World Health Organization

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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	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan P.O Box: 963166 Amman 11196 Jordan
Name and Address of Bioanalytical Research Site	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan P.O Box: 963166 Amman 11196 Jordan
Name and address Statistical Site	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan P.O Box: 963166 Amman 11196 Jordan
Corporate address of Organization	Sport City Circle, Amman, Jordan P.O Box: 963166 Amman 11196 Jordan
GPS coordinates	GPS coordinates 31.98549° N 35.89714° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Study no: SUPY-T0121/13 bioequivalence study to evaluate the bioequivalence of the test product SWIDAR (Sulfadoxine/Pyrimethamine) 500/25 mg immediate release tablet

Inspection details	
Dates of inspection	20 – 23 June 2022
Type of inspection	Routine
Introduction	
Summary of the activities	IPRC offered the following services: - Bioequivalence/ Bioavailability Studies - Clinical Trials (Phase II - IV) - Bioanalytical Services - Data Management / Pharmacokinetics & Biostatistics / Medical Writing
General information about the company and site	IPRC is a privately owned Clinical Research Organization (CRO), established by Prof. Naji Najib in 1997 to provide clinical & bioanalytical services for the pharmaceutical industry.
History	IPRC was inspected by local and foreign authorities, such as US FDA, EMA, Turkish MOH, and SFDA. WHO had previously inspected the organization in May 2015.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility, including observing ongoing studies. Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations, analytical testing and the respective audit trail. 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
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 in detail.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organizational chart was dated 5 Aug 2021, authorized, and kept up to date.

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 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 SOPs were implemented and followed. Maintenance of a historical file of all SOPs was organized.

The JFDA regularly accredited the bioanalytical and clinical sites. The respective documentation was available.

The organization's general working hours were from 8 am to 5 pm.

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.

There were a sufficient number of computers to enable personnel to perform data entry and required data handling 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.

The software programs were randomly selected to review their validation status, at time of inspection.

Software programs used, storage of data, and the procedure for backups and long-term archiving of all relevant electronic data were specified in SOP for the Backup strategy in the IPRC. The methods covered the process of labelling of tapes, daily, weekly, monthly, and yearly backups, as well as system state backup. Backup data were periodically rewritten as part of the backup procedure, and the data from the previous backup was archived. Another SOP was available to describe the backup and recovery procedure for Watson LIMS.

Data restoration was also specified in the same procedure, and the documentation for the most recent restoration was available and reviewed. The last evidence was provided on the form for "Testing the Backup Form" performed on 10 Apr 2022.

customized software programs were available for their intended use:

- For registration and tracking of stock records in the store, including chemicals used in the analytical laboratory
- Access application used in the medical laboratory for recording lab results through data entry.

Networks, including the complete server architecture, were designed, 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 respective SOP.

Excel sheets were used for the calculation of some of the descriptive statistics based on predefined acceptance criteria. The SOP for Calculation of the concentration of stock solutions and weighing of RS was reviewed. The analysts should weigh the exact amount of Reference Standard ±0.1 % to reach the required CCs and QCs, as per the SOP.

Observations made concerning the Computerized system were adequately addressed in the respective CAPA plan.

3. Quality management

The CRO had QA and QC systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and the applicable regulatory requirements.

A CRO Master File was implemented to replace the 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.

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

The investigation of root cause analysis, tracking for trends, and implementing appropriate corrective and preventive action (CAPA) were found adequate through the evaluation of the respective CAPA plan.

Issuance of templates used for study-related activities was described in the respective SOPs for BA-related templates. The issuance of templates was carried out under the supervision of the QA. The templates were numbered, and a tracking record was kept for used and unused templates after the completion of the study.

There was an SOP for the management of SOPs. The responsible person should go through the list on a word document and identify the SOPs which need to be updated. The SOPs were revised every two years based on this list.

Observations made concerning Quality Management System were adequately addressed in the respective CAPA plan.

4. **Archive facilities**

The CRO had sufficient and appropriately secure storage space, which was relative humidity-controlled and pest-controlled, for archiving the trial-related documentation.
Archives were protected from flooding and equipped with smoke detectors and fire extinguishers.

The archiving activities were managed in accordance with the applicable SOP.

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

Records of document access and return were maintained. The length of time for which study documentation, including raw data, was kept in the archive, and defined in the respective SOP, i.e., a minimum of 25 years for clinical study-related documentation and five years for other types of documentation. This period was also specified in the contract between the sponsor and the CRO, which included provisions for the financing of the archiving.

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

Observations concerning the Archive facility were sufficiently addressed in the respective CAPA plan.

5. **Premises**

During days 2 & 3 of the inspection, a facility tour was conducted.

The facilities were 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 adequate safety for 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 key-card access. Any entry to and exit from the facility were recorded in the main reception area for visitors, with exception of volunteers. However, the entrance used by the volunteers was different from the main entrance, and their entrance was monitored for COVID-related measures. The payment for respective study activities was recorded at the time of the subjects' departure.

Sites where clinical activities took place included a pharmacy where investigational products were stored under appropriate conditions with entry and exit restricted by access control. Relevant entry/exit records of each visit to the pharmacy were maintained.

The temperature and related humidity of storage facilities were monitored using the Data logger. Data loggers were associated with an application.

Laboratory premises were designed to suit the operations to be carried out in them. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Adequate storage space was available for samples, standards, solvents, reagents, and records. Biological samples, i.e., plasma samples were stored in the main Deep Freezer area in the basement under the supervision of a Freezer-keeper. The samples were transferred to a Deep Freezer area within the Laboratory facility on the 4th floor as soon as the sample analysis plan was approved to be used for the ongoing studies. The thermometer sensor used for randomly selected Deep Freezer was tested, and the respective temperature mapping was reviewed. The hot spot was identified for the location of the sensor. An email notification was generated upon triggering the alarm.

Laboratory premises were designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, 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. Staff was instructed to wear laboratory uniforms, coats, and other protective clothing, including eye protection. Safety cabinets to avoid the risk of contamination were available. 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 waste, and safety cabinets were in use. The environment was required to be protected in conformance with local or national regulations.

Diesel Backup Generator (DG) and UPS systems were available to generate electrical energy in case public power supply outage. The logbook for weekly maintenance of DG was reviewed.

Synchronized clocks were located throughout the facility to document the exact time study activities occurred. The server room was well organized, with restricted access and an entry/exit record-logbook. Gas cylinders were kept safely.

Observations made concerning Premises were adequately addressed in the respective CAPA plan.

6. Personnel

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. 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. The number of staff members counted to 108 at the time of inspection. Contract workers were employed to perform certain activities, such as study dietician. The respective contract was verified.

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 in six different units spread over six floors of the CRO.

The CPUs were equipped with 180 beds. Systems were in place in the accommodation facilities so that subjects could alert CRO staff in case of need.

Lockable toilets were alarmed, and doors were designed to ensure they could be opened from the outside should a medical emergency occur. The alarms for the CPU and the respective washroom were tested.

The clinical site consisted of

- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy;
- 6 x CPUs;
- Subjects' recreation area;
- Pharmacy;
- Room for the administration of the investigational products and sample collection;
- Sample processing (e.g., plasma separation) and storage (freezer);
- Archive facility;
- Preparation of standardized meals in the kitchen and a cafeteria;
- ICU

Provisions were made for the urgent transportation of subjects to Istikal Hospital. A notification was sent to the hospital before the initiation of the study, which the hospital admitted.

Access to the randomization list was restricted to the pharmacist in charge of the study after being verified by IRB and QA Unit. The list was kept under lock, and the procedure was specified in the 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.

Observations concerning the Clinical phase were adequately addressed in the respective CAPA plan.

8. Clinical laboratory

A suitable clinical laboratory was used for analysing samples. The laboratory was accredited. The facility belonged to the CRO.

Hematological 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 were ensured full traceability and sample integrity using a barcoding system.

A dated list of laboratory normal ranges was available, and a list of acceptable ranges was appended to the protocol, as annex 6 to be used during the study in the scope of inspection.

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

Individual reports were created by the laboratory for each subject and were included in the CRFs. The laboratory archived source of raw data for all tests performed in paper formats.

Data integrity requirements were ensured for all tests related to the study through adequate validated systems used for sample analysis. The laboratory used hematology analyser and biochemistry analyzer. Both systems' applications were reviewed to ensure the data integrity of the results. Modification, edit, and deletion options were not available.

9. Ethics

The Institutional Review Board of IPRC, Amman, Jordan endorsed the ethical conduct of the study and approved a favourable opinion on the protocol. The Board was constituted and operated in accordance with the principles and requirements described in Guidelines on Research Involving Human Subjects. The IRB of IPRC reviewed the study protocol. The study protocol was approved on 25 Feb 2021, and version 01 approval was issued on 14 Mar 2021. The WHO prequalification team also reviewed this protocol. The clinical trial was authorized by the Jordan Food and Drug Administration (competent authority of Jordan) on 14 Mar 2021.

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.

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

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through an Insurance policy, i.e., EuroArab Insurance.

The volunteers or subjects 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

The site initiation visit report was available. The primary responsibility of the monitor, who was the sponsor representative for a BE study, was to ensure that the study was conducted in accordance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. This included verifying the use of correct procedures for completion of CRFs and confirming the accuracy of data obtained.

In total, three visits, as well as a site initiation visit during the conduct of the trial, were performed. The monitor prepared a written report for the site initiation visit and a verification letter for the subsequent visits.

Observations related to Monitoring were sufficiently addressed in the respective CAPA plan.

11. Investigators

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

The sponsor and the CRO signed an agreement for the study protocol in accordance with the requirements.

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. Additionally, the information about the shipment, delivery, description, storage conditions, dispensing, administration, and reconciliation of any remaining pharmaceutical products, were verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date were reviewed.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through a digital data logger and the records for controlling temperature and relative humidity were available.

Randomization was performed following the respective SOP, and the records were maintained, including the randomization list and seed.

The randomization list was prepared by Data management Unit. The list was submitted with other study-related documentation to the IRB by the person responsible per the local requirements. After receipt of IRB approval, the list was e-stamped, verified and scanned by the Quality Control group before being handed over by the data management Unit to the pharmacist for dispensing IMPs.

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.

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.

Dispensing and packaging procedures were performed in accordance with the applicable requirements. Dosing was performed in accordance with the applicable SOP, under the supervision of the investigator and 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 and a penlight, in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. A second verification check was also performed. Dosing was directly documented in the CRFs.

Samples of the product in the original container were retained for possible confirmatory testing in the future for at least one year after the expiry date of the newest product. Sample retention was defined and described in the respective SOP. Upon completion of clinical conduct, the quantities provided by the sponsor were reconciled. The remaining unused samples were counted and compared with the expected final balance by the responsible pharmacist and then verified by another pharmacist. The remaining quantities of IPs were stored in the pharmacy until ready for shipping back to the sponsor or to be destroyed. The procedure was specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

Observations concerning the Handling of IMP were adequately addressed in the respective CAPA plan.

13. Case report forms

Randomly selected CRFs from the study 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 dosing, intake of food and fluids, medical record, sample collection, inclusion & exclusion records, etc., was recorded in the CRFs.

The study investigator File and TMF were reviewed and verified.

14. Volunteers, recruitment methods

The subjects were recruited by word of mouth. JFDA had established an External JFDA subject database to register all the volunteers/study subjects attending any clinical trial in Jordan, to avoid cross-participation and to specify a minimum time, i.e., 80 days that should elapse between a volunteer's participation in one study and the next. The CRO recorded the subjects by name, personal ID number, sex, DOB, and nationality. The CRO was not allowed to recruit volunteers before being verified in this database. Access to the database was password controlled. The data could not be deleted or modified. However, new volunteers could be added to the list. Only JFDA was authorized to delete any volunteer or amend errors. The system was successfully tested, and the NRA deleted the erroneous addition of volunteers upon request from CRO. The email correspondence was provided and available.

Identification of volunteers and subjects was ensured using their Jordanian ID cards and the respective unique social security number.

The informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study. The clinical trial protocol described criteria for subject selection (inclusion and exclusion criteria) and screening procedures. The breath alcohol tester was tested to verify its proper functionality.

Observations concerning the Recruitment method were addressed sufficiently in the CAPA plan.

15. Food and fluids

Meals were standardized and adequately controlled and scheduled during the study days. The CRO was able to arrange for standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol in the in-house kitchen.

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

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

Chromatograms and their integration, absence of signals in the blank samples, and absence of any unexplained interruptions in the injected sequences were verified. The reason for the study sample repeat analysis and instrument failures was reviewed. The provisions and the documentation of the ISRs were confirmed.

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

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

The method development process was adequately described and documented, and the usage of IS was justified based on the applicable literature. After method development, an analytical plan was provided as a basis for the method validation. A stable isotope-labelled internal standard for each analyte was used in the MS methods, and Lithium Heparin was applied as an anticoagulant.

During the method validation as per SOP for Bioanalytical method validation, , the maximum number of injections per run was validated by injecting standard calibration curve, blanks, and QCs at a minimum of three levels (low, mid and high) in size equivalent to prospective analytical run of study samples. A minimum of one set of QCs was spread throughout each analytical run.

A full validation was carried out on the instrument. Partial validation was carried out in accordance with the applicable protocol on two other instruments. The two latest instruments were used for sample analysis.

A selective, sensitive and rapid liquid chromatography-tandem mass spectrometry method for determining Sulfadoxine & Pyrimethamine in human plasma (Li-heparin) was validated. The procedure involved liquid extraction of the drugs (Sulfadoxine and Pyrimethamine) and their internal standard (Sulfadoxine-d3 and Pyrimethamine-d3). The chromatographic separation employed a C18 column and the mobile phase consisted of Ammonium acetate buffer, Methanol, and Acetic acid. To evaluate the linearity of Sulfadoxine and Pyrimethamine in the Quattro premier mass spectrometer detector, three intra-runs were carried out in multiple reactions monitoring (MRM) mode using electro ion spray with positive ionization. The total run time was about 5 minutes, and the standard curve range was (1.000-150.000 & 0.010-1.500) µg/ml for Sulfadoxine and Pyrimethamine, respectively. The partial validation started on 19 May 2021 and ended on 23 May 2021. The partial validation was performed in accordance with the respective validation protocol. The attachment was written according to the applicable SOP, and all raw data, source documents, and related documents were retained as per respective SOP.

Instruments used for the sample analysis were listed and reviewed.

The sample processing was documented in the respective forms. When appropriate, a separate template was also provided to record any unexpected activity during sample processing.

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 prior to the issuance of the study reports.

The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. The matrix plasma used for preparing QC and CC stock solutions in separate batches was donated by the National blood bank institute of Jordan. Upon receipt, the containers were assigned specific numbers and tested for HIV, Hepatitis B, and Hepatitis A. The receipt of the plasma from the bank (based on an agreement between the CRO and the National Blood bank) was documented on the form for the medical laboratory testes request from.

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 reviewing the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. The procedure for repeat analysis in case of pre-dose concentration above LLOQ was defined in the respective SOP.

A system suitability test was done before the start of runs on each day.

After completion of the analytical run, the data was transferred to Watson LIMS for regression calculation (to process the batch for batch acceptance).

The analytical runs were accepted or rejected in accordance with the applicable SOPs.

When almost 50 % of subject samples were analysed, samples from these subjects were re-analysed as per the available SOP. Later, samples from the rest of the subjects were analysed after the completion of the study. The samples were obtained around C_{max} and the elimination phase according to the sample size calculation.

Total Samples per study (A)	ISR sample size (About)
≤ 1000	10% of (A)
> 1000	Calculated as 10% for the first 1000 samples and 5% for sample # ≥ 1001 **e.g.:** Total # samples = 1500, then sample size = (1000x10% + 500x5%) = 125 samples for ISR

Observations concerning the Method development, Method validation & Analysis of study samples were addressed in the respective CAPA plan.

18. Sample collection, storage and handling of biological material

The specification of samples (blood plasma), sampling method, volume, and the number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transfer of samples from the clinical unit to the Deep Freezer area, and storage were in accordance with the applicable SOP.

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

Labelling of collected samples was clear to ensure correct identification and traceability. All storage conditions were controlled, monitored, and recorded throughout the storage period and transportation. Records of storage and retrieval of samples were maintained. Sample duplication was verified using a custom-made software system.

Observation concerning the handling of biological material was addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based and 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 the batch acceptance, were defined in the SOP for Chromatography guideline and SOP or Sample set (batch) construction and acceptance criteria for calibration curve and QC samples in the analytical run. When the analysis was repeated, the source data for all the analytical runs contained information about the initial evaluation of runs (collecting all calibration samples). The calibration range was adequately truncated. Internal standard variations were trended and used as part of the verifications of result validity.

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

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented 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 trails of Chromatography software systems 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, a time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

20. Good laboratory practices

A tour of the facility on Day 3 was performed to verify the suitability in terms of arrangement and safety.

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

Deep freezers for storage of samples and refrigerators for storage of the Reference standards were adequately qualified, calibrated, and maintained. There was an alarm system associated with the digital thermometer to trigger email notifications and call notifications to the staff responsible for the

maintenance of the facility. The automatic alarm system was tested during the inspection. The daily monitoring and all alarm checks were documented.

The usage of RS was recorded in the respective logbooks in chronological order with all applicable information. Standard materials usage logbook was reviewed. The use of sulfadoxine and IS was reviewed in this logbook for development purposes. For validation purposes, a new logbook was opened.

For the purposes of qualification verification, the temperature mapping of the Deep Freezer was reviewed to verify the Hot spot and the location of the respective sensor. The temperature mapping process was adequately carried out at the time of inspection.

Temperature mapping used in the sample processing room was performed based on the respective SOP. The hot spot was identified, and the sensor was appropriately placed.

Balances, other measuring devices and equipment, and instruments used during the conduct of a trial were periodically calibrated and verified before use to be fit for their intended purpose.

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

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

Observations concerning Good Laboratory Practice, were addressed in the CRO's CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The statistical model underlying the BE analysis was stated in the respective protocol.

The Data management unit made the calculations. The analytical study results were available in Watson^{TM} LIMS. The Data management unit received an email notification from the QA unit once the data was completed. Sample collection time deviations were obtained on a paper template from the clinical department, and the respective calculation was incorporated into the respective sample collection time points. The data was processed in a Notepad file.

A second qualified person double-checked the input of data values in the QA unit in accordance with the applicable SOP.

The trial records were maintained in a database, i.e., Watson^{TM} LIMS, and locked once the Data management group received the email notification from the QA Unit. Once the database was locked, the study was unblinded, and statistical analysis was performed using WinNonlin. The statistical analysis was documented and mentioned in the study report, and the process was defined in the applicable SOP.

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 were identified between the results stated in the report and the original (raw) data.

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

Miscellaneous	
Samples taken	NA
Assessment of the CRO master file	The CRO master (CROMF) file was reviewed. The company's master file provided introductory information of the organization and didn't cover all information required by the guidelines for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7). According to the above-mentioned guideline, the CRO master file should be a document prepared by the CRO containing specific and factual information about the CRO and the conduct of clinical studies, as well as the analyses of samples and related operations carried out at the named site. It was expected that a CROMF provided information on the policies, approach and general activities of a CRO. It should serve as general information by regulatory inspectors in addition to the trial-specific data and information submitted for assessment. It should also provide an overview of the organization's approach to GCP, GLP and other guidelines pertaining to its activities.
Annexes attached	NA

Part 3	**Initial conclusion – inspection outcome**

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at ***International Pharmaceutical Research Center (IPRC)*** located at ***Sport City Circle, Amman, 11196; 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
   WHO_TRS_850.pdf

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
http://apps.who.int/medicinedocs/documents/s23245en/s23245en.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://digicollections.net/medicinedocs/documents/s23697en/s23697en.pdf

16. OMCL guideline on Qualification of Equipment: Annex 1 Qualification of Liquid Chromatography Equipment, PA/PH/OMCL (11) 04 R6, European Directorate for the Quality of Medicines (EDQM), August 2018

17. OMCL guideline on Qualification of Equipment: Annex 7 Qualification of Mass Spectrometers, PA/PH/OMCL (10) 86 R6, European Directorate for the Quality of Medicines (EDQM), August 2018

18. OMCL guideline on Qualification of Equipment: Annex 8 Qualification of Balances, PA/PH/OMCL (12) 77 R11, European Directorate for the Quality of Medicines (EDQM), September 2020