

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

Part 1	General information
<b>Organization details</b>	
Company information	
Name and Address of Clinical Research Site	Micro Labs Ltd, Micro Advanced Research Centre Clinical Pharmacology Unit Nos. 9 to 14, Katha Nos. 390/395 Situating at Kudlu, Near Grama Panchayath Office Singasandra Post, Sarjapura Hobli, Anekal Taluk Bengaluru District Bengaluru -560068 India
Name and Address of Bioanalytical Research Site	Micro Labs Ltd, Micro Advanced Research Centre 58/3, Kudlu Village, Anekal Taluk Bengaluru -560068 Karnataka India
Name and address Statistical Site	Micro Labs Limited Clinical Pharmacology Unit, Nos. 9 to 14, Katha Nos. 390/395 Situating at Kudlu, Near Grama Panchayath Office Singasandra Post, Sarjapura Hobli, Anekal Taluk Bengaluru District Bengaluru -560068 India
Corporate address of Organization	<b>Head Office:</b> 31, Race Course Road Bangalore -560001 Karnataka, India Tel no. +91 80-22370451-57 Email: info@microlabs.in
GPS coordinates	BA site: 12.89192°N 77.65049°E

WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	Bioequivalence study of Artemether and Lumefantrine Dispersible Tablets 20mg/120mg
<b>Inspection details</b>	
Dates of inspection	6 – 9 December 2022
Type of inspection	Routine
<b>Introduction</b>	
Summary of the activities	<p>This facility performed analyses of samples collected during Bioavailability and Bioequivalence (BA/BE) studies conducted to support marketing authorization in various markets for in-house developed products.</p> <p>The organization has initiated a Clinical Pharmacology Unit focusing on conducting the Clinical Phase of Bioavailability and Bioequivalence studies. The clinical facility received approval from CDSCO in December 2018, and the clinical operations started in January 2020.</p>
General information about the company and site	<p>The organization was established in 1973 as a fully integrated pharmaceutical company across the entire pharmaceutical value chain.</p> <p>The bioanalytical facility received approval in January 2017 from CDSCO and started its operation in February 2017.</p>
History	The Bioanalytical facility was recently inspected by WHO in April 2022. A new application was submitted to the WHO after the inspection for which the clinical part was performed at the CRO's clinical facility. Since the clinical facility was not inspected by the WHO, a new inspection was initiated to cover both bioanalytical and clinical facilities.
Brief report of inspection activities undertaken	<p>The following scope and study-related activities were reviewed:</p> <p>The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.</p> <p>Regarding the bioanalytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.</p>

	A review of the clinical study data, analytical method validation, and analytical study data were conducted, along with comparing the source data to the study reports.
<b>Scope and limitations</b>	
Out of scope	The CRO's clinical pathology laboratory was not operational during the inspection and it was not inspected because it was not used for the study in the scope of this inspection.

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioavailability
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
	GMP	good manufacturing practice
	HPLC	high-performance liquid chromatograph
	LC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form
	ICH	International Conference on Harmonization
	(I)EC	(Independent) Ethics Committee
	IMP	investigational medicinal product
	ISF	investigator study file
	ISR	incurred sample analysis

	IQ	installation qualification
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification
	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

<b>PART 2</b>	<b>SUMMARY OF THE FINDINGS AND COMMENTS</b>
---------------	---

<b>General section</b>
------------------------

## 1. Organization and management

A presentation was provided explaining the clinical and bioanalytical activities of the organization in detail, as well as the changes since the last WHO inspection. The study-specific bioanalytical and clinical activities were also presented.

The Clinical Pharmacology Unit of Micro Labs Limited was approved by the Drug Controller General of India (DCGI) office in December 2018 and subsequently on 23 May 2022 to conduct BA/BE studies in healthy human volunteers.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organization chart was dated and authorized for BA and CL departments on 3 & 7 November 2022, respectively.

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

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

## 2. Computer systems

The CRO's computerized systems were previously inspected in April 2022. Since then, the CRO has added two new software systems to the list of software systems:

A new database management system (SDMS) was implemented to achieve better compliance. The system was used to assort data and for archiving of electronic data generated in the chromatography software system. The qualification documentation of the software system was available, and the respective PQ documentation was reviewed. The system was added to the flow chart for data backup.

The implementation of a new LIMS software application was ongoing at the time of inspection.

At the clinical site, there was a database used for the registration of new volunteers. The database search engine only allowed filtering the data by volunteer number. However, none of the CRO's personnel, even the administrator, had the right to modify the volunteers' information, except for addresses and contact numbers. Any other modification should be made through a request submitted to the administrator. The administrator would then contact the vendor to incorporate the change. The qualification documentation of the software system was available and reviewed.

The software application associated with the ECG machine had deletion and edit options, only available for the IT person. The software was also equipped with an audit trail. The application memory had the capacity to store up to 200 ECG records. The records were automatically transferred into the file server. The ECG records were deleted once the machine memory was full. However, a paper print with complete information was also provided during ECG uptake and stored with the rest of the clinical raw data.

Data backup and restoration were described in the respective SOPs. The transfer of data was illustrated in the respective flowcharts for data backup. An additional flowchart was provided at the time of inspection to indicate the transfer of data from the ECG machine to the Network switch and to the CPU file server to be stored in five server folders with specific names. It was recommended to include the flowchart in the respective SOP.

The qualification documentation of the application used to prevent the cross-participation of volunteers was available and reviewed.

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

### **3. Quality management**

A controlled list of SOPs was available. SOPs related to clinical and bioanalytical activities were reviewed and discussed when applicable.

The CRO had an emergency preparedness plan. The plan covered emergency fire and chemical spillage. An SOP was available to cover the medical emergency mock drill records. Documentation of the Mock drill performed on 23 Nov 2022 and 30 Jun 2022 was available and reviewed.

SOP for Internal audits was available and discussed. QAU personnel verified all the activities performed during a project/study, including electronic result tables, chromatograms, and audit trails. The review was documented on the chromatography instrument's audit trail by accessing the software system through QA-reviewer rights, and the action was recorded on the respective checklist. The SOP for LC-MS/MS system access control using Analyst software system was available.

In addition, the QA checked the Analyst software system's data following the respective SOP.

### **4. Archive facilities**

The CRO had sufficient and appropriately secure storage space in the clinical facility, which was fireproof, and pest-controlled, for archiving the trial-related documentation.

The archiving activities were managed in accordance with SOP for Document archival and maintenance of the archive facility.

Access to archive storage areas was controlled and restricted to authorized personnel. The entry and exit information were recorded in the respective logbook.

Records of document access and return were maintained. The length of time for study documentation, including raw data, should be kept in the archive as defined in the SOP.

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

## 5. Premises

During the inspection, a tour of clinical and bioanalytical facilities was conducted. Since the bioanalytical facility was recently inspected, the focus was to visit and inspect the clinical facility.

The CRO had added two new LC-MS/MS, two deep freezers, one combination refrigerator, and one freezer to the BA facility.

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 safety of the subjects. The potential risks involved in the respective activities were considered in the facility's design.

Entry to the clinical facility was restricted and controlled. The Exit doors were adequately monitored, and CCTV systems were installed throughout the Premises. The Emergency evacuation was ensured. Entry to and exit from the facility were recorded. The documentation of CCTV performance verification was available and reviewed. A performance check was carried out every three months.

The Clinical site included a pharmacy where investigational products were stored under appropriate conditions, with restricted entry and exit. Proper entry/exit records of each visit to the pharmacy were maintained. The pharmacy section and the respective walking chamber should be expanded to have more space for IMP storage to avoid mix-ups or similar mishappens.

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.

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.

A Diesel generator with 500 KW supplied the electricity power of the entire facility in case of electricity load shedding and interruptions. Additionally, the laboratory equipment, ICU, sample processing area, and IT systems were supported by UPS systems, when applicable.

Safety data sheets were available to staff before testing was carried out. Staff working in the laboratory was 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 coats or other protective clothing, including eye protection. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison,” “flammable”) whenever appropriate.

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

## **6. Personnel**

There was enough medical, paramedical, technical, and clerical staff with the appropriate qualifications, training, and experience to support the trial and to be able to respond effectively to reasonably foreseeable emergencies. The number of staff members counted to 57 at the BA site and 114 at the Clinical site, including QA, IT, and statisticians, at the time of inspection. At all stages of the trial, including at night, there were qualified and trained personnel to ensure that the safety and well-being of the subjects were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities such as phlebotomists.

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

## **Clinical section**

## **7. Clinical phase**

The clinical phase of the studies was performed on the premises of the CRO at the clinical site. The clinical and bioanalytical sites were located within walking distance on the same premises.

The CPU was equipped with 62 + 2 ICU beds. Beds were equipped with corded handsets, and in the washrooms and the bathroom, Emergency Pull Cord Modules were available to be used by subjects for calls to alert CRO staff in case of need. There was a nurse station on the Ground and First floors to monitor the entry and exit of the study participants.



Facilities for changing and storing clothes and for washing and toilet purposes were clean, well-ordered, easily accessible, and appropriate for the number of users. Lockable toilets were alarmed, and doors were designed to ensure they could be opened from the outside should a medical emergency occur.

The clinical site consisted of four floors, including the basement and Ground floor, divided into the following sections:

- Reception
- Screening
- ICF Presentation
- Store
- Clinical Pathology Lab which was not operational at the time of inspection.
- Housing Area- I, II & III
- ICU
- Pharmacy
- Sample processing and storage
- Work desk
- Conference room
- PK/STAT
- Quality Assurance
- Archival
- Staff Dining
- IT and Server

Access to the randomization list was restricted. The list was kept under supervision in form of a hard copy, and the respective distribution was documented.

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.

The observation related to the Clinical phase was addressed in the respective CAPA plan.

## **8. Clinical laboratory**

A suitable clinical laboratory was used for analysing samples. The laboratory was accredited, and the accreditation was valid until 22 February 2023.

Haematological tests, urine analysis, and other tests were performed before and/or after the clinical trial as specified in the study protocol.

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

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

The laboratory created individual reports for each subject and included them in the CRFs.

## **9. Ethics**

The trial was approved by the independent ethics committee before the study was conducted. The Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list. Detailed minutes were kept of the discussions, recommendations, and decisions of the IEC meetings. The IEC was given time to review protocols, informed consent forms (ICFs), and related documentation.

### Informed consent form

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

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

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through the Insurance company.

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

Language Translation Services performed the applicable translation.

## **10. Monitoring**

The Cliniserve Monitoring partner was responsible for independent monitoring of all clinical periods in accordance with a monitoring visit plan 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 completing CRFs and verifying the accuracy of data obtained.

The monitoring visits were documented, and the respective reports were provided to the site after the completion of the study.

## **11. Investigators**

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

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

The information concerning the receipt, storage, handling, and accountability of investigational products at every stage of the trial was recorded. The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products were also verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through a digital temperature and humidity device. The records were printed and reviewed daily.

Randomization was performed in accordance with SOP for Generation of Randomization Schedule, and records were maintained, including the randomization list and seed. The randomization list was accessible only to the authorized personnel.

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

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

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

Dispensing and packaging procedures were performed in accordance with SOP for Dispensing of IMP 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 to ensure that the subject had swallowed the IP. Dosing was directly documented in the CRFs.

Samples of the product in the original container were retained for possible confirmatory testing in the future for at least one year after the expiry date or two years after the completion of the study or until the test product has received approval, whichever longest in accordance with the study protocol. Dispensed products that were not administered were also retained.

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

Randomly selected CRFs from the study were reviewed.

The data to be 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 the vital examination, demographics, exclusion & inclusion criteria, intake of meals, dose administration, blood sample collection, adverse events, concomitant medication, possible withdrawal, etc., was recorded in the CRFs.

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

Procedures for recruiting volunteers were specified in SOP for Volunteer Recruitment for Biostudies and included a description of the potential methods the CRO used for this purpose. A database was maintained only for the registration of new volunteers. Another database was established to avoid cross-participation and to specify a minimum time that should elapse between a volunteer's participation in one study and the next by recording the first dose

administration at the station located at the CPU. The software system was a central repository used by the CROs in the district to find out whether any of the subjects had participated in a previous trial, and participation data was uploaded to prevent over-volunteering. Access to the database was password controlled to secure confidential information on volunteers. A biometric system using thumb and index fingerprints ensured the identification of volunteers and subjects.

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

## **15. Food and fluids**

The CRO was able to arrange for standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol and as per the agreement with the catering services.

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.

The provided meals were standardized and 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 to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of serious adverse events.

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.

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

## Bioanalytical section

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

Chromatograms and their integration, the absence of signals in the blank samples, absence of any unexplained interruptions in the injected sequences were verified. The reason for the study sample repeat analyses and instrument failures was reviewed. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the requirements.

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

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

Bioanalytical method of determination of Artemether and Dihydroartemisinin was validated for calibration curve ranging from 2.000 ng/mL to 350.294 ng/mL for Artemether and 2.001 ng/mL to 350.391 ng/mL for Dihydroartemisinin in K<sub>2</sub>EDTA human plasma using LC-MS/MS as per the respective Method Validation. Artemether D3 and Dihydroartemisinin 13C D4 were used as internal standards.

Bioanalytical method for determination of Lumefantrine was validated for calibration curve ranging from 50.167 ng/mL to 20086.702 ng/mL in K<sub>2</sub>EDTA human plasma using LC-MS/MS as per the applicable Method Validation. The analysis was performed on LC-MS/MS system (TRIPLE QUAD™5500).

The method development process was adequately described and documented. The usage of IS was justified based on the relevant literature for Artemether, Dihydroartemisinin, and Lumefantrine in the respective notebook for method development. The source of literature was available. After method development, a description of the analytical method for Artemether, DHA & Lumefantrine was provided as a basis for the method validation. Stable isotope-labelled internal standards were always used in the MS methods, and K<sub>2</sub>EDTA was applied as an anticoagulant.

During the method validation as per SOP for Bioanalytical Method Validation, a run was performed to determine the batch with 120 samples of QCs and CCs (so-called Analytical run batch determination) that was comparable in length to those that were expected to be used for analysis.

The sample processing was documented in the respective forms. A note to file was also provided to record any unexpected activity during sample processing, when applicable.

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

The review of the full method validation included Aqueous Linearity, Carry Over, Selectivity, Matrix Effect, Interconversion, P&A and Sensitivity, Recovery, Long Term Stock Solution and Dilution Stability, Whole Blood Stability, Screening, Ruggedness, Extended Batch, interfering Potential by Concomitant Drugs. According to the requirements, partial validation was performed on specific instruments.

The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants. The purchase documentation of the plasma from New Life Blood Centre, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed, and discussed.

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 review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per applicable SOPs, such as SOP for Subject Sample Analysis and Analytical Run Acceptance Criteria. A system suitability and stabilization test (optimization) were done prior to the start of sample analyses on each day and in accordance with SOP for Peak Integration and Chromatographic Acceptance Criteria.

Preparation of spiked calibration curve standards (CS) and quality control (QC) samples were recorded on the respective template with adequate information to ensure traceability in accordance with the applicable Standard Testing Procedure (STP). The records of the stock solution preparation and stock dilution used to provide the CS and QCs were also available. The Reference Standards used for preparing stock solutions were adequately documented in the respective logbooks.



At least 10% of the samples were selected for ISR for the first 1000 samples and 5 % for the remaining samples. A designated person identified and reviewed the samples to be taken for ISR in the following manner: At least two samples per period of all the accepted batches of analysed samples were selected as incurred samples, i.e., one sample which had a concentration near the  $C_{max}$ , and one sample in the elimination/terminal phase having a concentration greater than LQC. The acceptance criteria were clearly defined in SOP for Incurred Sample Reanalysis.

The system audit trail review was carried out at the time of the studies in the scope of the inspection, reviewing the paper records. However, the practice was changed to review the electronic raw data, and adequate training was provided to the responsible personnel. The training was sufficiently documented.

Only subject no. 25 had a predose above 5 % of  $C_{max}$ , which was treated as per the applicable procedures.

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

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

Three aliquots were provided for the sample analysis and the respective backup samples. The aliquots were shipped and stored separately. The QC and CC samples were discarded and documented. A reconciliation for consumption of QC and CC samples was available and reviewed. Aliquot 1 & some of the samples from aliquot 3 were used for the sample analysis of Arthemeter and DHA, while aliquot 2 was used for Lumefantrine.

Information about storage condition and specifications, study date, anticoagulant used, number of received samples, number and specification of haemolyzed samples, and usage of dry ice was documented and verified in respective controlled templates.

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.



Labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained following SOP for Receipt, handling, storage, and disposal of study samples & SOP for Labelling Procedures in the Clinical Pharmacology Unit.

Approval was required to be provided by Test Facility Management for the disposal of study samples, and the details should be recorded in the respective form. After approval, the custodian disposed of study samples in the presence of QC personnel as per SOP for Safety in Laboratory. All the aliquots were stored until analysis, and aliquot 3 with sufficient volume was retained for at least six months after approval of the bioanalytical report. The samples were available during the inspection in the respective storage facility.

## **19.Data processing and documentation**

Integration settings were science-based and justified. 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 SOP for Subject Sample Analysis and Analytical Run Acceptance Criteria. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. Variations in response to Internal Standards (IS) and the respective acceptance criteria were described in the SOP. The calculation of IS response related to Artemether and DHA was reviewed.

Full audit trails were activated on all analytical instruments before, during, and after the method validation and the sample analyses. Verification of checksum was confirmed.

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

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

## 20. Good laboratory practices

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

Deep freezers for storage of the samples and refrigerators for storage of the Reference standards were adequately qualified, calibrated, and maintained. There was an alarm system associated with the digital thermometer to trigger email notifications to the custodians responsible for the maintenance of the facility. The automatic alarm system was tested during inspection to verify its proper functionality. The daily monitoring and all the alarm checks were documented.

For qualification verification, the temperature mapping of the Deep Freezer used for the sample processing, was reviewed to verify the hot spot and the location of the respective sensor. The temperature mapping study was available. Transfer of samples to equivalent storage units was appropriately considered in case of emergency, maintenance, or repair.

The operation, use, calibration, checks, and preventive maintenance of equipment were previously inspected in April 2022.

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.

## Pharmacokinetic, statistical calculations and reporting section

### 21. Pharmacokinetic, statistical calculations

The statistical model underlying the BE analyses was described. The pharmacokinetic parameters such as  $C_{max}$  and  $AUC_{0-t}$  for Artemether and Dihydroartemisinin (DHA) and  $C_{max}$ ,  $AUC_{0-72}$  and  $T_{max}$  for Lumefantrine were estimated using Phoenix WinNonlin and the statistical analysis was calculated using SAS®.

QA verification was required to be carried out following the respective SOP of vertical format concentration data of Artemether, DHA and Lumefantrine under fed condition.

The observation related to Pharmacokinetic and statistical calculations was addressed in the respective CAPA plan.

## 22. Study report

Procedures were established to ensure the quality and integrity of the study report.

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

Miscellaneous	
<i>Samples taken</i>	<i>N/A</i>
<i>Assessment of the CRO master file</i>	A CRO Master File for the Bioanalytical site, effective 7 Nov 2022, and another CRO Master File for the Clinical site, effective 7 Nov 2022, were available.
<i>Annexes attached</i>	<i>N/A</i>

Part 3	Conclusion
--------	------------

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 *Micro Labs Ltd, Micro Advanced Research Centre*, located at the following addresses:

***Clinical Pharmacology Unit  
Nos. 9 to 14, Katha Nos. 390/395  
Situating at Kudlu, Near Grama Panchayath Office  
Singasandra Post, Sarjapura Hobli, Anekal Taluk  
Bengaluru District  
Bengaluru -560068  
India***

***Bioanalytical Unit  
58/3, Kudlu Village, Anekal Taluk  
Bengaluru -560068  
Karnataka  
India***

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

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

<b>Part 4</b>	<b>List of guidelines referenced in the inspection report</b>
---------------	---

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.  
**Short name: WHO BE guidance or TRS996 Annex 9**  
<https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>
2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009  
**Short name: WHO GCLP**  
<https://apps.who.int/iris/handle/10665/44092>
3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137). **Short name: WHO GCP**  
<https://www.who.int/publications/i/item/9241208503>
4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. **Short name: OECD GLP**  
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
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**  
<https://www.who.int/publications/i/item/9789241502948>
6. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised). **Short name: Glove use information leaflet**  
[https://www.who.int/publications/m/item/glove-use-information-leaflet-\(revised-august-2009\)](https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009))

7. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.  
**Short name: WHO CROMF Guidelines or TRS No. 957, Annex 7**  
[https://www.who.int/publications/i/item/WHO\\_TRS\\_957](https://www.who.int/publications/i/item/WHO_TRS_957)
8. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. **Short name: WHO storage and transport guidance or TRS 961 Annex 9**  
[https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f\\_2](https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f_2)
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 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**  
<https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf>
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**  
<https://www.who.int/publications-detail/978-92-4-000182-4>
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**  
<https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations-3-good-manufacturing-practices-guidelines-on-validation>