

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

Part 1	General information
Organization details	
Company information	
Name and Address of Clinical Research Site	Sitec Labs Ltd. Plot No: Gen-40, TTC, MIDC Behind Millenium Business Park Near Nelco bus stop Mahape Navi Mumbai-400710 India <u>Screening and pathology site:</u> 1 st floor, Jayashree Plaza, Near Dreams Mall, LBS Marg, Bhandup(w) Mumbai 400 078, India
Name and Address of Bioanalytical Research Site	Sitec Labs Ltd. Plot No: Gen-40, TTC, MIDC Behind Millenium Business Park Near Nelco bus stop Mahape Navi Mumbai-400710 India
Name and address Statistical Site	Sitec Labs Pvt. Ltd. Gen 40, TTC Industrial Area, MIDC, Behind Millennium Business Park, Near Nelco Bus Stop, Mahape Navi Mumbai - 400 710. India
Corporate address of Organization	Sitec Labs Ltd. Plot No: Gen-40, TTC, MIDC Behind Millenium Business Park Near Nelco bus stop Mahape Navi Mumbai-400710 India

Sitec Labs Pvt. Ltd., Navi Mumbai India - CRO

20-23 March 2023

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Contact: prequalinspection@who.int

GPS coordinates	Latitude: 19°1'58.98"N Longitude: 73°1'46.78"E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	WHO application no. HA779 Bioequivalence study of Abacavir, Dolutegravir, and Lamivudine tablet for oral suspension 60/5/30 mg WHO application no: HA770 Bioequivalence study of Efavirenz 400 mg + Lamivudine 300 mg + Tenofovir Disoproxil Fumarate 300 mg tablet WHO application no. CV021 Bioequivalence study of Molnupiravir 200 mg capsule
Inspection details	
Dates of inspection	20-23 March 2023
Type of inspection	Routine
Introduction	
Summary of the activities	Sitec is a Contract Research Organisation that develops and validates new analytical methods to run bioequivalence/bioavailability studies. The CRO provides services in three different categories: <ul style="list-style-type: none"> - Analytical services: Analytical Method Development and Validation. ICH Stability studies Comparability studies Forced Degradation studies Leachable, Extractable studies Excipient & API analysis Finished Product analysis - Clinical services: Bioavailability & Bioequivalence studies - Bioanalytical services: Bioanalytical Method Development and Validation Bio Sample analysis
General information about the company and site	Sitec Labs Pvt. Ltd is a Private Limited company established in 2004 in Mumbai. The organization expanded the facility in 2010 from approx. 30000 sq. ft to approx. 75000 sq. ft. by relocating to Navi-Mumbai, India.

History	<p>The CRO was inspected by the US FDA, MCC, UAE Ministry of the Health Department, Department of Drug Control, MHRA, and ANVISA.</p> <p>An onsite inspection was performed by WHO in August 2018.</p>
Brief report of inspection activities undertaken	<p>The following scope and study-related activities were reviewed:</p> <p>The company’s history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.</p> <p>Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.</p> <p>A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with comparison of the source data to the study reports.</p>
Scope and limitations	
Out of scope	N/A

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
DMF	drug master file
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
OOS	out of specification
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

PART 2**SUMMARY OF THE FINDINGS AND COMMENTS****General section****1. Organization and management**

A presentation was provided explaining the activities of the organization in detail.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The Director authorized the organization chart on 17 Feb 2023.

DCGI issued a registration certificate in form CT-09 on 17 Jun 2020, valid for five years.

There was a job description for each employee, including his/her responsibilities. It was randomly verified that every job description was signed and dated by the staff member to whom it applied.

A list of signatures of the authorized personnel performing tasks during each study was available and verified. The service agreement with the sponsor was available.

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

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

The official working hours of the office were from 8:30 to 17:15.

2. Computer systems

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

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and were validated, operated, and maintained in accordance with the principles of GCP and GLP, as appropriate.

An inventory of all computerized systems on the network was available. Changes to the network, including the temporary addition or removal of systems from the network, were documented in Change Request forms following the respective procedures.

There were a sufficient number of computers to enable personnel to perform data entry and data handling required for calculations and compilation of reports. Computers had adequate capacity and memory for the intended use.

Authorized personnel unlocked the computer systems with their dedicated username and password. User levels were assigned for different activities in the software systems, wherever applicable.

The software programs used to perform key activities were evaluated through GAP assessment and risk assessment in accordance with 21 CFR PART 11 and EU Annex 11. A URS was prepared for each software system. IQ, OQ, and PQ documentation were available to verify that the system was developed in a controlled manner in accordance with the applicable procedures. The qualification and/or validation certificates were provided under the user's supervision. The qualification of randomly selected systems was reviewed.

The specific user requirements, regulatory/guideline requirements for BE studies, the operating environment in which the system was used, and the usage of the system in the studies were considered in the Performance Qualification of the applicable systems. Quality risk management was applied when deciding which components needed to be validated. All phases of their life cycle were considered. SOPs for usage of each software program used to perform activities of a BE study were available.

Regular updates to key software programs were carried out in accordance with the applicable SOP. A periodic review schedule with information on application software, the respective equipment, workstation ID, frequency of review, date of validation, date of last periodic review, and following periodic review, and the completion date was provided, dated 30 Jan 2023. The process described in the SOP included an assessment of the documentation, procedures, records, and performance of a computerized system to determine whether it was still in a validated state or what actions, if any, were necessary to restore its validated state. The frequency of review depended on the system's complexity, criticality, and rate of change but should be within the annual review frequency. The schedule was specific to each department, i.e., clinical, bioanalytical, and pathology.

The backup and restoration process was detailed in the SOP for the backup and restoration of electronic data. Networks, including the full client/server architecture and interfaces such as the laboratory information management systems, were designed, qualified, managed, and controlled in accordance with the applicable procedures. The backup validation report dated 11 Jan 2023 was available and reviewed. Evidence for the folder's readability and size was provided in screenshots.

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

The disaster recovery and business continuity of IT systems were specified in the respective documentation. Cluster server failure, storage failure, loss of data, switch failure, and other types of breakdowns were addressed in this documentation.

The observation related to the computerized systems was adequately addressed in the respective CAPA plan.

3. Quality management

The CRO had appropriate QA and QC systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and the applicable regulatory requirements. Every SOP should be revised every two years, and if no changes were required, the Master copy would be stamped to indicate that the SOP was reviewed, and the validity of the SOP was extended.

An integrated Quality manual version no. 23, effective 7 Oct 2022, was provided in accordance with ISO 9001:2015 & 21 CRF 211.

QA personnel were not directly involved in trial-related activities, and an in-process QA personnel audit did not replace another person's oversight when required.

The QA unit was responsible for

- verifying all activities undertaken during the study,
- ensuring that the quality management systems were followed, reviewed, and updated,
- determining that the protocol and SOPs were made available to study personnel and were being followed,
- checking all the study data for reliability and traceability,
- planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP, and following up on any corrective action as required, to determine if all studies were conducted in accordance with GCP and GLP,
- ensuring that contract facilities adhered to GCP and, if applicable, to GLP: this included auditing such facilities and following up on any corrective action required,
- verifying that the trial report wholly and accurately reflected the data from the study and the methods and procedures followed,
- promptly reporting audit findings in writing to management, the investigator, and the study director, as applicable.

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

The Change control form for SOP updates was available in accordance with the revised ICH M10 guidelines. The respective SOP was updated accordingly, and the change request was completed on 17 Mar 2023. The impact of the change on the other activities was evaluated by either the user department or the QA.

4. Archive facilities

The CRO had appropriately secured temporary storage space, equipped with a fire resistance door (two hours fire rated), relative humidity-control, and pest-control devices, for archiving the trial-related documentation for approximately six months before being sent to the offsite archive facility. A dehumidifier was installed in the facility. A letter from the service provider was provided on 23 Mar 2023 to certify that pest control treatment, i.e., disinfection, rodent, gecko, fly control treatment, spider, and mosquito control treatment at the premises, were carried out to avoid any pest from entering the premises and to remove any pests that have already established their presence within the premises.

The archiving activities were managed following the procedures established in the applicable SOP.

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

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

All inspection requests for retrieval and traceability of the study-related documents were successfully met during the inspection.

5. Premises

A facility tour was conducted during the inspection on days 2 & 3.

The site was divided into a bioanalytical department and a clinical department. Check-in and ambulatory area were located at the adjacent Plot, i.e., No. PAP-A-417, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai. However, the screening activities took place at a different facility about 14 km from the clinical department.

The facilities were kept clean and had adequate lighting, ventilation, and environmental control at the time of inspection. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

Clinical trials were carried out under conditions that ensured adequate safety for the subjects.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site had adequate facilities, including laboratories and equipment.

Entry to the facility was restricted and controlled through key cards/biometric access. Alarm systems to detect the exit of subjects from clinical facilities were installed, and/or the doors were locked. The Emergency evacuation was ensured. Any entry to and exit from the facility were recorded.

Sites where clinical activities took place included a pharmacy where investigational products were stored under appropriate conditions kept in the stability chambers, monitored by a digital thermometer software system, with restricted entry and exit. Proper entry/exit records of each visit to the pharmacy were maintained.

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 protect all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Safety data sheets were available to staff before testing was carried out. The team working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff was trained to use the firefighting equipment, including fire extinguishers, fire blankets, and gas masks. Staff was instructed to wear laboratory

coats or other protective clothing, including eye protection. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings (e.g., “poison”, “flammable”) whenever appropriate and kept in secure cabinets in a separate room.

First-aid materials were provided, and the staff was instructed in first-aid techniques, emergency care, and antidotes. Express feeder connection for an uninterrupted electricity supply was available. In case of power failure, three interlinked diesel generators were available with a total capacity of 920 kva. An uninterrupted power supply (UPS) with a total capacity of 250 kva was provided.

Volatile organic chemicals were handled under certified fume hoods or air extractors, and safety and eye showers were available in the laboratory.

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

6. Personnel

Induction training programs were organized for new employees, in addition to the on-the-job training and periodic training on various aspects conducted by trained personnel. Training on unit operations and processes, use of equipment, safety, GCP, and GLP were carried out by in-house and outside specialists.

Records relating to training and post-training assessment were maintained. The number of members of staff counted to over 450. Contract workers were employed to perform certain activities, such as a dietician.

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

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO.

The CPU had 112 beds, divided into four units on the same floor. Systems were in place in the accommodation facilities so subjects could alert CRO staff in case of need.

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

The clinical site consisted of

- Subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy,
- CPU,
- Subjects' recreation,
- Pharmacy,
- Room for the administration of the investigational products and sample collection,
- Sample processing (e.g., plasma separation) and storage (freezer),
- Archive facility,
- A dining hall,
- ICU

Provisions were made for the urgent transportation of subjects to the hospital in accordance with an agreement dated 12 Jan 2023. A mock drill was performed to verify the safe transportation of volunteers to the hospital in an emergency.

Access to the randomization list was restricted to the pharmacist in charge of the study. Such documents were kept under lock and key (if in the form of a hard copy), and their distribution was documented. The list was provided in a sealed envelope to the pharmacist.

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

After the Pandemic, the CRO started using test kits to perform alcohol and drug panel tests during the applicable activities. The certificates of analysis of the 6 drugs multi-dip and alcohol test devices were available. However, the calibration report of the Breath Alcohol Analyser, dated 21 Oct 2022, was also available and reviewed.

The X-ray facility was subcontracted to an external vendor, close to the screening facility within walking distance. The vendor's personnel physically provided the X-ray image and description.

An observation related to the clinical phase was successfully addressed.

8. Clinical laboratory

A suitable clinical laboratory was used for analyzing samples. The laboratory was accredited by NABL in accordance with ISO 15189:2012.

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

The samples had unique identification numbers and were traceable by test requisition form to an identified individual.

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. Source or raw data for all tests performed were archived by the laboratory in electronic and paper formats, depending on their source and the laboratory's storage capacity.

Data integrity requirements were ensured for all tests related to the study through adequately validated systems used for sample analysis.

9. Ethics

The Independent Ethics committee approved trials before any study activity was conducted. This Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation.

Informed consent form

Information for study participants was given to them in English or vernacular language, i.e., either Hindi or Marathi, and at a level of complexity appropriate to their understanding, both orally and in writing. The volunteers should be literate.

Informed consent was given by the subject and documented in writing before starting any trial-related activities. The information clearly stated that participation was voluntary, and the subject had the right to withdraw from the study on their initiative at any time without giving a reason. The reasons for withdrawing from the study were included in the records, if applicable. The CRO had changed its procedure to exclude audio-video recordings of the informed consent process while conducting clinical trials.

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 policy.

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.

The certificate of translation and back translation of the informed consent were reviewed. The translation was performed and documented internally by the CRO. An external translation agency completed the back translation of the ICF.

10. Monitoring

The studies were monitored by monitors employed by the sponsor.

The monitor prepared a written report after each site visit to be submitted to the sponsor, and the sponsor communicated any issues to the CRO if applicable to enable prompt corrective action.

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

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor.

Randomization was performed in accordance with SOP for Randomization process, and records were maintained, including the randomization list and seed. The randomization list was accessible only to the statistician and a dispensing pharmacist.

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 the information was not lost once the lid was removed.

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

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

Dispensing and packaging procedures were performed in accordance with the requirements and SOP for Dispensing of investigational products. Dosing was performed in accordance with SOP for Dosing.

The surface on which the product was handled was thoroughly cleaned before bringing bottles of the product into the area. Any product containers (full or empty), lone dosage formulations, labelling materials, contaminants, dirt, and debris were removed from the area. A second person verified that the surface area/line was clear and clean before bringing in and opening product containers. The IMPs were handled with appropriate utensils. Tablets were distributed into each container in accordance with the randomization list for the comparator or the test product as appropriate. The two products, i.e., Test & Reference, were handled at different times. This also applied to the labelled containers. Every step was recorded sequentially in detail. The surface upon which the product was handled, and its surroundings were cleared and cleaned immediately before and after initiating the dispensing of the following product, also in the same study.

Investigational product accountability and dispensing records were always maintained. Each activity was documented when performed, including records of doses administered and returned or destroyed and records of verification by a second person of each step.

Dosing was carried out under the supervision of the PI, dosing supervisors, and qualified staff members from QC and QA to whom this task was explicitly delegated in writing. A new software system was implemented to digitalize the clinical activities from screening activities throughout the clinical phase, including dosing administration, sample collection, and sample processing. Hence, an IT person was also available during these activities to attend to any system failure.

The IP's label was checked before dosing, and the exact time of dosing was documented on the CRF's/e-CRF's designated page. A mouth check was performed by looking under the tongue, under the lips, in the corners of the mouth, and between gums and cheeks, using a tongue depressor or a spatula in the case of solid oral dosage forms to ensure that the subject had swallowed the IP. Dosing was directly documented in the e-CRFs at the time of inspection. However, the new digitalized system was implemented in October 2022 and did not exist at the time of the studies in the inspection scope.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for possible confirmatory testing for at least one year after the expiry date of the newest product in accordance with SOP for Management of IMP. The sample retention time was also specified in the contract between the sponsor and the CRO. According to the contract, the IMPs should be retained depending on the regulatory agency's agreement, as mentioned in a table in the agreement. Dispensed products that were not administered were also retained.

13. Case report forms

Randomly selected CRFs from the studies CV021, HA799 & HA770 were reviewed.

The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about inclusion /exclusion criteria and all procedures required by protocols was recorded in the CRFs. Documentation regarding IMP administration and blood sample collection was available. Investigators verified patients' eligibility, and the approval process was adequately documented. The quality of documents was sufficient, and ALCOA principles were followed. There were no cases of discrepancies or incomplete information. All CRFs were readily available and provided in a timely manner on request of the inspection team.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in SOPs for Screening and for Check-in and checkout of the volunteers/subjects from CPU and included a description of the potential methods the CRO used. Both male and female volunteers were recruited for the studies. A database containing a module for registration of volunteers, was maintained on volunteers to avoid cross-participation and specify a minimum time that should elapse between a volunteer's participation in one study and the next. Access to the database was password controlled to secure confidential information on volunteers or subjects.

A biometric system using both thumbs ensured the identification of volunteers and subjects. The biometric system was periodically validated.

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. The CRO was a member of OVIS, i.e., Online Volunteers Information System, to avoid the cross-participation of the volunteers between the CROs. Participation data was uploaded to this central repository to prevent over-volunteering.

15. Food and fluids

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

Timing, duration, and amount of food and fluids consumed were recorded. Before samples were obtained from ambulatory subjects, they were asked about their food and drink consumption. A dietitian with appropriate qualifications, training, and experience designed standardized meals.

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 a serious adverse event.

First-aid equipment and appropriate rescue medication were available in the ICU. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the ICU.

The CRO had adverse event registration and reporting forms as part of the CRF. The usage of concomitant medication was properly recorded in the CRF.

Bioanalytical section

The focus of the inspection of the bioanalytical part was on studies CV021 (determination of β -d-N4-hydroxycytidine (NHC), i.e., initial metabolite of molnupiravir) & HA779 (determination of abacavir, dolutegravir, and lamivudine). More specifically, the following records and activities were arbitrarily investigated:

- Auditing source documentation and raw data for validation of the bioanalytical methods.
- Analysis of subject plasma samples and a review of the electronic data.
- Audit trails for electronic data capture and handling related to the BE studies.
- Results of calibration standards, quality control samples (QCs), subject plasma samples in analytical runs, and chromatograms generated from the analytical runs.
- Preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and interruptions in the injected sequences were verified. The reason for the study sample repeat analyses and all 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 provisions.

The inspection team received adequate support from well-informed and transparent personnel to review the study documentation.

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

The method development process was adequately described and documented, and the usage of IS was justified based on the relevant literature. A copy of the literature was available. After method development, an analytical plan was provided as a basis for the method validation. A stable isotope-labelled internal standard was used in the MS methods. The expenditure of selected Reference standards was verified.

During the method validation as per SOP for validation of the bioanalytical method, a run was performed to determine the batch with adequate samples of QCs and CCs (so-called analytical run batch determination) comparable in length to those expected to be used for analysis in accordance with the applicable SOP. The SOP was revised on 17 Mar 2023 to include the Analysis of Long Precision and Accuracy batch to cover the number of study samples in the analytical run (Sample processing and analysis on LC-MS/MS) for subject analysis/ISR. After implementing the new process, a P&A long batch analysis was performed for the studies in the inspection scope to include the new requirements per ICH M10. The analytical experiments, and the respective raw data were properly recorded.

The method validation for Abacavir Lamivudine was reviewed. The examination related to the presence of concomitant medication (Other Drugs) was performed on 2 Aug 2022.

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 storage period was available before the start of the studies, except for the long-term stability, which was performed after the termination of sample analysis.

The random review of the method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including stock solution stability), haemolytic effect, recovery, and reinjection reproducibility. Partial validation was performed according to the requirements. The biological matrix used in method validation was similar to that obtained during the bioequivalence study. The anticoagulant was also the same as that used in bioequivalence studies. The clinical department's documentation of the plasma preparation, including the volunteer's ICF, 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 a review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs.

The preparation and verification of the System Suitability analyses were reviewed. It was confirmed that the Incurred Sample Reanalysis (ISR) was performed to assess the reproducibility of a bioanalytical method to analyze incurred samples. ISR was executed for all pivotal studies.

The observation related to the sample analysis was adequately addressed in the respective CAPA plan.

18. Sample collection, storage and handling of biological material

The specification of samples (blood plasma), sampling method, volume, and the number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport, or shipping and storage of samples occurred per the applicable SOPs.

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 labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots, shipped, and stored separately.

SOPs for Preparation of calibration and quality control levels in plasma and for Receipt, storage, and disposal of study samples specified the management of the study samples, QC samples, and CC samples, including their disposal. The respective record for the Molnupiravir study was available and reviewed. The retention time for the biological materials was specified in the contract between the CRO and the sponsor.

The observation related to the storage of biological samples was adequately addressed in the respective CAPA plan.

19. Data processing and documentation

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

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

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

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

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, the 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 on Day 2 to verify the suitability of the facility in terms of arrangement and safety.

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

Deep freezers for storage of the samples and refrigerators for storage of the Reference Standards were qualified, calibrated, and maintained. There was an alarm system associated with the digital temperature monitoring system to trigger a notification call 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 in the system.

The most recent temperature mapping of the Deep Freezer was reviewed to verify the hotspot and the location of the respective sensor. The temperature mapping process was properly carried out in full, partial, and no-load conditions. Transfer of samples to the equivalent storage units was appropriately considered under maintenance and repair.

Balances, other measuring devices, equipment, and instruments used during a trial were periodically calibrated and verified before use to be fit for their intended purpose. Periodic verification of randomly selected balance and micropipette was verified during inspection. The balance room temperature was properly monitored using a digital thermometer.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. These activities were verified by random review of the equipment, e.g., LAF bench used to dispense IMP and LC-MS/MS. Equipment and its components were labelled with the respective ID number, calibration date, and next calibration date. The analytical sheets and the respective logbooks for instrument usage adequately documented the equipment usage. The use of columns was recorded in the logbook for the usage of columns.

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

Information concerning the source, preparation date, and stability was available on the label or the CoA.

The observation related to Good Laboratory Practices was addressed in the applicable CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

A presentation explaining the pharmacokinetic and statistical department's activities was provided during the inspection on Day 4. The statistician's qualification was verified through his CV dated 6 Jan 2023.

The statistical model underlying the primary BE analysis was stated in the respective protocol and/or a statistical analysis plan. The sample size was decided based on the information received from the sponsor.

The randomization scheme was generated using the Proc Plan procedure in SAS software. The computer & the printer used to create a copy of the randomization list were password protected. This document was accessible only by the statistical department.

The Excel sheet with the sample collection time points, together with any applicable deviations, was prepared and shared with the statistician by the Data entry operator. The records were verified by the QC as part of the Report writing team. At the time of the studies in the inspection scope, the data entry was done using the paper CRF. The activity is currently completed through the software system, i.e., a platform to design, process, and monitor the eCRFs.

PK calculation was carried out following SOP for Pharmacokinetic and statistical calculation using Phoenix WinNonlin software. The summary table, graphical presentation, and BE output, including ANOVA, were generated in SAS software.

The data lock procedure was now forecasted in the new software system. Any unlocking of data will be registered, and it should be justified. Before implementing this system, any data revision was based on paper record requests when applicable.

22. Study report

The process of study report writing was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies were identified between the results stated in the report and the original (raw) data.

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

Miscellaneous	
<i>Samples taken</i>	NA
<i>Assessment of the CRO master file</i>	The CRO Site Master File version no. 17, effective 19 Jan 2023 was provided and reviewed.
<i>Annexes attached</i>	NA

Part 3	Conclusion – inspection
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Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines of *Sitec Labs. Ltd.*, located at the following addresses:

Clinical & Bioanalytical site

Gen 40, TTC Industrial Area, MIDC, Behind Millennium Business Park, Near Nelco Bus Stop, Mahape Navi Mumbai - 400 710.

India

Screening & Pathology site:

1st Floor, Jayashree Plaza, Near Dreams Mall, LBS Marg, Bhandup(w) Mumbai 400 078, 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.

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

16. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
Short name: WHO GPPQCL Guidelines or TRS No. 957, Annex 1