

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

| Part 1 | General information |
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| Organization details | |
| Company information | |
| Name and Address of Clinical, Bioanalytical and Statistical Research Site | Nuvisan GmbH (Neu-Ulm) Wegenerstrasse 13 Neu-Ulm 89231 Germany |
| Corporate address of Organization | Nuvisan GmbH Wegenerstrasse 13 89231 Neu-Ulm Germany Tel: +49-731-9840-0 Tel (24/7): +49-731-9840-333 and +49-172-6379339 Fax: +49-731-9840-280 Email: hello@nuvisan.com |
| WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles | Bioequivalence study of the coated Cesol tablet formulation |
| Inspection details | |
| Dates of inspection | 14 to 16 September 2022 |
| Type of inspection | Initial |

| Introduction | |
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| Summary of the activities | Nuvisan has had a GLP certification as a test site since 1994 for analytical tests on biological materials and chromatographic studies of formulations for toxicological studies. |
| History | <p>GLP/GMP certificates and licenses for the manufacturing and testing activities were based on the most recent inspection by the pertinent regulatory authority. All current certificates and licenses were available in CROMF Appendix 02:</p> <ul style="list-style-type: none"> • Audit certificate, BVMA • Statement of GLP Compliance, Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit • Certificate of GMP Compliance of a Manufacturer Human Medicinal Products, Regierung von Oberbayern • Certificate of GMP Compliance of a Manufacturer Human Investigational Medicinal Products, Regierung von Oberbayern • Certificate of GMP Compliance of a Manufacturer Veterinary Medicinal Products, Regierung von Oberbayern <p>The CRO has undergone various GCP inspections in the last four years, performed by ZAB, Regierung von Oberbayern, US FDA, and EEC GCP (BfArM, EMA).</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 | Not applicable |

| Abbreviations | | |
|---------------|----------|---|
| | ADR | adverse drug reaction |
| | AE | adverse event |
| | ALCOA | attributable, legible, contemporaneous, original and accurate |
| | BE | bioequivalence |
| | BDL | below detection limit |
| | CAPA | corrective actions and preventive actions |
| | CC | calibration curve |
| | CPU | clinical pharmacology unit |
| | CRA | clinical research associate(e) |
| | CRF | (electronic) case report form |
| | CRO | contract research organization |
| | CTM | clinical trial manager |
| | CoA | certificate of analysis |
| | CSR | clinical study report |
| | DQ | design qualification |
| | ECG | electrocardiogram |
| | GAMP | good automated manufacturing practice |
| | GCP | good clinical practice |
| | GLP | good laboratory practice |
| | GMP | good manufacturing practice |
| | HPLC | high-performance liquid chromatograph |
| | LC-MS/MS | liquid chromatography–mass spectrometry |
| | IB | investigator’s brochure |
| | ICF | informed consent form |
| | ICH | International Conference on Harmonization |
| | (I)EC | (Independent) Ethics Committee |
| | IMP | investigational medicinal product |
| | IQ | installation qualification |
| | LIMS | laboratory information management system |
| | LLOQ | lowest limit of quantification |
| | LOD | limit of detection |
| | MS | mass spectrophotometer |
| | MVR | monitoring visit report |
| | NCS | non clinically significant |
| | NRA | national regulatory agency |

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|--|-------|---|
| | 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 |
| | SDV | source data verification |
| | SOP | standard operating procedure |
| | SUSAR | suspected unexpected serious adverse reaction |
| | ULOQ | upper limit of quantification |
| | URS | user requirements specifications |

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

A presentation was provided by the site detailing the activities of the organization.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organization chart was dated 31 Aug 2022, authorized, and kept up to date. The organizational chart consisted of 77 pages. A complete explanation of the relation between the management, Clinical department, and BA department, as well as Quality Management Nuvisan Group and the respective reporting line, was provided.

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

A list of signatures of the authorized personnel performing tasks during each study was available and verified. The documentation was arranged by staff role in the study, together with the information about items of training and delegation tasks.

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 duties 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 in the digital Data Management System (eDMS).

The service agreement between the CRO and Merck Healthcare KGaA was available. Nuvisan agreed with the sponsor to retain the subject identification list and study documents for 25 years.

In contrast to the GLP and GMP regulations, the GCP regulations do not prescribe GCP certificates therefore, none is issued by the German or European authorities. As members of BVMA, the Nuvisan GCP facilities at Neu-Ulm were regularly audited by independent external auditors. A certificate of compliance with the applicable GCP guidelines was available at Nuvisan.

The general working hours were flexible from Monday to Friday from 9 am until 5 pm. At the time of inspection, 296 staff members were working for the company.

2. Computer systems

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

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and were validated, 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, clearly identifying those GxP regulated. Changes to the network, including the temporary addition or removal of systems from the network, were documented.

There were enough computers to enable personnel to perform data entry and handling, required calculations, and compilation of reports.

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

The software programs used to perform key steps were validated for the intended use. The qualification and/or validation certificates were provided under the user's supervision to ensure that the software was validated for its intended use.

The validation of the following computerized systems was reviewed. The documentation contained a risk assessment to define the category of the system, validation plan, URS, test plan, test script, and test summary report. The OQ and PQ of software systems were replaced by a test script which was provided based on the respective URS and system acceptance.

The validation documentation of randomly selected software 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 validation of the computerized systems. Quality risk management was applied when deciding which components needed to be validated. All phases of their life cycle were considered. SOPs on the use of each software program that was used to perform activities of a BE study were available.

Regular updates to key software programs, whenever required, following an appropriate risk assessment on the potential impact that it could have on current data and qualification or validation status, were carried out in accordance with the applicable SOP.

Software programs used, and frequency of virus testing, storage of data, and the procedure for backups and long-term archiving of all relevant electronic data were specified in the SOP, including frequency of backups and archiving. Data generated by chromatography software systems and LIMS were backed up on the respective application. Data were incrementally backed up on the server, and a full backup was carried out each weekend on the magnetic tapes. Monthly and yearly backups were performed on different magnetic tapes as part of the backup procedure. The data from the previous backup was archived in a secure place. Data generated via eDMS and the Clinical database were separately backed up in the cloud.

The reliability and completeness of these backups were verified through a monthly automated restoring process documented in the Restorage log and supported by documentation about the session details. The last documentation related to 8 September 2022 was reviewed.

Observations related to the Computerized systems were 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. In case of overdue, the SOP remained effective until the next revision.

The Nuvisan QMS distinguished four hierarchical levels of quality documents. At each level, the next level's leading documents must be considered to avoid contradictions. In unintentional contradiction, always the upper level overruled the lower level document.

A Quality manual was provided. The purpose of the Quality Manual was to:

- a. Communicate 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

QA personnel were not directly involved in trial-related activities.

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed. The study audit was carried out in accordance with the SOP for Documentation and Review of bioanalytical projects.

The site had three audit groups:

- GLP
- GCP
- GMP

The quality management system included root cause analysis, ensuring data integrity, and implementing appropriate corrective and preventive action (CAPA) using the respective modules in the eDMS software system. The activities were verified through a review of the audit program 2022 and the audit report for GLP on 19 May 2022.

Tracking for trends was followed by a Quality status report that collected information about all deviations and the respective corrective/preventive actions.

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

4. Archive facilities

The CRO had sufficient and appropriately secure storage space, which was fireproof for 90 minutes, relative humidity-controlled and pest-controlled. The facility was protected from flooding.

The archiving activities were managed according to the appropriate SOPs.

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

Records of document access and return were maintained. The length of time for the retention of study documentation, including raw data, was defined in the applicable SOP. This period was also specified in the agreement between the sponsor and the CRO, which included provisions for the financing of the archiving.

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

5. Premises

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

The facilities were clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate.

The trial site had adequate facilities, including laboratories and equipment. The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. Entry to the facility was restricted, and keys and/or electronic chips were available.

Video surveillance to detect the exit of subjects from clinical facilities was installed, and/or the doors were locked. Emergency evacuation was ensured.

Sites where clinical activities took place included an IMP storage facility where investigational products were stored under appropriate conditions. The CTS (Clinical Trial Supplier) department was responsible for receiving and preparing IMP shipments under GMP conditions before being transported to the IMP storage in the clinic for dispensing and dosing administration. The retained samples were returned and kept in the CTS department.

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. The temperatures in freezers and refrigerators were monitored.

Laboratory premises were generally designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples. Smoke detectors were installed on the main corridor that connected the different laboratories, but only within some laboratories.

Safety data sheets were available to staff on request. Staff working in the laboratory was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Staff was trained to use the firefighting equipment, including fire extinguishers and fire blankets. 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," or "radioactive") whenever appropriate.

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

Synchronized clocks were located throughout the facility to document study activities' exact times. The PC and radio clocks were synchronized against the atomic centralized radio clocks to show the same time for recording the time of activities.

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

6. Personnel

There was enough medical, paramedical, technical, and clerical staff with the appropriate qualifications, training, and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies.

At all trial stages, including at night, there were qualified and trained personnel to ensure that the rights, safety, and well-being of the subjects were safeguarded and to care for the subjects in emergencies. Contract workers were employed to perform certain activities.

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.

The training of SOPs took place in the applicable software system from August this year. The training SOP was under process to incorporate the new procedure.

Clinical section

7. Clinical phase

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

The CPU was equipped with 40 + 84 beds. Alarm buttons were in place in the accommodation facilities for night shifts so subjects could alert CRO staff in case of need. However, the beds used for activities during day times were not equipped with any alarm due to the presence of staff.

Facilities for changing, storing clothes, washing and toilet purposes were clean, 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 and a backyard.
- IMP storage and CTS facility;
- Space for the administration of the investigational products and sample collection in the clinic, where they also kept the emergency equipment for first-aid;
- sample processing (e.g. plasma separation) and storage (freezer);

- Archive facility;
- preparation of standardized meals and a dining hall;

Provisions were made for the urgent transportation of subjects to the hospital available according to the rules in Germany. The Emergency could be dialled using 110/112 numbers. In addition, when required by the study, an external emergency physician was available at the time of the study to monitor the volunteers' condition.

The equipment used was appropriately calibrated at predefined intervals. In addition, the adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified at appropriate intervals.

ECG machines were directly connected to a barcode system and the applicable software system. The Alcohol tester was equipped with an indicator to show sufficient air to be blown into the device.

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

8. Clinical laboratory

A suitable clinical laboratory was used for analysing samples. The CV of the head of the Laboratory was available and reviewed. The laboratory participated in proficiency testing provided by external vendors such as "Referenzinstitut für Bioanalytik" in accordance with the applicable SOP.

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

Full traceability and sample integrity during sample labelling, receipt, storage, and chain of custody were ensured using the LIMS system at the time of the study. A new LIMS system was implemented to generate the barcode and automated interface with some clinical laboratory instruments.

The CRO received information about the analytical methods used in the laboratory, and a list of laboratory normal ranges was appended to the study protocol.

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

9. Ethics

Trials were approved by the independent ethics committee (IEC) before any study was conducted, i.e., 18 Feb 2020. This Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list.

The IEC meetings' approval, recommendations, and decisions were kept in the ISF. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation. The submission took place on 15 Jan 2020.

Informed consent form

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

Informed consent was given by the subject and documented in writing before starting any trial-related activities. The information was clear: 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 study records.

The information about insurance and other procedures for compensation or treatment should the subject be injured or disabled by participating in the trial or during was available through an insurance policy. An insurance certificate was provided in the ISF by HDI insurance company for the period 23 March 2020 to 31 December 2021.

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 was available in the TMF at Merck. However, a back translation of the informed consent was not provided.

10. Monitoring

The CRO had their own monitors. Documentation of site initiation visits log, site visit log, site initiation visit report, closing out visit and report, and communication on monitoring visits were available in the ISF and reviewed.

QC procedures were implemented in the bioanalytical laboratory.

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. The PI signed the protocol (9 January 2020 / Version 1.0) agreement on 14 January 2020.

12. Receiving, storage and handling of investigational drug products

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

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through the system for temperature control.

Randomization was performed in accordance with the applicable SOP, and records were maintained, including the randomization list and seed number.

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

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, but only for test medications. Labels of Test medication were designed to have two identical labels to have one portion be pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The unused containers were labelled separately for the test and the reference investigational products and remained segregated in a secure area under a lock at the CTS after the completion of the study and transferred from the IMP storage room.

The IMPs were shipped from the CTS after initial labelling to the IMP storage room under the study coordinator and PI supervision and kept in the locked closets under environmentally controlled conditions.

Dispensing and packaging procedures of test IMP were performed per requirements. Dosing was performed in accordance with the respective SOP under the supervision of the investigator and qualified staff member to whom this task was explicitly delegated in writing. The exact time of dosing was documented on the CRF's designated page.

A mouth check was performed by looking under the tongue, under the lips, in the corners of the mouth, and between gums and cheeks, using a spatula and a penlight, in the case of solid oral dosage forms, to ensure that the subject had swallowed the IP. Dosing was directly documented in the software system and the form for the arrangement of study medication. The volunteer was identified using the barcode on the wristband provided to the volunteer at check-in time.

Samples of the product in the original container were retained for possible confirmatory future testing for at least seven years. Sample retention was defined and described in the applicable SOP.

Dispensed products that were not administered were returned to CTS after completing the study report in accordance with the appropriate procedure. The documentation was available and reviewed.

Observations related to the IMP handling were addressed in the respective CAPA plan.

13. Case report forms

Randomly selected CRFs from the study were reviewed.

The Site administration team designed the CRFs according to protocol and under the supervision of PI and sent them to the study coordinator.

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 screening procedure, restriction about the study and the volunteer agreement, alcohol breath test, collection of blood and urine samples, adverse events, concomitant medication, randomization sequence number, IMP administration, collection of biological samples for PK analysis, fluid intake, treatment termination, laboratory reports were recorded in the CRFs for all four periods.

The screening failures were indicated on the list of screened volunteers, and the respective documentation was available in the ISF, which was randomly verified.

A different volunteer registration database was used during the study in the scope of inspection. The respective study data on the software system was available upon the inspection request. During the review of the CRF related to subject no. 101 with screening number S009, it was noted that the system did not have the option to capture the reason for changes. However, the new system was properly configured to record the respective information.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers specified in SOP for Recruitment and inclusion of study participants and included a description of the potential methods that the CRO used for this purpose. A database was maintained on volunteers to avoid cross-participation and specify a minimum time 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.

The Recruitment team was responsible for identifying volunteers for each study through advertisement measures. The EC and authorities approved advertisement materials before being used. The advertisement took place by posting on social media, such as CRO's Facebook, Instagram, and website. Volunteers contacted the team and left their telephone numbers to be contacted by the team. A pre-screening questionnaire was deployed to identify the potential volunteers who were given an appointment to show up at the site for ICF and screening procedures.

The volunteer ID card and personal number ensured the identification of volunteers and subjects.

The informed consent was sent to the potential subjects via email to register an appointment for screening. The ICF was obtained physically for any screening procedures required to determine the study's eligibility and 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. Participation data was uploaded to this central repository to prevent over-volunteering. Usage of this software system was not mandatory in Germany.

15. Food and fluids

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

A significant positive food effect is known for PZQ and was also shown for the orally dissolving tablet formulation (Bagchus 2019). The WHO guideline for rac-PZQ stated that “the bioequivalence study should be conducted in the fed state as praziquantel was recommended to be taken with food. Timing, duration, and amount of food and fluids consumed were recorded.

It was documented that the subject was fasting for at least ten hours before breakfast, and the medication was administered after breakfast.

The dietitian who designed a standard breakfast, had appropriate qualifications, training, and experience. Her CV, agreement, and study documentation were available and reviewed.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of serious adverse events.

First-aid equipment and appropriate rescue medication were available in the clinic and ready for emergency use at the study site. Any treatment given to a subject was documented and included in the CRF and the supporting documentation on the study site.

The CRO had adverse event registration and reporting forms to be collected and documented by the study physician and personnel. The study physician transferred the information to the designated section in the CRF. The practice was carried out in accordance with SOP for reporting AE and concomitant medication.

Bioanalytical section

The inspection included the audit of source documentation and raw data for validation of the bioanalytical method, and analysis of the respective subject plasma samples as well 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), and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from the analytical runs. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited.

Chromatograms, their integration, and the evaluation of the response of the instrument with regard to the different concentrations of the calibration curve samples were reviewed. Compliance with existing procedures on sample integration was confirmed. The absence of signals in the blank samples and the absence of signals for carry-over were verified.

The records on any unexplained interruptions in the injected sequences were verified, and 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.

For a review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The inspectors were given access to a copy of all raw analytical data generated by chromatography software system. The analytical raw data in the LIMS were available in the inspection room.

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

The method development process was controlled by the applicable SOP and described and documented by means of electronic raw data. The usage of IS was justified based on a method description provided by the sponsor and literature. After method development, an analytical plan was provided as a basis for the method validation. A stable isotope-labelled internal standard was always used in the MS methods, and K₂EDTA was applied as an anticoagulant.

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

The sample processing was documented in the respective forms. Any unexpected events were reported as additional entries in the raw data.

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 review of the full method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), and extraction recovery. A partial validation was performed at the request of the sponsor. The partial validation was documented in accordance with the requirements. The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. The purchase documentation of the plasma from “BioChemed,” including receipt and storage, 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. A system suitability and stabilization test were done before the start of runs on each day.

An adequate number of samples were selected for Incurred Sample Reanalysis (ISR). The samples were chosen with concentrations around C_{max} and in the elimination phase. The acceptance criteria were clearly defined in the respective SOP. Selection, evaluation, and reporting of ISR were supported by the LIMS system.

Observations related to the Method validation were addressed in the respective CAPA plan.

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

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

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

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

According to the Laboratory Manual related to the protocol in the scope of the inspection, the remaining samples were stored at Nuvisan BA Dep for six months after the finalization of the clinical study.

Observations related to the biological sample handling and storage were addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based. The practice of changing the applied integration algorithm after validation without performing partial validation experiments was discussed. Furthermore, the relevance of smoothing factors, mainly the importance of keeping them low enough not to mask possible interferences and changes in peak geometry, were explained. Selected validation runs were integrated using the algorithm applied to the study samples, with a lower smoothing factor and the respective data was made available to the inspectors.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. When the analysis was repeated, the source data for all the analytical runs contained all information about the original, and first evaluation of runs (containing all calibration samples). The calibration range was properly truncated. Internal standard variations were trended and used as part of the verifications of results 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, 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 facility tour was performed to verify its suitability 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. An alarm system was associated with the monitoring system to trigger SMS and call notifications to the responsible custodian.

The process of temperature mapping and the practice of applying the temperature mapping obtained from one device to another, even though they were not of the same model and type, were discussed during the inspection.

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

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

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, either on the label or on the CoA.

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

Pharmacokinetic, statistical calculations and reporting section**21. Pharmacokinetic, statistical calculations**

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

Calculations were made by the biostatistician in the Biostatistics Department using software systems in accordance with the applicable SOP.

Pharmacokinetic parameters and descriptive statistics were evaluated for the analytes using SAS and Phoenix®/WinNonlin® Software (Pharsight Corporation, USA).

Data values input was double-checked by the Site administrator and Nuvisan CRA in accordance with the applicable SOPs.

A database was maintained and locked as soon as possible after the completion of the study and SDV by monitors. Once it was locked, the study was unblinded, and statistical analysis was performed. The dates of locking and statistical analysis were documented and mentioned in the study report, and the process was defined in the applicable SOP. The data from the study in the inspection's scope was uploaded on 25 September 2020, defined as the Hard Lock date. Hard lock was when the data was locked, and no query could be raised any longer. At that date, the data was uploaded into the DM folder to be accessed by a statistician for statistical purposes.

At the end of the study, the Site administrator requested IT to move the study data to Drive K by email. The Drive K only allowed read access to study data.

22. Study report

The process of study report writing was verified during the inspection. SOP for preparation, review, and QC of clinical study reports was established to ensure the quality and integrity of the study report. The study report for the study in the scope of inspection was prepared in accordance with the sponsor's applicable SOP.

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 was transferred to the statistical department. 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> | N/A |
| <i>Assessment of the CRO master file</i> | Nuvisan GmbH – CRO Master File / Neu-Ulm Site Revision 01, dated 31 August 2022 was provided. |
| <i>Annexes attached</i> | N/A |

| Part 3 | Conclusion – outcome of inspection |
|--------|------------------------------------|
|--------|------------------------------------|

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at *Nuvisan GmbH (Neu-Ulm)*, located at *Wegenerstrasse 13 Neu-Ulm, 89231 Germany*.

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 |
|--------|--|
|--------|--|

- Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
Short name: WHO BE guidance or TRS996 Annex 9
<https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>
- Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
Short name: WHO GCLP
<https://apps.who.int/iris/handle/10665/44092>
- Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137). **Short name: WHO GCP**
<https://www.who.int/publications/i/item/9241208503>

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. **Short name: OECD GLP**
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011. **Short name: WHO Ethics Committee Guidance**
<https://www.who.int/publications/i/item/9789241502948>
6. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised). **Short name: Glove use information leaflet**
[https://www.who.int/publications/m/item/glove-use-information-leaflet-\(revised-august-2009\)](https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009))
7. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7. **Short name: WHO CROMF Guidelines or TRS No. 957, Annex 7**
https://www.who.int/publications/i/item/WHO_TRS_957
8. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. **Short name: WHO storage and transport guidance or TRS 961 Annex 9**
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f_2
9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6. **Short name: TRS 1003 Annex 6**
<https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf>

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

Short name: WHO TRS No. 1025, Annex 4

<https://www.who.int/publications-detail/978-92-4-000182-4>

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

<https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations-3-good-manufacturing-practices-guidelines-on-validation>