

**Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Bio-Equivalence Study**

Part 1	General information
Organization details	
Company information	
Name and Address of Clinical Research Site	<p>Aizant Drug Research Solutions Private Limited Clinical Development Division (CP-I) Survey No.: 172 & 173, Apparel Park Road Dulapally Village, Dundigal- Gandimaisamma Mandal Medchal- Malkhajgiri District Hyderabad, Telangana India – 500100</p> <p>Aizant Drug Research Solutions Private Limited Clinical Pharmacology Unit-II (CP-II) St. Theresa’s Hospital, 2nd Floor Premises No. 7-1- 645/A Sanath Nagar Hyderabad, Telangana India - 500018</p> <p>Web: www.aizant.com</p>
Name and Address of Bioanalytical Research Site	<p>Aizant Drug Research Solutions Private Limited Clinical Development Division Survey No.: 172 & 173, Apparel Park Road Dulapally Village, Dundigal- Gandimaisamma Mandal Medchal- Malkhajgiri District Hyderabad, Telangana India – 500100</p>
Name and address Statistical Site	<p>Aizant Drug Research Solutions Private Limited Clinical Development Division Survey No.: 172 & 173, Apparel Park Road Dulapally Village, Dundigal- Gandimaisamma Mandal Medchal- Malkhajgiri District</p>

Aizant Drug Research Solutions, Hyderabad, India-CRO

7-11 March 2022

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	Hyderabad, Telangana India – 500100
Corporate address of Organization	Same as above
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	<p>WHO application no. HA697 Bioequivalence study of Lopinavir/Ritonavir Granules (2 Sachets X 40/10 mg) 40 mg / 10 mg</p> <p>WHO application no. HP016 Bioequivalence study of Daclatasvir Tablets 60 mg</p> <p>WHO application no. HA754 Bioequivalence study of Flucytosine Tablets 500 mg</p> <p>WHO application no. HA746 Bioequivalence study of Test product Dolutegravir, Lamivudine, Tenofovir Disoproxil Fumarate tablets 50mg/300mg/300mg</p> <p>WHO application no. TB365 Bioequivalence study of Linezolid Tablets 600 mg</p> <p>WHO application no. HA749 Bioequivalence study of Atazanavir Sulphate/Ritonavir tablets 300/100 mg</p> <p>WHO application no. HA426 Bioequivalence study of Test product Lamivudine, Zidovudine and Nevirapine Tablets 150 mg/300 mg/200 mg</p> <p>WHO application no. HP025 Bioequivalence study of MyHep DVIR™ (Daclatasvir/Sofosbuvir) 60 mg/400 mg comprimés pellicules (Tablets)</p> <p>WHO application no. HP026 Bioequivalence study of sofosbuvir and velpatasvir 400 mg/100mg film-coated tablets</p>

	<p>WHO application no. HA762 Bioequivalence study of isoniazid, pyridoxine, sulfamethoxazole, and trimethoprim tablets (300mg/25mg/800mg/160mg)</p> <p>WHO application no. HA756 Bioequivalence study of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg Tablets</p> <p>WHO application no. HA766 Bioequivalence study of Efavirenz, Lamivudine, Tenofovir disoproxil fumarate tablets (equivalent to 245 mg of tenofovir disoproxil) 400mg / 300mg/ 300mg</p> <p>WHO application no. HA764 Bioequivalence study of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate tablets 600 mg/ 300 mg/ 300mg</p> <p>WHO application no. HP030 Bioequivalence study of Tenofovir disoproxil fumarate Tablets 300 mg</p> <p>WHO application no. HA752 Bioequivalence study of Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg tablets</p>
Inspection details	
Dates of inspection	7-11 March 2022
Type of inspection	Routine
Introduction	
Summary of the activities	<p>The CRO consisted of two sites with the capacity to perform bioequivalence/bioavailability and in-vitro studies in healthy subjects/patients.</p> <p>The CRO provided the following services:</p> <ul style="list-style-type: none"> • Clinical pharmacology • Clinical diagnostic • Method development • Method validation • Study sample analysis • Pharmacokinetic and statistics

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General information about the company and site	Aizant Drug Research Solutions Pvt. Ltd. was a drug development solutions provider established in 2006. The company consisted of two facilities with one of the facilities dedicated to the clinical part of the studies, i.e., Clinical Pharmacology Unit-II. This unit was established in 2017, located on the second floor of St. Theresa hospital on the northern part of the city.
History	A list of inspections performed by various authorities since April 2008 was provided. WHO previously inspected the CRO in October 2011, March 2015, and July 2017.
Brief report of inspection activities undertaken	<p>The following scope and study-related activities were reviewed:</p> <p>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.</p> <p>Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.</p> <p>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.</p>
Scope and limitations	
Out of scope	Not applicable

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis

CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
LC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator’s brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

Part 2**Summary of the findings and comments****General section****1. Organization and management**

A presentation was provided explaining the activities of the organization.

An organization chart depicting key positions and the names of responsible persons for both CP-I and CP-II was provided.

A job description for all personnel, including a description of their responsibilities was available. Every job description was signed and dated by the staff member to whom it applied. Randomly selected CV, job description and training documentation of applicable staff were reviewed and verified.

A total of 158 employees at CP-I and 53 at CP-II were engaged in clinical operations and a list of signatures of the authorized personnel performing tasks during each study was available.

Good Clinical and Good Laboratory Principles were established for both clinical and bioanalytical part.

Agreements were signed between the CRO and the respective sponsors.

The general working hours were from 9am to 6pm on weekdays, in addition to first and third Saturday of the month.

2. Computer systems

A list of software and computerized systems used to run the studies was provided and reviewed. It was verified that the CRO did not use the Microsoft XP system in their operations.

A digital Laboratory Information System (LIS) was recently implemented. The system is currently used solely for handling data from haematology, biochemistry, and serology analyzer machines used at the clinical pathology laboratory (incl. generation of laboratory result reports and evaluation of results by investigators). Urine sample results were added to the study report separately.

The software systems linked to the HPLC-MS/MS instruments were installed on stand-alone desktop PCs (one per instrument). Each PC was equipped with two independent hard disks (one being the primary hard disk and another capturing a 100% copy of all data stored on the primary hard disk).

A backup procedure was implemented. All the backups were saved as .bkf files into the space available in the Storage Module affixed to the IBM Server Chassis. External Hard Disks were used for the CPU – II unit. All the hard disks in the Storage Module were configured in RAID-5. All the backup sessions were password-protected, and restoration of any kind required a password linked to an individual username. IT Administrator maintained the password as per applicable SOP for Password Policy and Computer Access.

For automatic backups, the data was currently on the servers. The backup was provided through the Symantec BackupExec 12.5 Software installed in Aizantsrv04. Once the backup jobs were created, the backup was automatically executed in the service mode according to the scheduled time.

Twice monthly, a random qualification of backed-up data was performed to verify the size of folders. A complete restoring process, i.e., the reliability and completeness of these backups, were verified every six months according to the respective procedures. The documentation for the short-term verification for a complete restoring check, incl. content of folder and readability, was provided and reviewed.

Qualification and validation of chromatography software systems were planned and carried out. The respective tests were recorded to demonstrate that the equipment and/or system could perform as intended.

The validation documentation of the Laboratory Information software system linked to the Haemolysis analyser, consisting of Installation, Operational, and Performance qualifications as well as the risk assessment reports, and the respective protocols, were reviewed and approved by the QA manager of Aizant and associated director – QA. However, the validation was carried out by the service provider, i.e., Implement technologies, with an address in Hyderabad. The system was not adequately challenged during the performance qualification. The validation documentation was signed on 6 Aug 2016. Revalidation of the software system was in process. Nevertheless, it was confirmed that the recent validation was not different from the available one, and the system was not sufficiently challenged in the recent validation either. The validation documentation of the Laboratory Information software system linked to the biochemistry analyser was also available.

The chromatography software systems used in the CRO were not networked.

A Manual was available for the Onsite emergency plan. A corporate certificate for an emergency evacuation mock drill dated 29 Aug 2019 was the only mock-up action performed to test the individual disaster plan.

The available chromatography software systems were all upgraded. A risk assessment and a respective change request were provided. The risk assessment report of the software for the LC-MS/MS system linked to the instrument and the respective document was reviewed. Data storage hard disk failure was considered a risk, and measures were presented.

SOP for Allocation of Operational Rights and Defining Security Levels to Chromatographic Equipment Software systems was reviewed.

Observations made in relation to computerized systems were adequately addressed in the respective CAPA plan.

3. Quality management

The CRO had appropriate QA systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, and the other applicable regulatory requirements. A complete list of SOPs dated 5 Mar 2022 and all the SOPs was prepared on a pen drive ahead of inspection for inspectors' perusal.

The CRO's QM highlighted the company's quality objectives and addressed the requirements for a QMS of the organization's departments, i.e.:

- Clinical Pharmacology
- Bioanalytical
- Pharmacokinetics and biostatistics
- Project management
- Diagnostics
- QA
- Purchase
- Engineering

QA personnel were independent of the work they were quality assuring, including:

- Establishing the systems and procedures required for the various operations as per GCP, GLP and various regulatory authorities
- Review and approval of SOPs
- Handling of deviations/ incidents and CAPA
- Management of change control

- Management of Qualification of equipment and instruments
- Conducting periodic internal audits in various departments
- To conduct study specific in-process and retrospective audits
- Review and approval of bioanalytical method validation and study reports
- Review and approval of clinical study reports

Change request procedures were established in accordance with the applicable SOP. The SOP was reviewed to verify the implementation of the process. The change request forms for procurement of new instruments were provided and reviewed. Three forms were used to report the change request: Change control note to initiate the request

- Change control assessment
- Additional sheet to list the layouts to be modified due to the respective change
- Verification of change effectiveness

A list of approved vendors with information about name, address, contact person details, service provided, date of approval, and status was provided. Metagenome Labs limited clinical laboratory was contracted to provide diagnostic services in case of instrument failure or other issues. The laboratory was in accordance with SOP for Clinical vendors selection and qualification.

The organization had the arrangement to control the issuance of templates. Each template had a unique number, issued by QA in a respective logbook. Compliance with the procedures for the issuance of templates was verified through a review of selected templates such as volunteer reporting records, and monitoring visit log. The reconciliation of unused templates was also randomly substantiated.

4. Archive facilities

An SOP for archiving was implemented. The archive processes were tested through the successful recall of requested documents and records during the conduct of the inspection and found effective.

A temporary archive facility was designated to secure the storage space of the trial-related documentation. The facility was monitored to maintain the acceptable humidity and temperature. The archive facility of CP-II was inspected. The facility was located on the second floor of the Premises. Pest control was carried out every two weeks. The agreement with pest control service provider was provided. The facilities were equipped with CO₂ fire extinguisher system.

A third-party agreement was made with a service provider to provide an off-site archive facility. It was noted that the contract was in renewal process. There was no provision for preventive actions to avoid any early destruction of documentation in the contract.

However, the service provider was regularly audited. The vendor was requalified, and the implementation of preventive measures were verified at the time of audit.

Access to archive storage areas was controlled and restricted to authorized personnel. The list of authorized personnel was displayed at the entrance of the archive facility.

The length of time for which study documentation, including raw data, was kept in the archive was defined either in their SOP or in agreement with the sponsor.

Observation made in relation to archive facility, was sufficiently addressed.

5. Premises

During the inspection, a tour of facilities was conducted. CP-II facility was visited on Day 2 of inspection.

CP-I facility consisted of:

- 80 beds clinical wards divided in two clinics of 40 bed
- Dedicated registration/medical screening area
- Well-equipped ICU, Bed lift, Ramp
- Ambulance to take care of emergencies
- Dedicated Pharmacy with restricted access
- Clinical diagnostic laboratory
- Bioanalytical laboratory
- X-ray room

CP-II facility consisted of:

- Registration/Medical screening area
- 84 beds clinical wards divided in two clinics with 54 beds in Clinic-I & 30 beds in Clinic-II
- Well-equipped ICU's to take care of emergencies associated with tertiary care hospital (Within the facility)
- Dedicated Pharmacy with restricted access
- X-ray room

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

Adequate safety measures appropriate to the potential risk involved for the subjects were implemented. Entry to the restricted facilities was controlled by using individual digital keys. A visitor log was available to record the entry and exit information of the facilities' visitors, including volunteers, pharmacy, sample storage room, etc.

The floor plans were reviewed to verify that the facility layout and design suit the operations to be carried out in them. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Adequate storage space suitable for samples, standards, solvents, reagents, and records was available.

Premises had systems in place to dispose of waste.

Digital temperature monitoring systems were used for temperature monitoring of cold storage facilities, whereas hygro thermometers were used for other facilities such as archive facility and pharmacy.

The facility was equipped with UPS and a diesel generator. A daily check of the generator took place and was recorded in a maintenance logbook.

The CP-I facility was associated with a close tertiary care hospital (10 min drive from the facility). The agreement was available. The initiation of the study was communicated with the hospital in advance, via email.

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

The procedures for the handling of ECG instruments and the associated logbooks in CPU-II, together with the respective access control, functionalities of the associated software system, and the availability of audit trails were inspected.

Pharmacy

For each clinical unit, an independent pharmacy area was established. The premises of the pharmacy located in CPU-II was visited and inspected.

Access to the pharmacy was restricted and controlled by access rights assigned by the management. The entry/exit information was documented in the respective logbook. The pharmacy was monitored for humidity and temperature. Records on actual, as well as minimum and maximum temperature values, were maintained.

The pharmacy area had an independent storage section for quarantined and retained investigational products, as well as test and reference products used for ongoing studies. Any movement in and out of these cabinets was documented in logbooks.

Dispensing of IMPs was performed in a qualified safety cabinet. In addition, a balance was kept in the pharmacy to be used for dispensing applicable IMPs, such as creams.

Observation made in relation to Premises was adequately addressed.

6. Personnel

There was a sufficient number of 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 foreseeable emergencies. Each employee had a training folder containing a CV, JD, training schedule and training records, questionnaire, certificate, personnel credentials, and other related documentation. The delegation of significant trial-related duties was documented in writing. Contract workers might be employed to perform certain activities when needed.

There was also confidentiality, non-disclosure, non-compete, and non-solicit agreement between the organization and the staff.

Observations made in relation to personnel, were adequately addressed.

Clinical section

7. Clinical phase

The CRO had rooms to meet applicable requirements for a clinical site. Facilities for changing and storing clothes and for washing and toilet purposes were clean, well ordered, easily accessible, and appropriate for the number of users.

The study site had rooms or areas for subject registration, screening activities, exchange of information, questions related to the informed consent form, administration of IMP, sample collection and processing, dining room, etc.

Provisions were made for the urgent transportation of subjects to a hospital or clinic equipped for their emergency care when required. For CP-I, an agreement was signed with a hospital to provide medical care in emergency cases. An email notification sent to the hospital for study C20105 (WHO application no HP030) was verified.

Access to key documents, such as the randomization list, was restricted to specific personnel, i.e. Study QA staff. The randomization list was distributed to the applicable staff in a sealed envelope or via password-protected emails.

The adequate function and performance of emergency-use equipment (e.g., defibrillators & nebulizer) were verified at appropriate intervals. The maintenance of randomly selected equipment was verified, and the list of medication stored for emergency use, and its respective logbook for usage were inspected.

Urine tests were carried out to detect the presence of alcohol in the subjects' blood system instead of alcohol detector device, during the Pandemic. However, a digital alcohol tester breath analyser was also available to be used as per protocol requirements prior to the Pandemic. The use of a tester was demonstrated to verify the device indicator's ability to show whether a sufficient quantity of lung air was blown into the device.

Observations made in relation to Clinical phase, were adequately addressed.

8. Clinical laboratory

A clinical laboratory was located and accredited at the CP-I facility for analysing samples. Haematological and clinical chemistry tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol. Procedures for sample labelling, receipt, storage, and chain of custody could ensure full traceability and sample integrity. However, the instruments were not equipped with adequate audit trails to ensure the integrity of laboratory reports.

A dated list of laboratory normal ranges and the accreditation certificate of the laboratory, including the current and signed curricula vitae of the responsible person, were available and reviewed. The respective SOP for recruiting volunteers also defined the acceptance of non-significant laboratory abnormal results.

The laboratory created individual reports for each subject and included them in the CRFs. Raw data for all tests performed were archived by the CRO in electronic format in the respective software system through an automated process.

Observations made in relation to the clinical laboratory were addressed in the respective CAPA plan.

9. Ethics

Trials were approved by an independent ethics committee (IEC) before any study was conducted, in accordance with the applicable requirements. The Ethics Committee's approval, i.e., MAARG Independent Ethics Committee, for study HP030 was reviewed to verify the independence of the members and the list of submissions, including a new version of ICF, translation, and back translation documentation, as well as a protocol Errata, dated 19 Oct 2020.

Study HP030 was insured through an agreement from 4 Jun 2020 until 3 Jun 2021 by an insurance company. The policy would be renewed and applied to any study conducted for the respective period.

10. Monitoring

The conduct of studies was generally monitored by a sponsor-designated monitor. The monitoring documentation of Study C17401 (WHO application no. HA426), including monitor visit log, site initiation visit report, interim visits reports, and close out visit report, and response to the monitoring report and the respective CAPA plan was reviewed.

Observations made in relation to monitoring, were adequately addressed.

11. Investigators

The principal investigators (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 of the protocol and the final study report.

Qualification, training of study investigators, and their experience in the conduct of BE studies were randomly selected to be reviewed and verified. A medically qualified investigator was always responsible for the integrity, health, and welfare of the subjects during the trial and for the accurate documentation of all trial-related clinical data. The investigators were permanent employees of the CRO through a respective contract, as per the organization's procedures.

If any of the clinical laboratory parameters were found to be beyond laboratory range but otherwise deemed to be clinically non-significant, i.e. normal by the physician and PI, the same was denoted as NS with the physician's medical justification and signature along with the date on the laboratory report, in accordance with SOP for pre-study evaluation of volunteers for study enrolment (Screening) and handling of volunteers failed in screening.

12. Receiving, storage and handling of investigational drug products

The CRO recorded all the information concerning the receipt, storage, handling, and accountability of investigational products. The records of information about the shipment, delivery, receipt, description, storage, and dispensing were available. At the time of inspection, a reconciliation of one of the IMPs was performed to verify the process.

An adequate number and suitably qualified pharmacists were available. Study medication was kept in securely locked cupboards, and access to the pharmacy was restricted to authorized personnel.

Procedures for the generation and handling of the randomization list were available. Access to the randomization list was limited to the statisticians, the pharmacist, and quality assurance. In case of emergency, a sealed envelope containing the randomization list was available for PI and delegated staff.

Generation of labels reduced the potential risk for mislabelling by applying the procedures for line clearance and a number of quality controls. The content of the labels included all required information. During the inspection, the content of the labels affixed on the dispensing containers and the CRF-specific page, as well as compliance with the randomization list, were verified during the administration of the IMP.

All surfaces used for dispensing and packaging of IMPs were cleaned, and any material not required for the activity was removed before bringing bottles of the product into the area. A reconciliation of all materials used and remaining after completion of the respective activity was performed. Line clearance was ensured. Records were adequately documented.

Quality control personnel were required to verify adherence to the provisions during dispensing and packaging and to document these verifications in detail.

Remaining IMP, as well as empty containers, were retained and found to be adequately stored. The retention period of the IMP was defined in the respective agreement/documentation.

During the inspection, the reconciliation of the IMP for study CT_G07 1.2 was reviewed. The number of remaining and used IMPs was compared to the information provided in the study report. The records were found to be adequate, and all required activities, including quality controls, were documented.

The administration of IMPs for study HP030 (C20105) was reviewed. Dosing was performed in accordance with the applicable SOP and protocol under the supervision of the investigator / designated person and directly documented in the CRF with exact information about the time of dosing. It was verified that the subject had swallowed the product through a mouth check. Investigational product reconciliation after dosing was confirmed by a second responsible person.

13. Case report forms

CRFs were properly designed to record data on each subject during the trial, and the issuance of the forms was controlled in accordance with the applicable SOPs. Therefore, the templates were numbered with a unique issuance number. The CRFs had a section for drug dispensing with information about the time of administration (scheduled and actual time). ID cards were issued and verified. Mouth checks, water consumed, and swallowing checks were all confirmed on the CRF.

The volunteers' visit log was also reviewed to verify the general screening of volunteers prior to the study-specific screening.

A number of subjects pertaining to studies C20105, C17401, and C17401 were randomly selected to verify compliance with the protocol with regard to collection of data, data integrity, source data, investigators' certification, administration of IMP, sample collection actual timing, medical history, use of concomitant medication, adverse event reporting, obtaining of ICFs, inclusion & exclusion criteria and ECG, X-ray, and laboratory reports. The reason for the subjects' withdrawal was confirmed.

The Audit trail of the respective software system for the period of running the abovementioned studies was provided and reviewed.

Observations made in relation to ECG reports were adequately addressed.

14. Volunteers, recruitment methods

Prospective volunteers reported to the CP-I or CP-II facilities through word of mouth. New volunteers were registered in the database for volunteer registration.

Volunteers were received at the gate security where they were registered upon their arrival in a logbook for screening or study logbook respectively.

Initially, volunteers underwent the registration process by documenting their details, as well as confirming adequate literacy skills, in the volunteer registration form, after giving the volunteer consent for registration in the Aizant's database. Volunteers' personal details were updated in the volunteer database and a unique five-digit volunteer registration

number was allotted to each volunteer and a volunteer photo identity card was generated. Subsequent visits of volunteers to the CRO facility for any purpose would be identified by a unique registration number in the database. The database was currently used only for verification of eligibility of volunteers already registered in the system through a biometric device (left index finger and right index finger – depending on subjects’ gender and photo). Screening validity (21 days window prior to the check-in period) and project eligibility to avoid double participation were checked by the staff responsible for registration. The VCPVS database was used to avoid cross-participation in clinical studies.

Volunteers underwent the screening process after giving their consent for screening as prescribed in the respective SOP. During the screening, the volunteer's medical information was verified and documented in respective forms as defined in relevant SOPs. Volunteers’ data was maintained in a database with restricted access to only the concerned staff.

During screening activities, volunteers undertook study-specific x-ray, ECG, protocol-specific haematology, biochemistry, serology, and urine tests up to 21 days prior to the check-in process.

Volunteers selected in the screening and reporting for study participation underwent the study informed consent process. Informed consent presentation was given in groups in vernacular language by the designated study personnel followed by a One-on-One presentation with the Clinical Research Physician and/or CRA to resolve medical/general study-related queries. The group presentation abstained during the Pandemic. Volunteers could proceed with study-specific activities only after having obtained their consent for study participation. Ample time was given to the volunteers to take a decision on their study participation. The Informed consent process (Group and One-on-one) was video recorded. Concerned study personnel obtained consent for study participation from volunteers. The information regarding the general screening was recorded in the volunteer eligibility logbook for registration/screening.

Sample size per protocol was defined in accordance with SOP for Sample size determination for Clinical Studies using SAS software by a statistician. The result was communicated to the protocol writing group.

A Master List of subjects with the name of all study participants was provided for each study, in addition to a list of eligible volunteers provided prior to the study to select the appropriate subjects based on a first man first-served arrangement. This list was prepared based on the eligible volunteers who had participated in the general screening phase.

Observations made in relation to volunteers and recruitment methods were addressed in the respective CAPA plan.

15. Food and fluids

Standardized meals were designed by a dietitian with appropriate qualifications, training, and experience.

The preparation of food was outsourced to a catering service at CP-I.

An in-house kitchen was designated for the preparation of subjects' meals at CP-II. The preparation of food in accordance with the protocol requirements was supervised by a qualified dietician. The facility was not visited, due to time constraints.

Records of the timing, duration, and amount of food and fluids consumed were maintained in the respective subjects' CRFs.

16. Safety, adverse events, adverse event reporting

Adverse events were adequately documented in the Adverse Event Reporting form according to the applicable SOP for both adverse events occurring during the study and post-study.

Concomitant medication was also captured on the form if relevant. The logbook for the usage of medicines in emergency for the period of studies was reviewed.

Bioanalytical section

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

Several personnel involved in the bioanalytical activities were interviewed. The inspection team received adequate assistance for the review of the study documentation.

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

All analytical methods on which the analysis of the study samples was based, were developed and validated by Aizant's bioanalytical department. A set of SOPs provided a detailed description of how to develop and validate analytical methods. Method development was based on publications that were available on site and the selection of the

isotope-labelled internal standard was sufficiently justified. Method development was followed by pre-method validation experiments.

Method validation was based on the EMA and FDA guidance document on bioanalytical method validation. The execution of the required experiments incl. the acceptance criteria was thoroughly described. This included tests to be performed to support the stability of all analytes and various conditions. The general stability data (stock solution, bench top, freeze-thaw, autosampler, and short-term stability) were available at the time of analysis of study samples. Long-term stability data was partly performed in re-validation studies. The storage period of the study samples was covered.

The inspection included audit of randomly selected source documentation and raw data for validation of bioanalytical methods. Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs were inspected along with the chromatograms generated from analytical runs. The audit trail of HPLC-MS/MS instrument AIZ/BL/0238 was verified and conformance to the validation report was confirmed. The preparation of analyte stock solutions, calibration standards, QCs, and internal standards, and reagents were also audited.

As part of the validation, one validation run contained a number of samples comparable with the runs injected during the study samples analysis. Calculation of matrix factor and recovery was verified. The signals reported in the validation report were compared against analytical raw data. The LLOQ of the validated methods was found to be adequate to quantify at least 5% of the C_{max} of study subjects.

18. Sample collection, storage and handling of biological material

The conditions for storage of samples were specified in the analytical study plan as well as in the analytical method. All occurred temperature deviations were documented and evaluated as required by the applicable SOPs. Procedures were in place to ensure sample integrity in case of a power outage and failure of freezers and deep freezers. All freezers and deep freezers were temperature-monitored, and an alarm system was installed. Storage of samples was documented, and the records were maintained. Samples and backup samples were separately shipped. Risks for sample mix-up and cross-contamination were adequately addressed. The duration of storage of the samples was specified in the agreement with sponsors.

Actual sampling times and deviations from the prespecified sampling times were directly recorded in the CRFs. Deviations were noted to be reported in the study report and were considered when calculating the pharmacokinetic parameters. Labelling of collected samples was clear to ensure correct identification and traceability of each sample.

Samples were provided in two aliquots and separately stored/shipped. The storage conditions of the plasma samples were compared to the stability data available.

The inspectors verified raw data captured in forms and logbooks associated with sample transfer, from the clinical to the bioanalytical department.

The samples, sampling method, volumes, and quantity of samples were adequately specified in the study protocol. A detailed description of analytical procedures was captured in the analytical study plan and the analytical method. In addition, applicable procedures were established to define sample handling, processing, analysis, and storage, as well as run acceptance conditions, criteria for re-analysis of samples, and incurred samples re-analysis process.

Analytical runs included a set of calibration standards, QC samples, as well as all samples of one or more study subjects. The ID number of instruments used for sample analysis was documented. Although the absence of carry-over effects was ensured, samples were injected in accordance with their sampling time point to avoid the injection of low concentrated samples after high concentrated samples.

Blank plasma was used for the preparation of calibration standards and QCs in bulk. The individual aliquots were numbered and stored together with the study samples. A total of five freeze and thaw cycles were evaluated for all analytes in plasma. The same anti-coagulant used for the study samples was applied.

Procedures on incurred samples reanalyses were compliant with the EMA Guideline on bioanalytical method validation. The difference between the original results and the results of the reanalyses was evaluated and reported.

Observations made in relation to sample handling methods were adequately addressed.

19. Data processing and documentation

The designated operator exported the concentration data from Analyst® to the Excel sheet template. The data was required to be quality controlled by the QC group and stored in a folder that was only accessed by the Head of the PK and BA. An email was sent to the statistician when the list was transferred to the PK group for further usage.

Integration settings were science-based and fully justifiable. Smoothing was kept low enough not to mask possible interferences and changes in peak geometry.

The analytical raw data of randomly selected studies, i.e., C20105, C17276, and CT-G-071.2, were provided and inspected in detail:

- The records of the individual batches consisted of a system suitability test, batch processing records, evaluation of acceptance criteria and the run sequence. All time points associated with handling of samples, i.e. withdrawal, restorage, intermediate storage, start and end of processing, loading into auto sampler and start of analysis were documented.
- The maximum storage period for the individual conditions was calculated and compared with the stability data.
- Reinjection incidence reports, including reasons for reinjection were available and verified.
- Source documentation and raw data were reviewed and verified.
- Results of calibration standards, quality control samples (QCs), subject plasma samples in analytical runs were inspected along with the respective chromatograms.
- The preparation of analyte stock solutions, calibration standards, QCs and internal standards, as well as reagents were confirmed.
- Retrieval and restorage of study samples were reviewed and verified.
- The respective audit trail was verified against the study raw data.
- The reported concentrations were compared with the analyte concentrations documented in the reporting tables generated by the acquisition software.
- Handling of temperature excursions and documentation of relocation of study samples were verified. In addition, temperature records of deep freezers used for plasma samples of study C20105 were confirmed. The storage conditions of study samples were verified.

20. Good laboratory practices

Sample storage facilities were adequately qualified, calibrated, and maintained, equipped with an adequate monitoring system to control the temperature. If there was an automatic alarm system. The daily monitoring of temperature was documented. A temperature mapping of cold storage facilities was performed.

Balances, other measuring devices and equipment, and instruments used during the conduct of a trial were periodically calibrated and verified before use to fit their intended purpose. The performance verification of the micro-pipette was demonstrated at the time of inspection.

SOPs for the operation, use, calibration, checks, and preventive maintenance of equipment were available. Records of usage were documented in respective logbooks. Items of equipment used in the Laboratory were identified to enable verification that they had been appropriately qualified and calibrated.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration (if appropriate), expiry date, and specific storage instructions.

Observations made in relation to good laboratory practices were adequately addressed.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The statistical model was stated in the respective protocol and calculations were made by suitably qualified personnel in PK department. The biostatistician was responsible to generate the randomization schedule upon request from Pharmacist. The pharmacist requested the biostatistician for the randomization schedule through ‘The randomization Requisition Form (Attachment-3)’ which had the product details like Test(s), Reference(s), and Lot/Batch information. The completed form was reviewed by the QA designee. The biostatistician also received the IEC-approved study protocol provided by the QA/designee. The randomization list was generated using the respective software system. Reproducibility of the randomization list for study C18258 by using the specific seed number was verified during the inspection.

A software system was used for statistical analysis.

A database of trial records was maintained and was locked after the completion of the study. The dates of statistical analysis were documented and mentioned in the study report, and the process was defined in the respective procedures.

22. Study report

Procedures were established to ensure that the clinical study report accurately reflected all the study procedures and results.

The study report was randomly compared with the raw data to verify that discrepancies between the results stated in the report and the actual original (raw) data did not take place.

All parts of study report were required to be quality controlled by the designated QA-personnel.

Miscellaneous	
<i>Assessment of the CRO master file</i>	The CRO master files (CROMF) was reviewed. The company's master files provided introductory information of the organization and covered the information required by the guidelines for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7).

Part 3	Initial conclusion – inspection
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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 ***Aizant Drug Research Solutions Private Limited***, located at ***Survey No.: 172 & 173, Apparel Park Road, Dulapally Village, Dundigal- Gandimaisamma Mandal Medchal-Malkhajiri District, Hyderabad, Telangana; India.***

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

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of guidelines referenced in the inspection report
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- 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf
- 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://www.who.int/tdr/publications/documents/gclp-web.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 Annex 3
https://apps.who.int/iris/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1
4. WHO good practices for pharmaceutical quality control laboratories, 2010 (WHO Technical Report Series, No. 957), Annex 1.
Short name: WHO GPPQCL Annex 1
https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodpracticesPharmaceuticalQualityControlLaboratoriesTRS957Annex1.pdf
5. 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/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1
6. 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
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
7. 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://www.who.int/ethics/publications/9789241502948/en/>
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;jsessionid=B7F180F317E8BE2DB4289C7BF9A561FF?sequence=1

9. 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/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf?ua=1

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

Short name: Glove use information leaflet

http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

11. 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 No. 1033, Annex 4

<https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations>

12. 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 Technical Report Series, No. 1003, 2017, Annex 6

Short name: WHO multisource guidance

https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf

13. 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 1025, Annex 4

<https://www.who.int/publications-detail/978-92-4-000182-4>

14. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. WHO Technical Report Series, No.961, 2011, Annex 9.

Short name: WHO TRS No. 961, Annex 9

https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1

15. Ethical principles for medical research involving human subjects, 52nd WMA General assembly, Edinburgh Scotland, October 2000.

Short name: Declaration of Helsinki

[https://www.who.int/bulletin/archives/79\(4\)373.pdf](https://www.who.int/bulletin/archives/79(4)373.pdf)

16. Good manufacturing practices: guidelines on validation, WHO Technical Report Series, No. 1019, 2019

Short name: WHO TRS No. 1019, Annex 3

https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1