

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)	<u>Clinical site:</u> Synchron Research Services (Pvt) Ltd. 2nd Floor, Swagat Plaza II, Iscon – Bopal Road, Ambli, Ahmedabad 380056, India <u>Bioanalytical and statistical site:</u> Synchron Research Services (Pvt) Ltd “Synchron House” Behind Mondeal Park, Near Gurdwara, S.G. Highway Ahmedabad – 380059 Gujarat, India <u>Dispensing and logistics pharmacy department and Archiving facility – The Chambers</u> Sarkhej Gandhinagar Highway, Bodakdev, Ahmedabad, 380054 Gujarat, India
Corporate address of Organization	Synchron Research Services (Pvt) Ltd “Synchron House” Behind Mondeal Park, Near Gurdwara, S.G. Highway Ahmedabad – 380059 Gujarat, India
GPS coordinates	Synchron House Latitude : 23.0455 Longitude : 72.5129 Ambli Clinical site : Latitude: 23.0261 Longitude: 72.4823 Dispensing and logistics pharmacy department and Archiving facility; The Chambers Latitude: 23.0440 Longitude: 72.5150

WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Study no: RII/2016/1357 tablets 300 mg / 150 mg Study no: SLS-CL-0148-17 (Only bioanalytical part) tablets 250 mg
Inspection details	
Dates of inspection	11 – 15 June 2018
Type of inspection	Routine
Introduction	
Summary of the activities	The facility had the capacity to perform bioequivalence / bioavailability, pharmacokinetic studies, and phase I to III clinical studies on both healthy subjects and patients.
General information about the company and site	The CRO was founded in 1998 as Bio-equivalence Centre in Ahmedabad and their collaboration with Covance for global clinical trials was established in 2000. In 2004, the CRO collaborated with Parexel for global clinical trials management. In 2015, the bioanalytical facility Synchron House, and in 2017 Satva Clinical facility with 60 beds were added to the company.
History	A list of previous external inspections was provided, reflecting that the CRO was inspected by various inspectorates. In the last 5 years, the CRO was inspected by the USFDA and CDSCO. Synchron Research Services was inspected by WHO in 2010. The US FDA report pertaining to the inspection performed on February 2018 was studied.
Brief report of inspection activities undertaken	The Inspection team covered the following study-related activities under the scope of this inspection: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensing and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.

	Regarding the Analytical operations, the team covered good practices, qualifications of personnel and procedures used during the method validations and analytical testing. The clinical study data, analytical method validation, and analytical study data were reviewed, and the source data was compared to the 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
	LC-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 (where applicable)
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General section

1. Organization and management

The company presented the structure and operations of the organization.

Synchron Research Services Pvt. Ltd. is an Independent CRO, dedicated to providing clinical research services to pharmaceutical companies. Synchron was established in 1998 in Ahmedabad, by entrepreneur Dr. Shivprakash Rathnam, catering for a whole spectrum of clinical research including phase I-IV clinical trials and BA and BE activities. Their BA activities started in 2002. The CRO has been collaborating with Parexel international USA, starting in 2006, and with a 30-bed facility in Bangkok. The clinical study was performed in Swagat Plaza II (Ambli) which was located 5 km from the Bioanalytical site (BA).

The organization has two clinical facilities:

Location 01:

Clinical BA/BE & P- 1 Department,
2nd Floor, Swagat Plaza II, Iscon Bopal Road, Ambli,
Ahmedabad, Gujarat, Pincode-380056, India

Location 02:

New facility Under Expansion plan in 2016
Clinical BA/BE & P-1 Department, 201&301,
2nd & 3rd Floor, Satva, Opp Bhavin School
Thaltej, Ahmedabad 380059,
Gujarat, INDIA

Agreements and pertaining Master Service agreements with sponsors were reviewed. The biological samples were required to be retained for a period of time from the date of completion of the report.

The organogram of Synchron Research services Pvt. Ltd. Ahmedabad was included in the CROMF, depicting the departments. The organogram was verified by Managing Director on 3 May 2018. The organization was divided into 12 departments, with two clinical units, i.e. Ambli and Satva facilities.

A list of employees was provided in the CROMF, categorized in groups depending on the activities they were involved in. The regular working hours were from 9:30 to 18:30, Monday to Friday.

2. Computer systems

A list of software was provided. The available software programmes were used for both inspected sites (Synchron House and Ambli Clinical site) and controlled by the IT department. Statistical analysis was performed using SAS and Kinetica software, accessed by a limited number of trained staff. A system validation procedure, together with the Computer System Qualification (IQ, OQ, PQ) were presented.

VPMS Software

VPMS database was used for the registration and collection of volunteer information. At the time of inspection, the total number of registered volunteers was 10 659 with a quarter of these being female volunteers. This software was available on a limited number of computers at the Ambli Clinical site. The software was installed in 2008/2009.

LCquan Software

Bioanalysis of subject sample was performed using validated software. The validation of the software had been performed by external service provider. The validation covered all the

standard requirements; however, the audit trail of this software had not been included in the validation.

Access rights to the software and instruments were password protected with the IT department being responsible for administration rights. SOP for Installation and Operation Qualification and User Permission of Xcalibur and LCquan, with effective date 6 Oct 2017 was reviewed.

Four levels of security were defined in the LCquan software as Analyst, Administrator, QA auditor and Reviewer. These groups were provided appropriate permission levels. The permission levels were described as Disallowed, Signature list, Supervisor password, Allowed and Hidden. A document with the name of members was reviewed.

An overview was available called “Folder access Permission”, defining the type of employees’ access to the different instruments with the respective role. The documentation was signed and dated.

Procedures for back-up

A system was in place for the backup of software and data. The SOP for Electronic Access Control Procedure effective date 20 Apr 2018 and the SOP for Data backup and Recovery Process effective date 18 May 2016 were reviewed. The organization was in the process of implementing an additional backup process of storing information on the cloud. At the time of inspection, the organization was backing up the data on a twice daily, weekly and monthly basis using tapes that were stored within the secure server room. The SOP for Server room access process effective date 23 Nov 2016 was reviewed.

Access Control

Access control to the facilities was controlled by a software system. All staff were issued with swipe cards and access to rooms was controlled using this system. The IT department (two people located at Synchron House and one at Ambli clinic) were responsible for accessing entry rights. An audit trail was available for both the Synchron House site and Ambli site for movement within the buildings. Filters were available to search under the following categories including but not limited to zone, card number, holder name, department, room etc.

Observations made in relation to the computerized system were addressed in the CAPA plan provided by the CRO.

3. Quality management

A Quality manual was available. Synchron Research Services Pvt. Ltd. established a Quality system conforming to GCP, GLP and other applicable regulatory guidelines.

The Quality management – Quality assurance system was structured to house three groups, reporting to the QA-Head. The QA-Head directly reporting to the CEO. A weekly meeting took place regularly. A total tracking of deviation was undergone every 6 months. However, the urgent matters were reported immediately.

The QC-team was responsible for review and handling of in process checks and retrospective verifications for each and every project, preparation of the plan, and issuing the authorization of QC activities, after protocol training. Clinical and bioanalytical data underwent 100 % verification by the QC-team.

The QA-team (Audit team) was responsible for performing in-process audits, retrospective audits, system audits and vendor audits in line with approved audit plans. The retrospective review of data was performed for minimum 20 % of raw data. Critical data such as accountability of IP and concentration of analyte in analytical runs were 100 % reviewed.

The QMS-team was generally authorized to have an oversight of document-control issues, SOPs review, change-control, deviation, CAPA tracking and archiving management.

A list of SOPs was kept in an Excel programme to ensure their timely revision. A total of 262 SOPs were implemented in the Quality system.

The following SOPs were requested and reviewed:

- SOP for Computer System validation policy, effective date 19 Feb 2016
- SOP for calibration curve standards and Quality Control Samples Specification and Acceptance criteria
- SOP for Chromatographic Acceptance Criteria
- SOP System Suitability and Auto Sampler Carry over of chromatographic Systems
- SOP Calibration Curve Standards and Quality Control Samples Specification and Acceptance Criteria
- SOP for Repeat Sample Analysis
- SOP for Documentation Procedure for Method development, Validation and Bioanalytical Report Volume
- SOP for Incurred Sample Re-analysis
- SOP for Repeat Sample Analysis
- SOP for Receipt, Verification, Storage, Shipment, Retention and Disposal of Biological Samples
- SOP for Operation routine check and maintenance of ECG instrument
- SOP for Informed consent process

The process of obtaining of informed consent and the responsibility was explained explicitly.

- SOP for collection of blood and urine sample from human volunteer, effective 31 May 2018
- SOP for Biological samples transfer, centrifugation, separation, storage and Accountability process
- SOP for shipment of biological study samples
- SOP for SOP for SOP process
- SOP for training
- Volunteer Database management

The Annual vendor audit plans for 2017 and 2018, prepared in January each year, were provided and reviewed.

The Catering audit report pertaining to the audit performed on 29 Jul 2016 was provided. Findings were identified, and all addressed by the auditee. No remarks were made.

Templates used for study activities were issued by QA for each respective study. The lists of the template-reconciliation for both studies were provided. The template reconciliation for study SLS-CL-0148-17 and for study RII/2016/1357 were signed 6 Jun 2018 and 20 Apr 2018 respectively, after completion of whole projects and resolving all the issues. The reconciliation was reviewed, and the record was randomly verified.

A checklist for Audit trail verification of Thermo Quality Assurance was provided to be used by the QA-team. Acquired time, acquired file number, and pertaining activities were verified for randomly selected analytical runs.

A Logbook was kept recording the document/template issuance where all information regarding the type of templates issued, as well as the returning and discarding of unused templates were itemised.

Observations made in relation to the CROs QMS were addressed in the CAPA plan.

4. Archive facilities

The archiving facility was in a building together with the Dispensing and logistics pharmacy department, on 6th and 10th floor, accessed by authorized key card. The facility on the 10th floor was the recent one where the ongoing archiving activities took place.

As soon as the study was completed, the respective documentation was transferred to the archiving facility in boxes, together with a form containing the documentation index. The

process of archiving of documentation was described adequately according to their procedures. And the documentation was well-organized.

Preventive measurements such as monitoring of temperature and humidity control, pest control (once in a month by PCI), installation of gas-operated fire extinguishers, smoke detectors and rodent-traps were implemented.

A thorough company archive system was verified through the document requests for study documentation and supporting records.

Observations made in relation to the archiving was addressed in the CAPA provided by the CRO.

5. Premises

During the inspection, a tour of the two facilities was conducted.

The facility plan layouts for all facilities were provided in the CROMF.

All clocks were synchronized, connected to the main server operated by GPS to document the exact time of study activities. Medical examination equipment was labelled properly for installation and calibration information.

Clinical location Ambli:

The Clinical BA/BE & P- 1 Department facility at this location had three furnished and equipped CPU units with 90 Beds capacity with ICU, Screening area, Check in area, Body and baggage area, sample handling & separation area, Drug store (Investigational Products storage) area, Pantry for meal distribution, Subject Recreation area with sufficient wash rooms/toilets.

Upon the check-in procedures, the volunteers were allocated different colour gowns according to a colour code for separation of different groups. The clinical site consisted of three units:

Clinical pharmacological Unit-I (CPU-I) Bed capacity:	46 beds
Clinical pharmacological Unit-II (CPU-II) Bed capacity:	14 beds
Clinical pharmacological Unit-III (CPU-III) Bed capacity:	30 beds

The restricted areas were accessed by only authorized personnel by using their individual access cards. The SOP for Electronic access control procedure, together with the overview of access to the restricted area was provided by IT-person, signed 20 Apr 2018.

IT was responsible for updating the list of users and their pass control for respective doors, using a template which was attached to the abovementioned SOP, after issuing the access card.

The segregation room located in the clinical site was used for storage and centrifuging of collected biological samples. The room was equipped with two -70 °C freezer, two -20 °C freezers and three centrifuge machines. The freezers were monitored by digital thermometer connected to the data logger placed in the freezer, with the capacity of printing temperature measurements. The device had to be taken out of the storage for data-reading purposes with consistent intervals and placed back into the freezer. Hence, the initial reading of the data logger would show an increase of the temperature. The device would start measuring the real temperature in the freezer, shortly after the data logger was placed back into the freezer. One of the -20 °C freezers was tested to verify proper function of the alarm and notification procedure.

An additional hooter system was connected to the alarm system which separately monitored the temperature and notified the staff in case of excursion of temperature.

The temperature and humidity were recorded for the drug storage area. The temperature monitoring and the respective data logger pertaining to the freezer under the maintenance in the segregation room was reviewed for 5 Jun 2018 until 12 Jun 2018 to track the fluctuation of temperature. Additionally, the logbook for the retrieval of the samples to the safe freezer on 10 Jun 2018 was checked. The service report and instrument maintenance recorded were available. It was verified that actions were taken properly and in a timely manner.

Back-up Generator

The electrical control panel for Ambli site was located in a secure area. The back-up generator at Synchron House was located in the basement of the facility. The generator was connected to the deep freezers and UPS was connected to the LCMS-MS instruments. The facility was under 24-hour surveillance. The generator was tested weekly and was easily started upon request. The SOP for the Contingency Plan for Power Failure was reviewed. The maintenance and service records for the generator were available.

Safety Measures

The facility was adequately equipped with fire extinguishers and smoke-detectors. First aid kits were available in the laboratory areas with a list of first aid trained staff available.

During sample preparation, there was no absorbent bench material available, the bench was made of a porous material (timber) that could not be easily cleaned in case of a biological spill, and the positioning of the waste bin was inappropriate.

The disposal of waste was outsourced.

Clinical Pharmacology Unit

Testing of buzzers for the beds and toilets was required prior to conducting of each study. Verification was provided using a template “Buzzers of beds and toilets facility routine check log” with respective logbook.

The laundry service was also reviewed. An invoice was issued by the laundry service for the period of study at the CPU. The payment voucher was provided, dated 14 Nov 2017, paid for laundry expenses on Oct-17.

Toilets would be locked during the drinking restriction period.

ICU

ICU was handled by one physician and two qualified nurses.

The medication available for emergencies was randomly verified for expiration date by reviewing the usage and maintenance log of ICU medication, which was found compliant. It was noted that at the time of inspection the room temperature of the ICU was 30.1°C and the daily record log was recorded as 29.1°C. The comments column was blank. There were some medications (i.e. Adrenaline) that had a storage requirement of below 25 °C that were stored outside of their recommended storage requirements.

An anaphylactic kit was prepared and checked prior to each study with its own logbook.

Medical emergency equipment: oxygen device, defibrillator, ECG machine, suction machine, laryngoscope was verified. The defibrillator procedure was discussed with ICU personnel with medical responsibility. Sufficient knowledge was demonstrated.

A mock drill was performed on 29 May 2018, taking 17 minutes to carry out the medical emergency procedure. An ambulance was available in good working order.

The CV and training documentation for the medical personnel handling the emergency in ICU were provided and reviewed.

Bioanalytical laboratory

The Bioanalytical laboratory was located on the third floor of the Synchron House and consisted of rooms dedicated to bioanalytical activities, such as an instrument LS-MS/MS section, a weighing room with four analytical and micro balances. The deep freezer room for the storage of samples was situated on the 2nd floor. The alarm sensor connected to one of the freezers was tested to verify the proper functionality. The laboratory was well-organized. Safety measures such as an emergency shower, Safety data sheet (indexed binder) and first aid kits were available.

Log books were available in the laboratory for all items of equipment used within the facility along with temperature and humidity recording log books. All log book entries were legible, dated and signed.

The refrigerators and freezers within the facility were temperature mapped (by an external company) with the map displayed on each piece of equipment. All service records were available and up to date. The SOP for Calibration and maintenance of instruments was reviewed.

The dispatch records were reviewed. The procedure for the destruction of biological samples was reviewed, i.e. for receipt, verification, storage, shipment, retention and disposal of biological samples.

The following additional SOPs were reviewed:

- SOP for Operation, Calibration, Mapping, Cleaning and Maintenance of Cold Storage
- SOP for Operation, Calibration, Mapping, Cleaning and Maintenance of Deep Freezer
- SOP for Pipette Calibration
- SOP for Operation and Maintenance of Continuous temperature monitoring system
- SOP for Operation and monitoring of Temperature Data logger and Excursion Alarm System for the Deep freezer/Refrigerator

Dispensing and logistics pharmacy department was located at Chamber site Bodakdev on the 2nd floor, accessed by authorized personnel's key card only.

The pharmacy was well-organized. It was divided into storage, dispensing and receipt areas. All entries, exits, shipments and drug dispensing activities were recorded properly.

The Courier receipt of the last completed shipment was reviewed. The data logger ID number was recorded and "IP receipt acknowledgement form" was completed to verify CoA, import licence (if applicable), shipment details and other required documentation were verified. A sequential number was given to the IP containers and one container was randomly selected for an accountability check. Any discrepancy would be reported to the project manager and consequently to the sponsor.

The logbook for drug register; receipt, retrieval and retain was reviewed for the IMPs in the scope of the inspection.

The accountability of retained test drug for the study RII/2016/1357 was confirmed.

The overview of the personnel with access to the drug store at Ambli site was provided. The Director of Pharmacy, 2 pharmacists, an attendant and security had access to the pharmacy.

Temperature and humidity of the stability chamber were monitored by digital thermometer, connected to a software. The monitoring was run by computerized system. Temperature mapping of the chamber and refrigerators was done by external vendor. A Walk-in chamber was used for retained IPs.

The alarm was connected to the security who would inform the pharmacists in case of temperature excursion.

Observations made in relation to the premises were addressed in the CAPA plan provided by the CRO.

6. Personnel

During the inspection CVs and Job Descriptions (JD) of personnel were randomly reviewed.

A clearance certificate for a contract worker; designated as scientist at the BA department, was issued upon his resignation on 10 Apr 2018. IT was responsible for revoking access control card and laptop PC and peripherals. The Clearance certificate was issued according to the policy for resignation. The employee should collect the clearance certificate from HR, IT, respective department, accounts, QA and submit it to the HR. The IT would receive the clearance certificate form from the HR to deactivate the access card and record the details.

The SOP for training of the staff was reviewed.

Clinical section

7. Clinical phase

Inspectors visited the clinical facilities. The working area was well maintained.

Study No.: RII/2016/1357
Study period: 5 Oct 2017 – 20 Nov 2017
Period I: 14 Oct 2017
Period II: 26 Oct 2017

34 subjects were enrolled into the study, all male. According to the study report, attempts for recruitment of female subjects were made, but the subjects had not shown interest. One subject was withdrawn, due to abnormal value of serum C reactive protein after checking in of period I. 32 subjects completed the study activities.

The delegation lists for the studies RII/2016/1357 and SLS-CL-0148-17 for clinical and bioanalytical part, respectively were available.

The delegation list for study RII/2016/1357 was a combination of the delegation verification and protocol training.

Subjects' belongings were kept in lockers in the changing room where the amenities such as uniforms and wristbands in respective colour codes were handed over to the subjects for their use, before being directed to the CPUs.

Remarks in relation to the clinical phase of the studies and Good Document Practice were resolved in the CAPA plan provided by the CRO.

8. Clinical laboratory

The related activities were contracted. The Master Service agreement with the laboratory, dated 3 Jul 2014 was provided and reviewed. The laboratory was included in the audit plan for vendors.

Sample labelling, receipt, storage and handling were reviewed and verified. The vacutainers used for collection of the samples were prepared and shipped to the site by the laboratory.

Laboratory normal ranges were modified and adjusted according to the local population. The acceptable normal ranges were prepared as an appendix, added to the protocol which was submitted for Ethics Committee's approval. The laboratory results were verified to be within the acceptable range by reviewing the CRFs.

The results were kept with the CRF in paper form signed and verified by the investigator.

The list of volunteers screened for the study was compared with the list of samples shipped to the laboratory and verified, including the data logger ID.

9. Ethics

Ethic Committee submission and approvals for study RII/2016/1357 were verified. The name and qualification of the members of the IEC were noted in the approval letter for substantiation of the independency of the committee.

The CRO clinical facilities in Ambli and Satva were insured by the insurance company from period 5 Jul 2017 to 4 Jul 2018 to cover the period of the respective studies. The agreement was authorized and signed on 28 Jun 2017.

10. Monitoring

Monitoring visits records and monitoring observations during the conduct of the study RII/2016/1357, on 13, 14, 15, 25, 26 and 27 Oct 2017 were verified reviewing the respective visitor log.

Monitoring reports, their quality, as well as the provided CAPA and applicable follow up were all checked. Protocol deviations were captured properly.

11. Investigators

CVs, Job Description and training records, including GCP certificates of the PI and investigators involved in study RII/2016/1357 were reviewed and verified.

12. Receiving, storage and handling of investigational drug products

The shipment documentation for study RII/2016/1357, including the data-logger of the study drug from the pharmacy to the clinical site was reviewed and verified, for both periods I and II.

The Data logger was identified on the shipment documentation, together with the data logger's hard copies. The shipment started from 27 Sep 2017 until 5 Oct 2017. An excursion of the temperature was recorded as maximum 41.60 °C, starting 28 Sep at 12 pm until 2 Oct at 12:30 pm. Another excursion took place later. A letter was provided by the sponsor confirming that the IMP was still stable at 40 °C ± 2 as per 6 months accelerated stability data. Hence the product was still considered as fit for dosing. The stability report of analytes in study RII/2016/1357 was provided by the sponsor on 11 Apr 2018.

The shipment was sent on 27 Sep 2017 with the total of 504 tablets. A Data logger with specific ID was dispatched with the shipment.

The logbook for the storage and retrieval of the IMP, in the humidity chamber for dispensing purposes for both period I and II was verified.

Labelling of the IMPs was done according to the requirements.

A storage room was dedicated to storage and handling of the IMPs at the Ambli site, with restricted access by key card, authorized only for CRAs and investigators. The cleaning staff had access to the storage under CRA's supervision. Overview of the exit and entrance records for the period of the study no. RII/2016/1357 was reviewed. The room was equipped with a stability chamber with digital temperature and humidity monitoring. The IMPs were shipped to the site the day before of the dosing unless they were required to be stored between 2-8 °C. In that case, the IMPs were shipped to the site prior to the dosing.

The Ambli site was visited on 12 Jun 2018 to observe the administration of IMP dosing and blood sample collection. Volunteers were called to one of the three stations provided for dosing

and blood collection, and were assisted by two staff, in addition to the monitor and investigator present at the time of dosing and sample collection. Dosing schedule, labelling, completion of the CRF, badges provided to volunteers for identification purposes and process of dosing and sample collection took place effectively, according to the applicable procedures.

13. Case report forms

CRFs provided for the study RII/2016/1357 were reviewed for a number of subjects with respect to the clinical reference parameters and found within the specified limits of references as mentioned in the protocol.

The reconciliation records were also reviewed.

14. Volunteers, recruitment methods

Recruitment and registration:

Subjects were introduced to the CRO, either by word of mouth or they were contacted if they were already registered in the system, and eligible to participate in the study. Approximately 10 600 volunteers were registered in the database, of which 2 500 were female.

Volunteers who were referred to the CRO were registered in the visit log prior to registration in an internal database. Access to the database was password controlled to protect the volunteers' confidentiality. Subjects' personal data, height and weight were registered. BMI was calculated manually, recorded on a form for "Height, Weight and BMI Recording" and the SOP for Measurement of Height, Weight and Calculation of BMI at the time of screening was available at the site of measurement. Volunteer's identification was ensured by checking their ID, photo and fingerprints. A unique ID number was generated by the system for each volunteer registered in database. A routine check of scales and height measurement instrument was done daily.

The OVIS database was also checked by name/initials and fingerprint for cross participation purposes. Study participants who were registered in the dosing would be blocked in the system. The OVIS database was also checked prior to the volunteers' check-in to the CPU, on the day of study.

Screening procedures

All the subjects willing to participate in the study no RII/2016/1357 were screened prior to their enrolment, to assess their eligibility by satisfying all the inclusion and exclusion criteria. During screening, the medical history of the subjects was elicited, and they underwent a general clinical examination, physical examination, measurement of blood pressure, pulse rate, temperature and respiratory rate, 12-lead ECG, clinical laboratory evaluations, chest X-ray, immunological tests for HIV (Human Immunodeficiency Virus), HBsAg (Hepatitis B Surface Antigen), HCV Ab (Hepatitis C Virus) and P24 antigen test. This procedure was conducted within 21 days prior to

the dose administration in Period-I. The activities were supervised by the inspection team, following one of the volunteers through the process.

X-ray was performed at Ambli site by Pal Imaging centre. The instrument located at the site belonged to the Pal Imaging centre and the centre's radiograph was present to perform the X-ray at the time of need.

The SOP for obtaining of the Informed Consent was reviewed, and the process was followed to assess their compliance with the applicable requirements. The process was performed satisfactorily, and all volunteers were given the opportunity to meet one by one with the investigator to raise their concerns, if any.

The project specific ICF and the additional ICF approved by the IEC was verified against the visitors' log to confirm the availability of the volunteers for the screening process.

The ECG machine didn't have an option to save or edit. However, there was a F6 key that was password protected accessible by IT. A screenshot was provided to demonstrate the steps after logging in as an administrator. System setup would appear with 12 different options. However, the machine did not have a memory to save the records of ECG results.

A Breath alcohol analyser device was used prior to the check-in process. The device was demonstrated to verify that the device had an indicator to show whether or not the quantity of the lung air was sufficient. The usage of the device was logged in the respective logbook.

The process for blood and urine collection was described adequately. The Laboratory requisition form and vacutainers were prepopulated by study number, screening number and date. Containers were labelled by subject ID number, initials, study number, date, phase of the study (screening) and bar code.

The refrigerator in the sample collection room was reading -1.2 °C at the time of inspection, although no samples were stored in the refrigerator, the phlebotomist was collecting samples. The acceptable temperature range for this equipment was between 2-8 °C. The logbook for the period of 28 March to mid-April recorded temperatures of below 2 °C and above 8 °C. There was no process available for equipment that was out of specification.

The volunteers received the honorarium for the participation right after the completion of each phase of the study; PI, PII and post study, in cash. The payment documentation was verified. The list verified that two volunteers were not participating in the study.

15. Food and fluids

Preparation of food for volunteers was outsourced.

16. Safety, adverse events, adverse event reporting

A complete review of reporting of the adverse reports pertaining to the study in the scope of inspection was performed.

Bioanalytical section

The inspection included auditing of source documentation and raw data for validation of bioanalytical methods and analysis of subject plasma samples as well as auditing 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 was also audited.

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

Study SLS-CL-0148-17	
Start date of validation	1 Sep 2017
End date of validation	9 Sep 2017
Date of sample collection:	
Period I: sub 1 – 40:	5 Oct 2017
Period II: sub 1- 40:	12 Oct 2017
Method development	
Preparation of analyte stock solution and ISTD stock solution, as well as dilution preparation was documented adequately.	<u>Method of detection:</u> LC-MS/MS <u>Data generation:</u> Computer-based software LC-Quan; 3.0 Thermo Manufacturers <u>Matrix:</u> Human Plasma <u>Anticoagulant:</u> K3EDTA
Method validation: Data was adequately recorded and readily retrieved.	
The COA was reviewed:	Specificity: Specificity was evaluated by using 8 batches with specific Plasma ID

The CC range was established from 4.999 ng/ml – 4980.995 ng/ml for the analyte. Reagents & Materials used were verified.	K₃EDTA Human plasma including Haemolytic plasma & Lipemic data demonstrating no influence of either, was reviewed. The origin of plasma used in the experiments was verified. Dilution integrity The records for the dilutions 1/5th and 1/10th was reviewed. Carry over was well within limits, < 20 % LLOQ and < 5 % for ISTD Interference factor was well within the limits < 20 % LLOQ and < 5 % for ISTD				
Precision and Accuracy	The raw data was reviewed and verified.				
Auto sampler stability was performed at 5 °C up to 99:38 hours	Freeze/Thaw The stability was verified using five F/T cycles.				
	The data used for long term stability stock solution of the analyte and the respective IS to demonstrate 224 days' stability was verified.				
	Long term stability of analyte in matrix was determined as 67 days.				
Analysis of samples Report authorized on 30 Nov 2017					
The protocol specified the number of subjects as 40 with 23 sampling time points at each period and 2 periods. 36 subjects completed the study.	<table> <tr> <td>Date of first run</td><td>23 Oct 2017</td></tr> <tr> <td>Date of last run</td><td>3 Nov 2017</td></tr> </table>	Date of first run	23 Oct 2017	Date of last run	3 Nov 2017
Date of first run	23 Oct 2017				
Date of last run	3 Nov 2017				

Number of samples received was 1748 and number of samples analysed was 1656, since 4 subjects had not completed the study.	
Analytical run	Randomly selected analytical runs were reviewed to verify their system suitability, acquisition time, IS area, appropriateness of use of QCs and CCs, interspersing of QCs, Chromatograms and pertaining factors across the batches. The invalid runs were studied to confirm the reason for invalidity, together with the respective reporting. A memo-to-files for all runs which had errors or were modified, was provided dated 6 Nov 2017. All issues were resolved properly.
Repeat analysis: The relevant SOP for repeat analysis was studied.	15 samples were re-analysed. Repeat analyses were carried out according to their procedure either due to AULs (above upper limit samples) or ISV (internal standard variation).
Re-integrated chromatograms	Not applicable
ISR	Number of sample used: 168 97.6 % of sample results met the acceptance criteria. ISR samples were randomly verified.
Back calculations	The range of accuracy and precision of the back-calculated concentrations of the standard curve points for the analyte was from 99.4 % to 100.5 % and 0.9 % to 2.0 % respectively.

Acceptable ranges fulfilled:	ISTD variation was reviewed for all batches. The mean of the results was calculated, and the acceptable range was considered as any result within $\pm 50\%$ of the mean. Any sample outside of this range would be repeated, and if more than 30 % of the samples had IS variation outside the range, the whole batch would be repeated. Calculation was done manually.
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The observations made regarding section was addressed adequately.

18. Sample collection, storage and handling of biological material

Study no RII/2016/1357

The pre-dose and post-dose blood samples were collected in pre-chilled and pre-labelled vacutainers containing K₂EDTA (anticoagulant). Vacutainers were placed upright in a rack kept in ice-cold water bath below 4 °C before blood collection and until centrifugation.

Temperature was measured using calibrated temperature recording device.

06 mL blood per sample was withdrawn; Out of this, 03 mL blood was transferred in to pre-labelled & pre-chilled vacutainers containing K₂EDTA as anticoagulant and 300 µL of 1M Ascorbic acid solution (buffer solution) for analyte and its metabolite and 03 mL blood was transferred in to pre-labelled & pre-chilled vacutainers containing K₂EDTA as anticoagulant for the other analyte.

Immediately after each tube of blood was drawn, it was inverted gently several times to ensure the mixing of tube contents. Vacutainers were placed upright in a rack kept in ice cold water bath below 4 °C before blood collection and until centrifugation. The blood was centrifuged at 4000 rpm for 2 minutes below 4 °C.

The separated plasma was transferred to pre-labelled polypropylene tubes in four aliquots as mentioned below:

- First and second aliquot was used for the analyte and its metabolite.
- Third and fourth aliquot was used for the other analyte.

The checklist for sample shipment was signed and verified on 27 Oct 2017, at the end of period II. Missing samples were recorded.

One subject was withdrawn due to an adverse event and another subject didn't show up. The Subject with AE was present for post study check. The records were checked for verification purposes.

The shipment documentation for the sample transfer from Synchron to Lambda was reviewed. The data logger started prior to the shipment of the blood samples from the site and stopped after it was received by Lambda. The data logger showed that the temperature had increased above the upper limit during the shipment, but it was documented that the temperature excursion was related to the period after the receipt of the shipment by Lambda.

The record for collection and the centrifugation of the samples for study RII/2016/1357 was reviewed.

The samples were shipped to the BA-department Deep freezer room for storage and handling of samples for analysis purposes. Samples were shipped to the BA-facility in ice-boxes with a data logger. A checklist was provided to verify the details of shipment and samples received. All documentation was submitted to the QC-department for quality control and archiving. Samples were later withdrawn from the freezer for one-by-one verification, recorded in the logbook for usage of freezer. Retrieval of samples for analysis purposes took place according the procedures adequately.

Working standards were also kept in a refrigerator in the Deep freezer room. An overview of the working standards with their respective expiry date was available next to the refrigerator. Disposal of the expired working standards was carried out once a month.

21 set of STD samples and 102 sets of QC samples were used for the analytical runs in study SLS-CL-0148-17. The record of the remaining QCs and CCs was reviewed.

The observations made in relation to re-analysis of retained samples were addressed in the CAPA provided by the CRO.

19. Data processing and documentation

Integration settings of the analytical runs were reviewed. Smoothing was kept the same throughout the runs.

A full audit trail was activated on the analytical instruments used for the study in the scope of inspection.

Raw data were generally documented in a manner that enabled the traceability with respect to sample and equipment identification and time and date of activity and the respective delegate.

Logbooks were consistently used to record the activities and usage of equipment throughout the organization.

There was a system in place for the validation of data entry with entries being checked by a second person. Changes made to patient information was not possible without administrator rights and approval of these changes.

20. Good Laboratory Practices

The laboratory situated at Synchron House was well maintained. There was a separate analytical balance room, wash room, and laboratory area. There was a large and separate area for the LCMS/MS and other analytical instruments. Computers for these instruments were in another area. Laboratory areas were access controlled. All staff in the facility were observed wearing appropriate personal protective equipment.

The organization had a mature maintenance program, with most of maintenance activities being performed through external providers. All equipment was labelled with a unique identifier, calibration date and next due date. The following maintenance and calibration records/certificates were reviewed:

- LCMS/MS – One equipment
- Deep freezer – One equipment
- Walk-in freezer
- Freezer mapping report – One equipment
- Analytical Balance – One equipment
- Weights used for calibration of analytical balance
- Calibration of pipettes – last 4 months of calibration records for all pipettes within the facility were reviewed.
- Breath alcohol analyser
- Patient defibrillator
- ECG machine

There was an SOP for Calibration and Maintenance of Instruments available. During the inspection, the calibration check of pipette was witnessed.

Log books were available for all equipment within the laboratory. All chemicals and solutions were adequately labelled.

A procedure was in place for the monthly testing of alarms for all temperature-controlled devices.

Pharmacokinetic, statistical calculations and reporting section**21. Pharmacokinetic, statistical calculations**

The department for statistical calculation and pharmacokinetic was staffed by 4 statisticians, 5 medical writers, 5 data management officers.

The number of subjects for studies run at the site was determined by the statistician.

Randomization

SAS 9.1.3 was used to generate the randomization list using the seed number. The Randomization list was printed, and the hard copy was verified by the QC-team.

There were designated people from the CRO responsible to transfer the list to the pharmacist.

As soon as the protocol was approved, a notification was sent to the designated personnel by email. The email for study SLS-CL-0148-17 dated 15 Dec 2016 and all respective notifications were available. The randomization process started as soon as the team received the schedule from the management team. The SOP for generation of the seed number was available.

The Archival request form for archiving of 14 + 2 files pertaining to the project no. RII/2016/1357 dated on 28 Feb 2018 signed by designated personnel was provided.

The CV, JD and training documentation of the responsible person for biometrics and data management were available.

The statistician received the original CRFs from the clinical site. The data was entered, and double entry was performed using SAS phedIt. The data entry database was run by modules. Bioanalytical data was received from the BA-site.

It was verified that 5 people had access to the system.

Software Kinetica which was a standalone system, used for processing of PK parameters. Additionally, a program in SAS was customized for calculation purposes. Only one licence was provided accessed by 2 PK-designated personnel.

The customized SAS program was used for calculation of PK parameters as well as the calculation of 90 % confidential intervals.

PK calculations were performed by two statisticians in parallel, using Kinetica and SAS. This was to ensure the same results using two different tools for quality control reasons.

Every data generated by the statistician site, was submitted to the QC/QA to be verified.

The results go to the medical writing after completion of the PK-calculation.

22. Study report

After completion of the PK-calculation, the results were submitted to the medical writing team.

Study reports were arranged by using a template.

Study reports were provided for inspection team's review.

Miscellaneous	
<i>Samples taken</i>	20 samples were randomly selected from the study no. SLS-CL-0148-17 to be re-analysed. The re-analysis process identified as CC-22 was carried out under supervision of the inspector from CDSCO on 13 Jun 2018. The batch acceptance criterion which was considered as at least 67 % of re-assayed samples having concentration value within 20 % of original value, was not met. The re-analysis was repeated on 14 Jun 2018 with ID no CC-23, with samples from only subjects 30 and 31 as mentioned above. This run also failed. Calibration standards used in the run were identified as STD BS-23 and the sets of QCs used were identified as 103-104 for the first run on 13 Jun 2018 and 105 -107 for the second run on 14 Jun 2018 which were stored together with the subject samples. Freshly made QCs were not prepared in the re-analysis of the subject samples. The calibration curve in both runs met the acceptance criteria. Due to time constraint, the runs could not be repeated and consequently no conclusion could be drawn. It was not clear whether the failure was due to QC failure or degradation of the analyte in the samples.
<i>Assessment of the CRO master file</i>	The CRO master (CROMF) file was reviewed. The company's master file provided introductory information of the organization and did not 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 abovementioned 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.
<i>Annexes attached</i>	Not applicable

Part 3	Conclusion
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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
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1. Guidance for organizations performing in vivo bioequivalence studies. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties 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. Fifties 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>
Short name: WHO GLP
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
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>