World Health Organization

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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 Clinical Research Site	Spinos Life Science and Research Private Limited No.29 A, "Krishna Madhuravanam", VellakinarPirivu, Thudiyalur, Coimbatore- 641029 Tamil Nadu, India
Name and Address of Bioanalytical Research Site	**Study no. SLS-CL-0123-17** Norwich Clinical Services Pvt. Ltd, 147/F, 8th Main, 3rd Block, Koramangala, Bangalore-560 034, Karnataka, India **Study no. SLS-CL-0175-17** VerGo Pharma Research Pvt. Ltd (Division - VerGoClinicals), Plot No 24/1, D-1 Mologa de OroraCorlim, Tiswadi, Goa- 403110, India **Study no. SLS-CL-0126-17** **For two analytes:** Norwich Clinical Services Pvt. Ltd, 147/F, 8th Main, 3rd Block, Koramangala, Bangalore-560 034, Karnataka, India. **For another two analytes:** VerGo Pharma Research Pvt. Ltd (Division – VerGo Clinicals), Plot No 24/1, D-1 Mologa de Orora, Corlim, Tiswadi, Goa- 403110, India **Study no. SLS-CL-0148-17** Synchron Research Services Pvt. Ltd. "Synchron House" Behind Mondeal Park, Near Gurudwara, S.G. Highway, Ahmedabad – 380059, Gujarat, India
Name and address Statistical Site	Spinos Life Science and Research Private Limited No.29 A, "Krishna Madhuravanam", VellakinarPirivu, Thudiyalur, Coimbatore- 641029 Tamil Nadu, India
Corporate address of Organization	Spinos Life Science and Research Private Limited No.29 A, "Krishna Madhuravanam", VellakinarPirivu, Thudiyalur, Coimbatore- 641029 Tamil Nadu, India

GPS coordinates	Latitude 11,0647 Longitude 76,9373
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Study no. SLS-CL-0123-17 150mg/150mg Tablets Study no. SLS-CL-0175-17 400mg and 150mg Tablets Study no. SLS-CL-0126-17 150 mg, 75 mg and 275 mg Tablets Study no. SLS-CL-0148-17 250mg Tablets
Inspection details	
Dates of inspection	11-13 April 2018
Type of inspection	Routine
Introduction	
Summary of the activities	The facility had the capacity to perform bioequivalence / bioavailability and in-vitro studies in healthy subjects / patients. The company served the pharmaceutical and biotechnology industries in India and abroad through the clinical research services.
General information about the company and site	Spinos Life Science and Research Private Limited was an independent Clinical Research Organization located in Coimbatore, Tamil Nadu. The CRO started its operation in April 2016 by taking over a well- established clinical facility of Micro Therapeutic Research Labs and Private Limited.
History	The CRO was inspected by DCGI on 10 Oct 2016. The company was also accredited by NABL with certificate number MC-2065, valid from 17 Mar 2017 until 16 Mar 2019
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The history of the site, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article

	accountability, dispensing and storage, processing and handling of biological (serum) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Pharmacokinetic, statistical calculations and reporting section, coverage was provided to confirm practices, qualifications of personnel, and procedures used during the randomization, statistical and pharmacokinetic calculations. A review of the clinical study report was carried out.
Scope and limitations	
Out of scope	Bioanalytical facility and bioanalytical part of the studies were not covered. The site was only responsible for the clinical activities of the studies in the scope of the inspection.

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
	GMP	good manufacturing practice
	HPLC	high-performance liquid chromatograph
	HPLC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form
	ICH	International Conference on Harmonization
	(I)EC	(Independent) Ethics Committee

IMP	investigational medicinal product
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

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

1. Organization and management

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

The CRO's organogram signed and dated on 18 Jan 2018 and 05 Feb 2018 was provided in the CROMF. A total of 78 employees were working in two different shifts in the company (one shift covering time interval 09:00 am - 7:00 pm and the second one covering the hours between 7:00 pm - 07:00 am). They were involved in different activities based on their roles described in their respective job descriptions.

The facility was spread over an area of almost 36,000 sq. ft., with a built-up area of about 20,000 sq. ft. distributed over two floors (Ground and First). The clinical facility for housing study volunteers was equipped with 97 beds. The bioanalytical facility was equipped with 2 LC-MS/MS.

2. Computer systems

Spinos Life Science and Research Pvt. Ltd had a network of computers which enabled the collation of data from all operations throughout a project.

Spinos was utilizing computer systems for maintaining the digital records and processing, analyzing and storing of the generated data. All the computers and laptops in Spinos were identified with a unique identification number. The IT structure consisted of four main servers. All the end-user computers were connected to the main server via the local network area.

Regular Back up was performed according to the applicable SOP.

A daily back-up was run, as well as the weekly and monthly full back-up of the data generated by the software. Back-ups were provided on tape and shipped to the remote archiving facility. The respective agreement valid from 12 Nov 2017, together with the audit report, was reviewed. An audit was performed by the CRO on November 2017 to verify the suitability of the archiving facility.

All computers were installed with licensed Microsoft office 2003/2007/2010 version.

A list of software and the corresponding validation plan were provided in the CROMF.

Software validation was carried out as per the applicable SOP. SOP for Validation of laboratory computerized system and software of 5 Aug 2016 was reviewed.

According to the applicable SOP, whenever a revalidation of Computer system / software was planned to be carried out, the choice between partial and complete validation was decided based on the level of risk related to the respective modification. If the created risk was low, then the partial validation approach with Performance Qualification would be considered suitable. All computerized systems were assessed to be validated every two years, based on the changes made to the computerized systems.

The validation plan was provided.

The access to the databases in use was provided by the IT administrator, based on the request issued by the Head of the department or designated personnel.

SOP for Preparation and maintenance of data backup and restoration, effective 5 Aug 2016 was reviewed to verify the restoration procedure.

There was a regular check of back-up tapes once in three months for tapes archived in the offsite archiving facility, and once in a month, one tape was retrieved from the in-house archiving facility to verify the accuracy and completeness of the data stored on the tapes. The retrieval request for 2017 and 2018 was reviewed, respectively from internal and external facility.

The record for the material inward, and retrieval record logbook, dated 3 Mar 2018, pertaining to retrieval of a specific tape was reviewed. The tape was run/restored, and the job log was printed out, with "Completed Status" mentioned as successful.

Smart forms software:
The qualification protocols and reports for Smart forms software approved on 4 Jan 2018 was reviewed.

The system was a web-based application developed on Microsoft Net technology. Smart form was three-tiered layered solution and built in user control system and dynamic role-based menu system. Appropriate menu items were shown to the user, based on the user-role which would be assigned by the administrator.

The User Specification requirement was elaborated in the documentation and Performance Qualification was carried out, respectively.

The concerns raised during the inspection was addressed adequately.

Volunteer registration database – web-based (VMS)
The database was inspected by performing a mock registration. The audit trail was only accessed by designated IT-personnel for read-only purpose. Search option via both subject and period of time in audit trail was available. Data registered in the database could only be changed if the change was approved by PI.

3. Quality management
Spinos Life Science and Research Pvt. Ltd had four level documentation structures:

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

The quality management was explained in detail by QA. Original SOPs were kept in hard copy with QA-stamp and the soft copies were stored on their QA-data system, protected by a specific password. The database was only accessed by the QA-personnel. The Quality Manual version 01 dated 27 Sep 2016 was available.

CRO Master File was also provided and structured according to the requirements.

The QA department was an independent department, managed by the QA manager who reported directly to the director of the CRO.

The QA was also responsible for performance of audits, including vendor audits, maintaining the quality procedures and management of documentation. The job description of QA-Head was verified.

Following SOPs were reviewed:

- Quality assurance
- Procedure for Archival and Retrieval
- Emergency care of subjects
- Dosing Procedure
- Blood Sampling during Study
- Transport and Receiving Pharma or Biological Samples
- Entry & Exist Procedure
- Handling of Investigational Medicinal Products
- Dispensing of study medication
- Statistical analysis using statistical analysis system (SAS) and Preparation of Statistical Report
- Incident reporting and procedure for conducting investigations

Reconciliation list of study SLS-CL-0175-17 for the issuance of number of templates issued through Smart Form system was available. The list contained project no, form name, sequence number, total requested form, used and remained. The returned templates (unused) were logged in a logbook and discarded accordingly. The forms used for "clinical freezer usage log" and the respective logbook was reviewed.

The reconciliation list was sealed, signed and dated on 19 Dec 2017. The process was described in SOP for Issuance and numbering of logbooks and forms, effective date 28 Feb 2018.

An index of Trial Master File was present to issue the number of forms necessary for conduct of specific studies. The respective index was reviewed for study no SLS-CL-0175-17

An annual audit plan for outsourced service providers and vendors would be prepared, approximately in August/September and would be revised throughout the respective year, if necessary.

4**. Archive facilities**

The archiving facility was only accessed by the authorized personnel with their individual key card.

The process for archiving and retrieving of the documentation was described in detail by the archivist and documentation was randomly selected to be examined by inspection team to ensure their compliance with the procedure. A password protected Excel sheet was provided to maintain

the overview of available documentation in archiving facility, with necessary back-up. E-copies of source documentation in paper form were also provided.

The archiving facility was sufficiently equipped with smoke-detectors, rodent trap, fireproof door, water leakage sensor. Pest control was carried out by designated maintenance-personnel, twice a week.

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

The entry and exit within the facility was restricted by access-controlled doors through all the critical areas such as pharmacy, archive facility and sample separation area.

The organizational structure of Spinos Life Science and Research Pvt. Ltd was consisting of the following departments:

- Clinical
- Bioanalytical
- Diagnostic
- Quality Assurance
- Pharmacokinetic/Statistics
- Medical Writing
- Project Management
- Administration

Security room was provided at the entrance of the facility with security guard. Visitors' logbook was maintained at the security room for capturing the details of individuals entering the facility. Separate entrance was available for entry of visitors/staff.

The Ground floor was accommodating 7 self-contained CPUs of 97 beds capacity. The beds were spread over 7 housings: Housing I with 28 beds, Housing II -07 beds, Housing III - 19 beds, Housing IV - 08 beds, Housing V - 08 beds, Housing VI - 08 beds, Housing VII - 19 beds. The volunteers' registration, screening areas, ICU, X-Ray room, Phlebotomy and Sample Separation area were located at the Ground floor, as well.

Clinical Diagnostic Lab, Bioanalytical lab, Pharmacy, archiving facility, Server room, Administration and the Quality Assurance offices were located at the first floor. Ample office space was available to the technical and support personnel including space for data analysis and documentation teams. Additionally, the facility was equipped with UPS, Diesel Generator and Power distribution installations.

To ensure the smooth flow of the activities, the facility was clearly demarked into volunteers waiting area / counselling area, volunteer screening area, volunteer housing area along with the wash rooms, investigational product administration area, phlebotomy area, access-controlled pharmacy, recreation and dining rooms for the study volunteers.

Registration of the volunteers and their details were captured in the volunteer registration Software.

The volunteer registration database was used for registration of volunteers by means of their biometrics (finger print), name and photo. Subjects were primarily identified by fingerprints. The cross-check study participation was performed through OVIS.

A separate area was provided for Informed Consent process managed by Audio Video Recording.
The inspectors verified the audio/video recording process.

Biological waste was stored and disposed in a separate area near the security room within the premises located in the Ground floor. Waste disposal based on biological and non-biological waste was periodically managed by an external independent vendor.

Monitoring of Temperature and Humidity:

- Online temperature recording system was available in all critical areas and for all critical instruments like Pharmacy, archiving facility, Ultra Low Temperature freezer, Low Temperature Freezer, humidity chamber and refrigerators.
- Any excursion from the set temperature was alerted through a hooter alarm installed in the security area and in all facility floors.
- An e-mail pop-up was received by the responsible persons for any temperature / humidity excursions (tested and confirmed during the inspection)
- Excursions were documented in an incident report and impact analysis was carried out as per applicable SOP
- 24 hours' maintenance personnel deputed to ensure the proper maintenance of temperatures.

The overview of personnel with access to the restricted areas was provided in a documentation called Master List of access card (IT structure), dated 26 Mar 2018. The access was coded, and codes were defined in another documentation dated 26 Mar 2018.

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

Screening areas were separately provided for male and female volunteers with a space to accommodate around 100 volunteers.

ICU room was equipped with two adjustable beds, required equipment, stock of emergency drugs to handle medical emergencies. ICU was centrally located within easy access to all the clinical processing units and ambulance in the event of an emergency through the emergency exit. Ambulance was stationed in designated area close to the ICU exit point.

The following equipment available in the ICU was verified during the inspection:

- Defibrillator
- Nebulizer,
- Oxygen Cylinder,
- Suction Apparatus
- Pulse oximeter
- Laryngoscopes
- Multi parameter monitor.

Equipment maintenance logbook was verified for all devices mentioned above.

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

Randomly selected emergency medication was verified for expiration date.

The calibration certificate for Pulse oximeter was verified.

Issues raised during the inspection was sufficiently addressed.

Power supply system
Primary power back-up was ensured by 3 UPS installed in the facility with a total capacity of 55 KVA, covering all critical equipment and instruments available.

Secondary power back-up was covered by the Diesel Generator of 160 KVA, 3 phases supply, 400 volts, 50 Hz capable to ensure at least 24 hours of operation supporting 100% of presently installed instruments and utilities.

The maintenance logbook for generator was verified.

Pharmacy
The in-house pharmacy was access-controlled, and only authorized personnel were allowed to enter. Entry and exit information for each visit were recorded in the logbook including the reason for visiting the area. Pharmacy area was divided in two separate zones: buffer area and dispensing area. The pharmacy was overall monitored for temperature and humidity through online temperature monitoring system. For study IMPs, storage stability chamber was available inside the pharmacy. Records pertaining to the pharmacy activities were documented in the study specific controlled forms. The archival area for storage of retained IMPs was segregated.

6. Personnel

The qualification of personnel was verified by providing their CV and maintained by appropriate training. Their CV and job description, as well as training documentation of randomly selected personnel were reviewed.

Clinical section

7. Clinical phase

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

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

The delegation logs for studies 0123-17, 0126-17, 0148-17 and 0175-17 were verified.

Handling and processing of blood samples was observed during the running of study SLS-BE-0152-17 with 12 subjects.

The site had signed contracts with the hospital situated 2 km from the facility, for any emergency situations.

According to the SOP for emergency situations, the site should inform the responsible person at the emergency hospital about the study initiation visits. The communication with the hospital and the acknowledgment of the receipt of study initiation information were verified.

The alcohol test breath-analyzer device was tested.

The ICF process was discussed with the medical staff. All the ICFs for the following studies were verified:

Study SLS-CL-0175-17
Study SLS-CL-0148-17
Study SLS-CL-0126-17
Study SLS-CL-0123-17

All the equipment/instruments installed at Spinos were calibrated by the external calibration agency as per the schedule mentioned in the applicable SOP. External calibration certificate was authorized by Spinos Quality Assurance unit before it was released to the end-user.

The CRO was equipped with all the major equipment/instruments such as ECG machine, digital X-Ray, alarm systems attached to every bed in housing areas, toilet alarm systems in all the toilets, water leak detector system with an alarm hooter in archival , -70 degree Ultra Low temperature Freezers, -30 degree Low temperature freezers, refrigerators, refrigerated

centrifuges, humidity chambers for Investigational product storage , BP cuff, thermometers, alcohol breath analyzer, weighing machine, stature-meter for measuring height.

The alarm installed for temperature monitoring, attached to the freezer in blood sample processing area, was tested. The instrument engineer called the responsible custodian and the maintenance person showed up to follow up the alarm notification. The facility was supervised by maintenance-personnel for any emergencies at all time.

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

8. Clinical laboratory

Spinos had an In-House diagnostic facility accredited by NABL. NABL certificate MC-2065 from 17 Mar 2017 to 16 Mar 2019 was provided. The biological samples for screening purpose were collected in a separate sample-collection area, located on the Ground floor. The samples of specific volunteers were collected in a vacutainer which were bar-coded using a software. The collected samples were transferred to the in-house diagnostic laboratory in a thermal box. During the blood sample collection, the samples were kept in icy water.

The time and date on the computer in the pathology lab could not be changed, however the time-zone on the computer was not locked. They explained that this computer was in upgraded process and software installation was running at the moment of inspection. The documentation regarding this upgrade was provided by IT personnel. After the installation, the time-zone was blocked in the same day and verified by inspector.

The samples collected in the collection area were transferred to the access-controlled diagnostic facility which was equipped with Random Access fully automated Biochemistry analyzer, fully automated Immunoassay analyzer, fully automated Hematology Cell counter, Urometer (Automated) and refrigerated Centrifuge and temperature-controlled refrigerators for storage of the kits.

The samples were analyzed after performing the in-house QC run/test. Strict TAT was followed for all the samples received in the diagnostic laboratory. All the source data of the lab results were archived as per the in-house SOP.

9. Ethics

Research Ethics Committee was used for approvals for all studies. All EC approvals were verified for following studies:

Study SLS-CL-0175-17
Study SLS-CL-0148-17
Study SLS-CL-0126-17
Study SLS-CL-0123-17

Spinos had a contract with Institutional Ethics committee and Independent Ethics Committee. The Company utilized services of Ethics Committee for the approval of protocol and SOPs.

Insurance certificate was verified issued with validity from 29 Jan 2017 to 28 Jan 2018.

10. Monitoring

Monitors' visits were verified in the visitor's logbook.

The monitoring visits were verified for the following studies:

- Study SLS-CL-0175-17
- Study SLS-CL-0148-17
- Study SLS-CL-0126-17
- Study SLS-CL-0123-17

The qualification of the monitor was provided through his CV.

The agenda for the monitoring visits was shared prior to each visit through e-mails. The monitoring was carried out according to the schedule. The e-mail correspondence was provided to the inspectors.

11. Investigators

CV and job description of Principal Investigators were verified.

Training record comprised of the following documentation:

- Index of the training file
- CV with responsibilities
- Copies of Educational, Training and Experience Certificates
- Induction Training-Checklist
- Identification of training requirement and schedule during induction
- Training Matrix card
- Employee Training Card
- Group -Training Card
- Training Evaluation Forms / Questionnaires
- Assessment of Job Specific Training during Induction
- Job Description

12. Receiving, storage and handling of investigational drug products

The pharmacy was accessed by two pharmacists supervising the handling of investigational medicinal products.

Once the study was confirmed, the shipment was arranged by the sponsor. If the protocol was approved by the time of receipt of IMP, the IMP would be stored in the storage. Otherwise, the IMP would be quarantined.

Upon the receipt of the shipment, the respective documentation, such as cover letter, CoA, package label, batch no., log no. and expiry date, as well as the shipment condition was verified. The process for the last shipment received was reviewed.

Randomization was requested by PI on a respective form. As soon as the randomization list was ready, the pharmacist was notified by the designated bio-statistician to pick it up personally.

All templates used in the pharmacy for recording of the activities were controlled documentation with specific ID no., study number and date and time of issuance.

Label preparation was performed by the pharmacist on templates in word format, prepared for this purpose. Labels prepared for both periods of study 0175-17 were compared to the randomization list. Dispensing and accountability details for the respective reference product were also reviewed.

13. Case report forms

The CRFs were reviewed for study no. SLS-CL-0126-17.

14. Volunteers, recruitment methods

Recruitment of volunteers was based on the promotional material in the form of brochures, SMS, phone calls, flipcharts and by word of mouth. Volunteers were recruited through intensive counselling in all the areas surrounding Coimbatore and entire Tamil Nadu. Separate volunteer recruitment team worked on recruitment of volunteers, through IEC approved promotional materials like advertisements and brochures. The EC approval was verified for the respective advertising.

The volunteers were briefly informed about company as an organization doing research, clinical study, its objectives, risks, benefits and the procedures involved in the study, process of registration in volunteer data bank, the process of screening and the tests done during screening and the criteria for selection for participation in studies and clarified doubts if any.

Registration of the volunteers into the volunteer database to participate into the clinical research studies was performed by using the validated software. Volunteers were identified by fingerprint and photograph. The subjects signed a registration consent form prior to the registration in the database. The EC approval for registration consent was verified.

After the screening, depending on the drug's therapeutic class and safety profile, special medical investigations were carried out before, during and after the completion of the study.

Separate area was provided by the firm for Informed Consent process for Audio Video Recording, recreation and dinning.

Facility was controlled by restricted access doors throughout all the critical areas, such as pharmacy, archive, and sample separation area.

Fire Extinguishers and smoke detectors were installed in all areas of the facility to handle any emergency. Fire Extinguishers were verified for expiry date.

Facility was equipped with in-house ambulance services with two emergency exits.

Emergency escape routes were clearly displayed throughout the facility to ensure the evacuation during emergencies.

15. Food and fluids

Standardized meals were provided to the volunteers at the predefined intervals as per the protocol.

Dietician was interviewed and the condition of preparation of food was discussed. Food samples were tested regularly, recently on 11 Jan 2018 by service provider Alpha labs and technologies. Test was carried out for different yeast and bacteria on rice, Dhal, rasam, vegetable, curd and boiled egg. Drinking water was also microbiologically tested by service provider Seeds enviro labs, and report was provided on 19 Mar 2018.

Dietician's JD, dated on 6 Apr 2018 was reviewed.

16. Safety, adverse events, adverse event reporting

This part was not inspected.

17. 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 phlebotomist / sample collection.

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

18. Data processing and documentation

This part was not inspected

Pharmacokinetic, statistical calculations and reporting section

19. Pharmacokinetic, statistical calculations

After the completion of the bioanalytical phase, the QC-audited concentration data was sent to the PK investigator for the analysis via email. The data regarding the blood collection time and other required information was submitted by the clinical site, also through email.

The process of randomization generation via SAS software was inspected by regeneration of the randomization list of one of the studies in the scope of the inspection by using the study's seed number.

Biostatistician / designated personnel checked for the completeness of PK input, PK parameters, etc. according to the protocol, in-house SOPs and applicable regulatory requirements. PK analysis was performed using another software. All data was stored in folders with restricted access.

PK data and respective report was submitted to the sponsor through Hyper link text transport protocol, which was a server-based link, such as FTP.

20. Study report

Study reports were used to verify the study data without any remarks.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CROMF was provided and reviewed.
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:

Spinos Life Science and Research Private Limited
No.29 A, "Krishna Madhuravanam",
VellakinarPirivu, Thudiyalur,
Coimbatore- 641029
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. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP". http://www.who.int/tdr/publications/documents/glp-handbook.pdf

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

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

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

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

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

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

12. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
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
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