

**Prequalification Team Inspection services**  
**WHO PUBLIC INSPECTION REPORT**  
**(WHOPIR)**  
**Bio-Equivalence Study**

<b>Part 1</b>	<b>General information</b>
<b>Organization details</b>	
Company information	
Name and Address of Clinical Research Site	Raptim Research Pvt. Ltd. A-226, T.T.C., Industrial Area, Mahape M.I.D.C. Navi Mumbai – 400710 India
Name and Address of Bioanalytical Research Site	Raptim Research Pvt. Ltd. A-242, T.T.C., Industrial Area, Mahape M.I.D.C. Navi Mumbai – 400710 India
Name and Address of Screening site	Raptim Research Pvt. Ltd. PAP-A-218, PAP-A-219, T.T.C., Industrial Area, Mahape M.I.D.C. Navi Mumbai – 400710 India
Name and address Statistical Site	Raptim Research Pvt. Ltd. A-242, T.T.C., Industrial Area, Mahape M.I.D.C. Navi Mumbai – 400710 India
Corporate address of Organization	Raptim Research Pvt. Ltd. A-242, M.I.D.C., T.T.C., Industrial Area, Mahape Navi Mumbai-400 710 India Tel.: +9 1 22 2778 1 889
GPS coordinates	<b>Bioanalytical &amp; Statistical site</b> 19.11424° N 73.02302° E  <b>Clinical site</b> 19.11492° N 73.02204° E  <b>Screening site</b> 19.11733° N

*Raptim Research Pvt. Ltd., Navi Mumbai-CRO*

12-15 December 2022

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	73.02297° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	<p><b>HA729</b> Bioequivalence Study of Fixed Dose Combination of Tenofovir Disoproxil Fumarate 300mg + Lamivudine 300 mg + Dolutegravir 50mg tablets</p> <p><b>HA696</b> Bioequivalence study of Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate tablets 50mg/300mg/300mg</p> <p><b>MA161</b> Bioequivalence study of Artemether and Lumefantrine tablets 20mg/120mg</p> <p><b>HA758</b> Bioequivalence study of Darunavir and Ritonavir Tablets 800 mg/100 mg</p> <p><b>MA163</b> Bioequivalence study of Sulfadoxine and Pyrimethamine 500 mg / 25 mg dispersible tablets</p> <p><b>HA722</b> Bioequivalence study of comparing fixed dose combination of Dolutegravir 50mg, Lamivudine 300mg and Tenofovir DF 300mg tablets</p> <p><b>CV010-0</b> Bioequivalence study of Molnupiravir capsules 200 mg</p> <p><b>CV012-0</b> Bioequivalence study of Nirmatrelvir tablets 150 mg and Ritonavir tablets 100 mg</p> <p><b>MA088</b> Bioequivalence study of Fixed Dose Combination containing Artemether 20 mg and Lumefantrine 120 mg tablets</p>
<b>Inspection details</b>	
Dates of inspection	12-15 December 2022
Type of inspection	Routine

<b>Introduction</b>	
Summary of the activities	The facility had the capacity to perform bioequivalence/bioavailability and in-vitro studies in healthy subjects/patients.
General information about the company and site	Raptim Research was established in the year 2005. A broad spectrum of services like Pharmacokinetic studies (BA/BE), IVRT, IVAD, Pharmacodynamic studies Phase II & III trials, and Dermatology studies were rendered by Raptim to Pharmaceutical industries and/or to CROs.
History	The CRO was previously inspected by WHO in October 2017.  Other inspections were conducted by US FDA, MHRA, ANVISA, NPRA, BfArM, HPRA, CHILE & DCGI.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed:  The company’s history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.  Regarding the analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.  A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with comparison of the source data to the study reports.
<b>Scope and limitations</b>	
Out of scope	Not applicable
Restrictions	Due to time constraints, the inspection team has verified the implementation of the CRO’s procedures in relation to the integrity of the studies’ data and the safety of study participants based on a risk-based approach with a focus on the selected studies.

Abbreviations		
	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioavailability

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
ISF	investigator site file
ISR	incurred sample reanalysis
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

<b>PART 2</b>	<b>SUMMARY OF THE FINDINGS AND COMMENTS</b>
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<b>General section</b>
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## 1. Organization and management

A presentation was shared with the WHO Inspection team on the activities of the organization and recent changes since the last WHO inspection.

The organization had offices in India, specifically an operational facility in Navi Mumbai, a clinical facility in Gandhinagar, Gujarat, and a marketing office in New Jersey, USA.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organization chart was dated & authorized on 5 Nov 2022. The organization was headed by Dr. Rajen Shah & Mr. Viraj Shah as Directors.

There was a job description for each employee, including their responsibilities. The job description of randomly selected personnel was randomly chosen to be verified that it was signed and dated by the staff member to whom it applied.

A list of signatures of the authorized personnel performing tasks during each study was available and verified.

It was ensured by the management that appropriate and technically valid SOPs were implemented and followed. Maintenance of a historical file of all SOPs was adequately organized.

The facilities were also approved by the National regulatory authority, i.e., DCGI (The Drug Controller General of India), for conducting clinical studies with 170 beds. DCGI Approval letter for each facility was attached to the CRO Master File.

The service agreement with the sponsors was available. The agreement with Emcure was reviewed and discussed.

Both bioanalytical and clinical departments had a 24-hour work schedule.

## 2. Computer systems

An inventory of software and computerized systems used in the studies was provided.

Since 2016, the CRO has implemented a software system to be used for registration and screening of volunteers, pathology laboratory data processing, electronic sample management, SDMS print, and LIMS for the purpose of electronic data and information management. The URS of the software system, approved on 2 Nov 2020, was available to define functional, security, interface, ER-ES, business and reporting, and mapping of data integrity requirements. The following processes were covered by the software as part of automation efforts:

- ✓ Clinical study
- ✓ Screening since 2021
- ✓ Pathology Lab
- ✓ Sample management
- ✓ Laboratory Information management since 2021
- ✓ Scientific Data Management (SDMS) since 2016
- ✓ Training

A performance qualification, i.e., Experiment Batch result validation test cases, was carried out on 3 Jun 2021.

An SOP for Qualification Operation and Security Configuration of the application for LIMS and SDMS was available. This SOP was modified to adopt the new procedure of project execution till project archival. Procedures for Computer System Validation were also provided.

There were a sufficient number of computers to enable personnel to perform data entry, and data handling required calculations and compilation of reports. Computers had the adequate capacity and memory for the intended use.

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of people who had access to the selected database systems was verified. Secure and unique, individual-specific identifiers and passwords were used. Selected software systems used for the various study activities were reviewed. SOPs for usage of each software program used to perform activities of a BE study were available.

Software programs used, storage of data, and the procedure for backups and long-term archiving of relevant electronic data were specified in SOP for the Backup of a computer system, including frequency of backups and archiving. Backup data were periodically rewritten as part of the backup procedure, and the data from the previous backup was archived. The restoration process was also included in the same SOP. eScan Antivirus (Internet Security SU or SMB) was installed for data protection.

Data entry procedures, including data validation methodology (proof reading, double data entry, etc.), were designed to prevent errors.

Observations related to the Computerized systems were adequately addressed in the respective CAPA plan.

### **3. Quality management**

The CRO had QA and QC systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and the applicable regulatory requirements. The CRO started using a software system for the digital management of the SOPs. A Quality Manual was provided.

QA personnel were not directly involved in trial-related activities.

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed.

Observations related to the QMS were adequately addressed in the respective CAPA plan.

### **4. Archive facilities**

The Archive facility was located on the top floor of the Bioanalytical facility. The CRO had sufficient and appropriately secure storage space for archiving the trial-related documentation. The facility was fireproof and relative humidity-controlled, and measures for pest control were in place.

The archiving activities were managed in accordance with the applicable SOP. Access to archive storage areas was controlled and restricted to authorized personnel.

Records of document retrieval were maintained. The length of time for which study documentation, including raw data, should be kept in the archive was defined in the SOP.

This period was also specified in the contract between the sponsor and the CRO, which included provisions for the financing of the archiving.

The archiving procedures of the trial-related documentation were verified through successful retrieval and traceability of the documents during the inspection.

## 5. Premises

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

The facilities were generally clean and had adequate lighting and ventilation. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

The clinical facility consisted of three floors (ground + 2). Each floor had a clinic with a separate changing room, a housing area for male and female subjects, sample collection and processing and storage, a recreational area and dining area, and a separate ECU. Clinical trials were carried out under conditions that ensured the safety of the subjects. The potential risks involved in the activities were considered in the premises' design.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site had adequate facilities, including laboratories and equipment. Entry to the facility was restricted and controlled through biometric access. The Emergency evacuation was ensured. And the volunteer's presence was monitored by 24-hour staff supervision. Any entry to and exit from the facility were recorded.

The temperature control of the cold storage facility was monitored by the digital system.

The site, where clinical activities took place included a pharmacy where investigational products were stored under appropriate conditions, with entry and exit restricted by access control. Appropriate entry/exit records for each visit to the pharmacy were maintained.

Laboratory premises were designed to suit the operations to be carried out in them. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Storage space for samples, standards, solvents, reagents, and records was available.

Observations related to the Premises were sufficiently addressed in the applicable CAPA plan.



## 6. Personnel

There was enough medical, paramedical, technical, and clerical staff with the appropriate qualifications, training, and experience to support the trial and to be able to respond effectively to reasonably foreseeable emergencies. The number of members of staff at the time of inspection counted to:

- 150+ including QC team at the clinical site
- 350+ including QC team at the bioanalytical site
- 20+ members as QA team

At all stages of the trial, including at night, there were qualified and trained personnel to ensure that the rights, safety, and well-being of the subjects were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities for which they were trained.

Randomly selected current curricula vitae and study-related training records of personnel involved in trial activities for full-time and contract workers were reviewed to be verified.

### Clinical section

## 7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO. The clinical facility was close to the bioanalytical and screening facilities on the same road.

The CPU was equipped with 170 beds and six separate beds in the ECU. Alarm buttons were in place, next to each bed in the housing facilities so subjects could alert CRO staff in case of need.

Facilities for changing and storing clothes and for bathing and toilet purposes were clean, well-ordered, easily accessible, and appropriate for the number of users at the time of inspection. The toilets were equipped with alarm buttons, and doors were designed to ensure they could be opened from the outside should there be a medical emergency.

Provisions were made for the urgent transportation of subjects to the contracted emergency hospital.

The biostatistician generated the randomization schedule and kept it in a specific folder accessible only to pharmacists. The pharmacists were informed once the randomization plan was stored in the respective drive through email.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) should be verified at appropriate intervals or prior to the study. The records were documented in the respective logbooks.

## 8. Clinical laboratory

A suitable clinical laboratory was located at the clinical premises to analyze samples. The Clinical Pathology Laboratory was accredited by NABL (National Accreditation Board for Testing and Calibration Laboratories). The Accreditation Certificate was attached to the CRO Master File. In case the Laboratory did not have the capability of testing any parameter, then the samples were sent to the external accredited laboratory. An agreement was signed with this external lab.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol. A barcoding system ensured full traceability and sample integrity through sample labelling, receipt, storage, and chain of custody.

The laboratory normal ranges were specified in the respective SOP. However, older versions were applicable at the time of studies in the scope of the inspection. The SOP was recently made effective, i.e., 2 Dec 2022, based on comments from the WHO assessment team.

The current and signed curricula vitae of the Head of the Clinical Laboratory were reviewed.

The laboratory created individual reports for each subject and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic and/or paper formats, depending on their source and the laboratory's storage capacity. All the raw data were transferred into the applicable software system, which was available during the inspection and reviewed.

Observation related to the data integrity of data produced by the laboratory's instruments was addressed in the respective CAPA plan.

## 9. Ethics

Studies in the scope of inspection were submitted to the Independent Ethics Committee in accordance with the applicable SOP before any study activity was conducted. The Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list. Discussions, recommendations, and decisions made

during the IEC meetings were documented. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation.

#### Informed consent form

Information for study participants was given to them in vernacular language and at a level of complexity appropriate to their understanding, both orally and in writing.

Informed consent was given by the subject and documented in writing before starting any trial-related activities. Informed consent was also recorded by video. The information was clear that participation was voluntary and that the subject had the right to withdraw from the study on his or her own initiative at any time without giving a reason. The reasons for withdrawal from the study were included in the study records.

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through an insurance policy. The study participants were insured through an insurance agreement with the Insurance company.

The volunteers or subjects were allowed to discuss with a physician their concerns regarding potential side effects or reactions from using the investigational products before participating in the trial.

### **10. Monitoring**

The studies were monitored by sponsor representative when applicable. The monitoring visit log and correspondence were available and reviewed.

### **11. Investigators**

The Principal Investigator (PI) had the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee and signing the protocol and the final study report.

The qualification of investigators was captured on their CV and the GCP related training evidence.

### **12. Receiving, storage and handling of investigational drug products**

The information concerning the receipt, storage, handling, and accountability of investigational products at every stage of the trial was recorded. The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining

pharmaceutical products were also verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored in formulation cabinets or refrigerator under appropriate conditions as specified in the official product information provided by the sponsor. The storage conditions were monitored through a digital temperature monitoring system (Eurotherm). The room temperature was also monitored using a thermo-hygrometer.

Randomization was performed in accordance with the applicable SOP, and records were maintained, including the randomization list and seed number. The randomization list was accessible in a secure folder only to the statistician who generated it and the dispensing pharmacist.

The IPs were properly labelled. Compliance of all labels with the randomization list was verified once they were printed and before the labelling of the containers. Labels were pasted onto the container to ensure that the information was not lost once the lid was removed.

Good routines for labelling and documenting the administration of the IP were established to verify that each subject did receive the product dispensed for him or her by using labels with a tear-off portion. Labels were designed to have two identical labels with one portion pasted onto the container and the second label pasted onto the CRF at the time of dosing.

Dispensing procedures were performed in accordance with the respective requirements. Dosing was performed in accordance with the respective SOP. The exact time of dosing was documented on the CRF's designated page. A mouth check was performed by looking under the tongue, under the lips, in the corners of the mouth, and between gums and cheeks, using a tongue depressor or a spatula and a penlight, in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. Dosing was directly documented in the CRFs.

Samples of the product in the original container were retained for possible confirmatory testing in the future for at least one year after the expiry date of the newest product. Sample retention was defined and described in the SOP and was specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

### **13. Case report forms**

Randomly selected CRFs from the studies in the scope of inspection were reviewed.

The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. The lab results' raw data were kept in the laboratory, and the results were entered into the respective software system.

Information about ICF, demographic, physical examination, AE report, Post-study safety assessment, SAE report, subject dropout, withdrawal details, pre-enrolment day activities, pregnancy test, if applicable, breath alcohol test, urine drug test, inclusion & exclusion criteria, post-dose vital exam, concomitant medication, dosing administration, blood sample collection, together with the actual time of collection, discharge summary, check-in and check-out time and date, was included in the CRFs.

### **14. Volunteers, recruitment methods**

Procedures for recruiting volunteers were specified in the respective SOP which described the potential methods the CRO used for this purpose. The registration module of the applicable database was maintained on volunteers to avoid cross-participation and specify a minimum time between a volunteer's participation in one study and the next. Access to the database was password controlled to secure confidential information on volunteers.

A biometric system using index fingerprints ensured the identification of volunteers. The volunteer was registered in the system on arrival at the screening visit and received a barcoded wrist band which was used for identification traceability for screening and other related study activities.

The informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study. The clinical trial protocol described criteria for subject selection (inclusion and exclusion criteria) and screening procedures.

OVIS Software application was used to determine whether any of the subjects had participated in a previous trial by other CROs in the area. The study participation date was uploaded into this central repository to prevent over-volunteering. Access to the database was password controlled.

## 15. Food and fluids

Meals were standardized, adequately controlled and scheduled during the study days. The CRO was able to arrange for standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol, SOP for Meal management, and as per the agreement with catering service.

The timing, duration, and amount of food and fluids consumed were recorded. Prior to samples being obtained from ambulatory subjects, they were asked about their food and drink consumption. A dietitian with appropriate qualifications, training, and experience designed standardized meals.

## 16. Safety, adverse events, adverse event reporting

The studies were planned, organized, performed, and monitored so that the safety profile was acceptable, including to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of serious adverse events. The procedure was implemented in accordance with the applicable SOP.

First-aid equipment and appropriate rescue medication were available in the ECU and ready for emergency use at the study site. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the ECU.

The CRO had adverse event registration and reporting forms as part of the CRF.

Observation related to reporting of adverse events was adequately addressed in the respective CAPA plan.

### **Bioanalytical section**

The inspection included the audit of randomly selected source documentation and raw data for validation of the bioanalytical methods and analysis of subject plasma samples, as well as a review of the electronic data, audit trails for electronic data capture and handling related to the BE studies, with a focus on selected studies. The results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from the analytical runs. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited.

Chromatograms and their integration, the absence of signals in the blank samples, absence of unexplained interruptions in the injected sequences were verified.

During the method validation according to the applicable SOP, a run was performed to determine the batch with a specified number of QCs and CC samples (so-called Long Batch Performance) comparable in length to those expected for analysis. The documentation of the ISRs was confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the requirements.

For review of the study documentation, the inspection team received adequate support from the personnel, who were well-informed and transparent.

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

The method development process was adequately described and documented, and the usage of IS was justified based on the applicable literature. The literature used for the development was mentioned in the respective notebook. After method development, an analytical plan was provided for the method validation. A stable isotope-labelled internal standard and appropriate anticoagulant reagent were always used in the MS methods.

The documentation for the purchase and transfer of plasma used for method validation and sample analysis, as well as lipemic and haemolyzed plasma from suppliers, was available and reviewed. The documentation comprised receipt, storage, retrieval, preparation, and consumption of the pooled plasma.

The CRO used the chromatography software system to facilitate the chromatography-based analysis. The application was upgraded on most computers. A list of computers running the application with the respective license ID numbers was provided during the inspection.

The sample processing was documented both in paper and electronic forms. A note to file was also provided to record any unexpected activity during sample processing, when applicable.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the studies, except for the long-term stability data, which were generally performed before the issuance of the study reports.

The review of the full method validation in the selected instrument included precision and accuracy testing (three batches of P&A), selectivity, matrix effect, calibration curve, autosampler carry-over along with the system suitability, dilution integrity, stability (including freeze-thaw stability, stock solution stability, haemolytic effect, recovery, and reinjection reproducibility). Partial validation was performed according to the requirements.



The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact sequence of processing was defined and documented. All samples collected from a given subject during all trial periods were analyzed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs, using the applicable module in the applicable software system for the respective calculations. A system suitability and stabilization test were done prior to the start of runs on each day.

10% of the total samples were used to run Incurred Sample Reanalysis. The samples were selected with a concentration around  $C_{max}$  and in the elimination phase. The acceptance criteria were clearly defined in the SOP.

## **18. Sample collection, storage and handling of biological material**

The specification of samples (blood plasma), sampling method, volume, and the number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport, and storage of samples took place in accordance with SOP for Receipt, Handling, Storage, and Disposal of Biological Matrix and Biological Samples.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were considered when calculating the pharmacokinetic parameters.

Labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period using a digital thermometer associated with a software system. A datalogger with specific serial numbers, was used during transportation from the clinical site to the BA site. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots which were shipped and stored separately.

The studies' QC, CC, and biological samples were retained or discarded according to the applicable SOP and the respective agreement with the sponsor. The records of samples retained for the study in the scope of inspection were documented in the respective Deep Freezer's logbook and reviewed.



Blood samples retention time was specified in the respective agreement with the sponsor.

## 19. Data processing and documentation

Integration settings were science-based and justifiable. The smoothing factor was kept low enough in general not to mask possible interferences and changes in peak geometry. However, there were incidents where higher smoothing factors were used due to a need for peak integration. Result tables before and after re-integration were available and reviewed for WHO application CV010 batch 4, 5 & 6, and batch 7, 8 & 9.

During the inspection of sample analysis data, randomly selected system suitability and stabilization failure was investigated and compared with the result tables and audit trail records. The form for Investigation was available, and the failure incident was adequately addressed. After system rectification, the batch was reanalysed, as applicable, and all the activities were recorded in the respective logbooks.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as the batch acceptance, were clearly defined in the applicable SOP. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. The calibration range was adequately truncated. Internal standard variations were trended using a validated Excel sheet and used as part of the verifications of result validity in accordance with SOP for Subject Sample Analysis. A sample could be re-analyzed if the Internal standard (IS) area was not within 50-150% of the acceptance limit (mean of the internal standard area observed for the acceptable CC standards and QC samples) or if there was no IS area. The current SOP was effective 14 Oct 2022. However, in the SOP version 01, valid from 3 May 2019 until 4 Sep 2019, the acceptance criteria for variations related to the labelled-Internal Standards was between 20 to 185 %, which applied to the studies performed before Sep 2019, e.g., WHO application HA758.

Full audit trails were activated on all analytical instruments, before, during and after the method validation and the studies of interest.

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented and stored in the SDMS software system with adequate traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). All audit trail files were retained in the SDMS software, e.g., results table audit trail, project audit trail, and instrument audit trail.

The documentation for reinjections, the respective error notification, result tables, and other investigation and sample processing documentation were available. The screenshots were provided of the error notifications.

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

## **20. Good laboratory practices**

A tour of the facility was performed to verify the suitability of the facility in terms of arrangement and safety.

Laboratory premises provided protection for all employees and handled chemicals and biological samples safely. Staff were instructed to wear laboratory coats or other protective clothing, including eye protection.

The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE studies with an established QA system.

Deep freezers for storage of the samples and refrigerators for storage of the Reference Standards were adequately qualified, calibrated, and maintained. An alarm system was associated with the digital thermometer to notify the sample custodian and the CRO's security personnel. The automatic alarm system was tested during inspection to verify its proper functionality. The daily monitoring and the alarm checks were documented.

For the purposes of qualification verification, the temperature mapping of the randomly selected refrigerator and Deep Freezer were reviewed to verify the hot spot and the location of the respective sensor. The process of temperature mapping was properly carried out. Transfer of samples to equivalent storage units was appropriately considered under maintenance and repair.

Balances used during a trial were periodically calibrated and verified before use to fit their intended purpose.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. These activities were verified by random review of the equipment used in study-related activities. Equipment and its components were labelled with the respective ID number, date of calibration, and date of next calibration. The equipment usage was

adequately documented in the analytical sheets, as well as the respective logbooks for the instrument usage.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA.

Premises had systems in place to dispose of waste, treat fumes, and protect the environment in conformance with local or national regulations.

## Pharmacokinetic, statistical calculations and reporting section

### 21. Pharmacokinetic, statistical calculations

The statistician provided a presentation explaining the data processing activity procedures which were followed by the statistical department.

The department was responsible for study protocol inputs by studying the pilot study and the literature, requirements for the BE study design, type of formulation, intra/inter subject variability, applicable pharmacokinetics, selection of study design, and sampling time points.

Sample size estimation was done based on study design and regulatory acceptance criteria, intra or inter subject variability, test/reference ratio, type-I-error, and power of the study. The intra/inter subject variability could initially be determined based on a pilot study and/or respective publications.

The randomization list was generated using SAS<sup>®</sup> software.

Exclusion of subjects from statistical and pharmacokinetic calculations, e.g., pre-dose concentration less than 5 % of  $C_{max}$  or withdrawal of subjects, was determined in accordance with the regulatory guidance and the respective statistical plan in the study protocol.

The Pharmacokinetic analysis plan included a list of pharmacokinetics parameters recommended by the regulatory guidance, information on software used for pharmacokinetic parameters estimation, and information on the model used for the analysis.

The ANOVA model effect factor, the descriptive statistics, and the acceptance criteria for bioequivalence, e.g., 90 % CI for T/R ratio to be within BE limits of 80 – 125 %, were defined in the study protocol, section for statistical analysis plan in compliance with the regulatory guidance.

After completion of the study, decoded subject analysis sheet and concentration data were reviewed and verified by QA before the performance of pharmacokinetics and statistical analysis. The data was stored electronically in a secure designated folder.

The statistical report and the respective appendices were verified and compared with the software-generated outputs.

## 22. Study report

The process of study report writing was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies between the results stated in the report and the actual original (raw) data were identified, through the random review of data.

The study report included a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and the report of the validation of this method. The clinical study reports were approved by the Principal Investigator. The bioanalytical reports were also approved by the responsible staff and management. Monitoring and audit reports were available before release of the final study report.

<b>Miscellaneous</b>	
<i>Samples taken</i>	<i>N/A</i>
<i>Assessment of the CRO master file</i>	A CRO Master file was provided and reviewed.
<i>Annexes attached</i>	<i>N/A</i>

<b>Part 3</b>	<b>Conclusion</b>
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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 studies were considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at **Raptim Research Pvt. Ltd.**, located at the following addresses:

***Clinical site:***

***A-226, T.T.C., Industrial Area, Mahape M.I.D.C.***

***Navi Mumbai – 400710***

***India***

***Bioanalytical & Statistical site***

***A-242, T.T.C., Industrial Area, Mahape M.I.D.C.***

***Navi Mumbai – 400710***

***India***

***Screening site***

***PAP-A-218, PAP-A-219, T.T.C., Industrial Area, Mahape M.I.D.C.***

***Navi Mumbai – 400710***

***India***

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for three years, provided that the outcome of any inspection conducted during this period is positive.

<b>Part 4</b>	<b>List of guidelines referenced in the inspection report</b>
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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 or TRS996 Annex 9**  
<https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>
2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009  
**Short name: WHO GCLP**  
<https://apps.who.int/iris/handle/10665/44092>
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**  
<https://www.who.int/publications/i/item/9241208503>
4. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.  
**Short name: WHO TRS 1010, Annex 9**  
<https://www.who.int/publications/m/item/trs-1010--annex-9-who-good-practices-for-desk-assessment-of-compliance-with-good-manufacturing-practices-good-laboratory-practices-and-good-clinical-practices-for-medical-products-regulatory-decisions>
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.  
**Short name: OECD GLP**  
[https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem\(98\)17&doclanguage=en](https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en)
6. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.  
**Short name: WHO Ethics Committee Guidance**  
<https://apps.who.int/iris/handle/10665/44783>
7. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.  
**Short name: WHO CROMF Guidelines or TRS No. 957, Annex 7**  
[https://www.who.int/publications/i/item/WHO\\_TRS\\_957](https://www.who.int/publications/i/item/WHO_TRS_957)

8. 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 storage and transport guidance or TRS 961 Annex 9**

[https://apps.who.int/iris/bitstream/handle/10665/44079/WHO\\_TRS\\_961\\_eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y)

9. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).

**Short name: Glove use information leaflet**

[https://www.who.int/publications/m/item/glove-use-information-leaflet-\(revised-august-2009\)](https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009))

10. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.

**Short name: TRS 1003 Annex 6**

<chrome-extension://efaidnbmninnibpcjpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf>

11. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.

**Short name: WHO TRS No. 1025, Annex 4**

<https://apps.who.int/iris/handle/10665/331814>

12. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.

**Short name: WHO TRS 1033, Annex 4**

<https://apps.who.int/iris/handle/10665/340323>

13. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).

**Short name: Declaration of Helsinki**

<https://apps.who.int/iris/handle/10665/268312>

14. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022

**Short name: ICH M10**

[https://database.ich.org/sites/default/files/M10\\_Guideline\\_Step4\\_2022\\_0524.pdf](https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf)

15. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.

**Short name: WHO TRS No. 1019, Annex 3**

<https://www.who.int/publications/m/item/trs-1019---annex-3-good-manufacturing-practices-guidelines-on-validation>