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Prequalification Team (PQT), Inspection Services (INS)
WHO PUBLIC INSPECTION REPORT
WHOPIR
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Chengdu Xinhua Hospital** **Phase I Clinical Research Center Team** 180 Shuangqiao Road, Chenghua District Chengdu, Sichuan Province P. R. China
Name and Address of Bioanalytical Research Site	**Chengdu Finelyse Pharmaceutical Technology Co., Ltd** 1st Floor, Building B, No. 5, Keyuan South Road High-tech Zone Chengdu, Sichuan Province P. R. China
Name and address Statistical Site	**Shanghai Zenith Data Technology Co., Ltd.** 12th Floor, Building 2, No.2388 Chenxing Road Minhang District, Shanghai P. R. China
Corporate address of the Organization	**Chengdu Gencore Pharma Medical Technology Co., Ltd.** ***This is the primary Contract Research Organization subcontracting the study to the centers mentioned above.*** Floor 11, Building B, Rongyao Building, No. 5 Keyuan South Road, High-tech Zone Chengdu, Sichuan P. R. China
GPS coordinates	BA Site: Latitude: 30°36'46" Longitude: 104° 1' 38" CL Site: Latitude: 30° 39' 9" Longitude: 104° 6' 3"

WHO product numbers covered by the inspection	**WHO application no. CV026** Bioequivalence Study of **Nirmatrelvir 300 mg** (2 x 150 mg Film-coated tablets) + **Ritonavir 100 mg** (1 Film-coated tablet)
Inspection details	
Dates of inspection	15-17 July 2024 Bioanalytical site 18-19 July 2024 Clinical site
Type of inspection	Initial
Introduction	
Summary of the activities	The primary Contract Research Organization (CRO) subcontracted the BA Site to conduct the bioanalytical component of the study. Founded in 2016, Chengdu Finelyse Pharmaceutical Technology Co., Ltd. (hereinafter referred to as "BA Site") is a private enterprise specializing in trial design, clinical monitoring, and biological sample analysis for clinical trials. This laboratory specializes in bioanalytical studies for drug pharmacokinetics and bioequivalence studies of small molecule drugs, with an annual capacity of 60 projects. The BA Site currently employs more than 200 analytical methods, covering active substances in therapeutic areas such as antibiotics, antivirals, hypertension, diabetes, anticoagulation, and cancer. Furthermore, the CRO subcontracted Chengdu Xinhua Hospital's Phase I Clinical Center (hereinafter referred to as "CL Site") to conduct the clinical component of the study. The hospital has a dedicated unit for Phase I studies.
General information about the clinical site	Chengdu Xinhua Hospital is affiliated with and serves as an education base for North Sichuan Medical College, providing treatment, healthcare, and rehabilitation services. In addition to conducting clinical investigations, the hospital specializes in five key disciplines, including the National Phase I Drug Clinical Research Center, general surgery, respiratory, cardiology, and orthopaedics. The clinical center shared the following functions with the rest of the hospital: - Pathology laboratory - IT systems and helpdesk - Food supply

	The site's staff communicated in Chinese, with interpreters facilitating translation for the inspectors. The study and Quality Management System (QMS) documentation were also primarily in Chinese.
History	Since its operation, the BA Site has passed 43 on-site inspections conducted by the National Center for Food and Drug Inspection. This inspection marks their first WHO inspection or any inspection by external authorities. The CL Site was inspected by the National Authority as part of pre-approval inspections in March 2021.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed, The sites' 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. Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with the comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Statistical and pharmacokinetic components of the study

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

CNAS	china national accreditation service for conformity assessment
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
DF	deep freezer
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 chromatography
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
LTNW	ritonavir
MS	mass spectrophotometer
MVR	monitoring visit report
NMTW	nirmatrelvir
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance

	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

PART 2	SUMMARY OF THE FINDINGS AND COMMENTS

General Section

1. Organization and management

Presentations were provided detailing the activities of the sites. The sponsor had an agreement with the CRO, Chengdu Gencore Pharma Medical Technology Co., Ltd., which subcontracted the bioanalytical and clinical portions to Chengdu Finelyse Pharmaceutical Technology Co., Ltd. (bioanalytical laboratory) and Chengdu Xinhua Hospital (clinical site), respectively. The study-specific agreements between the CRO and both the bioanalytical laboratory and the clinical site were available and reviewed.

The bioanalytical site had an organizational chart depicting key positions and names of the responsible persons. The chart, dated April 26, 2024, was authorized, and kept up to date.

The clinical site organizational chart, dated January 3, 2022, was part of the Quality Management system. The chart accurately reflected the current functions and hierarchy of the organization. The clinical site was certified, operating as a separate entity within the hospital, ensuring focused oversight and management.

There was a job description for each employee, detailing their responsibilities. It was randomly verified that every job description was signed and dated by the respective staff member.

A list of signatures of the authorized personnel performing tasks during each study was available and verified. It was noted that on the study delegation list, at the BA site, only the Project Lead and the respective analysts were recorded. Other parties involved, such as sample managers, were not recorded on the list as per the applicable SOP. Their signatures could be verified using other measures, such as signatory lists.

The principles of Good Laboratory Practices were sufficiently established, clearly defining the responsibilities of the facility management. The BA Site compiled its quality system documents in accordance with relevant regulations and guidelines, tailored to its specific requirements. As a result of this effort, it obtained CNAS accreditation on December 31, 2022. The accreditation of the BA Site was appended to the QM and reviewed during the inspection.

The management ensured that appropriate and technically valid SOPs were implemented and followed. The maintenance of a historical file of all SOPs was adequately organized.

The assurance of confidentiality was mentioned in the Quality Management system.

The working hours at the BA Site were from 8:30 am until 5:00 pm.

Observations related to Organization and Management were sufficiently addressed in the respective CAPA plan.

2. Computer systems

A list of software and computer systems used in the studies at both the BA and CL Sites was provided.

The laboratory's mass spectrometers used an appropriate chromatography software system for sample injection analysis and peak area data integration. Laboratory personnel then imported this data into the LIMS software for linear regression and blood drug concentration calculations. The original data from these processes were stored in their respective systems until a review conclusion was obtained.

To ensure the integrity and security of electronic data, the servers were equipped with disk arrays (RAID) to prevent data loss from hard disk damage. These systems were deployed within an internal local area network, secured by a firewall and antivirus software. Additionally, automatic backup software performed daily full backups of the databases, with the backups written to tape for long-term preservation.

Procedures for Computer System Validation, specifically for the BA Site, 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. A system retirement plan must be prepared and approved prior to the system's retirement following SOP for System Retirement. The IT department filled in the "Facility and Equipment Change Record Form" in the facility and equipment change application. Implementation could only proceed after confirmation by the

technical leader, review by the supervisor of the quality assurance department, and approval by the system leader (laboratory director).

An inventory of all computerized systems on the network was available at the BA Site. The above-mentioned SOP included a provision that any change to the computerized systems, including the temporary addition or removal of systems from the network, must be documented.

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

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of individuals with database access was maintained. Secure, unique, individual-specific identifiers and passwords were used.

The software programs used to perform key steps were required to be suitable and validated for the intended use. The qualification and/or validation certificates were reviewed. It was ensured that the documentation was provided under the user's supervision and that the software was fit for its intended use and in accordance with a QA system. The qualification of the 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. Quality risk management was applied when deciding which components needed to be validated. SOPs for each software program used to perform activities of a BE study were available. The operating SOPs for the chromatography system and the LIMS were requested and reviewed.

The storage of data and the procedure for backup and archiving of all relevant electronic data were specified in the applicable SOP, including the frequency of backup at the BA Site. Backups were periodically rewritten as part of the backup procedure, and the data from the previous backups were archived.

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

3. Quality management

The sites 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, and the applicable regulatory requirements.

At the CL Site, the SOP for SOP was reviewed and discussed. The SOPs have to be reviewed annually and revised, if needed. The list of SOPs reviewed was documented in the annual report, dated January 2024. The QMS of the CL Site was managed in accordance with the respective SOPs.

The BA Site's Quality manual was reviewed. The purpose of the Quality Manual was to:

a. Communicate a quality management plan
b. Communicate information regarding quality procedures, control, and assurance
c. Provide evidence of conformity to the national and international regulatory requirements
d. Share knowledge
e. Provide evidence of management's commitment to quality

The 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 following an SOP, and following up on any corrective action as required, to determine if all studies were conducted following 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 accurately and completely reflected the data from the study and the methods and procedures followed;
- promptly reporting audit findings in writing to management, to the investigator and to the study director, as applicable.

At the BA Site, annual internal audits were conducted in accordance with the respective SOP to inspect personnel training, equipment calibration and maintenance, biological sample and reference material management, computerized systems, project implementation, compliance with quality system documents and industry regulations, and laboratory facilities. These audits confirmed adherence to the quality system and reviewed the documents. Revisions were made as necessary to ensure they remained up to date with industry requirements and customer needs.

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed at the bioanalytical and clinical sites. A form for project-specific review titled “Internal Quality Audit Plan” was used. This form was referenced in another SOP.

In situations when laboratory activities repeatedly failed to meet expectations, non-compliance work procedures were initiated. A root cause analysis of these situations was conducted, targeted preventive and corrective measures were proposed, and the quality system documents were revised if necessary.

At the BA Site, the templates used in study activities were issued in accordance with the applicable SOP. The color-controlled paper was printed out by the Quality Assurance Department and handed over to the archivist. The project team members filled in the "Controlled Paper Distribution and Recycling Record" before the start of the trial and then approached the Quality Assurance Department to issue the paper number. They collected the controlled paper from the Archives, where the archivist issued it with an item number added. To use the blank controlled paper for archived items, the "Application for Approval Form for Defiling" and the "Controlled Paper Release Recycling Record" were required to be filled in.

Change control requests were carried out in accordance with the respective SOP at the BA Site. The requests and the respective actions were documented in a form. The documentation for the new system incorporated for the data lock was reviewed. The Site modified the user privileges accordingly. The data could be closed by the project manager and IT, but could only be unlocked by the IT.

The evaluation of supplies, including product and service suppliers, was carried out in accordance with the applicable procedure at the BA Site. The desk assessment of the plasma supplier was available and was performed on 6 November 2023.

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

4. Archive facilities

The sites maintained a secure storage facility for archiving the trial-related documents.

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

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

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

The archivist at the BA Site was also responsible for pest control following the applicable SOP where the instruction was given. The archiving activities were managed following the applicable standard procedures.

Observation related to the Archive facility was adequately addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facilities was conducted.

The facilities were kept clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate. The sites 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 facilities was restricted and controlled through keycards and biometric access. The subjects at the clinical facilities were adequately supervised. Emergency evacuation procedures were ensured. All entries to and exits from the facility were recorded.

The BA Site was visited on Day 3, and the clinical CL Site was toured on Day 5. The BA facility was located on the 11th floor of its respective building, while the CL Site was situated within the hospital. The hospital is a non-profit private institution, with three and a half floors dedicated to Phase I clinical trials.

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

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

The laboratory at the BA Site premises was 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.

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

Safety data sheets (in Chinese) were made available to staff before testing was carried out. Staff working in the laboratory were familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff were instructed to wear laboratory coats or other protective clothing, including eye protection. All containers of chemicals were fully labeled and included prominent warnings (e.g., "flammable") whenever appropriate.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Staff were aware of the need to avoid working alone in the laboratory. First-aid materials were provided, and staff were instructed in first-aid techniques and emergency care.

Containers containing volatile organic solvents, such as HPLC eluents were closed with an appropriate seal. Volatile organic chemicals were handled under fume hoods, and safety and eye showers were available in the laboratory.

Premises at the BA Site had suitable systems in place to dispose of waste. These activities were handled following the Liquid Waste and Waste Disposal Control Procedure.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. At all trial stages, including at night, qualified and trained personnel were present to ensure that the subjects' rights, safety, and well-being were safeguarded, and to care for the subjects in emergencies.

The team at the CL site was well-trained with a total of 38 full-time staff, including 5 medical staff, 13 nursing staff, and 20 pharmacists. Among the team members, 29 had bachelor's degrees or above, including 13 with master's degrees or above. The Research Center Director, qualified as Chief Pharmacist, engaged in clinical research for more than 30 years, and had extensive project experience in the field of clinical pharmacy.

The CVs of the Principal Investigator (PI), Sub-Investigator (SI), and one of the MDs of the study were checked and verified, along with their GCP certificates and training lists. The staff involved in the study activities had received protocol training from the PI, and the evidence, including their signatures, was provided, reviewed, and discussed.

The personnel of the BA Site (42 persons) were trained according to the respective SOP.

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of Chengdu Xinhua Hospital, i.e., Phase I Clinical Research Center's environmental facility. A complete layout of the facility used for the clinical trials was available and was followed during the tour to verify its correctness.

The facility consisted of one subject screening area, six independent wards with corresponding functional areas and 208 expandable hospital beds, six biological sample processing rooms, one GCP central pharmacy, and one archive for documents. The facility featured two-way access control for the wards, Wi-Fi coverage on all floors, three levels of electronic monitoring, a dual municipal power supply with a standby generator, and a temperature monitoring system capable of real-time temperature and humidity monitoring and alarm.

Elevators to the screening area were operated only when volunteers were invited for study-specific screening activities. Volunteers were checked in, using the registration system outside the screening area before being led to the area. Study information was

shown on a TV in the screening area prior to providing informed consent in a group. The checkout activity also took place in the same area.

During the study conduct, a trolley was prepared with medication and devices needed for emergency situations. If the study required, one of the rooms was available to set up as an emergency room with a defibrillator and other devices in the respective CPU.

The equipment used was appropriately calibrated at predefined intervals.

Information about blood collection and storage of the respective blood samples was recorded in the respective system during the study. Blood collection activities were observed during the inspection. Each volunteer had a badge with a barcode generated by the applicable system, which was read through the system once the volunteer was called to the dosing or blood collection station. This barcode was used in all study-related activities to record the study data in the system. The badge also carried the volunteer's picture for identification purposes.

The entire screening flow was visited and reviewed during the inspection, including the rooms for informed consent, vital signs, height and weight, and ECG recording.

The device for measuring height and weight was a digital system interfaced with the applicable clinical data system to transfer the data into the system. In addition, a printout was generated to record the volunteer's name, date and time, and the respective values. The printout was scanned and uploaded into the system.

A breath alcohol tester and a KIT were used respectively for alcohol and drug tests when required by the protocol.

Observations related to the Clinical Phase were adequately addressed in the respective CAPA plan.

8. Clinical laboratory

A suitable clinical laboratory at the hospital was used for analyzing samples. The laboratory was accredited, and a certification issued by NCCN EQA, valid until the end of 2024, was available. The facility was not visited during the inspection due to time constraints.

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

Sample labeling, receipt, storage, and chain of custody ensured full traceability and sample integrity through the Laboratory Information System (LIS) belonging to the hospital. A barcode was generated for both sample collection and used by the investigators to generate the barcode for their prescription, prescribing the screening activities required as per the respective 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 curriculum vitae of the Head of the Clinical Laboratory was reviewed.

The laboratory created individual reports for each subject, and the results were uploaded to the LIS and sent to the CL Site. The system user selected the results and clicked on them to be imported into the respective clinical data system. A paper copy was also included in the volunteers' study binder. The transfer of data between the LIS and the clinical data system was validated by a third-party software company.

The barcode used for biological samples for safety data (screening and post-study) was generated using the LIS, while the barcode used for study activities (screening, check-in) was generated using the applicable clinical data software system.

9. Ethics

The trial was approved by Chengdu Xinhua Hospital Ethics Committee, on 29 September 2022 before any study activity was conducted. This committee’s independence from the sponsor and the CRO was verified through the respective member list. The committee had 14 members; 11 members were present, and one vote was avoided since it belonged to the PI of the study. The PI was a permanent member of this ethics committee and had the right to vote for the clinical trials requested by other hospital departments. Detailed minutes of the meetings documented the discussions, recommendations, and decisions of the IEC. The IEC was given sufficient time to review protocols, informed consent forms, and related documentation. The ethics committee also performed a closing meeting for the study, which was documented in a separate document dated 21 March 2023.

Informed consent form

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

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

Insurance was available through the insurance policy of the Insurance Company.

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

An observation related to Informed consent was adequately addressed in the respective CAPA plan.

10. Monitoring

The study was monitored by a monitor representative from the CRO, Gencore. There were four monitors during the study. The monitors were appropriately qualified 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 the data obtained.

A pre-and post-study visit and a monitoring visit during the trial were performed. The monitor prepared a written report after each site visit and communicated any issues to the CRO and the sponsor as quickly as possible, even while the study was being conducted, if possible, to enable prompt corrective action. The respective communications and corrective actions were documented.

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 the protocol and the final study report.

The PI's qualifications were mentioned in her CV as a bachelor's degree in pharmacy. She had experience in different fields of clinical trials, primarily with the handling of IMPs. She had worked as a PI since December 2009. Since June 2018, she had been working for this hospital as a clinical pharmacist/PI. The list of her relevant training in GCP was reflected in her CV, with training provided from 2001 until now. Numerous

GCP-related training sessions were provided to her throughout her career as a GCP employee. The GCP training was also provided, and the certificates were available and reviewed. Therefore, the criteria for PI qualification outlined in Section 4.1 of ICH GCP E6 were met.

The medical care of the subjects was handled by the medical doctors involved in the study as Sub-Investigators (SI).

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 IP package was received and labeled with sequential numbers. The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, and return of any remaining pharmaceutical products was also verified. Details of the IP included dosage form and strength, lot number, and expiry date.

The SOP for storage condition control of the IMP was reviewed.

IP was stored under appropriate conditions as specified in the official product information provided by the sponsor. The temperature and humidity of the pharmacy area were controlled by the temperature control system. The records were available on the pharmacist's mobile and could be reviewed at any time. A temperature mapping was performed by placing the probes at spots exposed to more risk. The pharmacy was equipped with cabinets for room temperature, a refrigerator for cold, and another chamber for 15°C storage.

Randomization was performed by the statistician company Shanghai Zenith Data Technology Co., Ltd. The records, including the randomization list and seed, were sent to the CL Site in a sealed envelope addressed to the SI. The randomization list was accessible only to the SI and the CRA (Contract Research Associate) to input the information into the system. Later, the pharmacist received the information for drug dispensing. The envelope was only opened after the completion of screening, and the date of opening was recorded on the envelope.

The IPs were properly labeled. The labels were generated in a system and pasted onto the containers to ensure that the information was not lost once the lid was removed.

Adequate routines for labeling and documenting the administration of the IP were established to verify that each subject received the product dispensed for them by using labels. The labels were designed to be single sided to be pasted onto the containers.

Dosing, dispensing, and return of the IP were carried out by SOP for distribution, dosing, recovery, and return.

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), individual dosage units, labeling materials, contaminants, dirt, and debris were removed from the area. Tablets were distributed into each container in accordance with the randomization list for the comparator or the test product as appropriate. The two products, Test and Reference, were handled at different times. Every step was recorded.

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

Dosing was carried out under the supervision of the investigator and a qualified staff member to whom this task was explicitly delegated in writing. The label was checked through the applicable clinical data system, and the exact time of dosing was documented in the same system. A mouth check was performed using a tongue depressor and a penlight to inspect under the tongue, under the lips, in the corners of the mouth, and between the gums and cheeks, in the case of solid oral dosage forms, to ensure that the subject had swallowed the IP. Both dosing and blood collection were video recorded, but only the records of the dosing were kept with the rest of the study records.

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. Sample retention was defined and described in the respective SOP and was specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

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

13. Case report forms

Randomly selected CRFs from the study were reviewed.

A Clinical Trial Electronic Data Acquisition System, which belonged to a third-party eCRF system, was entrusted by the sponsor. The Site recorded the study information either in paper form, such as ECG records, or electronically in the applicable clinical data system. The data recorded in the applicable clinical data system was downloaded after the completion of the study and sent to the CRO by email to be uploaded into the eCRF. The transfer of data to the eCRF took place manually and was verified by the PI. Evidence of verification, dated 9 February 2023 (after the completion of the Fed study), was available and reviewed. Documentation and instructions were also in place to explain the transcription of the data between these two systems.

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.

An observation related to the CRF was adequately addressed in the respective CAPA plan.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the SOP for subject recruitment, screening, inclusion, and information security. This included a short description of the potential methods the CRO used for this purpose. The hospital had established a WeChat group where volunteers were added, and prior to the planned study, they informed the group about the upcoming study and also released advertisements on other social media accessible to their volunteers. A database was maintained on volunteers to avoid cross-participation and to 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.

Each subject was identified by their official ID card at the time of visit using the volunteer registration system. The ID card was swiped, and a picture was taken to be compared with the ID picture using the system to verify identity. Staff were allowed to participate in studies according to local law. A urine or blood sample was collected before each check-in for drug usage and pregnancy, if applicable.

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. A software system was used to determine whether any of the subjects had participated in a previous trial in any CRO registered in the system. Participation data was uploaded to this central repository to prevent over-volunteering. Access to the database and the audit trail was managed by the Beijing Municipal Science and Technology Commission on a national basis. The search in this system worked only by swiping the ID card of the volunteer; therefore, a search using the name of the volunteer was not possible. Once the volunteer was registered in the system as enrolled/dosed, the site had access to his/her folder and could add information about dosing and completion of the study. After that, cross-verification was only possible through swiping the ID card.

The recruitment was study-specific, and the remaining volunteers were sent home even if they had passed the screening criteria.

15. Food and fluids

Meals were prepared and scheduled during the study days following the guidelines provided in the reference book “PK Drug Interactions.” The site arranged meals, snacks, and drinks for the study subjects as per the clinical trial protocol, using the hospital’s kitchen, which was visited during the inspection.

Timing, duration, and amount of food and fluids consumed were recorded. A dietitian designed the standardized meals in cooperation with the Sub-Investigator (SI).

Observation related to the Food arrangement was adequately addressed in the respective CAPA plan.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including 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.

A logbook to record the usage of medication in case of adverse events was not available at the time of the study. It was noted that the site was in the process of preparation of an adequate practice to record the information in a reliable manner.

The following records and activities of the study of Nirmatrelvir & Ritonavir were selectively investigated, including the associated validation projects:

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

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were verified. The reasons for the study sample repeat analyses and all instrument failures were reviewed.

The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions.

For the review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The inspector had direct access to the study data generated by the chromatography and LIMS software systems.

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

The method development process was adequately described and documented, and the usage of internal standards was justified based on relevant literature. The literature was available. After method development, a method validation project was provided as a basis for the method validation. Analytical method validation was completed before the analysis of the research sample. However, sample analysis could begin before the issuance of the formal validation report, provided that the method validation trial had been completed and accurately documented in the study folder, and the completed experiments demonstrated that the analytical method was quantitatively capable (i.e., the analytical method was valid), which was the case with this study. The completed method validation was recorded in the project leader's study folder, and a statement was available to verify that the method had been validated and accepted. The document was reviewed and approved by appropriate management on 4 November 2022 for V1.0, and 5 December 2022 for V1.1. The version history was available and reviewed. The practice was performed in accordance with the respective SOP for Method validation.

Stable isotope-labeled internal standards were used in the MS methods, and K_2-EDTA was applied as an anticoagulant.

The instrument parameter setting and the preparation and pretreatment of biological samples were carried out in accordance with the analytical method document issued by the method validation project team.

The clinical trial protocol included both fasting and fed conditions because the product was being registered also in China. However, only the data from the fasting part was available for submission to WHO. In the laboratory, both the fasting and fed condition trials for this study were conducted under the same study number.

A study plan, dated 5 Dec 2022, was used during the study sample analysis. This study plan was updated to version V1.1 after the completion of the study on 19 January 2023. The study plan was revised because the concentration of NMTW in the dilution accuracy quality control (QC.DIL.1) could not cover the concentration of the sample that exceeded the upper limit of quantification during the determination of unknown samples. This updated version was used for the fed part of the study, which took place between 12 January 2023 and 20 January 2023. This QC was only used for ISR analysis of the fed part of the study sample analysis.

During the method validation as per the applicable SOP, a run was carried out to determine the batch with 273 samples of QCs and CCs (so-called Analytical Run Batch Determination) comparable in length to those expected to be used for analysis. The regression model was also described in the respective SOP and was calculated using the LIMS application. During method validation, for each analytical run requiring standard curve quantification, two sets of standard curve samples were used. According to the protocol, linear regression was performed to fit an accompanying standard curve. The linear correlation coefficient of the standard curve had to be greater than 0.9800. The deviation between the measured value and the labeled value at the lowest concentration point of the standard curve needed to be within ± 20%, and the deviation at other concentration points needed to be within ± 15%. At least 75% of the samples had to meet this requirement. Points failing to meet the standard were excluded, and the standard curve was recalculated. In the final regression calculation for standard curve samples, there had to be at least 6 non-zero standard curve concentration levels, with at least one duplicate sample at each concentration level.

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 before the issuance of the study reports.

The CRO carried out the method validation and sample analysis in accordance with the previous version of the ICH M10 guidelines and the SOP dated 30 August 2022, which did not consider the new matrix effect testing requirement.

The review of the method validation included precision and accuracy testing (P&A), sensitivity, selectivity, calibration curve, carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and haemolytic effect), recovery, and reinjection reproducibility. Carry-over was calculated using blank plasma aliquots injected after the highest concentrations in each batch. The calculation was done after the completion of all batches, and the results were available. Partial validation was performed according to the requirements; however, only one of the instruments was used for the sample analysis. Whole blood stability was also assessed by comparing the analyte ratio of fresh whole blood with that of samples stored for 2 hours.

The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. Method validation evaluated the long-term stability of the drug-containing matrix for 74 days, fully covering the period from collection to completion of testing of the biological samples.

The purchase documentation of the plasma for both method validation and sample analysis, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed and discussed.

Each analytical run included calibration curve standards, and 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 analyzed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention times, the accuracy of calibration standards and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs.

A Pre-Injection Equilibration (EQU) and a System Suitability Test (SST) were performed before any run-in case there was a pause or interruption between two consecutive runs.

For EQU Run:

To confirm that the instrument had reached the equilibrium state at the time of injection, the response of continuous injection of the same concentration sample was used to verify equilibrium before the injection of the analysis batch. The equilibrium sample could be obtained by making a new sample or using a sample from the injected analysis batch. The instrument user judged whether the subsequent analysis batch could be submitted based on the actual project situation. If there were abnormalities in the baseline, target peak response, peak shape, and retention time of the continuously balanced sample, and no improvement trend was observed, subsequent injections were paused, the cause was investigated, and the project leader decided on the follow-up treatment.

For SST:

The system suitability test was performed after each instrument was balanced. For analysis batches interrupted within 5 hours, the system suitability test had to be passed before submitting subsequent samples. For sequential injections of two or more sample batches, only the system suitability needed to be investigated prior to the first analysis batch. When the system suitability results met the acceptance criteria, the instrument performance was considered normal, and the subsequent analysis batch could continue. Otherwise, the next analysis was suspended, and the instrument was maintained or repaired to restore performance and pass the system suitability evaluation before continuing with the subsequent analysis batch. The acceptance criteria for SST were specifically mentioned in the respective STP, and the evaluation of the results was documented in the analytical sheet.

The laboratory had prepared 21 aliquots (sets) of QC, each totaling 300 μL for each concentration, plus 3 sets for DI. All 21 aliquots were used for the sample analysis. No DI was used during the study sample analysis.

Any deviations were noted and appropriately documented, and deviations were assessed following the SOP for Detection Method Deviation Control.

The provisions and documentation of the Incurred Sample Reanalysis (ISRs) were confirmed. The procedure was defined in the Biological Sample Proposal. When the first ISR (ISR1) was tested, the accuracy of the quality control samples, namely “NMTW (Nirmatrelvir) QC.1” was not within the acceptance criteria, while all LTNW (Ritonavir) quality control samples met the acceptance criteria. Therefore, the data results for NMTW in this analytical run were rejected, while the data results for LTNW were accepted.

The samples in this analytical batch underwent another reanalysis for NMTW. An investigation took place to identify the reason for failing the NMTW part of the analytical run. It was concluded that the reason was likely accidental. The investigation considered why Nirmatrelvir had failed but Ritonavir had not.

Observations related to Method validation and sample analysis was adequately addressed in the respective CAPA plan.

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

The specifications of samples (blood plasma), sampling method, volume, and number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, shipping, and storage of samples took place in accordance with the SOP for the reception of biological samples in the BA laboratory and another SOP at the CL Site.

At the BA Site, study samples were managed and recorded by the LIMS system. The sample manager entered the samples into the system, selected the reason as "Arrived," and the location as “Dry ice,” and manually entered the arrival time. In some cases, the sample label did not contain a Custom ID number, requiring the sample manager to generate a Custom ID in the LIMS, print the label, and attach it to the sample vial (this step was performed on dry ice). The sample manager then transferred the sample to the storage freezer and synchronized the operation in LIMS with "Internal Movement" as the reason, including information about the appropriate freezer number for the location and the temperature shown by the digital thermometer on the dry ice when finished. For blank biological samples, the sample manager transferred the sample to a storage freezer and manually recorded the time. The collection or return of study samples and stability samples for the respective analysis was requested & recorded through the LIMS.

At the CL Site, the collection of blood and the respective storage in the DF were recorded in the applicable database system. There was a journal for the usage of the centrifuge machine in paper form.

The samples collected in the fasting study were transported to the BA Site on December 1, 2022, using dry ice throughout shipment, with the temperature maintained below -60°C. No overtemperature, sample loss, damage, or other abnormalities occurred during transportation.

Actual sampling times and deviations from the pre-specified sampling times were recorded, and the respective deviations were to be considered when calculating the pharmacokinetic parameters.

The labeling 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 using the Temperature (Humidity) Monitoring system. Samples were duplicated in aliquots. Aliquot 2 was not shipped to the bioanalytical laboratory and remained at the CL Site.

As per SOP for sample management at the BA Site, QC samples, and pooled matrix were discarded. The reconciliation of the pooled plasma, along with the record of the disposal of remaining stock solution, QC, and CCs, was recorded in the logbook for the respective DF as per the respective procedure.

The retention period of study samples met the requirements of the technical service contract. When the technical service contract did not stipulate the retention period, study samples were retained beyond the verification period of the sample. Clinical study samples, in general, were saved until the clinical study report was completed or published. If the storage time exceeded the time specified in the contract with the client, the client was notified to confirm whether the study samples should be processed or continued to be stored.

The observation related to the Sample management was adequately addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based and justifiable. The smoothing factor was kept low enough (3) to avoid masking possible interferences and changes in peak geometry.

In this project, an automatic integration method was used, with one integration method applied for each analysis batch, and manual integration was prohibited in principle. A LIMS was used for regression and concentration calculation. For the reprocessing of calculation results, such as the calculation of mean and standard deviation, the report function of the LIMS was preferred. When the results listed by the LIMS did not meet the requirements, supplementary calculations were completed.

The criteria for acceptance and exclusion of calibration curve standards and QC samples, as well as batch acceptance, were defined in the applicable SOP. The source data for all analytical runs contained all information about the original first evaluation of runs (including 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 verification of result validity.

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). The audit trail function of the chromatography software was permanently activated. All audit trail files were retained (e.g., results table audit trail, project audit trail, and instrument audit trail).

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

20. Good laboratory practices

A tour of the bioanalytical laboratory was conducted to verify the suitability of the facility in terms of arrangement and safety.

The bioanalytical facility covered an area of about 1,100 square meters, with the laboratory occupying approximately 700 square meters on the 11th floor of a commercial building. The laboratory area was divided into functional sections, including office space, archives, balance room, computer room, sample receiving room, sample storage room, data processing room, mass spectrometry room, pre-treatment room, cleaning and drying room, and a hazardous waste temporary storage room. The layout of the facilities was shown in Appendix 1 of the CRO MF.

Deep freezers for storage of the samples and refrigerators for storage of the reference standards were visited. These storage facilities were in the Deep Freezer room with controlled access. Access to the restricted facilities at the BA Site was controlled by a key card. There was an alarm system associated with the digital thermometer to trigger SMS and call notifications to the custodians responsible for the maintenance of the facility. The automatic alarm system was tested during the inspection to verify its proper functionality for one of the Deep Freezers. The daily monitoring and all the alarm checks were documented in the software application. No alarm log was generated during the storage of samples in the DF used during the study. For the purposes of qualification verification, the qualification of the respective Deep Freezer was reviewed to verify the hot spot and the location of the respective sensor.

Balances were periodically calibrated and verified before use to be fit for their intended purpose.

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

- Balance (BA facility)
- HPLC (BA facility)
- Centrifuge machine (CL facility)
- DF (CL facility)

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

Observations related to Good Laboratory Practices were adequately addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

These activities and aspects were outside the scope of this inspection.

22. Study report

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

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The CRO Master File (CROMF) was reviewed.
Annexes attached	N/A

Part 3	**Conclusion – inspection outcome**

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at the following sites:

Chengdu Xinhua Hospital
Phase I Clinical Research Center Team
180 Shuangqiao Road, Chenghua District
Chengdu, Sichuan Province
China

Chengdu Finelyse Pharmaceutical Technology Co., Ltd
1st Floor, Building B, No. 5, Keyuan South Road
High-tech Zone
Chengdu, Sichuan Province

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

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

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***

5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
   Short name: WHO Ethics Committee Guidance

6. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
   Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
   Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***

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

9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6

10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4

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

12. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).
Short name: Declaration of Helsinki

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

14. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3

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