

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

Part 1	General information
Organization details	
Company information	
Name and Address of Clinical Research Site	Cliantha Research Limited Head Office, Opposite Pushparaj Towers Near Judges Bungalows, Bodakdev, Ahmedabad 380 054, Gujarat, India Tel# +91-79-2685 3088, Fax# +91-79-2685 3093 Cliantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India, Tel# +91-79-66135628/674 , Fax# +91-79-66135602
Name and Address of Bioanalytical Research Site	Cliantha Research Limited Head Office, Opposite Pushparaj Towers Near Judges Bungalows, Bodakdev, Ahmedabad 380 054, Gujarat, India
Name and address Statistical Site (delete if not applicable or if the same as the above)	Cliantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India, Tel# +91-79-66135628/674 , Fax# +91-79-66135602
Corporate address of Organization	Cliantha Research Limited Head Office, Opposite Pushparaj Towers Near Judges Bungalows, Bodakdev, Ahmedabad 380 054, Gujarat, India Tel# +91-79-2685 3088 Fax# +91-79-2685 3093
WHO product numbers covered by the inspection/ Product names/	TB305 (Cycloserine capsule 250mg) HP001 (Sofosbuvir 400mg tablets)

WHO Public Inspection Report:

Cliantha Research Limited, Ahmedabad, India- BE site

25-29 June 2018

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Study numbers/ Study titles	
Inspection details	
Dates of inspection	25-29 June 2018
Type of inspection	Routine inspection
Introduction	
Brief summary of the activities	Cliantha Research, is a global Contract Research Organization (CRO) providing integrated clinical offerings in Early Phase (Phase I/IIa), Late Phase (Phase II-IV), Bioequivalence (BA/BE), Clinical Endpoint Trials, Bioanalytical, Biosimilars, Dermatology, Biometrics, and Personal Healthcare services. Head office, Ahmedabad, <u>Clinical Facility:</u> ○ 2 Clinics with total 96 beds: 2 independent ICUs ○ Check-In & Compliance area ○ 2 freezers temp set at -20°C ○ 3 freezers temp set at -70°C ○ Walk-in freezer temp set at -20°C ○ Controlled access pharmacy ○ Ambulatory Visit Area <u>Bioanalytical Lab:</u> ○ 24 LC/MS/MS (6 API 5500, 18 API 4000) ○ 1 ICP-OES ○ 1 Walk in freezer temp set at -20°C ○ 2 Upright freezer set at -20°C ○ 8 Ultra Low freezers temp set at -70°C <u>Quality Assurance:</u> ○ Independent QA/QC for Clinic, Bioanalytical Lab & Stats Sigma, Ahmedabad <u>Clinical Facility:</u> ○ 3 Clinics with total 100 beds: 3 independent ICUs ○ Check-In & Compliance area ○ 1 Walk-in freezer temp set at -20°C ○ 3 freezers temp set at -20°C ○ 3 freezers temp set at -70°C ○ Volunteer screening area ○ Controlled access pharmacy ○ Ambulatory Visit Area <u>Bioanalytical Lab:</u>

	○ 4 LC/MS/MS API 4000 ○ 3 Walk in freezer temp set at -20°C ○ 1 Upright freezer set at -20°C ○ 17 Ultra Low freezers temp set at -70°C <u>Quality Assurance:</u> ○ Independent QA/QC for Clinic, Bioanalytical Lab & Clinical lab									
General information about the company and site	Cliantha was established in 2004 and based at Ahmedabad (HQ) with clinical, bioanalytical and statistical services. In 2009, a 100 bed clinical facility was established in Ahmedabad (Sigma) including a Clinical Lab. In 2016, Cliantha added a bioanalytical facility to the Ahmedabad (Sigma) site. <table><tr><th>Sites</th><th>Clinic</th><th>Bioanalytical</th></tr><tr><td>Ahmedabad, HQ</td><td>96 beds</td><td>24 LC/MS/MS + 01 ICP-OES</td></tr><tr><td>Ahmedabad, Sigma</td><td>100 beds</td><td>4 LC/MS/MS</td></tr></table>	Sites	Clinic	Bioanalytical	Ahmedabad, HQ	96 beds	24 LC/MS/MS + 01 ICP-OES	Ahmedabad, Sigma	100 beds	4 LC/MS/MS
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Ahmedabad, HQ	96 beds	24 LC/MS/MS + 01 ICP-OES								
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History	Cliantha Research Limited (former BA Research India Limited) has been regularly inspected by WHO-PQ. The last WHO-PQ inspection was performed on 19-22 March 2013 which covered both clinical and bioanalytical facilities. The site has also been regularly inspected by USFDA, the latest of which was in March 2018. In addition, the site is also inspected by UKMHRA (April 2017), EMA (November 2015) and other agencies.									
Brief report of inspection activities undertaken										
Scope and limitations										
Trial protocol code (TB305)	Study Number: BA15577119-01 Single Dose Oral Bioequivalence Study of Cycloserine Capsules 250 mg and ‘CycloSERINE’ (Cycloserine) Capsules USP 250 mg In Healthy Adult Male Subjects Under Fasting Conditions.									
Trial protocol title (HP001)	Study Number: BA15101179-01 Single dose oral bioequivalence study of Sofosbuvir film coated Tablets 400 mg and ‘SOVALDI™’ (Sofosbuvir) film coated Tablets 400 mg in Healthy Adult Human									

	Subjects under Fed Conditions.
Out of scope	Bioanalytical part of HP001 was not inspected as it was performed by the sponsor at their own laboratory.

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CRA	clinical research associate
	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
	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
	IEC	(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
	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	the upper limit of quantification
	URS	user requirements specifications

Part 2	A brief summary of the findings and comments
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1. Organization and management

As part of the opening meeting, the President of Cliantha gave a presentation on an overview of the organization. The organization charts for the clinical and bioanalytical facilities (HQ and Sigma) was available which depicted key positions and the names of the responsible persons. Their job descriptions and their responsibilities were maintained. Also, a list of signatures and initials of the authorized personnel was maintained. Training plan and records were available for the staff taking part in the conduct of the studies.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

2. Computer systems

A list of systems used to perform clinical and bioanalytical work was obtained. The computer systems were qualified and validated before their use in clinical and bioanalytical areas. Computer systems used for the bioanalytical work were networked. The computer system used for the statistical and pharmacokinetic applications was access control. A list of personnel who have access to the database was maintained.

Source documents (electronic) were verified by the inspectors using Analyst Audit Trail Manager. *Analyst* software allows for three audit trails namely, Project audit trail, instrument audit trail, and quantitative audit trail.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

3. Quality management

SOPs were in place which covered the necessary quality assurance aspects of the trial. The SOPs appeared to be understood by all employees interviewed and were followed.

The contract between sponsor and Cliantha was in place. The responsibilities have been agreed between the two parties for protocol, IEC and other responsibilities. A master service agreement between sponsor and Cliantha was also in place valid for 5 years. Project contract dated 4th May 2015 was in place which defined study specific responsibilities. The clinical study was conducted in Cliantha whereas the bioanalytical part was done at sponsor site.

Informed consent document in English was reviewed. Gujarati version was also available. The ICF document was written in layman's language. The subjects ICFs were reviewed and verified against the subject arrival record. It was noted that all subjects had signed the ICFs.

The CV of the Principal Investigator was in place which was submitted to the IEC in September 2015.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

4. Archive facilities

The CRO has the archive facilities at Noida, Vadodara, Sigma and Matoda. The inspectors visited the archive facility at Matoda which consisted of about 7 storage rooms including an IT archive room. All the rooms were labeled. The rooms were temperature and humidity monitored using Eurotherm thermohygrometers which were calibrated. A compactor and pallet racking system was provided for the storage of archive materials. The hard copies were packed in boxes and labeled according to the study name. The racks were themselves appropriately labeled to ensure easy identification. The alarm system was provided for an emergency. There were automated gas based sprinklers provided to automatically suppress and fight the outbreak of fire. Fire extinguishers were also provided. A pest control system was in place for rodents, but the number of baits provided was insufficient.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

5. Premises

The facilities were generally clean with adequate lighting and ventilation. The bioequivalence studies were carried out under conditions adequate to ensure the safety of the subjects.

The clinical and laboratory premises used to perform clinical and bioanalysis were generally spacious and adequate for their use. The inspectors visited the clinic facility on day 3. The Clinic consisted of the following areas:

1. Orientation
2. Consent enrolment

3. Screening Consent
4. Study Consent
5. Sample collection
6. Phlebotomy Rooms
7. X-Ray
8. Bedding Area
9. Dining Area and Recreational Area
10. Intensive Care Unit (ICU)
11. Clinical Laboratory
12. Extraction Lab 1 and 2
13. LC-MS/MS Lab

Recruitment

The facility has three stages for recruitment of a subject. The subject who is the first timer goes through the enrolment consent. Here preliminary checks are done on the eligibility of the participant. The subject is then taken through an audio-video clip explaining the dangers of cross participation. Participant also goes through the enrolment consent form in either Gujarati, Hindi or English. If the participant is found eligible, then screening consent is conducted, the subject is then entered into the Clientrix Volunteers Data Management system (CVDMS for Cliantha and its affiliates) for his details including biometric (2 thumbs and 2 index fingers). He is also checked for cross participation on OVIS (Online Volunteers Information System) within the state of Gujarat. The participant before checking in as a subject of a study undergoes the third stage of consent known as study-specific consent where the molecule under study is well explained to him or her and further clinical checks are conducted.

ECG

At the ECG room, a bed was provided for subjects, SOP was available for the recordings of the ECG and a logbook for the screening details. The Job description of the in-charge of ECG was verified as was also engaged in the counseling of female subjects. It was confirmed that counseling was part of the duties.

Sample collection

After a participant is declared to be clinically fit to join the study, sample tubes are barcoded and referenced to a subject.

X-ray Area

The area was provided with a digital X-Ray machine which is connected to a server. Study number is not available on X ray films as it is part of general screening. X ray identification is through volunteer registration number for the study.

Entry into Clinic

Two audio recording areas were provided for subjects to make their final Informed consent declaration in either Gujarati, Hindi or English. Alcohol test, urine specimen, and others are taking for the final examination of the subject. Toilets are provided with colored water to ensure that subjects do not temper with samples by diluting with clear water. Screen Test devices which could indicate positive, negative and invalid test were provided. After the examination, consent declaration and sample collection, the study subjects are provided with their numbers before entry into the clinic. A body and baggage area are available and equipped with lockers. Here the subjects are provided with their clinic dress, towel, and other necessities. The clinic can only be entered and exited by staff. No subjects have a pass to leave the clinic on his or her own. A dining and recreational area were provided. The Phlebotomy room was equipped with various shades of lightening to suit the needs or preference of subjects.

ICU

The ICU comprised of the following equipment:

- Two defibrillators
- Pulse Oximeter
- Refrigerator
- Suction Machine.

Lockers were provided for storage of medicines. The temperature for the storage of some medicinal ampoules was not stated appropriately or was not well interpreted by personnel of the CRO. Store in “cool area” was indicated in some products. There was a need for the CRO to ensure that medications are properly labeled and stored at their appropriate conditions. Log books for drug inventory, equipment, sphygmomanometer, blood glucose monitor, maintenance were available. Emergency contacts were provided.

6. Personnel

There was a sufficient number of medical, paramedical and technical staff with the appropriate qualifications, training, and experience. From the opening meeting presentation, it was noted that a total of 397 personnel were responsible for the day to day operations reporting to the President. In addition, a total of 241 personnel responsible for quality assurance, training, and other support functions reported to the Chief Executive Officer of Cliantha. This personnel were responsible for all Cliantha facilities located at the four different sites in India.

Training of personnel was reviewed. It was noted that the procedure was applicable to all employees and contractual staff of Cliantha. The procedure requires retraining on relevant SOPs if some personnel is on leave or absent for more than six months. Also, retraining on SOPs, regulatory guidelines and practical procedures will be conducted on a need basis, to ensure compliance.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

Clinical section

7. Clinical phase

The CRO has sufficient rooms meeting the required WHO Guidance for organizations performing in-vivo bioequivalence studies.

The protocol was found compliant to applicable WHO-GCP regulations; no discrepancies between the protocol and the informed consent were noted. Both studies were found to have been conducted in accordance with the protocol. The informed consent was reviewed and did not cause concern. The trial subjects were apparently sufficiently and appropriately informed about the trial, the drug, their compensation and the duties they were supposed to have. The document was couched in simple and plain language for the understanding of the subject. All the subjects that entered into the clinic for the study were required to sign the form.

The Investigator conducted training on the study protocols. The trainees consisted of personnel of the CRO, those contracted by the CRO and the three sub-Investigators. All the participants signed to indicate that they were trained.

8. Clinical laboratory

The clinical laboratory was accredited by the College of American Pathologists (CAP) in January 2018 and NABL in October 2017. The laboratory comprised of the following areas/sections:

- Special Chemistry Area
- Cell Culture Lab
- Instruments
- Refrigerator
- Biochemistry analyzer
- Hematology Machine
- 2 Architect plus Equipment, one under validation. Available for clinical chemistry.
- Multifuge

Disposal waste containers were provided for three kinds of waste. Red disposal waste container for gloves, syringes, and cannulas, a blue disposable waste container for glass and yellow containers for infectious disposal waste such as cotton, bandage, vaccines, and gauge. Sample retention policy for handling serum, EDTA, Blood smear and citrated Plasma was provided. Desired temperature and period of holding these samples were provided. Digital temperature device was available for monitoring temperature of the laboratory. SOP to review audit trails on

the various equipment was not available. User rights for accessing equipment were in place. No deputation was in place for some administrators. The user accessible rights documents refer to “modify” and “delete” which is not supported. The SOP for password policy and equipment log books was available.

An in-house Guideline for evaluation and reporting of clinical laboratory parameters effective date was available and reviewed.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

9. Ethics

The ethics Committee IBIOME was employed for the study. SOP for the independent Ethics Committee effective was reviewed. Correspondences between the ethics committee and CRO for the approval of protocol were available. The Ethics Committee uses ICH, GCP guidelines and Schedule Y for their operations.

A meeting of the ethics committee was reviewed. The document was prepared by the secretary of the committee and signed by the chairperson. The meeting duration of 31 minutes for the study protocol and its associated documents, was found inadequate to allow sufficient discussion.

The CV of Principal Investigator was reviewed. It was updated yearly. His qualification and training records both internally and externally were provided. The document was found to be satisfactory.

10. Monitoring

Monitoring reports for Sofosbuvir study were reviewed. A total of 6 visits were made by the sponsor. For Cycloserine study, monitoring visit reports was available for Period-I (dosing),

Period-II (check-in and dosing) and study close-out visits. These visits were verified against the visitor sign-in log and were found acceptable. In general, the monitoring reports were detailed and monitored most of the areas during their visit.

11. Investigators

The principal investigator was generally present during the study, in addition, a comprehensive delegation log was in place. The delegation log was reviewed and was found satisfactory. The delegation took place prior to the study.

12. Receiving, storage and handling of investigational drug products

The certificate of analysis for innovator product (IPs) and test product from sponsor was reviewed. The shipping records were available. The IPs were dispensed and verified against the randomization schedule.

Label and Shipment Records

The COA of both the test product and the reference product were available. Chart for monitoring the storage temperature was provided and reviewed.

Randomization schedule

The randomization was done by SAS Version: 9. 4 which was followed in the dosing of the subjects.

Pharmacy

The pharmacy was under lock and key. Apart from the card key used to have access, there were two locks with keys under the custody of the pharmacist-in-charge and another key with the QA person. It was under negative pressure to the corridor and air curtains were provided at the entrance. A changing area was provided and shoes covers and hardcover are required before entry. Cupboards were provided for the storage of the various study products. These were labeled. Hand gloves, trays and other kits used for the dispensing of drugs were available and properly stored. A stainless-steel change over bench was in place. The temperature and humidity were monitored. A dispensing booth with laminar air flow was provided.

Log Books were provided for the following activities; Access to pharmacy and IPs in – out records

Reconciliations records of IPs used for one of the studies was reviewed and were found to be accurate according to documented records and physical retained left-over stocks in place.

13. Case report forms

The case report forms for the subjects for both studies were reviewed and language was found to be simplified for the understanding of subjects. This document was available indicating the subject name, subject ID, signature or initials and date of consent.

Study delegation records were reviewed. The various professionals involved in the study had their functions indicated as assigned by the PI. These were duly signed by the personnel.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

14. Volunteers, recruitment methods

The procedure on enrolment of volunteers into Clientrix Volunteer Data Management System (CVDMS) was available this being the first procedure in place for the enrolment of volunteers.

Screening of enrolled volunteers was reviewed. Another procedure outlines the screening procedure to confirm the health status of enrolled volunteers for clinical studies conducted at Cliantha. It was claimed that this procedure was used to enroll volunteers in their database.

Informed consent procedure was in place which outlines the procedure for presentation, discussion and documentation of project specific ICD to the volunteers during the clinical studies conducted by Cliantha.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

15. Food and fluids

Food and fluid were provided according to the protocol requirements.

Administration of investigational products to subjects was used when dosing was performed for Sofosbuvir tablet 400mg. Separation records for centrifuge and deep freezer were verified and samples were collected in K3 EDTA vacutainer. The samples (3476, aliquot 1) were shipped to sponsor.

16. Safety, adverse events, adverse event reporting

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

Bioanalytical section**17. Method development**

For Cycloserine study, the method was developed (optimized) and validated in-house at Cliantha Research Limited. Laboratory notebook was used for the development of Cycloserine analytical method. The literature referred for the development of the method was part of the binders reviewed.

Sofosbuvir method was developed, validated and used by the sponsor at their laboratory. Hence, this was not covered during this inspection.

18. Method validation

A method for determining Cycloserine in human plasma has been validated using an API 4000 LC/MS/MS system and solid phase extraction method with detection in the range of 0.2000 to 30.00 µg/mL. The data was acquired by and calculated on Applied Biosystems “Analyst” version 1.6.2 software. Linear regression, with 1/x² weighting, was used to obtain the best fit of the data for the calibration curves. The lower limit of quantitation (LLOQ) was 0.2000 µg/mL and the upper limit of quantitation (ULOQ) was 30.00 µg/mL. Quality control samples (six sets) at concentrations of low 0.6000 µg/mL (LQC), medium 3.700 µg/mL (MQC-2), medium 10.00 µg/mL (MQC-1) and high 22.50 µg/mL (HQC) prepared in human plasma were analyzed with each assay validation batch to ensure acceptable assay precision and accuracy. Six (6) sets of LLOQ (0.2000 µg/mL) and ULOQ (30.00 µg/mL) samples were also included in each validation batch. The stability of Cycloserine in human plasma during freeze-thaw cycles, bench top stability at room temperature, processed stability of extracted samples at room temperature and at refrigerator temperature, stock solution stability at room temperature and at refrigerator temperature, working solution stability at room temperature and at refrigerator temperature, blood stability were studied. Also performed selectivity, interference check, cross specificity, carry over, recovery, reinjection reproducibility, ruggedness validation batch, matrix effect, matrix factor, extended validation batch, and dilution integrity.

19. Sample collection, storage, and handling of biological material

The ultra-deep freezers and freezers used for storage of plasma samples were inspected and found overall acceptable. The storage room was access controlled and entry and exit were recorded.

The SOP for storage and shipment of biological samples was reviewed. It was reviewed by the head of the department, QA person and approved by the management.

20. Analysis of the study samples

The number of smooths used to process subject sample chromatograms were 5 as compared to 4 used for the validation samples. In general, this section was found satisfactory.

21. Data processing and documentation

The SOP entitled Analyst Software Data Management was provided to manage the system. Five levels of access were provided to the user's base on the following acquisition method, analyst application Audit trail manager, batch and compound data base. The individuals with various access were System Analyst Administrator, project manager, Operator, Vendor engineer and the reviewer in decreasing rate of accessibility.

The deficiency noted under this section have been satisfactorily addressed, and the same shall be verified during next inspection.

22. Good laboratory practices

The inspectors visited the bioanalytical laboratory located on the 4th floor of Head Office. The laboratory is access controlled through the biometric system. Total of 6 sample custodian is responsible for the storage and issuance of subject samples. Custodian works in three shifts. Subject samples were issued to the analyst following a written request received the analyst. The laboratory was equipped with deep freezers (-70°C, -20°C) and refrigerators for storage of standard, calibration curve, and QC. It was noted that alarms connected to the deep freezers were challenged once every year. There was a procedure in place to acknowledge alarms as and when pop up.

The inspectors also visited the sample extraction area and LCMS/MS laboratory. Total of 24 LCMS/MS was in use (18 API4000 and 6 API5500). The calibration of these LCMS/MS was done once every 6 months (HPLC by Shimadzu and Mass by Cliantha's in-house instrument engineers).

Cold Room

Entry into the cold room was by biometric fingerprint access. It was manned by 6 samples custodians. Analyst makes a request for samples through a sample request form. The request is honored by a sample indicating the type of sample; HQC, HQC-1, MQC-2, LQC, Additional QC, SPC, SES. Eurotherm is provided to monitor the temperature and humidity of the room. Logs books for the various activities in the cold room provided for records. Waste bin was in place. Alarms were provided to announce temperature excursions.

Extraction Room

The area was spacious and well illuminated for its purpose. Centrifuges were provided and calibrated. Calibrated Analytical balances were used. Ice baths were provided.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

The confidence intervals reported in the study report were recalculated from the raw data listings using Phoenix[®] WinNonlin[®] 6.4 and matches was found for both C_{max} and AUC.

24. Study report

Cases of adverse events (AEs) occurred among the subjects. These AEs were categorized as mild, moderate and severe.

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 studies

- BA15577119-01 (TB305)
- BA15101179-01 (HP001)

were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Cliantha Research Limited.

All the non-compliances observed during the inspection that were listed in the full 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 5

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. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9 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 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) <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 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan, 1998. <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/cfcr/CFRSearch.cfm?CFRPart=11&showFR=1>
11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf
12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as “GLP”.
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
13. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf
14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf
15. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf
16. WHO Good Clinical Laboratory Practices (GCLP)
<http://www.who.int/tdr/publications/documents/gclp-web.pdf>