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

Part 1	**General information**
Organization details	
Company information	
Name and Address of the Site inspected (Clinical, Bio analytical and Statistical Site)	VerGO Pharma Research Pvt. Ltd (Division-VerGo Clinicals) Plot No 24/1, D-1 Mologa de Orora Corlim, Tiswadi Goa – 403110 India GPS coordinates: Latitude: 15.4915 Longitude: 73.8046
Corporate address of Organization	VerGO Pharma Research Pvt. Ltd 6th road, Santa Cruz, East Mumbai, Maharashtra – 400055 India
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**Study no. SLS-CL-0175-17 / 684-17** 400mg/150mg Tablets **Study no. SLS-CL-0126-17 / 664-17** 150 mg/75 mg/275 mg Tablets **Study no. 650-17** 150 mg/75 mg/400/275 mg Tablets
Inspection details	
Dates of inspection	16-19 April 2018
Type of inspection	Initial
Introduction	
Summary of the activities	The facility had the capacity to perform clinical trials and in-vitro studies in healthy subjects / patients.

General information about the company and site	VerGo Pharma Research Pvt. Ltd corporate office was registered, and located at 3rd floor, opulence building, 6th road, Santa Cruz, East, Mumbai, Maharshtra – 400055, with its clinical research Centre situated in Goa. The company was founded by Mr. Prasad Keni with the help of local domain knowledge in 2010, acquired a 100 bed clinical facility in Goa in 2012, and inaugurated the clinical facility after DCGI approval in 2013.
History	The company has previously been inspected by MHRA, UK and Malaysian authorities. The company was not previously inspected by WHO.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article 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, coverage was provided to confirm 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 comparisons of the source data to study reports.
Scope and limitations	
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 presented the structure and operations of the organization.

The organization's organogram was provided in the CRO master file, with details on employees' name and roles. It was approved and dated 5 Mar 2018.

The company had about 117 employees working in different departments and a pool of about 7000 volunteers in their registration database.

The CRO management was responsible to ensure compliance with the GCP and GLP principles, provide sufficient number of qualified personnel and equipment, maintenance of the qualifications, adequate QA and QMS and proper archiving.

Sponsor study agreement was reviewed. Storage of biological samples was specified in the project agreement. The agreement was signed and dated 18 Aug 2017. Communication with sponsor was made to confirm the sponsor's permission prior to the discarding of the biological samples.

The working hours at the site was established as 24 hours for running the clinical trials' activites, and 9-18 for running the BA activities.

Hospital used for handling the emergency situations was located 4.5 km from the site, which would normally take 10 minutes from site to get there. Mock situation was carried out to confirm the traveling time.

The organizational structure of VerGo Clinicals consisted of the following departments:

A. Clinical Research
B. Bioanalytical
C. Data Management
D. Quality Assurance
E. Project Management and Medical writing
F. Archival
G. Purchase and Stores
H. Human Resource and Administration
I. Information Technology
J. Engineering Department

K. Finance and Accounts
L. Additional Activities carried out at site
M. Pathology

2. Computer systems

VerGo Clinicals had a network of computers which enabled the CRO to collate data from all operations throughout a project. Bioanalysis of subject sample was done using validated software. Statistical analysis of project data was done through current version of validated statistical software. Backup and archival of all data generated at the Unit was done periodically.

Analyst software:

Analyst software was examined on one of the LC-MS/MS instruments.

The administrator (IT personnel) had the rights to copy/delete options to be able to transfer the folders from the software to the back-up server. Data was deleted by IT-administrators from the original folder accessed by other users as soon as the projects were completed. Source Data was stored in a folder called "Completed projects" only accessed by the administrator (IT personnel).

The IT personnel had access to the folders from staff personnel, since use of any external USB from the main instrument was not allowed. This was necessary in case the transfer of data was required, such as preparation for inspection request.

In order to acquire access to database for personnel, "User access" form was completed by Head of the relevant department, according to the role of the staff. Access would be given according to the SOP for Access administrative control and based on the User access form issued.

On the User access form, there was a provision for deactivation of the access, required to be completed upon the resignation of the employee from the organization.

Software installation and Operational and performance qualification (IQ, OQ and PQ) documentation was present. Risk assessment of the software was also provided.

SOP for Analyst software user privileges and Audit Trail, effective 12 Jul 2016 was reviewed.

VIMS software (Volunteer Information Registration System) – In-house database for registration of volunteers:

Database used for registration of volunteers was VIMS. The CRO was using the database OVIS to avoid the cross participation of volunteers.

Risk assessment of the database was carried out on 7 Apr 2018 according to the applicable SOP. All identified risks were having RPN (Risk probability Number) values less than 90, indicating that no action was required as per SOP.

The URS document was approved on 26 Mar 2018.

Volunteers referred to the CRO were recorded in the visit log prior to their registration in the internal database (VIMS). The access to the database was password controlled to protect the volunteers' confidentiality. Subjects' personal data, height and weight were registered. BMI was calculated manually by using a calculator. Volunteer's identification was ensured by checking their ID, photo and finger prints. A unique ID number was generated by the system for each volunteer registered in VIMS.

The VIMS was tested by mock registration of a new volunteer. A total number of 7262 subjects were registered in the VIMS.

The OVIS was also tested. The possibility of double participation was discussed.

Modifications were made to the mock registration to check the audit trail. All changes were appropriately captured in audit trail.

Procedures for back-up
All back-ups carried out daily into the cloud system, except to the pathology lab which was weekly backed-up. Source data was transferred to the server with the CRO domain control. The data from this server was transferred to another back-up system and synchronized with dropbox on cloud system.

CDs and DVDs might also be provided upon the request of the department and archived in the offsite archiving facility.

Observations made in relation to the computer system were addressed adequately in the CAPA provided by the CRO.

3. Quality management
VerGo Clinicals had a four level documentation structures, as provided in their Quality Manual, dated 28 Feb 2017:

- Quality policy
- Quality manual
- Standard operating procedures
- Farms/Logbooks

QA-Head acted independently and reported directly to the Managing Director.

Audit report status for vendor audit was provided, including all vendors being audited in 2017. The pertaining reports were available.

The vendor audit SOP was implemented.

Clinical In-process audit covered activities such as dispensing, dosing of IMP, eligibility of volunteers, as well as process of selection of volunteers, verification of cross participation and 90 days completion, compliance prior to recruitment.

BA In-process audit covered activities such as verification of preparation of stocking solutions, bulk spiking, batch processing and method validation.

Internal audit was carried out once every 6 months, covering all departments.

QA-activities were managed by five clinical QA-auditors, four BA QA-auditor, two documentation-staff, and Head of QA. Check lists were generated for each activity to be audited.

Concerns raised were forwarded to the Head of pertaining department, in addition to the Management Review meetings. Any major concern was directly submitted to the CRO-management.

Internal audit schedule for 2018 and 2017 and pertaining audit reports were provided. Each month a new area was assigned to be audited. The information about audit dates and audit report release dates were signed on the schedule.

List of SOPs was available, with SOP number, title, and effective date, as well as next revision date.

Observations made in relation to the QMS and QA were addressed adequately.

4. **Archive facilities**

The study related documentation was stored in the CRO's archiving facilities.

The ground floor facility was responsible to receive the documentation and carry out the primary activities, including verification of documentation and respectively recording them in the logbook, per the applicable SOP for Archiving.

The user department was responsible for labelling of the binders and the archivist was responsible for verification of the content of the binders.

After the primary archiving, the documents were transferred to the main archiving facility for storage of study documentation for applicable retention period. The main facility was access controlled by individual key cards. Two authorized archivists had access to the facility.

The facility was well-organized and equipped with racks labelled and indexed to provide a good overview of classified documentation. The facility was further protected by smoke-detectors and fire-extinguishers, including sensors sensitive to 40°C heat. Pest control was executed monthly. Pest control visits in March and February 2018 were verified in the logbook. Temperature and humidity was supervised twice daily, recorded in the logbook.

The process for retrieval and re-storage of documentation, using request form was verified, by checking the processing of retrieval of study documentation related to the ongoing inspection.

Observations made in relation to the archiving facility were addressed properly.

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

VerGo Clinicals employed facilities designed and organized to ensure the mode of operation. The building had five floors including a basement. The basement consisted of dedicated area for VerGo Pathology Centre and Chemical store.

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

The Ground floor consisted of the registration and screening Area, clinical unit I (14 beds), pharmacy, reception, admin block, archivist office, finance and account office, conference room, data management, walk-in cold room (-20°C), biomedical waste collection area and store room.

The area of first floor consisted of the clinical unit II (38 Beds) and bioanalytical laboratory. The Bioanalytical facility was designed keeping in mind the flow of process of sample extraction and analysis. First floor also consisted of server room, and a dedicated area for QA department, QA documentation, board room and office space for clinical staff.

Second floor had clinical unit III (48 beds), archival facility, rest room for staff and dining area for staff.

Kitchen, canteen and compressor room had heat alarms. The food provided to the subjects was prepared in-house. The hygienic condition of the area for preparation of the food was properly organised and maintained.

Each Clinical Unit had dedicated areas for dining and entertainment, phlebotomy, sample processing area and toilets, also equipped with CCTV for monitoring purposes.

Restricted areas were accessed using card keys.

One 380 KVA diesel generator was installed for power failure backup. During discussions, the site confirmed to have power cut issues every week. The maintenance logbook for generator was verified.

3 UPS devices providing a total of 320 KVA were available at site. Maintenance services for diesel generator and UPD devices were ensured every three months by the external vendor contracted.

Dispose of waste and other environment-friendly measures was properly done and outsourced.

The ICU was equipped with 2 beds, vital signs machine, ECG machine, BP measurement device, Oxygen cylinder etc. All physicians were trained by an external trainer to perform paramedics in emergency situations.

A logbook was kept recording the use of emergency medicines. An inventory log was also provided.

The medication available for medical emergencies was verified for expiry date, and none of them found to be close to expiry date or expired.

The following equipment available in the ICU was verified during the inspection:
- Defibrillator
- Nebulizer
- Oxygen Cylinder,
- Suction Apparatus
- Pulse oximeter
- Laryngoscopes
- Multi parameter monitor.

Medical site staff was interviewed on the applicable emergency procedures. A demonstration was provided for laryngoscope, nebulizer, pulse oximeter and defibrillator procedures. The site staff was well-trained on the different emergency procedures and aware of the use of equipment and emergency medication.

<u>Bioanalytical lab</u>
Bioanalytical facility was visited to verify the presence of the equipment used in the studies.

The bioanalytical department was designed to have separate instrument and activities rooms.

Material safety data sheet for chemicals and solvents was available at the BA laboratories. All chemical containers were adequately labelled, with project number, name of solution, ingredients, preparation date, expiry date, batch no, storage condition and the person responsible for preparation. The lab was also equipped with safety shower in case of chemical exposure accident.

The sample storage room equipped with deep freezers was accessed by responsible custodians and Engineering personnel, with provided overview. Temperature was monitored by digital thermometers Eurotherm connected to central alarm system, supervised by the security staff. The temperature monitoring for deep freezer was tested during the inspection to verify its functionality. Notification was received in a timely manner as soon as the temperature started increasing. Data logger and any documentation for any temperature excursion were reviewed.

The process of receipt and handling of samples was explained by the custodian. Samples were received in ice-box provided by clinical site in frozen condition, with a completed form. After verification of the shipment, another form was completed with recording the missing samples, study number, number of subjects, and number of samples received, aliquot numbers, as well as any observed discrepancy. Quality control of handling of samples was also carried out adequately.

Samples were labelled by study no, period no, aliquot no and subject no. The individual sample containers were also labelled with the respective time-point.

The logbook for biological sample receipt was reviewed. Date, project no, sample details, number of samples stored, aliquot number, number of missing samples, receipt of samples, freezer ID number, discarding of samples and verification of activities were all recorded in the logbook.

The temperature mapping documentation for freezer used for the study in the scope of inspection was studied.

Weighing room was equipped with analytical and micro balances. Daily calibration and monthly calibration to verify the linearity and repeatability of the measurements were documented. The room was also equipped with two refrigerators for storage of shipping solution and working standards. A complete overview of working standards was available for quality control purposes.

Pharmacy

The pharmacy area, with restricted access limited to the authorized personnel (pharmacist) was utilized for receipt, storage, dispensation and archival retention of study medications. All entries and exits in/from the pharmacy were to be recorded in a logbook.

Following CV and qualification verification, an interview was conducted with the pharmacist. The pharmacist was qualified, with sufficient experience and knowledge.

Medications were stored in cabinets, humidity chambers and refrigerators including drug archival area, depending on their storage conditions, all monitored by Eurotherm digital thermometers.

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

Observation made during the inspection was addressed adequately.

6. Personnel

The qualification of personnel was verified by assessing their CV and their undergoing appropriate training. A general plan was available based on the job description and responsibilities for each new employee to provide them with adequate training.

Two statisticians were involved in statistical and pharmacokinetic calculations. Their CV and Job description documentation, together with their activation/deactivation form for user and e-mail ID was reviewed and verified.

The form for activation and deactivation of user and mail ID was reviewed for the last employee who had left the organization.

The delegation list for method validation of Ethambutol was reviewed, dated 13 Sep 2017.
Training on STP and MV requirements was provided on 13 Sep 2017 signed by trainer.

SOP for Emergency response action plan, effective on 10 Feb 2017 and pertaining training documentation from 8 Feb 2017 for all personnel was provided. New employees were also trained based on their general training program. Training on this SOP was repeated every year and was included in the training matrix.

Training matrix was prepared for each year, organized by month, departments to undergo training and area/topic. The Plan was signed and dated by the trainer.

Clinical section

7. Clinical phase

The working area was in general well maintained.

There were three units with 100 beds to accommodate the subjects in the CPUs.

Medical and Para-medical staff were available round the clock.

All units had separate dosing, dining, phlebotomy and medical monitoring areas, as well as separate sample processing areas for centrifugation and storage before analytical processing. The process of sample collection was performed under hygienic conditions.

Screening X-Ray examinations were performed by outsourced facility when required.

The respective protocol training and delegation of the study activities were verified.

Subjects' belongings were locked in lockers in the changing room where the amenities were handed over to the subjects for their use, such as uniforms and wristbands in respective colour codes, before being directed to the CPU. At the entrance, the volunteers signed a record for their belongings.

The fire alarm was tested during the inspection. All staff members were informed about the alarm testing procedure. The reason for testing was that all emergency doors could be opened only if the alarm was activated. The site staff was informed and reacted properly.

The Entry/Exit logbook for volunteers was reviewed at the security. Volunteers were recorded in the visitor-log upon their arrival and before heading to the pre-screening area.

During the facility tour, alarms on bedsides and showers were tested. All of them functioned properly.

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

SOP for Handling Acute Medical Emergencies During a Study and SOP CR for Operation, Calibration and Maintenance of Defibrillator were discussed.

The site had a contract signed on 05 Oct 2016 with hospital for any emergency situations which was valid for 5 years.

The communication with the hospital and acknowledgment of receipt regarding the study initiation were verified.

A company owned ambulance (including appropriate medication and monitoring equipment) was available.

8. Clinical laboratory The laboratory was accredited using ISO 151819:20012.

Approved Pathology Lab was adequately equipped with required devices.

The Clinical/Pathology laboratory premises used were generally spacious and adequate for their use.

9. Ethics
Ethic Committee submission and approval were verified for following studies:

Study no. SLS-CL-0175-17 / 684-17
Study no. SLS-CL-0126-17 / 664-17
Study no. 650-17

Insurance certificate covering the period from 08 Mar 2017 until 07 Mar 2018 was checked.

10. Monitoring
The monitoring visits for study no. 650-17 were checked.

11. Investigators
CVs, Job descriptions and training logs were verified for Principal Investigator and study physicians.

Investigators had appropriate qualifications, training and sufficient experience in the conduct of BE studies, as confirmed by their CVs.

12. Receiving, storage and handling of investigational drug products
The study drug shipment was controlled adequately, once it was received. Activities were recorded in respective logbooks.

13. Case report forms
CRFs for randomly selected subjects were verified.

14. Volunteers, recruitment methods

After registration in VIMS, the volunteers were led to the informed consent area where the details of the specific ICF were explained to them and a copy of the ICF was provided. In addition, general screening forms such HIV, X-ray, IC for screening and medical screening record, and registration of volunteer into the volunteer database were requested to be signed.

If the volunteer decided to proceed, he/she was directed to the consent room to have one-on-one meeting. The volunteer would have the opportunity to raise any concern regarding the study during the consent process. The medical concerns were addressed by medically qualified personnel (i.e. investigator).

Following registration and ICFs procedures the volunteers were asked to perform a writing/reading test to verify their reading abilities and the language used.

The screening procedures were performed as per protocol requirements. The drug abuse and alcohol tests were performed. If the tests results were negative, the physical examination and ECG process were carried out. Physical examination process was discussed with study physician.

Observations made in relation to this section were addressed adequately in the CAPA provided by the CRO.

15. Food and fluids

The food provided to the subjects was prepared in-house. The area was clean, well maintained and organised.

The CV, job description and training logs for dietician were checked. Food and fluid were provided according to the protocol requirements.

16. Safety, adverse events, adverse event reporting

This section was not inspected.

Bioanalytical section

The inspection included audit of source documentation and raw data for validation of bioanalytical methods, and analysis of subject plasma samples as well as audit of the electronic data, audit trails for electronic data capture and 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 quality of the chromatograms generated from analytical runs. The preparation of analyte stock solutions, calibration standards, QCs and internal standards, and reagents were also audited.

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

VerGo clinical was responsible for analytical run of three analytes in the studies in the scope of the inspection.

Hence, the organization had performed one method validation on each analyte used in the studies.

<table>
<tr><td colspan="2">Study no. 684-17</td></tr>
<tr><td colspan="2">Method development</td></tr>
<tr><td colspan="2">The COAs for working standards, as well as the working standard consumption log was reviewed.

The method of detection was noted as mass spectrometry, using the Solid Phase extraction method / Protein Precipitation. The matrix used was human plasma with K_2EDTA as anticoagulant.</td></tr>
<tr><td colspan="2">Method validation</td></tr>
<tr><td>Preparation of CCs and QCs, starting from the stock solution to the spiking of the aliquots were reviewed, together with the logbook for disposal of the remaining volumes.

Reconciliation of number of CCs and QCs prepared vs. used samples was reviewed.

The instruments used for the method validation purposes were available.

The main validation was done in August 2017. Delegation list and pertaining training was available and signed 14 Aug 2017.

To confirm the method, P&A and stability tests were carried out in the presence of other co-administered analytes. The QCs were prepared with fixed concentration of analytes and their metabolite.</td><td>Matrix effect
Individual plasma using for Matrix effect was provided either by external laboratories. Both Lipemic and hemolyzed samples were also provided by vendors.

According to their current practice the lipemic and hemolyzed samples were provided in-house.

Specificity/Selectivity/Screening
Documentation was reviewed.

Dilution integrity, Carry over, Auto-sampler Carry over test
Documentation was reviewed.</td></tr>
</table>

Performance check of pipettes were carried out prior to the initiation of process activities. Stock solution preparation was reviewed. A list of experiments done was provided on a form called Experiment details, with the date of performance, whether accepted, or not and reason for failure. 28 experiments were performed starting August 16, ending 21 August 2017.	
Precision and Accuracy	Documentation for runs P&A 02, P&A 04, P&A 06 and P&A 05 together with Ruggedness and Re-injection reproducibility was reviewed.
Stability: Freshly spiked CC and LQC and HQC for comparison reasons were prepared. QC samples and CC samples were prepared independently. The disposal of remaining solutions was recorded in the respective logbook. Another form was available for Biological samples Disposal to be communicated with the sponsor. For calculation of acceptability, validated excel sheets were used.	**Stock solution preparation:** Stock solution for LTS and FTS prepared on 16 Sep 2017.
	Freeze/Thaw Documentation for one of the method validations was reviewed. Freeze thaw sample storage details for four cycles was reviewed.
	Bench Top Documentation was reviewed. The sample processing from the time of retrieval of samples by custodian to re-storage of samples was randomly checked.
	Long term stability stock solution Preparation of stock solution and storage and retrieval time of samples was recorded properly (30 days).
	Long term stability of analyte in matrix Documentation was reviewed.

Analysis of samples	
Transfer of periods I and II of aliquot 1 and 3 was carried out by Spinos Life Science on 13 Nov 2017. Aliquot 2 and 4 of periods I and II were sent to the CRO on 16 Nov 2017. The shipment documentation and the respective dataloggers were reviewed and verified. The sample processing for randomly selected samples was reviewed. Stock solution and spiking solution preparation was documented adequately. The addition of analytes as CAD/concomitant analyte to the QC samples was verified. The arrangement of the samples during the run was verified to be in accordance with the respective procedures. The usage of LC-MS/MS instrument for selected analytes was reviewed to verify the sequence of analytical runs performed in specific dates and the related instrument failures. The usage of instrument was recorded properly in the logbook for LC-MS/MS, used in the study. The run information for randomly selected subjects was verified. The documentation for re-injection and repeat of analyses was reviewed for verification purposes. The reason for re-injection and repeats was properly investigated and documented.	
Re-integrated chromatograms	Not applicable
ISR	ISR 01 and ISR 02 runs using 55 samples each, were performed in different dates, and met the respective acceptance criteria.

Study no 664-17
Analysis of samples
Stock solution preparation for QC and CC samples, respective spiking solution preparation, COAs, as well as the logbook for usage of working standards were verified.

The observations made during the inspection were addressed adequately.

18. Sample collection, storage and handling of biological material

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 phlebotomy / sample collection.

The haemolysed samples were identified by the respective chart, coded from A to D, and samples were recorded in the form. The missing samples were also documented, accordingly.

Labelling of study medication, monitoring check list and blood sample collection form, verification of vital signs and subjects' well-being, hygienic condition of restrooms were verified.

The temperature excursion of the deep freezer was reviewed to observe if the retrieval of samples from the freezer for sample processing purposes had any impact on the excursion of the temperature during the action. No visible fluctuation of temperature was observed. The door of the freezer was kept open for less than one minute to remove and restore the samples.

Missing and hemolyzed samples were reported by the sample provider; Spinos Life science in the respective template.

Logbooks were provided to verify the records of the retrieval and restorage of the samples used in the studies within the scope of inspection.

The whole process of transfer of subject samples from Clinical site to Bioanalytical site and the respective logbooks were reviewed. The shipment was carried out under controlled condition with data-logger IDs and temperature logs provided.

The purchase of dry ice documentation for 2017 was reviewed.

The shipment documentation for study no. 650-17 was reviewed. According to the SOP for Segregation and transfer of biological samples to the BA department, the samples should be placed in the zip lock bags subject-wise in the insulated box containing dry ice/ frozen gel packs. Frozen gel packs used at the site were re-usage of the gel packs received from IP shipment sent by sponsor. The bag was equipped by a thermometer device, to be read upon receipt, by the custodian at the BA Deep Freezer room. Respective documentation was reviewed.
Temperature of retrieval time and transfer time was noted on the subject sample transfer record.
Inventory of transferred samples was provided.

SOP for Preparation and verification of Labels prepared for sample collection storage tubes, effective 6 Aug 2016 was studied. Labels were prepared with study no., sub no., period no., time point, and serial no. as per format of sample format for sample collection tubes.

Subject samples for analysis purposes were inquired on a request form prepared by the designated analyst and submitted to the custodian of the Deep freezer room through the opening window at the entrance. The process was reviewed for the studies in the scope of the inspection.

Retention time of blood samples was performed according to the contract with the sponsor. All samples pertaining to the studies under the scope of the inspection were discarded and documented according with the agreement with the sponsor.

19. Data processing and documentation

Integration setting was predefined in the applicable SOP, and the different iterations used to obtain CC were saved. The smoothing factors used were kept as low as possible and was the same throughout the analytical runs.

Internal standard variation was trended, and the documentation was reviewed.

Audit trails were activated and foreseen for software in use.
Each data point was traceable to a specific sample, including sample unique number, time of collection and time of centrifugation. The logbooks were generally kept in a proper manner.

Issuance of templates was supervised by QA per SOP QA014-04, effective 24 Nov 2017.

Reconciliation of templates issued by QA was requested.

Observations made in relation to data processing and documentation were addressed adequately.

20. Good Laboratory Practices

The Master List of equipment and instruments used in the BA laboratory was provided.

The BA laboratory was equipped with LC-MS/MS instruments, deep freezers, sample processing area and other necessary equipment. Lab equipment was labelled with calibration date and validity, as well as a unique ID number. Cross contamination of samples on the working benches was foreseen. The total number of Micropipettes was noted on the inventory log.

Calibration certificates were available.

The calibration documentation dated 07 Jul 2017 for balances was reviewed. Calibration was externally performed by applicable vendor.

Observations made in the relation with Good Laboratory Practices were addressed adequately.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

Software SAS was used for randomization of the study participants. SAS was server-based database. A request form was generated by PI and received by the statistician prior to the generation of the randomization list. Randomization list was printed out on a password-protected printer. The password was created by the statistician by the time a print-out was required.

The process was inspected by regeneration of the randomization list of one of the studies in the scope of inspection and using the same seed number.

For Pharmacokinetic and statistical calculations, the generated data was submitted to the designated personnel. Time deviations from blood collection timepoints was provided by PI on a hard copy. Data from bioanalytical part was provided on an Excel sheet stored in a folder only accessed by the statisticians and BA-department. The file was copied in a folder by PK-designated personnel and all the data on the Excel was incorporated in software database WinNonlin. A data transfer form was also completed containing the file name and the name of the path on the server.

The Excel sheet received from BA was not editable, only enabled to be copied. Hence, it was copied by the PK-personnel to add the sequence, period, treatment, blood collection timepoint and actual blood collection timepoint and any other required information to the protected sheet provided by BA.

The PK-data processing was reviewed by the inspection team, without any remarks.

PK-data was submitted to the QA-team as hard copy for quality control purposes.

Both SAS and PK software were installed on password protected computers, only accessed by statisticians and IT-administrator.

After the completion of the study by BA, followed by the respective QA-review and verification, the data was locked and password-protected by the BA-department Head.

22. Study report

Study reports procedure was done by a designated team. This section was not inspected.
However, the study reports were provided prior to the inspection and were used during the inspection for verification purposes.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CRO master file (CROMF) was reviewed. The company's master file provided introductory information of the organization and didn't cover all information required by the guidelines for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7). According to the above mentioned guideline, the CRO master file should be a document prepared by the CRO containing 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 named site. It was expected that a CROMF provided information on the policies, approach and general activities of a CRO. It should serve as general information by regulatory inspectors in addition to the trial-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, most of the activities pertaining to 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 the CRO:

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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 Computerized 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.
Short name: WHO TRS 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

Short name: WHO TRS No. 957, 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