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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical, Bioanalytical and statistical Research Site	**ACDIMA Center for Bioequivalence and Pharmaceutical Studies (ACDIMA BioCenter)** 18th Salah Shimat St. Sweifieh - Amman Hashemite Kingdom of Jordan Tel: + 962 6 582 1618 Fax: + 962 6 585 3719 Mobile: + 962 795616375 (7days /24 hours) Website: www.acdimabiocenter.com E-mail: biocenter@acdima.com
Corporate address of Organization	As mentioned above
GPS coordinates	31.95794° N 35.86948° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. TB387** Bioavailability study to compare Rifampicin/Isoniazid/Ethambutol HCL/Pyrazinamide Film-Coated Tablets (150 mg rifampicin / 75 mg isoniazid / 275 mg ethambutol HCL / 400 mg pyrazinamide) **WHO application no. MA187** Bioequivalence study to compare Maldox tablets (500 mg sulfadoxine / 25 mg pyrimethamine)
Inspection details	
Dates of inspection	21-23 September 2022
Type of inspection	Routine

Introduction	
Summary of the activities	ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies (ACDIMA BioCenter) is a Contract Research Organization (CRO) that was established in 2000 to provide principally bioequivalence and clinical studies services, based in Amman (Jordan). The center is considered one of the multi-projects invested by the Arab Company for Drug Industry and Medical Appliances (ACDIMA) Board of Directors.
General information about the company and site	The CRO provided the following core business services: - Clinical Development Support Services. - Bioanalysis and Pharmaceutical Analysis Services. - Technical and Techno logistical Support Services - Total Quality Management Services. - Training and Professional Qualification Services - Bioequivalence studies. - Bioavailability studies.
History	The CRO was previously inspected by WHO in 2016, in addition to inspections performed by Turkey and JFDA authorities in recent years.
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, software system validation/qualifications, employee training, computer controls, and a tour of the facility, including the Medical Laboratory and the respective equipment with associated software systems. Regarding the Analytical operations, coverage was provided to firm 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.
Scope and limitations	
Out of scope	Not applicable

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

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PART 2	SUMMARY OF THE FINDINGS AND COMMENTS

General section

1. Organization and management

A presentation was provided explaining the organization's activities in detail by Dr. Rabab Tayyem as CEO/Executive Director and Dr. Mohammed Abufara as Assistant Executive Director / Medical Director.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organization chart was authorized, and kept up to date.

There were over 80 employees at the time of inspection. There was a job description for each employee, including a description of their responsibilities. It was randomly verified that every job description 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.

The principles of Good Laboratory Practices had sufficiently established the responsibilities of the test facility management. The CRO management was aware that as the investigator was an employee of the CRO, some of the responsibilities usually assigned to the investigator would, in a similar way, reside with the CRO management.

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 agreements for the conduct of a BE/BA study between the CRO and the sponsor were available. The requirements for archiving study documents (10 years), confidentiality, and study medications (5 years) were specified in the agreement. The requirement for the retention of samples was defined in the study protocol.

2. Computer systems

A list of software and computer systems used in the studies was provided.

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and were validated, operated, and maintained in accordance with the principles of GCP and GLP, as appropriate. Risk assessment was required alongside change control to assess the possible impact of the change so that action could be taken to reduce or eliminate risk. The evaluation might be used to determine the extent of validation required.

An inventory of all computerized systems on the network was available.

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.

The 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 database was maintained. Secure and unique, individual-specific identifiers and passwords were used.

Randomly selected software programs used to perform key steps were reviewed to verify whether they were suitable and validated for the intended use. The qualification and/or validation certificates were requested to provide insurance that the software was validated for its intended use and that it was developed and controlled by a QA system.

SOPs for usage of each software program used to perform activities of a BE/BA study was available.

Software programs used, frequency of virus testing, storage of data and the procedure for backups, and long-term archiving of all relevant electronic data were specified in SOP for Electronic data archiving and backup, including frequency of backups and archiving. Electronic data was backed up at regular intervals. The reliability and completeness of these backups were verified monthly according to the procedure. The documentation of the last data restoration performed on 1 Sep 2022 was available and reviewed. The agreement with the Cloud system provider was prepared and available. A flowchart for data Backup was provided during inspection to illustrate the backup flow adequately.

Networks, including the full client/server architecture and interfaces such as laboratory information management systems (WATSON LIMS), were designed, qualified, managed, and controlled.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.), were designed to prevent errors. The data entry process was specified in the SOP for Data entry.

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

3. Quality management

The CRO had appropriate 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.

A Quality manual was provided. A Quality Policy was implemented in the CRO's QM.

QA personnel were not directly involved in trial-related activities, and an in-process audit by QA personnel did not replace oversight by another person when required. The direct line report of the QA unit to the CEO was illustrated in the CRO's organizational chart. An audit plan and program for the vendors used for the study activities were also available

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed in accordance with SOP for Routine analysis report and data audit and SOP for Good Clinical Practice audit.

The quality management system included root cause analysis, ensuring data integrity, and the implementation of appropriate corrective and preventive action (CAPA).

The observation in relation to Quality management was sufficiently addressed in the respective CAPA plan.

4. Archive facilities

The CRO had sufficient and appropriately secure storage space, fireproof, relative humidity-controlled, and pest-controlled, for archiving the trial-related documentation. A water sensor was installed in the archive facility located in the basement to ensure the detection of any water intrusion.

The archiving activities were managed in accordance with SOP for Archiving, retention, and trailing of paper-based documents.

Access to archive storage areas was controlled and restricted to authorized personnel.

A list of authorized personnel was prepared to be displayed at the entrance of the archiving and pharmacy facilities at the time of inspection.

Records of document retrieval and return were maintained. The length of time for which study documentation, including raw data, should be kept in the archive as defined in the SOP. This period was also specified in the contract between the sponsor and the CRO.

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 kept clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

Clinical trials were carried out under conditions that ensured the safety of the subjects. The site selected was appropriate to the potential risk involved.

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 electronic key-cards/chips. Alarm systems to detect the exit of subjects from clinical facilities were installed, and/or the doors were locked. The Emergency evacuation was ensured. Any entry to and exit from the facility were recorded.

The Clinical Unit 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 of each visit to the pharmacy were maintained. During the visit, it was emphasized to use shoe covers to ensure adequate hygienic operations within the facility.

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

Laboratory premises were designed to provide adequate protection to all employees and authorized external personnel, including inspectors, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Safety data sheets were available to staff before testing was carried out. Staff working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff was trained to use the firefighting equipment, including fire extinguishers and gas masks. Staff was instructed to wear laboratory coats or other protective clothing, including eye protection. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison,” “flammable,” or “radioactive”) whenever appropriate.

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

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

Observation related to Premises was adequately addressed in the respective 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 all reasonably foreseeable emergencies. At all trial stages, including at night, there were qualified and trained personnel to ensure that the subjects' rights, safety, and well-being were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities.

Randomly selected current curricula vitae and 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 CPU was equipped with 110 beds. Systems were in place in the accommodation facilities so subjects could alert CRO staff in case of need.

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. Lockable toilets were alarmed, and doors were designed to ensure they could be opened from the outside should a medical emergency occur.

The clinical site consisted of:

- subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- CPU;
- subjects' recreation area;
- pharmacy;
- room for administration of the investigational products and sample collection;
- sample processing (e.g., plasma separation) and storage (freezer);
- archive facility;
- a dining hall;
- ICU

Provisions were made for the urgent transportation of subjects to the hospital through the Emergency call. A Mock drill was required to be carried out every six months. The last Mock training was documented on 8 Jun 2022 to Al-Istihari hospital. The length of duration was verified to be 17 minutes.

Access to the randomization list was restricted to the staff involved in the clinical study activities in charge of the study by the applicable SOP.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified at appropriate intervals.

8. Clinical laboratory

An in-house clinical laboratory was used for analysing samples. The laboratory was accredited by JFDA on 14 Sep 2021, by Ministry of Health on 24 May 2012 and by ISO 15189 (JAS Accreditation Unit) on 2 Jan 2020.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol.

Sample labelling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

The CRO had the information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges, and the accreditation certificate of the laboratory.

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

The laboratory created individual reports using the Medical Laboratory software system (MABS) for each subject and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic or paper formats, depending on their source and the laboratory's storage capacity.

It was noted that the classification of the out-of-range results as clinically significant was the clinical decision of the clinical investigator/principal investigator. Such decisions were guided by a predefined criterion, i.e., based on either clinical manifestation or a predefined threshold of deviation from the reference range in accordance with for Reference range determination and review. The results were considered not clinically significant if the result deviated by less than 5 % from the reference range for indices and less than 10 % from the reference range for other lab tests.

9. Ethics

Trials were approved by ACDIMA BioCenter IRB. The composition of the Ethics committee was available in the study file, together with the endorsements. The final approval of the protocol for study in the scope of inspection was reviewed. The process of ethics approval was completed 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. The IRB was given sufficient time for reviewing protocols, informed consent forms (ICFs), and related documentation, as appended to the protocol.

The study subjects were adequately insured through a study-related policy number with Arab Orient Insurance Company.

The end of the studies was reported to the IRB on 16 June 2020.

All applicable regulatory approvals were also available and archived in the ISF.

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 the start of any trial-related activities in the presence of an external witness. The information was clear that participation was voluntary and that the subject had the right to withdraw from the study on their 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 was available through an insurance policy.

The volunteers were given the opportunity 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

A monitor as sponsor representative from Molecule Contract Research Organization was present during dosing administration of Period I, Period II and before the initiation of study in the scope of inspection. A brief monitoring report was provided.

The site did not keep a monitor visit log; however, the date and type of visits were mentioned in the Monitoring statement provided by the monitor at the end of study. Moreover, an adequate corrective action was implemented.

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 for signing the protocol and the final study report.

His adequate qualification and experience were verified through his CV, signed and dated, which was available in the ISF.

12. Receiving, storage and handling of investigational drug products

The information concerning the receipt, storage, handling, and accountability of investigational products at every trial stage 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 under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through a software system and data logger. Records of temperature control were appropriately kept.

Randomization was performed in accordance with the applicable SOP, and records were maintained.

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.

Adequate 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 identical labels. Labels were designed to have two identical portions to have one portion pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The empty containers were labelled separately for the test and the reference investigational products. They remained segregated in a secure area under lock and key to avoid the risk of any potential mix-ups until the dispensing stage.

The dispensing and packaging procedures were performed according to the appliable SOP. Dose administration was carried out under the investigator's supervision and a qualified staff member to whom this task was explicitly delegated in writing. 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 in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. Dosing was directly documented in a template for the Investigational product administration form". The templates were issued in accordance with the applicable procedures, and the documentation was available and reviewed.

Sample retention was defined and described in the respective 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 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. Information about screening procedures, physical examination, subject history, and personal information, inclusion & exclusion criteria, dosing administration time, vital signs during the study, sampling time points, alcohol and drug test verification, intake of food, withdrawal information, concomitant, and AE was recorded in the CRFs.

The raw data regarding the time points for food and fluid intake, vital sign records, etc., were documented in the respective form and kept in the ICF with the rest of the essential documentation.

At the time of study in the scope of inspection, the CRO used a kit to verify alcohol consumption using saliva (under the tongue). For drug tests, the CRO used a kit.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers specified in SOP for Subject recruitment and SOP for Screening Procedures included a description of the potential methods the CRO used for this purpose. A database maintained by JFDA (Participants in Clinical trials database) was deployed on volunteers to avoid cross-participation and to specify a minimum time (80 days) that should elapse between a volunteer's participation in one study and the next. Access to the database was password controlled and limited to the study staff to secure confidential information on volunteers or subjects.

Identification of volunteers and subjects was ensured by specific national personal ID and/or passport numbers.

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.

15. Food and fluids

Meals were standardized and controlled and scheduled during the study days. Meals, snacks, and drinks for the study subjects were provided as described in the clinical trial protocol and as per an email with the catering service.

Timing, duration, and amount of food and fluids consumed were recorded. Before samples were obtained from ambulatory subjects, they were asked about their food and drink consumption,

Observation concerning Food & Fluids was adequately addressed in the respective CAPA plan.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including the volunteers. The principal or co-investigator was responsible for medical decisions in the case of adverse events and for notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of a serious adverse event.

First-aid equipment and appropriate rescue medication were available in the ICU 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 ICU.

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

Bioanalytical section

The inspection included the audit of paper-based source documentation and raw data for validation of the bioanalytical methods in the respective documents, as well as the compliance of the method execution with the applicable SOPs and guidelines.

A review of the electronic data and audit trails for electronic data capture in the chromatography data management system, LIMS and data handling related to the BE/BA studies was carried out. The method description and parameters applied during method validation, and study sample analyses were verified.

The analysis of plasma samples and 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 performed during method validation during the BE/BA study. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited. The rationale for selecting

rifampicin-d4, ethambutol-d4, [^{2}H4] Isoniazid, and Pyrazinamide-d3 for the study was discussed.

Chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were randomly verified. Determination of the regression curves, in the software systems, was confirmed. The reasons for the study sample repeat analyses and all instrument failures were reviewed. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions. The procedures associated with reporting the final concentrations of the study samples were verified.

For a review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The inspectors were given access to a copy of all analytical raw data generated in the chromatography software system. The analytical raw data in LIMS were accessible within the inspection room.

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. The internal standards used were adequately characterized and handled. A copy of the literature was available.

An analytical plan was provided after the completion of method development related to the study. Due to limitations in analyte stability, two methods had to be developed; one method demonstrated adequate evaluation of the concentration of the analytes, i.e., ethambutol, isoniazid, and pyrazinamide, while the other method demonstrated sufficient assessment of the concentration of rifampicin. A stable isotope-labelled internal standard was always used in the MS methods, and lithium heparin was applied as an anticoagulant.

During the method validation, all parameters were tested in accordance with the applicable SOP. The samples to be analysed, the evaluation of the individual parameters, and the acceptance criteria to be met were controlled in detail. A run was performed to determine the batch with more than 140 samples of QCs and CCs (so-called Analytical run batch determination) that was comparable in length to those that were expected to be used for analysis.

The forms, used for documentation of method validation were controlled following the respective SOP. The sample processing was documented in the respective forms. Any unexpected events were reported, and the respective decisions were adequately justified.

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, which was performed before the issuance of the study reports.

The review of the full method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability and reference standard storage 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 and additives. The plasma used was in general received from the clinical department. The plasma was tested and released for use in the bioanalytical laboratory. The storage conditions as well as any usage of plasma were documented and signed to individual projects. Additionally, all plasma used during sample validation was tested for the absence of interferences before being used.

During study samples analysis, 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 analysed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. A system suitability and stabilization test were done before the start of runs on each day.

Of the first 1000 samples, 10% were used to run Incurred Sample Reanalysis (ISR); of the subsequent samples, 5% were used for ISR. The samples were selected with a concentration around C_{max} and in the elimination phase. The acceptance criteria were clearly defined in the SOP.

The system audit trail review was carried out at the time of the studies in the scope of inspection, and adequate training was provided to the responsible personnel.

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

The specification of samples (blood plasma), sampling method, volume and number of samples were stated in the clinical trial protocol and in the information provided to the volunteers. The collection, preparation, transport or shipping and storage of samples took place in accordance with SOP.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were to be considered when calculating the pharmacokinetic parameters. All time points associated with plasma separation, harvesting, and storage were documented in forms and logbooks associated with analytical equipment or deep freezers.

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 and during transportation. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots, shipped, and stored separately. The shipment of primary samples from the clinical department to the bioanalytical department and the secondary samples from the clinical department to the storage unit in the basement of the facility was reviewed.

19. Data processing and documentation

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

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. When the analysis was repeated, the source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples). The calibration range was properly truncated. Internal standard variations were trended and used as part of the verifications of result validity.

Full audit trails were always 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 in a manner that ensured 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 (e.g., results table audit trail, project audit trail and instrument audit trail).

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.

Observations in relation to Data processing and documentation were addressed in the respective CAPA plan.

20. Good laboratory practices

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

The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE/BA studies, with an established and appropriate QC and QA system.

Deep freezers for storage of the samples and refrigerators for storage of the Reference standards were adequately qualified, calibrated and maintained. There was an alarm system associated with the monitoring system to trigger SMS, emails and call notifications to the custodians responsible for the maintenance of the facility.

For the purposes of qualification verification, the temperature mapping of the randomly selected deep Freezer was reviewed to verify the “hot spot” and the location of the respective sensor. The hot spot was identified on a little scheme available on all deep freezers and refrigerators. The temperature mapping process was adequately carried out at the time of inspection. The possibility of transferring samples to equivalent storage units was verified in case of maintenance and repair.

Balances, other measuring devices, equipment, and instruments 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 and under the control of a dedicated maintenance team. Records were maintained in accordance with the requirements that were asked for. 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 usage of equipment was adequately documented in the analytical sheets, as well as the respective logbooks for usage of the instrument. The usage of columns was recorded in the logbook for usage of columns.

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

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The statistical model underlying the BE/BA analyses was stated in the respective protocol and a statistical analysis plan.

A randomization list was provided based on the code related to the study design using SAS software system.

Sample collection time deviations were provided by the Data Entry group in the clinical unit and sent to the statistical analyst after being QA-checked. As soon as the list was provided, the raw data related to the clinical studies were sent to the archive to be retained for the required period. The table of time deviation was forwarded to the statistical department in an Excel sheet via email. The document was locked, and no modification could be done to the file's content.

The table of concentration was sent to the statistical unit in an Excel sheet and through the LIMS software system. The statistical department ran the data in both formats to verify the statistical results.

The Pharmacokinetic parameters and descriptive statistics were evaluated for C_{max} and AUC using Phoenix WinNonlin Software.

A second qualified person double-checked the data values input by an applicable SOP.

Paper study trial records were maintained and archived as soon as possible after the completion of the study. Once it was locked, the study was unblinded, and statistical analysis was performed.

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.

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

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The CRO site master (CROMF) file was provided in accordance with the guidelines for preparing a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7).
Annexes attached	***N/A***

Part 3	**Initial conclusion – inspection**

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 ***ACDIMA Center for Bioequivalence and Pharmaceutical Studies (ACDIMA BioCenter)***, located at ***18th Salah Shimat St., Sweifieh, Amman; Hashemite Kingdom of Jordan***.

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

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

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

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

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)

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://efaidnbmnnnibpcajpcglclefindmkaj/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

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