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Prequalification Team Inspection Services
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study
WHOPIR

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Norwich Clinical Services Pvt Ltd. (NCS)** Ground and First Floor, #147/F, 8th Main, 3rd Block, Koramangala Bangalore - 560 034 India
Name and Address of Bioanalytical Research Site	**Norwich Clinical Services Pvt Ltd.** Ground Floor, #147/F, 8th Main, 3rd Block, Koramangala Bangalore - 560 034 India
Name and address Statistical Site	**Norwich Clinical Services Pvt Ltd.** #147/I, 8th Main, 3rd Block, Koramangala Bangalore - 560 034 India
Corporate address of the Organization	**Norwich Clinical Services Pvt Ltd.** #147/F, 8th Main, 3rd Block, Koramangala Bangalore - 560 034 India Tel: +91-80-42772400 regulatoryncs@norwichclinical.com
GPS coordinates	Latitude: 12.9286 Longitude: 77 .6286
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. MA190** Bioequivalence study of Amodiaquine Hydrochloride Dispersible Tablets (153 mg base) **WHO application no. HA751** Bioequivalence study of Dolutegravir Tablets 50 mg
Inspection details	
Dates of inspection	23-26 September 2024

Type of inspection	The inspection was conducted as a routine assessment and constituted as a joint inspection by the US FDA and WHO.
Introduction	
Summary of the activities	The facility had the capacity to perform bioequivalence/bioavailability in healthy subjects or patients, with NCS offering services in pharmacovigilance, bioavailability/bioequivalence studies, bioanalytical research, and corporate training, all delivered in strict conformity with regulatory standards.
General information about the company and site	NCS operations started in 2010 with the introduction of pharmacovigilance (PV) services. In 2011, the company expanded its portfolio by initiating bioanalytical services. Bioavailability and bioequivalence (BABE) studies began in 2012. The organization received CDSCO approval for its bioanalytical facility at the current location and the clinical facility at the previous location on January 19, 2012. Subsequently, on July 27, 2017, approval was obtained for the relocated clinical facility.
History	The CRO had been inspected by various national authorities, including the US FDA, MHRA, BASG (Austrian NRA), NPRA (Malaysia), and the Turkiye Ministry of Health. The CRO was previously inspected by the WHO from June 18 to June 22, 2018.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, performance in clinical studies, informed consent procedures, ethics committee approvals, and related correspondence, test article accountability, including dispensing and storage, handling, and processing of biological samples (plasma) collected during the study, equipment calibration, employee training, and computer controls. A facility tour was also conducted. For the analytical operations, the review included practices, personnel qualifications, and procedures used in method validation and analytical testing. A review of the clinical study data, method validation, and analytical study data was performed, with source data compared against the final study reports.

Scope and limitations	
Out of scope	None

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BA	bioanalytical
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 study 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

PART 2	**SUMMARY OF THE FINDINGS AND COMMENTS**

General Section

1. Organization and management

A presentation was provided detailing the organization's activities, including specific changes implemented since the last inspection.

The CRO had an organizational chart displaying key positions and the names of responsible persons. The organizational chart was dated 24 July 2024, authorized, and regularly updated.

Job descriptions for each employee, outlining their responsibilities, were available. It was randomly verified that job descriptions had been signed and dated by the respective staff members.

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

The responsibilities of the test facility management were sufficiently established according to Good Laboratory Practice principles. CRO management acknowledged that, as the investigator was an employee of the CRO, certain responsibilities typically assigned to the investigator similarly resided with the CRO management.

Management ensured that appropriate and technically valid SOPs were implemented and followed. The change history of SOPs was documented in the change control form. As an example, the change control history form for one SOP was reviewed.

Sponsor master service agreements were available and reviewed, with provisions for the retention of IMPs, documentation, and biological samples clearly outlined in the agreements.

2. Computer systems

A list of software and computer systems used in the studies was provided. An inventory of all computerized systems on the network was available, with clear identification of GXP-regulated systems. The inventory included details such as the software name, status, compliance, and risk category.

The validation of GXP equipment and systems was maintained throughout the entire system lifecycle in accordance with SOP for Performing Validation Activity & Validation Master Plan. Periodic system reviews were required to assess and document whether the GXP equipment or system remained in a validated state or if revalidation of individual components or the entire system was necessary. In cases requiring revalidation, a risk assessment was conducted to determine the extent of revalidation needed. This assessment was carried out through a questionnaire included in the revalidation plan. Various scenarios were documented based on the answers to the risk assessment questionnaire, defining the extent of revalidation to be performed.

The periodic risk assessment was planned for at least once a year, typically during the internal software audit. The elements to be considered in these periodic reviews were defined in the applicable SOP. Changes to the location of equipment, functionality, or version of validated computer systems, areas, and processes were required to be managed through formal change control procedures. Regardless of any changes made to validated instruments, equipment, areas, or software, revalidation was mandated at least once every three years to ensure ongoing quality and compliance.

The procedure for decommissioning equipment or systems was outlined in the applicable SOP.

There were a sufficient number of computers available to allow personnel to perform data entry, data handling, calculations, and report compilation. The computers had adequate capacity and memory for their intended use.

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of individuals with access to the database was maintained. Secure, unique, individual-specific identifiers and passwords were utilized. An SOP for each computerized system was available, detailing the respective roles and access rights assigned to each user.

The qualification of randomly selected systems was reviewed for verification.

The storage of data, as well as the procedure for backup and long-term archiving of all relevant electronic data, was specified in the SOP for Data Backup and Archival Policy, including the frequency of backups. Backups were performed on Tape Media and conducted daily, weekly, and monthly. Weekly and monthly backups were created in duplicate, labeled as copy 1 and copy 2. Copy 1 was archived onsite, while copy 2 was archived offsite. The IT system was secured with a firewall and integrated applications to prevent cyberattacks or data loss, supported by a Business Continuity Plan.

The reliability and completeness of these backups were verified through two measures which were reviewed during the inspection.

The randomly selected self-designed software programs were reviewed during the inspection to verify their validated status.

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

3. Quality management

The CRO had appropriate QA and QC systems, supported by written SOPs, to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, and applicable regulatory requirements. Upon request, all current and relevant SOPs were provided to the inspection team through a secure computer file transfer service. This ensured that the inspection team had timely access to the necessary documents for review during the inspection process.

A Quality Manual, issued 5 Jan 2024 was provided. The purpose of the Quality Manual was to:

- Communicate the quality management plan
- Provide information on quality procedures, control, and assurance
- Demonstrate conformity to national and international regulatory requirements
- Facilitate knowledge sharing
- Provide evidence of management’s commitment to quality

The Quality Assurance Unit was independent of project conduct and has the following responsibilities:

- Conduct internal audits, facility audits, vendor audits, and project-specific audits in the Clinical Unit, Bioanalytical Laboratory, and Pharmacovigilance department.
- Perform random checks of processes across units such as the Clinical Unit, Bioanalytical Laboratory, GLP and Validation, IT, PK and Biostatistics, Pharmacovigilance, Medical Writing, and Training Activities.
- Manage other general activities as detailed in the respective document.

Both in-process and retrospective QA verifications, such as during bioanalysis when samples and standards were being prepared and tested, were conducted. Additionally, the CRO had a dedicated section called GLP and Validation, which was responsible for the calibration, maintenance, and validation of equipment. This section ensured that all equipment used in the studies was properly calibrated and maintained in accordance with regulatory standards.

The quality management system incorporated root cause analysis, ensuring aspects of data integrity were addressed. It also included the implementation of appropriate corrective and preventive actions (CAPA) and the proper handling of deviations. The management review (MR) dated 30 Jul 2024 for the Bioanalytical (BA) department was available and reviewed.

An internal audit was conducted at least once annually for all units. An audit schedule was developed as part of the internal audit process. Key audit findings and deviations were communicated to the audited unit by the audit team, followed by a detailed audit report submitted to the Unit Head. This report outlined the necessary corrective and preventive actions, in accordance with Internal Audit – Conduct and Follow-up.

The issuance and reconciliation of templates used in the study were overseen by the QA department, ensuring proper documentation and control. All records related to this process were accurately maintained. For the Amodiaquine study, the evidence of template issuance and reconciliation was thoroughly reviewed and verified, confirming adherence to established procedures and regulatory requirements.

The audit trail queries or reports to be used for the Analyst software system were defined in SOP for QA Project Activities in the Bioanalytical Laboratory. Examples of audit trail reviews and the recording of data were available and reviewed. The audit trail of the software systems was reviewed by QA according to the applicable SOP at the time of the

inspection. The version history of the SOP was documented in the Change Control documentation.

The CRO had SOP for conducting vendor audits. An annual audit schedule for vendors was available for 2024.

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

4. Archive facilities

The CRO maintained secure storage facilities on the ground floor and the 1st floor, adjacent to the sample processing room, for archiving trial-related documents. The storage facilities were equipped with measures to detect fire, control the humidity, and pest control. Overall, the CRO ensured the safety and integrity of the documentation through comprehensive security measures.

The archiving activities were managed in accordance with the SOP.

Access to the archive storage areas was controlled and restricted to authorized personnel, with a list of authorized positions displayed at the entrance of the facility. Records of document access and return were maintained, ensuring traceability.

The retention period for study documentation, including raw data, was defined in the SOP, and specified in the contract between the sponsor and the CRO.

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

Observations related to the Archive facilities were addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facility was conducted on Day 2 (Bioanalytical) and Day 3 (Clinical).

The Clinical Facility was located on both the Ground and First Floors, while the Bioanalytical Facility was situated on the Ground Floor. Additionally, there was a facility of M/s. Norwich Clinical Services located at 147/I, 10th Main, Koramangala 3rd Block, Bangalore-560 034, which housed the Medical Writing, Pharmacokinetics, Biostatistics, Regulatory Affairs, Administration, Quality Assurance, and Training units.

The Annex II facility of M/s. Norwich Clinical Services, located at 147/J, 10th Cross, 12th Main, 3rd Block, Koramangala, Bangalore-560 034, Karnataka, India, housed the Pharmacovigilance unit. This facility was not visited. The layouts of the Clinical and Bioanalytical facilities were attached as Annexures 01 and 02 to the CRO Master File (MF), and they were checked during the visit.

The facilities were clean and maintained with adequate lighting, ventilation, and environmental controls. Floors, walls, and workbench surfaces were designed to be easy to clean and decontaminate.

Clinical trials were conducted under conditions that ensured the safety of the subjects, and the site selected was appropriate to the potential risks involved. However, it was noted that there was no alternative method to open the Emergency Exit door in the event of an emergency, as they relied solely on the deactivation of the access control system and regular six-monthly checks.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site was equipped with appropriate facilities, including laboratories and necessary equipment.

Entry to the facility was restricted and controlled through keycard access. Alarm systems were installed to detect the exit of subjects from clinical facilities, and/or the doors were locked to ensure security. Emergency evacuation procedures were in place, and all entries and exits from the facility were recorded.

The sites where clinical activities occurred included a pharmacy with designated areas for dispensing and retention of investigational medicinal products (IMP). The IMPs were stored under appropriate conditions and monitored by data loggers. Access to the pharmacy was restricted through access control, and entry/exit records for each visit to the pharmacy were properly maintained.

The laboratory premises were designed to accommodate the operations carried out, providing sufficient space to prevent mix-ups, contamination, and cross-contamination. Adequate storage was available for samples, standards, solvents, reagents, and records.

The premises were also designed to ensure the safety of all employees and authorized external personnel, such as inspectors or auditors, particularly when handling or working in the presence of chemicals and biological samples.

Mock drills were regularly conducted to ensure the safe evacuation of staff during fire accidents or similar emergencies and to confirm that doors were disengaged in a timely manner during such events. Evidence of a mock drill conducted on 11 September 2024, including attendance sheets, was available for review.

Safety Data Sheets were made available to staff prior to the commencement of testing. Laboratory staff were familiar with and knowledgeable about the Safety Sheets for the chemicals and solvents they were handling. Additionally, staff were trained in the use of firefighting equipment, including fire extinguishers, and were instructed to wear appropriate laboratory attire.

In general, spark-proof and insulated electrical wiring and equipment, including refrigerators, were installed. Safety rules regarding the handling of compressed gas cylinders were strictly followed. First-aid materials were provided according to the applicable SOP; however, it was recommended that the contents of the first-aid kit be reconsidered to ensure that all necessary materials were readily accessible to staff. Notably, staff had not received instruction in first-aid techniques, emergency care, or the use of antidotes. However, medical doctors were available 24/7, and an SOP for managing hazards in the bioanalytical laboratory was in place.

Containers with volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were sealed with appropriate closures. Volatile organic chemicals were handled under certified fume hoods or air extractors, and safety showers and eye wash stations were available in the laboratory.

The premises had appropriate systems in place for waste disposal, fume treatment, and environmental protection, ensuring compliance with local or national regulations. SOP for Waste Management was available and provided detailed guidance on these processes.

For monitoring the temperature and humidity of the facilities (room temperature), a hygrothermometer was used, with daily recordings of maximum and minimum temperatures. Cold storage facilities were monitored using dataloggers. Each datalogger was connected to a display that showed the current temperature and an alarm system that notified security by activating an audible and visual alert in an alarm box installed at the security desk. Alarms were manually logged by the security staff in a logbook. The temperature records from the dataloggers were accessible via software, which allowed for monitoring in 30-minute intervals and provided a graphical presentation of the recorded data.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. At all stages of the trial, including night shifts, qualified and trained personnel were present to ensure the safeguarding of subjects' rights, safety, and well-being, as well as to provide care during emergencies. Additionally, contract workers were employed in specific activities to complement the core team's capabilities.

Randomly selected current curricula vitae and training records for both full-time and contract workers involved in trial activities were reviewed for verification.

The company employed a total of 140 staff members at the time of inspection.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted on the premises of the CRO. The CPU was equipped with 72 beds, and systems were in place within the accommodation facilities to allow subjects to alert CRO staff if needed.

The facilities for changing and storing clothes, as well as washing and toilet areas, were clean, well-organized, easily accessible, and suitable for the number of users. Lockable toilets were equipped with alarms, and the doors were designed to be opened from the outside in the event of a medical emergency.

The clinical site included the following areas:
- Registration and screening of subjects, with privacy ensured during the informed consent process
- Clinical Pharmacology Unit (CPU)
- Subjects’ recreation area
- Pharmacy
- Room for the administration of investigational products and sample collection
- Sample processing room (e.g., plasma separation) and storage (freezer)
- Archive facility
- Dining hall
- Intensive Care Unit (ICU)

Provisions were made for the urgent transportation of subjects to hospital in case of emergencies.

Access to the randomization list was restricted to the pharmacist in charge of the study. These documents were kept securely under lock and key (if in hard copy), and their distribution was documented accordingly.

All equipment used during the study was appropriately calibrated at predefined intervals. The functionality and performance of emergency-use equipment were verified at regular intervals to ensure readiness. The location of the defibrillator was adjusted to improve accessibility during emergencies.

8. Clinical laboratory

An external clinical laboratory was used for analyzing samples during the clinical trial.

Hematological tests, urine analysis, and other tests were conducted in accordance with the study protocol. The labeling, receipt, storage, and chain of custody of the samples ensured full traceability and maintained sample integrity throughout the process.

The CRO received information regarding the analytical methods used by the laboratory, along with a dated list of laboratory normal ranges and the laboratory's accreditation certificate. The inclusion and exclusion criteria related to the laboratory results were determined according to the list of acceptable reference ranges which was provided by the CRO.

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

The laboratory generated individual reports for each subject, which were included in the CRFs. The CRO logged into the laboratory's website, printed the respective reports, and stored them in the study binder. These reports were available on the laboratory’s website for 30 days. The laboratory retained the source data for 15 years in accordance with the applicable arrangements.

9. Ethics

The trials were approved by the applicable Independent Ethics Committee, which functioned as a partnership firm and was not affiliated with NCS, before the commencement of any study. The committee's independence from the sponsor, investigator, and CRO was verified through the member list. The decisions from the IEC meetings were available for review. The IEC was given adequate time to thoroughly review the protocols, informed consent forms (ICFs), and other related documentation.

The process for submitting documents to the Ethics Committee followed the applicable SOP.

The study was insured through an insurance company.

Informed consent form

Information for study participants was provided in their vernacular languages (English and Kannada) and presented at a level of complexity suitable for their understanding, both orally and in writing.

Informed consent was obtained from each subject and documented in writing before any trial-related activities commenced. The informed consent process was also recorded on video. The information provided was clear, emphasizing that participation was voluntary, and subjects had the right to withdraw from the study at any time without providing a reason. Reasons for withdrawal were documented in the study records.

Details about insurance coverage and procedures for compensation or treatment in the event of injury or disability resulting from participation in the trial were made available through the insurance policy.

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

The certificate of translation and back-translation of the informed consent forms were reviewed. The translation was conducted by the CRO's internal translator.

10. Monitoring

The study (Amodiaquine) was monitored by a monitor employed by the sponsor. The monitor was appropriately qualified and the CV was provided by the sponsor.

Due to COVID restrictions during the Amodiaquine study, monitoring was conducted remotely. A monitoring report was issued and sent to the CRO. Minor observations were noted and addressed through the respective CAPA plan.

11. Investigators

The principal investigator (PI) was responsible 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.

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

The information related to the receipt, storage, handling, and accountability of investigational products at every stage of the trial was recorded. This included details about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, and return of any remaining pharmaceutical products. The verification process also covered specific details of the pharmaceutical products used, such as dosage form, strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions, as specified in the official product information provided by the sponsor. These storage conditions were continuously monitored using dataloggers.

The generation of the randomization list was conducted in accordance with the applicable SOP, utilizing a software system. Records were maintained, including the randomization list and seed. Access to the randomization list was restricted to the person who generated it, the dispensing pharmacist, and the statistician.

The investigational products were properly labeled, and compliance of all labels with the randomization list was verified once printed, prior to labeling the containers. Labels were affixed in a way that ensured the information remained intact, even when the container lid was removed.

Adequate procedures for labeling and documenting the administration of the IPs were in place to verify that each subject received the correct product dispensed to them. This was achieved using labels with a tear-off portion, designed to have two identical labels. One portion was affixed to the container, and the second was pasted into the CRF at the time of dosing.

Empty containers were labeled separately for the test and reference investigational products and were kept segregated in a secure, locked area to prevent any potential mix-ups until the dispensing stage.

The dispensing, packaging and dosing procedures were carried out in accordance with the respective SOPs.

The surface on which the investigational product was handled was thoroughly cleaned before bottles of the product were brought into the area. All product containers (whether full or empty), lone dosage formulations, labeling materials, contaminants, dirt, and debris were removed from the area. A second person (QA) verified that the surface and surrounding area were clear and clean before any product containers were brought in and opened.

The IPs were handled using appropriate utensils, and tablets were distributed into each container according to the randomization list for the comparator or test product, as appropriate. The test and reference products were handled at different times to avoid any mix-ups. This procedure was also applied to the labeled containers. Every step of the process was recorded in sequential detail.

The surface and surrounding area used for product handling were cleared and cleaned both before and after the dispensing of each product, even when performed within the same study.

Investigational product accountability and dispensing records were meticulously maintained. Each activity was documented at the time it was performed, including records of doses administered, returned, or destroyed. Additionally, each step of the process was verified by a second person, and this verification was also documented in the records.

The inspectors observed the dosing administration and blood drawing on Day 3 of an ongoing study. Dosing was performed in accordance with the relevant SOP under the supervision of the investigator and a qualified staff member who had been explicitly delegated this task in writing. The volunteer’s badge was checked before dosing, and the exact time of dosing was documented on the designated page of the CRF. In the case of solid oral dosage forms, a mouth check was conducted using a tongue depressor or spatula and a penlight, examining under the tongue, lips, corners of the mouth, and between the gums and cheeks to ensure the subject had swallowed the investigational product. The dosing process was directly documented in the CRFs.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in their original containers were retained for possible confirmatory testing for five years, in accordance with the respective. After this period, the sponsor was contacted for further instructions regarding the handling of the retained samples.

13. Case report forms

Randomly selected CRFs from the study were reviewed.

The data collected for 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 times, adverse events, and any protocol deviations was also recorded in the CRFs.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the respective SOP, which included a description of the potential methods the CRO used for this purpose. The CRO primarily used the eBio application to inform volunteers about upcoming studies. A software system was maintained to avoid cross-participation and ensure that a minimum time elapsed between a volunteer's participation in one study and the next. Access to the database was password-controlled to safeguard confidential information about the volunteers or subjects. The database was recently updated to include the reasons for screening failure, and the identification of volunteers and subjects was ensured through a biometric system.

Informed consent was obtained from potential subjects for any screening procedures necessary to determine their eligibility for the study, in addition to the consent for participation in the research portion of the trial. The clinical trial protocol outlined the subject selection criteria (inclusion and exclusion) and the screening procedures. The OVIS software system (version 4.0) was used to check whether any subjects had participated in previous trials, with participation data uploaded to a central repository to prevent over-volunteering. OVIS was recently updated to Microsoft version 10. It was noted that only fingerprint identification was used to verify the volunteer's eligibility.

An appropriate device was used for alcohol testing, and urine samples were collected for drug testing.

The observation related to this section was addressed in the respective CAPA plan.

15. Food and fluids

Meals were standardized, adequately controlled, and scheduled during the study days. The CRO arranged standardized meals, snacks, and drinks for the study subjects, as outlined in the clinical trial protocol and in accordance with the agreement with the catering service.

The timing, duration, and quantity of food and fluids consumed by the subjects were recorded. Before samples were collected from ambulatory subjects, they were asked about their recent food and drink intake. A qualified and experienced dietitian, with appropriate training, was responsible for designing the standardized meals.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, conducted, and monitored to ensure that the safety profile remained acceptable, including for the volunteers. A medical doctor was responsible for making medical decisions in the event of adverse events and for notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, particularly 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 administered to a subject was documented in the CRF, along with supporting documentation from the ICU.

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

Bioanalytical section

The inspection focused on the Amodiaquine study, associated with WHO application no. MA190, as well as the related method validation. Additionally, spot checks were conducted for the Dolutegravir study, associated with WHO application no. HA751. The inspection specifically reviewed the following records and activities:

- Source documentation and raw data for validation of the bioanalytical methods.
- Analysis of subject plasma samples as well as the respective electronic data.
- 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, along with the chromatograms generated from the analytical runs.
- Preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

Furthermore, the chromatograms and their integration were verified, ensuring the absence of signals in the blank samples and any unexplained interruptions in the injected sequences. The reasons for the repeat analyses of study samples were reviewed. The provisions and documentation of the incurred sample reanalysis (ISR) were confirmed. The documentation and justification for the reinjection of analytical runs were verified and compared against the established provisions.

For the review of the study documentation, the inspection team received sufficient support from knowledgeable and transparent personnel. The associated study data package was made available for review and verification using the Chromatography software system.

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

The method development process was adequately described and documented, with the use of the internal standard (IS) justified based on relevant literature, a copy of which was available for review. Following method development, the Method Validation Protocol was provided as the basis for method validation. A stable isotope-labeled internal standard, e.g., Amodiaquine D10, was consistently used in the mass spectrometry (MS) methods, and K_2EDTA was applied as the anticoagulant in both studies.

The bioanalytical method used for the analysis was validated and approved for routine quantification of Dolutegravir in K_2EDTA human plasma (Dolutegravir Study related to application HA751). Norwich was responsible solely for the bioanalytical (BA) part of the study, while RA Chem Pharma Limited handled the clinical and statistical components.

The sample analysis for the Amodiaquine study was conducted in accordance with the analytical test procedure. The details of this procedure were annexed to the method validation report.

During the method validation, in accordance with the respective SOP, a run was performed to determine the batch size using 103 samples of QCs and CCs, referred to as the Batch Size Test. This was conducted with a run length comparable to that expected for routine analysis.

The sample processing was documented in the respective forms, following SOP for Recording of Raw Data in the Bioanalytical Laboratory. The request for biological samples for each analytical run was logged in the appropriate logbook, as well as in the corresponding Deep Freezer (DF) logbook. Additionally, a note to file was provided to record any unexpected activities during sample processing, when applicable. Study sample repeat analyses and the reporting of final concentrations were also thoroughly documented as per SOP for “Repeat analysis of clinical samples”.

Data supporting the stability of the samples under the specified conditions and storage period was available prior to the commencement of the studies, except for long-term stability, which was assessed before the issuance of the study reports. For Amodiaquine, this stability data was confirmed on 15 September 2020.

The review of the complete method validation included assessments of precision and accuracy (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and bench-top stability), hemolytic effect, recovery, concomitant drug interaction, and reinjection reproducibility. Partial validation was performed as required. The matrix used for the analytical method validation was consistent with the matrix used for the study samples, including the same anticoagulants.

For the preparation of stock solutions, the plasma matrix used in the method validation and study sample analysis of Amodiaquine was provided in-house. However, plasma may also be procured from external suppliers when necessary. The plasma used for the sample analysis in the Dolutegravir study was purchased from a supplier in Hyderabad. The documentation related to lipemic plasma was reviewed and verified.

The preparation of calibration curve (CC) standards, quality control (QC) samples, and dilution integrity (DI) stock dilutions was conducted using the Stock Dilution Manager software system. Each analytical run included CC & QC samples, and subject samples, all processed simultaneously. CC & QC samples were prepared as per SOP for Preparation of Calibration Curve Standards, Quality Control Samples, and Bulk Spiking Procedure, and were interspersed throughout the run. The exact sequence of processing was clearly defined and documented. All samples collected from a given subject during all trial periods were analyzed within the same run.

The acceptance criteria for the analytical runs were confirmed by reviewing the analytes' retention times, the accuracy of CC & QC samples, peak integration, and internal standard peak areas, in accordance with the applicable SOPs. A system suitability test, performed in compliance with SOP for System Suitability of the Chromatographic System, and a stabilization test, following SOP for Analytical Batch Acceptance Criteria, were conducted before the start of each day's runs, unless the batches were analyzed consecutively.

Incurred Sample Reanalysis (ISR) was performed in accordance with SOP for Incurred Sample Reanalysis.

The observation related to this section was addressed in the respective CAPA plan.

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

The specifications of the samples (blood plasma), including the sampling method, volume, and number of samples, were outlined in the clinical trial protocol and provided to the volunteers. The collection, preparation, transport, shipping, and storage of the samples were conducted in accordance with the respective 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.

The labeling of collected samples was clear, ensuring correct identification and traceability of each sample. All storage conditions, including freezer temperature, were controlled, monitored, and recorded throughout the storage period and during transportation. Records of sample storage and retrieval were meticulously maintained. Samples were duplicated in aliquots, with only aliquot 1 being transferred or shipped to the bioanalytical laboratory. Aliquot 2 would be requested and shipped only if necessary.

The Stock Dilution Manager software system was reviewed and discussed for the preparation of QC, CC, and DI during the study sample analysis. The preparation of the IS stock solution was performed on a separate form, as outlined in the applicable SOP, using a calculator for IS stock solution calculations. The preparation and calculation were reviewed and verified by a second person.

Documentation for the reconciliation of QC, CC, and pooled plasma was available and reviewed.

As per applicable, the study samples, QC samples, and pooled matrix were discarded, with the activity meticulously recorded. It was noted that the CRO had implemented a new practice for accurate accountability of pooled plasma to determine the exact consumption during the preparation of stock solutions for study analysis, in accordance with SOP for the procurement, handling, and storage of blank matrices. To track plasma consumption, the volume of matrix issued, consumed, and remaining was documented in the matrix inventory logbook by the sample custodian each time.

The system audit trail review was carried out during the study.

19. Data processing and documentation

The integration settings were science-based and fully justifiable. The smoothing factor was kept low to avoid masking potential interferences or changes in peak geometry.

The criteria for acceptance and exclusion of CC and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. The source data for all analytical runs included comprehensive information regarding the original evaluation of runs, which contained all calibration samples. The calibration range was appropriately truncated. Internal standard variations were employed as part of the process for verifying the validity of the results. However, at the time of the study, the CRO relied on an Excel sheet to calculate ±50% of the average IS peak area of QC and CC samples. This average was then compared with the IS peak area obtained for the study samples, and outliers were identified visually. In their updated practice, the CRO implemented trending plots to identify outliers after calculating the acceptable range.

Additionally, the CRO began using a tool for AC-code (to detect concentrations above the Upper Limit of Quantification, ULOQ), which was then reviewed by the QC reviewer to identify concentrations exceeding ULOQ. Another query used was the PD-code, which flagged pre-dose concentrations at 0 hours.

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

All original analytical raw data, including calculations, chromatograms, and their associated audit trails, were documented in a manner that ensured traceability regarding sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). All audit trail files, such as results table audit trails, project audit trails, and instrument audit trails, were retained.

Each data point was traceable to a specific sample, including the sample number, time of collection, time of centrifugation, time the sample was placed in the freezer, and the time of sample analysis. This ensured the ability to identify whether any aberrant results were due to potential sample mishandling.

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to prevent errors. Although the data entry process was outlined in the SOP for CRF data, this SOP did not apply to our studies. Nevertheless, the data entry procedures in place at the time were equally robust.

20. Good laboratory practices

A facility tour was conducted on Day 2 to verify its suitability in terms of arrangement and safety.

The general principles of Good Laboratory Practice were followed during the bioanalytical part of the bioequivalence studies, supported by an established and appropriate QA system.

Deep freezers for sample storage and refrigerators for the storage of reference standards were in use. An alarm system, connected to the Datalogger Records Management software, functioned as a digital thermometer to trigger notifications that were sent to the security front desk. Additionally, there was an indicator box to identify the respective cold storage facility associated with each alert. The automatic alarm system was tested during the inspection to verify its functionality. However, it was noted that the data logger for temperature monitoring could not retain alarm logs in an electronic format for trend analysis. An upgrade to the temperature monitoring system was in progress at the time of inspection.

For qualification verification purposes, the temperature mapping of the Deep Freezer used during the Amodiaquine study was reviewed to assess the hot spot and the location of the respective sensor. The temperature mapping was conducted under loaded conditions, using penetration (with the sensor placed inside a vacutainer filled with ethylene glycol), and included a door-opening test as part of the Performance Qualification. The temperature mapping process was properly executed at the time of the inspection. The transfer of samples to equivalent storage units was appropriately considered during maintenance and repair activities.

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, with records maintained in accordance with applicable requirements. These activities were verified through a random review of the equipment used in study-related activities. All equipment and components were properly labeled with the respective ID number, date of calibration, and the next calibration due date. Equipment usage was thoroughly documented in the analytical sheets, as well as in the respective logbooks for instrument usage. Additionally, the use of columns was recorded in a dedicated logbook for column usage.

The documentation of performance verification/calibration of the selected equipment was reviewed.

Chemicals, reference substances, reagents, solvents, and solutions were labeled to indicate their identity, purity, concentration (where applicable), expiry date, and specific storage instructions. Information regarding the source, preparation date, and stability was provided either on the label or in the Certificate of Analysis.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

Fixed factors such as subject, treatment, period, and subject sequence were used, with no amendments made to the statistical model.

The statistician's qualifications were verified through their CVs, and two statisticians were responsible for the respective activities.

A PK/PD analysis software system was utilized as the software package for both pharmacokinetic (PK) and statistical analysis. One statistician performed the calculations, while the other conducted a quality control check.

PK data underwent QA and QC processes in the designated software system and was locked before being transferred to the analysis software system.

22. Study report

The process of study report writing was verified during the inspection, and it was noted that procedures were established to ensure the quality and integrity of the study report.

The study report included a detailed description of the bioanalytical part of the trial, covering the bioanalytical method used and its validation report. The Principal Investigator approved the clinical study reports prior to the data transfer to the statistical department. The bioanalytical reports were approved by the responsible staff and management. Monitoring and audit reports were available before the release of the final study report.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The CRO master (CROMF) file with CMF number: CMF-10 dated 21 Oct 2021 was submitted and reviewed.
Annexes attached	N/A

Part 3	Conclusion – inspection outcome

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at ***Norwich Clinical Services Pvt Ltd.,*** located at ***#147/F, 8th Main, 3rd Block, Koramangala, Bangalore - 560 034; India***.

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

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

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***

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***

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***

4. 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***

5. 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***

6. 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***

7. 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***

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

9. 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

10. 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

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

12. 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

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

14. 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

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4