical analysis system SAS
- SOP for Pharmacokinetic analysis using phoenix WinNonlin software was applicable and reviewed.

The software used for purposes of Pharmacokinetic and statistical calculation was:

- SAS
- WinNonlin

24. Study report

Study reports were provided and found acceptable.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CROMF was reviewed. The company's master file provided introductory information of the organization, but it didn't cover all information required by the guideline for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7) The guidelines requires that the CROMF should contain specific and factual information about the CRO and the conduct of clinical studies, as well as the analyses of samples and related operations carried out at the site. In addition it should contain information on the policies, approach and general activities of a CRO. It should serve as general information to the regulatory inspectors, in addition to the trail specific data and information submitted for assessment. It should also provide an overview of the organization's approach to GCP, GLP and other guidelines pertaining to its activities. Nevertheless, all activities pertaining clinical and bioanalytical procedures were adequately described in the company's quality management system.
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: Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai – 600 059, Tamil Nadu, 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. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan, 1998.
Short name: WHO 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. 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

13. 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.
Short name: WHO TRS No. 961, Annex 9
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

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

15. 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

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