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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Clinical Study (Palatability)

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Lifepoint Multi-Speciality Hospital - LPR** Research room 3rd Floor, 145/1, Mumbai- Bangalore highway, Near Sayaji hotel Bhumkar Chouk Wakad, Pune-411057 Maharashtra India
Corporate address of Organization - CRO	**SIRO Clinpharm Pvt Ltd** Kalpataru Prime 1st Floor, Unit Nos. 3 & 4, Plot no. D-3, Road no 16 Wagle Industrial Estate Thane (W) – 400604 India
GPS coordinates of inspected site	Latitude: 18.5974 Longitude: 73.7553
WHO product number covered by the inspection/ Product names/ Study numbers/ Study titles	**Study no: Ipca/ZNDT/PIII-14** A Prospective, Open-Label, Multicenter, Phase 3 study to Assess the Acceptability of and Adherence to a 10-Day Regimen of Zinc Sulfate Dispersible Tablets for Treatment of Acute Childhood Diarrhea
Sponsor	IPCA Laboratories Limited Clinical Research and Development 142-AB, Kandivli Industrial Estate Kandivli (West) Mumbai 400 067 India
Inspection details	
Dates of inspection	04-06 December 2019
Type of inspection	Good Clinical Practice (GCP) inspection

Introduction	
Summary of the activities	The unit has the capacity to run Phase II, III, IV studies, Investigator Initiated Studies & Bioequivalence studies in disease population.
General information about the company and site	Lifepoint Hospital was established in 2015, covering various therapeutic indications. The hospital has currently 116 beds in addition to 12 beds in Intensive Care Unit. More than 50 studies have been conducted since 2015; including 22 completed and 16 ongoing studies. The research team comprises a team of 25 staff, i.e. Clinical Research coordinator, Phlebotomist, Accountant, office assistant, Quality manager and Site manager.
History	In addition to audits from Sponsors, the site was inspected by DCGI (April 2018) and US FDA (May 2018). The Pre-inspection audit visit report, performed on 11-12 Nov 2019 was reviewed. An audit certificate was also reviewed performed by sponsor on Nov 2019. The site has not previously been inspected by WHO.
Brief report of inspection activities undertaken	The inspection included one clinical study with the intention to evaluate the acceptability and palatability of and adherence to a 10-Day Regimen of Zinc Sulphate Dispersible Tablets. The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, IMP accountability, dispensation and storage, equipment calibration, employee training, and a tour of the facility. A review of the clinical study data, was conducted, along with comparison of the source data 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
	MOU	Memorandum of Understanding
	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**

A presentation was provided explaining the activities of the Research Unit in detail. Another presentation was provided by CRO SIRO Clinpharm to introduce the organization and the management of the study Ipca/ZNDT/PIII-14.

SIRO Clinpharm Pvt. Ltd., was responsible to handle and manage the clinical sites relating to the abovementioned study on the behalf of sponsor / WHO-applicant; i.e. IPCA. The organization was founded in 1996 in Mumbai and expanded its activities by launching operations in other cities in India, Asia and North America.

The study was conducted at 13 sites, i.e. in Malaysia (8 sites) and India (5 sites), with a total of 310 subjects.

The Lifepoint site was managed through Site's SOPs. An Organizational chart was provided and signed by Dr. Sunil Chaudhary; Director Lifepoint Research. The relationships between management, technical operations, support services and the quality management system were illustrated on the chart.

Study Delegation lists of tasks during the study, together with other essential documentation were available in the Investigator Study File (ISF). The list of studies for 2018 – 2019 was provided and reviewed.

The general site's working hours was established from 9:30 to 18:30 every working day.

The observation related to Organization and management was adequately addressed in the site's respective CAPA plan.

2. Archive facilities

Study related documentation was transferred to an offsite archive facility following the study closure meeting. A Memorandum of Understanding (MOU), version 1 dated 20 Mar 2017 for archival of study documents, Service level agreement, between LPR (Lifepoint Research) and the archive facility was available and reviewed.

The clinical facility had a temporary documentation room. The room was managed by a designated person who was responsible to assign the cabinets and the respective keys to the CRC responsible for the respective study. Each study was assigned a cabinet which was labelled with the study number. The cabinets were fire-resistant designed to withstand the fire for maximum of 4 hours. The room was also equipped with sprinkles and fire extinguisher. A pest control was carried out throughout the whole facility.

Documentation was arranged to be transferred in a lockable container to the offsite archive facility by the CRC responsible for the study.

The archive processes were tested through the successful recall of requested documents and records during the conduct of the inspection and found effective. The study documentation was retained for 15 years as per applicable requirements.

The observation related to Archive facility was adequately addressed.

3. Premises

During the inspection, a tour of Research Unit, including examination room, offices, documentation and IMP room, was conducted.

Clinical site was the Research part of the Lifepoint Multi-speciality hospital. The facility was clean and well organized. The patients' personal information; i.e. name, address, and telephone number, was recorded in the hospital registration database at the registration desk, at the first visit. Any data modification in the database required a password. The registration personnel did not have access to the password. Nevertheless, the database was not supported by an audit trail option. Hence, the database data integrity could not be verified.

4. Personnel

The investigator site training log for personnel involved in the study IPCA/ZNDT/PIII-14, together with the delegation list were available. The training was provided by the SIRO Clinpharm CRA on 27 Nov 2017. Personnel who joined the study after this date were trained by the PI.

Job description of randomly selected employees were reviewed.

Dr Sunil Chaudhary as Clinical Operations Director was responsible to support the clinical development programs for the investigation lead drug candidate in company and for conduct of trials.

Clinical section

5. Clinical phase

The protocol was amended twice, and the latest amendment was in use.

Protocol	Version no	Issue date
Original	1	26 Mar 2015
Amendment I	2	1 Feb 2016
Amendment II	3	14 Apr 2016

The objectives of the study included:

- To assess acceptability in terms of adherence to a 10-day regimen of zinc sulphate dispersible tablets in children aged between 3 and 59 months with acute diarrhea.
- To assess the acceptability in terms of palatability of zinc sulphate dispersible tablets in children aged between 3 and 59 months with acute diarrhea.
- To compare the efficacy of zinc sulphate dispersible tablets in children aged between 3 to ≤18 months and >18 to 59 months.
- To assess safety of zinc sulphate dispersible tablets in children aged between 3 and 59 months with acute diarrhoea.

The following endpoints were defined in the protocol:

- To assess adherence based on frequency of daily administration, duration of treatment, and preparation (dispersion) of the zinc tablets.
- To assess palatability of zinc sulphate dispersible tablets based on subjects' parent's/ guardian's report of his/her child behaviour after the zinc tablet was administered.

- To compare efficacy of zinc sulphate dispersible tablets between the 2 study groups (children aged 3 to ≤18 months and those aged >18 to 59 months) based on the following:
  a) duration of episodes of diarrhea
  b) frequency of episodes of diarrhea
  c) consumption of ORS treatment.

In addition to the above endpoints, safety was recorded for each subject in the study. The study included the following evaluations of safety:
- adverse events (AEs)
- vital sign measurements (including body temperature [axillary], pulse/heart rate, respiratory rate, and blood pressure)
- physical examinations (including body weight and skin examination at every indicated visit).
- Clinical laboratory evaluations would be performed if needed at Investigator's discretion.

The first patient at this site was recruited on 18 Dec 2017 and the last patient was recruited on 10 Feb 2018. The confidentiality agreement was signed by PI and the study agreement was available in the ISF and signed by parties on 7 Nov 2017.

Subject screening and enrolment log with study code, site no, PI name and country name was available, signed by PI on 27 Sep 2018. No screening failure of 31 subjects was recorded.

The subject identification list was documented on a template provided by CRO which was signed by PI on 27 Sep 2018 and retained at the investigator site only. Screening no, Subject's registration number in the hospital database, date of birth, subject's name and contact details were recorded on the form.

The observations related to Clinical Phase were adequately addressed.

6. Clinical laboratory

Two clinical laboratories could be used if necessary:
- Suburban diagnostics (India) Pvt. Ltd – with NABL national accreditation which was valid until 18 Dec 2019. This laboratory would be used if the sponsor required the subject's biological samples to be tested. An MOU was signed between the site and Suburban laboratory, dated 11 Jul 2017.
- Metro laboratory was the inhouse laboratory owned by the hospital.

The essential documentation including the laboratory normal reference ranges was available in the ISF.

7. Ethics

The study was not required to be notified to the regulatory authorities, as the investigational product was not a new molecule.

The study was approved by Lifepoint Research – Ethics committee. List of EC members, their qualification and a list of documentation submitted to EC were available in the ISF. The documentation was supplied by the CRO to the site in 10 CDs. The letter was available in the ISF, dated 23 Oct 2017.

The EC meeting was held on 28 Oct 2017 at 5pm at Lifepoint Multi-Speciality hospital, 4th floor, conference room, and the EC meeting consisted of chairperson, member secretary, clinician, legal expert, basic medical scientist, social worker, lay Person. Their Independency was verified. The committee was operated in accordance with their own SOPs, ICH GCP and Indian Council of Medical Research and Schedule Y.

Other relevant communication with EC was also available, such as registration of EC with the Government of India, dated 21 Apr 2015.

Notification of study closure was sent to the EC on 27 Sep 2018, by PI, at the same day the study closure meeting took place.

The study was insured through an agreement between the oriental insurance company limited and the sponsor, from 1 Jul 2017 – 30 Jun 2018. The policy covered the BE studies, and clinical trials conducted at different clinical centres in India, Malaysia and Russia.

<u>INORMED CONSENT FORMS</u>

Information for study participants (parents) were provided in Marathi, Hindi or English (English vs 1, dated March 2016, Site specific, vs 1, dated 18 Oct 2017). Certificates of accuracy for translation and back translation were available in the ISF.

Proof of parenthood and literacy of parents were verified prior to the screening activities. The ICF was complete and encompassed information about training received for filling out the diary card and instruction about dispensing of the tables, in section 8. Request regarding returning of used blister pack and tablet-splitter after completion of dosing was also mentioned in the ICF.

Randomly selected ICFs were reviewed and verified. There was adequate link to the registration database and the ICF to verify the existence of the subject.

8. Monitoring

A monitoring plan relating to study no IPCA/ZNDT/PIII-14 was available.

The visits of the monitors, together with their CVs were verified.

Site qualification and site initiation visits were performed by both the CRO and the sponsor. Three monitoring visits took place, before the study closure meeting on 27 Sep 2018.

A visitor log template was provided for all monitor visits. However, the registry logbook practice was initiated on April 2018. Hence, the monitors' visits could not be verified through the site's visitor logbooks.

Quality of monitoring reports and follow up of CAPA plan were adequate.

9. Investigators

Qualification documentation of PI and SI was reviewed. The confidentiality agreement, including the non-disclosure agreement signed by SI on 1 Dec 2017 was available.

The observation identified in relation to investigator's qualification was adequately addressed.

10. Receiving, storage and handling of investigational drug products

All the information concerning the receipt, storage, handling and accountability of investigational product was required to be documented. Information about the shipment, delivery, dispensing, receipt, administration and reconciliation/return of any remaining pharmaceutical products was recorded. A Clinical Research Coordinator (CRC) was appointed to handle the IMP. Site level accountability log for Clinical trial supply was reviewed. Two shipment orders were received:

- 15 Nov 2017
- 20 Jan 2018

The receipt of second shipment was not recorded on the subject level accountability log for CTS. However, a note to file was provided to clarify that.

All study medication was kept in securely locked area, equipped with locked cabinets assigned to each respective study. The environmental conditions were monitored, using hygrometers, reading the maximum and minimum temperature. The IMP was adequately labelled in accordance with the requirements.

Dosing was performed in accordance with the instructions given in the respective protocol.

The clinical trial supplies return form was reviewed for returned drugs, dated 18 Jan 2019. It was verified by SIRO on 21 Jan 2019 and was sent for destruction.

The observation related to Handling of IMP was sufficiently addressed.

11. Case report forms

The site had a paper based medical documentation. Source data was compared with CSR data listings and data entered in CRFs.

Source data verification included all source data for randomly selected patients both for the screening / enrolment visit and follow up / end of study visit.

12. Volunteers, recruitment methods

The volunteers' recruitment was described in SOP for Subject Identification Procedure. The study specific potential methods that could be used by the site for this purpose were also described in the respective SOP. Cross participation could only be verified by volunteer's declaration and/or if other study / medical records were available. Subjects were selected from the PI's own patient population and/or walk-in patients. Potential patients were selected and sent to the PI to receive the study information. Identification of volunteers and subjects was ensured by reliable means and a unique identification number was generated by the system as soon as the patient was registered in the database.

Criteria for subject selection (inclusion and exclusion criteria) and screening procedures were described in the clinical trial protocol.

Medical records were generated for each subject and included information obtained during each screening visit.

13. Safety, adverse events, adverse event reporting

No Adverse event was reported from this site.

The concomitant medication data-listing in the CSR was reviewed. Other sites had reported a few cases of use of concomitant medication. However, there was no case of concomitant medication prescription at this site. On the other hand, the other sites, involved in this study, had mainly reported the ORS as concomitant medication, although there was a separate data listing for ORS consumption. According to the available logbook, this site had accordingly reported the consumption of ORS. After discussion with the CRO representatives, it was concluded that the ORS recorded as concomitant medication was due to treatment of AE (worsening of the diarrhea) and not due to the study disease.

14. Study report

Clinical Study Report (CSR) was issued on 5 June 2018 (Ipca/ZNDT/PIII-14). In the CSR appendix 16 there were data listings which were used for the analysis of the study data. These data listings were used by the inspectors for the Source Data Verification. For more details, refer to section 11.

Miscellaneous	
Assessment of the CRO master file	N/A
Annexes attached	N/A

Part 3	**Conclusion – inspection outcome**

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 guidelines at ***Lifepoint Multi-Speciality Hospital – LPR***, located at ***Research room - 3rd floor, 145/1, Mumbai-Bangalore highway , near Sayaji Hotel, Bumkar Chouk,Wakad, Pune, 411057 MAHARASHTRA, 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 clinical site, 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".
   Short name: WHO GLP
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

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

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

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

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

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

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

12. 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