20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Clinical Diagnostic Centre of National University of Pharmacy (NUPh CDC) 27, Pushkinskaia Str. Kharkov – 61057 Ukraine
Name and Address of Bioanalytical Research Site	Laboratory of Pharmacokinetics (Kharkov) SE "State Expert Centre of the Ministry of Health of Ukraine" 33, Astronomicheskaia Str. Kharkov – 61085 Ukraine
Name and address Statistical Site	Laboratory of Pharmacokinetics (Kharkov) SE "State Expert Centre of the Ministry of Health of Ukraine" 33, Astronomicheskaia Str. Kharkov – 61085 Ukraine
Corporate address of Organization	Clinical site: Clinical Diagnostic Centre of National University of Pharmacy (NUPh CDC) 27, Pushkinskaia Str. Kharkov – 61057 Ukraine Bioanalytical site: Laboratory of Pharmacokinetics (Kharkov) SE "State Expert Centre of the Ministry of Health of Ukraine" 33, Astronomicheskaia Str. Kharkov – 61085 Ukraine
WHO product numbers covered by the inspection/	**Study no. TH-PRT-I;** 250 mg coated tablets

Product names/ Study numbers/ Study titles	
Inspection details	
Dates of inspection	Clinical Site: 12-13 March 2018 BA site: 14-16 March 2018
Type of inspection	Routine inspection
Introduction	
Summary of the activities	The clinical facility belongs to the National University of Pharmacy (NUPh) with capacity to perform clinical trials and in-vitro studies in healthy subjects / patients. The bioanalytical facility belongs to The State Expert Centre of the Ministry of Health of Ukraine with capacity to perform the bioanalytical part of BE / Bioavailability-studies allowing for a maximum of 5 studies per year.
General information about the sites	The clinical facility was started by Professor Igor Zupanets in 2000. The facility had conducted approximately 50 clinical studies of different products during recent years, sponsored by pharmaceutical companies. The bioanalytical laboratory was established in 2006 upon the decision of the Health Ministery in 2005. The laboratory, as the first laboratory authorized, was mainly responsible for performance of BE / Bioavailability-studies; BA-phase and PK calculations. The laboratory was deployed in the premises belonging to the State Research Centre of Drugs through a lease contract with State.
History	The list of inspections performed since 2003 was provided. The clinical site was inspected by the Lithuanian authority which was the sole foreign authority inspection.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The history of the two sites, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensing and storage, processing and handling of biological (serum) 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 comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Not applicable

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BA	Bioanalytical
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
HPLC-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
	IS	internal standard
	ISV	internal standard variation
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification
	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

Part 2	**Summary of the findings and comments**

General section

1. Organization and management

The inspection covered two sites:

1- Clinical site which belonged to the National University of Pharmacy in Kharkov, Ukraine.
2- Bioanalytical site which was under supervision of Ministry of Health in Ukraine.

The sites provided their respective organization charts depicting key positions, without the names of responsible persons. The organizational chart belonging to the clinical site was signed and stamped in 2014.

After receipt of the delegation list with signatures of authorized personnel performing tasks during a study, a number of job descriptions of authorized personnel were selected, reviewed and verified. As per the respective SOP, a new study delegation list would be provided by the Sponsor or CRO, where a line would be added to the template to record the PI signature if feasible.

Dr. Igor A Zupanets was by qualification a physician. He was also the Senior Specialist in Clinical Pharmacy of the Ministry of Health, Ukraine who established the first clinical facility for BE-studies in Ukraine.

The focal Point of the clinical site was Dr Natalie Bezugla as study coordinator, qualified as a physician with scientific interests in clinical pharmacology.

Dr Viktoriya Libina was the Head of the BE-site with pharmacology background and biochemist by education.

The Laboratory Deputy Head was specialized in biophysics and had experience in PK-studies since 1981.

The Sponsor representative, together with the monitor of the study was present during the inspection.

2. Computer systems

The software used at the clinical site was a Windows Microsoft database for the registration of volunteers. Additional information including a questionnaire completed by the subject, a copy of their passports and an overview of their participation was kept in hard copy format and was signed and dated as source documentation. Windows 10 was used, and the licence was provided with the last authorization date 31 July 2018.

The computer system for registration of volunteers will be fully in use following validation as per the requirements of GAMP 5, approval of its usage by administration of the CDC of NUPh, and testing. The corrective was provided and will be closed after completing the cycle of computer software preparation.

There was a plan to use electronic registration of the data, such as e-CRF in the future.

The software used at the BA-site for analytical runs was MassHunter linked to the Agilent Technologies 6420 Triple Quad LC-MS/MS. Data was generated by the software and stored in the computer's D: Drive.

Computer system validation was carried out by Agilent Technologies on 28 Apr 2012, supported by an applicable Qualification report:

- IQ – Documenting the characteristic of system
- OQ – Series of tests and the overall operational qualification inclusive of MassHunter Qualitative and MassHunter Quantitative

Other LC-MS/MS instruments were present, but not in use since 2013 and 2010 respectively, due to the absence of the mass-detector part.

WinNonlin pharmacokinetic software was used for PK calculations. Validated excel sheets – operated by Windows 7 was used for calculation of stock solutions concentrations and other relevant practices.

All the hardware i.e. desk-tops and computers had a responsible user for the respective computer who was knowledgeable of the password. Passwords were created by IT-specialist located at the Headquarter in Kiev through an apportioned line for communication.

The passwords were available to the Head of the laboratory to be printed out and kept in a sealed envelope to be opened in an emergency. The envelope was presented and the process for opening of the envelope was described.

The observations made were addressed adequately.

Backup procedure for MassHunter database:

The data generated in MassHunter software was backed up on the server and transferred by flash drive after completion of the study. The transfer of data to flash drive was QC-ed.

Hard copies of data generated (paper copy) were considered as source documentation, signed and dated. The data would be retained per protocol requirement for at least 15 years.

WinNonlin software package was delivered with system validation documentation by Certara Pharsight cooperation.

Programs on the computers were installed by the IT-specialist. In case of any concern regarding the validation of computer systems, the procedures were improved in cooperation with the IT-specialist in charge.

The observations made were addressed adequately.

3. Quality management

The QA system was established at the clinical site according to the requirements of ISO 9001:2015 for Quality Management Systems. Furthermore, PI and co-investigators were responsible to ensure the quality of the activities throughout the whole study. Quality was ensured through meetings, training (particularly SOP training) prior and during the study.

A Video surveillance system was in place to monitor the clinical activities 24 hours.

A list of SOPs was submitted.

The SOP for Development of Standard Operating procedure, effective 29 October 2013 was reviewed. According to the SOP, all SOPs should be revised every 5 years or upon any changes.

QA personnel were responsible to keep the overview and ensure the revision of SOPs within the timelines.

The following SOPs were reviewed:

- SOP for Updating Healthy Volunteers E-database. The SOP was reviewed to ensure that there was a change control in place when changes in the databases were required.
- SOP for Working with Healthy Volunteers E-database – Instruction
- SOP for Management of volunteers' day regimen during clinical trial
- SOP for Dispensation of study medication in fluid form
- SOP for Dispensation of study medication in solid form.
- SOP for Preparation to administration of study medication in solid form to volunteers / patients
- SOP for Evaluation of clinical significance of deviation from normal range of values of laboratory test of healthy volunteers, effective 10 Oct 2017.
- SOP for Chromatography, effective 15 Jan 2018
- SOP for Staff training at work place, effective 21 Sep 2017
- A Business contingency plan for the BA site

The clinical site was certified on 24 Apr 2015 valid until 2020 according to the ISO 9001:2009, issued by the certification body; State Enterprise in Kharkov.

An Accreditation certificate was also issued by the authority, valid until 28 Oct 2019.

A License was issued for clinical practice by the Health authority in Ukraine for different clinical activities since 2010 and valid for the sites' lifetime. Authorization accreditation would be performed once in two or three years according to the local law.

The BA-site:
All the aspects of the activities were supervised by QA personnel, starting from the monitoring of the facility. In addition to the preparation of SOPs, incoming reagents and reference standards were also supervised by QA personnel. The SOPs were prepared in paper format, and they were version controlled.

A regular review of the SOPs was carried out to keep the quality management system up-to-date, including training of the staff.

A weekly meeting/training took place for respective ad-hoc queries, in addition to the periodic training in relevant topics. Individual training documentation for the period 10 Oct – 26 Dec 2016 was provided.

During the study process, activities of analytical runs were supervised on appointed days based on the critical points by QA. Upon completion of an analytical run, the report was completed according to the SOP.

The report was cross checked to ensure that the correct raw data was fully reflected in the report.

The independency of the QA was verified. The laboratory was audited during November 2017. The audit report was available.

An Internal audit dated March and November 2017 was carried out. The plan and the respective reports were available.

Activities such as calibration of equipment, supply of reagents and recycling of wasted materials were outsourced to third parties.

4**. Archive facilities**

Clinical site:

The Archiving facility at the clinical site was located on the first floor of the premises. The facility was well-organized by using boxes coded with 4 digits, linked to the study protocol. An index was kept, including archiving date and required retention time.

The process of request for retrieval of documentation for inspection was reviewed. The documentation was retrieved and kept in a temporary archive, 6 weeks prior to the inspection which was unnecessary for the preparation of the inspection. Hence, the respective SOP was revised to implement the new practice to retrieve the documentation 30 days prior to the inspection. Documentation would be protected in a temporary archive during the retrieval.

When documentation reached the end of the retention time period, documents would be discarded only after permission from the respective sponsor.

BA site:

The archiving facility at the BA site was located on the 3rd floor together with the rest of the facility. The archiving facility was separated with a door with iron rods, locked by key. The Head of the laboratory and the Archivist were authorized to access the facility. However, the key was kept by the Head of the laboratory, only. The Head of the laboratory was accessible by two cell phone numbers at any time.

The facility was equipped with a thermohygrometer and barometer, to be read once daily.

The process for preparation of the documentation for archival and retrieval of the documentation was explained in detail. A log was kept recording the date of retrieval, reason and signatures. The archiving documentation was indexed for a complete overview.

Source documentation was sealed after the completion of the study by stamping, signing and dating of the stamp on the documentation package.

Concerns raised in relation to the archiving facility and routine were addressed adequately.

5. Premises During the inspection, a tour of the facilities was provided.

At the clinical site, the volunteers were received on the first floor, registered by the registration officer and handed the questionnaire form to be completed by the volunteer.

Volunteers were led to the second floor where the facility housed the pharmacy, dining /sitting area, physical exam room, ICU facility, administration office and CPU with rooms furnished with two, three or four beds, IP-dispensing room, and a room for handling and storage of biological samples. The CPU was under supervision of the Director of Clinical and Diagnostics Centre.

The restricted areas were accessed by key cards at the clinical site and by access code at the BA-site. GPS synchronized clocks were located throughout the clinical facility to document the exact time study activities occurred.

The facilities were kept clean and organized with adequate lighting and ventilation.

The backup generator was replaced by a backup electricity line at the BA site, as two independence sources, for the whole building. In a case where the cable collapsed, or power was cut, the backup line would be switched on. However, the backup was not automated, and the building's staff were responsible for proper operation.

ICU

ICU was organized in a way to ensure proper care of subjects who required emergency or other urgent medical care. First-aid equipment and appropriate medication in case of emergency was available. The ICU was furnished with one bed.

A hospital was contracted 500 meters from the site to be called in Emergency situations.

A temperature log was maintained by the study nurse to ensure proper temperature for storage of medication.

The ICU operation was supervised by an anaesthesiologist. His CV was reviewed. He was a specialist in anaesthesiology with PhD degree in medicine with 16 years of experience in relevant workplaces, signed and dated on 22 Jan 2018.

Issues raised during the inspection were resolved in the site's CAPA.

Pharmacy

The pharmacy was accessed by two authorized personnel at the clinical site.

The pharmacy was well-organized by zones: White, Yellow, Red and Green.
Once the drugs were received, they were kept in the white zone. If minor observations were made which could be fixed, the package was stored in yellow zone, and finally packages which could not be dispensed were transferred to the red zone. Approved IMPs were kept in the Green zone for further dispensing procedures.

The dispensing room was separate.

Observations made during the inspection were addressed sufficiently.

Working standard storage
Working standards were stored in identified refrigerators with respective logbooks to keep the records of receipt and usage at the BA site.

6. Personnel
Both sites had qualified staff to perform the delegated activities. Personnel were receiving adequate training in accordance with the applicable SOP for training.

The BA site consisted of a team of 6 staff responsible for QA, chromatography data, preparation of samples, analytical queries and mass-detector.
The Training plan of the first quarter of 2017 was reviewed.

The working hours at the BA-site were established to be from 9 am to 5:30 pm, from Monday through Friday. However, in case of ongoing studies that required longer working hours throughout a working day, the site staff with study-related responsibilities would start from 8 am and might continue until 8 pm.

Selected CVs of BA site staff were reviewed and verified.

Clinical section

7. Clinical phase
According to the sponsor, a meeting took place in Copenhagen with the WHO PQ-team, regarding the study protocol. Many remarks to the protocol received from the experts in Copenhagen, were resolved / implemented prior to the approval of the study protocol by the local authority.

The facility was monitored by video surveillance camera systems. All the rooms in the CPU were equipped with a bell.

According to the study coordinator and the BA site staff, the calibration of the equipment was done by the service provider, mainly SE “Kharkivstandardmetrology” and SE “Ukrmetrteststandard, in due time.

Equipment was identified by a specific number. However, the information regarding the calibration of equipment was stored in the study file and not labelled on the instruments at the clinical site. At the BA-site, the information regarding the calibration of equipment was labelled on the instruments.

Calibration certificates for a number of selected devices were reviewed.

Pulse-meter calibration:
Calibration valid until: 30 Nov 2018 (Annual calibration)

Device for alcohol measurement (Ethanol vapour):
Calibration date: 22 Jun 2017
Valid until: 22 Jun 2018
The use of device for alcohol measurement was successfully demonstrated.

Issues raised during the inspection were resolved in the site's CAPA.

8. Clinical laboratory

In addition to the site's pathology laboratory, the site was using two other laboratories for HIV and syphilis tests, where required.

The following documentation was reviewed:

- Agreement between the site and "The regional centre for prevention and counteraction for AIDS in Kharkov", dated 12 Jan 2015
  Accreditation and CV of the Head of laboratory were reviewed. CV was signed and dated on July 2016
- Agreement between the site and Alpha lab service was signed 19 Jan 2015
- The payment to the Alpha lab was invoiced 5 Dec 2015

During collection of the biological samples for screening purposes, a representative from the regional central laboratory was present to collect the samples.

A Courier service was used for transfer of samples to Alpha laboratory.

Samples were forwarded to the in-house lab with a cover letter, in special containers in ambient temperatures. Samples were transferred to the abovementioned laboratories in boxes with dry ice.

Comparison of a subject's laboratory test result versus a reference or "normal" range was a medical decision made by PI or sub-investigator in accordance with the applicable SOP, which was reviewed.

9. Ethics

The EC was established at the university. Previously, a central Ethics Committee was used. Currently, the EC was attached to the site, operating independently. It was verified that the PI did not participate in EC meetings. The members, including lawyers, did not work for the NPU or the Clinical and Diagnostics Centre and had no interest in the study.

The study was insured by the Insurance company. The insurance certificate was valid until 1 Oct 2017.

10. Monitoring

This part was not investigated due to time constraints.

11. Investigators

Four investigators were involved in the study. Resuscitation clinicians, who were members of the study team, were delegated in only the emergency care.

12. Receiving, storage and handling of investigational drug products

Study drugs were shipped by courier service, supplied with documentation from the Sponsor to certify the quality, serial and batch number. The data-logger (temperature recorder) was printed out in a specific report, attached to the shipment documentation (receipt report).

Randomization was performed in accordance with the applicable SOP and records were maintained, including the randomization list provided by the sponsor. The randomization list was submitted by the Sponsor. According to the Ukrainian legislation, the prescribed medication should be listed in the medical history, so the randomization sheet should be available to the investigators in the clinical site.

Issues raised with regard to the randomization list were addressed and a new SOP, as well as respective training was provided.

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

Dispensing was described to be performed adequately, followed by quality control carried out by QA-personnel.

The dispensed study drug package was handed over to the study nurse 10 minutes prior to dosing and documented. Lists of tests drugs and reference drugs were separate.

After completion of the clinical part, the study drugs would be returned to the sponsor and a receipt would be provided.

Documentation for receipt, labelling, dispensing, reconciliation and return of the study drugs was reviewed and confirmed.

Issues raised during the inspection was addressed adequately.

13. Case report forms

This was not inspected.

14. Volunteers, recruitment methods

The recruitment method was carried out according to the SOP for Recruitment of volunteers. No advertisement was ever used in recruitment of the studies. The site had a reputation through years of experience within the field. About 600 volunteers were registered in the database.

The Investigator reviewed the database used for registration of volunteers, to select subjects according to the criteria in the protocol. Further, the Investigator prepared a list of subjects who could qualify according to the predefined criteria. Subjects were contacted according to the list in alphabetical order.

Subjects' data was recorded in a pre-screening log. In general, the SOP was followed adequately.

The record of the payment to all subjects in the study was reviewed and verified. Payment clearance was provided by a third party.

Upon arrival, the volunteer was led to the registration room to be identified by presenting their passport. A questionnaire was completed where the volunteer also consented to be registered in the registration database, followed by measuring weight and height for the BMI calculation. BMI was calculated using an excel sheet incorporated in the registration database.

The last participation of a subject in a study, was verified in the registration documentation, stored in binders in the facility. The registration database did not have an audit trail and only registration documentation in paper form was considered as source documentation. The documentation was recorded in compliance with the requirements.

<u>Screening procedures</u>

The volunteer was given sufficient time to read the ICF and consider participation. After detailed explanation and a discussion with the investigator, the volunteer signed the ICF in duplicate. The ICF was signed and dated by both volunteer and investigator.

Later, the volunteer was assigned a screening number and a labelled blood sample container. A logbook was available to record the activities.

The first urine sample was provided by the subject prior to receiving a sheet with information about the screening procedure. Another urine sample was provided by the volunteer after site admission.

The process of blood collection (blood collection room) and physical examination was visited. The use of the blood pressure instruments, alcohol breath analyser tester and pulse-meter were demonstrated adequately.

The ECG machine used at the site did not have a memory option. Date of performance, time and subject's initials were recorded on the ECG printout.

The results from the pathology laboratories were available 1-2 days after completion of the screening activities, to verify the volunteers' eligibility.

Eligible volunteers were admitted for period I before 6pm within 21 days after the screening procedure was completed. At the time of arrival, the volunteer was physically examined, and tested for alcohol breath and narcotic substances. Dinner was served at 7pm since the study required fasting condition (at least 12 hours). Data was verified.

Subjects were sent to the room assigned by randomization number. They also carried badges with subject numbers. However, there was a risk of badges mix up or switching since the badges has no ID photo and was worn around the neck. During the inspection, the practice was changed to use wrist-bands with the subject identification number.

The issues raised during the inspection was addressed adequately.

15. Food and fluids

The invoice for payment of catering dated 8 and 24 Nov 2016, was reviewed.

16. Safety, adverse events, adverse event reporting

One subject was excluded from the study due to an adverse event of diarrhoea. The blood samples were not collected after 12 noon, on 24 Nov 2016 and the subject was withdrawn from the study.

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

The analytical method was developed by the BA site. The literature was investigated regarding the metabolism of the analyte, also the assay and analyte in matrix.

Serum vs Plasma:
Due to legislative and supply challenges in Ukraine, acquisition of plasma with proper anticoagulant for the methods used in the study was unlikely. Therefore, the site used serum as bio-sample instead of plasma.

The authority representative present during the inspection provided new information regarding the new guideline allowing use of K2EDTA as anticoagulant. The observation was escalated to the respective official department for further investigation and follow-up.

Study no.: **TH-PRT-I**	
Method development	
Bioanalytical method development was initiated with a review of publications, which were readily available, regarding the analysis of respective analytes and anti TB products, mostly for estimation of the analytes in plasma. Experiment details were readily available, tidy and logical, properly recorded, signed and dated. Validation included the investigation of effects of haemolysis on the analytical serum concentration results which showed lack of any interference.	
Method validation	
Method validation was performed in 2014 with partial validation conducted in 2016 including short-time stability.	
Analysis of samples	
The sample processing procedure took one working day, to analyse samples of three subjects. Each run took approximately 10 hours. The processing sequence of samples (calibration standards, QC samples and clinical samples) was given in Table 2 of the analytical plan. QC samples within each analytical run was arranged to detect possible deviations during the study.	
The templates for preparation of stock solutions for QC, CS, DIL and IS was provided on 11 Nov 2016 with pertaining weight script. The stock solutions were prepared independently. The Reconciliation process of working standards used was inspected. The sites prepared larger quantities of stock solutions than needed and discarded the excess, although the exact required number of QC and CS was calculated in the analytical plan. For reconciliation of working standards used, an overview of purchased working standard was kept, along with the number of QCs and CSs prepared and discarded. The variation of ISD and the trend was reviewed and verified. The acceptance criteria were pre-defined in a template developed for the respective SOP for Data processing.	
Repeat analysis	Repeat of analytical runs was pre-defined in the analytical SOP. Samples with an abnormally low or high IS response, which differed from the mean IS response in calibration standards and control samples within the given analytical run, by more

	than 50 %, could be subjected to repeat of the analytical run. The ISV trends were reviewed and verified.
Re-integrated chromatograms	The Procedure for re-integration of chromatograms was reviewed to confirm the re-integration of chromatograms in the study due to incorrect baseline. Chromatograms re-integrated by software were applied to following samples: ISR1 02-I-13-3 R2-05-II-10-1.75 Both were reported.
ISR	2 ISRs were run on two different days. 10 % of samples were reanalysed.
Back calculations	This part was not investigated.
Acceptable ranges were fulfilled	

18. Sample collection, storage and handling of biological material

The clinical site:

The dosing process was carried out while the inspection team observed subjects receiving their respective study drugs.

Each room, with up to four subjects, was managed by a study nurse who had already dispensed the study drug and water. Subjects had already received the peripheral venous access catheter in their veins. The volunteers were guided through the process by the study coordinator.

The administration of study treatments and first blood sample withdrawal: Subjects were seated on the side of the bed. At 07:59:50 the medication was removed by the subject from the test tube, taken by hand and at the time indicated, 08:00, transferred to the mouth followed by taking the water. An oral check was performed. Two study personnel observed this stage.

After administration of the dose, the blood collection process was performed in intervals according to the protocol in the room and on the bed, by the same study nurse. Any delays of more than 60 seconds were recorded in the logbook. Blood samples for each subsequent time-point were immediately transferred to the blood sample processing area for centrifugation and storage.

The next area visited was the blood sample processing area. Process and equipment were investigated. Samples were centrifuged according to the time, speed and temperature established in the respective protocol. Collected blood samples were kept in ambient condition since the serum was the required bio-sample per protocol. The process was recorded on a template “Aliquot

preparation process". Time received, exposed time, centrifuge time start and end, time of storage and the length of process were all recorded on the template. Haemolysed samples were identified and recorded.

The freezer was identified by an identification letter and temperature was monitored by an incorporated digital thermometer which did not generate notification in case of temperature excursions out of acceptable range. A CAPA plan was introduced to acquire freezers equipped with data loggers and remote alarms for monitoring of the temperature excursions.

According to the clinical site's CAPA, records of the temperature mapping of freezers and the refrigerator would be available during the autumn 2018. The clinical site planned to acquire a new freezer for storage of the blood samples to allow monitoring of the temperature according to the applicable requirements.

Sample containers were placed in a tray, both the main aliquot and the replicate used a cap with same colour (orange), labelled adequately according to the protocol.

Only the main aliquots of samples were sent to the BA site under controlled shipment condition. According to the study protocol, the BA site was blinded.

The BA site:
Information regarding the shipment of samples was sent to the Head of the laboratory by the clinical site prior to the receipt of the shipment to confirm the BA site readiness, followed by preparation of the relevant template for receipt of the samples.

Samples that were shipped were equipped with a data logger to monitor temperature conditions.

Replicate samples used in the study were permitted by the sponsor to be discarded on 25 Apr 2016. The main samples (1273 samples) were discarded on 4 Dec 2017 and signed by the director of clinical site and the senior nurse.

Concerns raised during the review of the blood sample processing and storage were adequately addressed by the CAPAs.

19. Data processing and documentation

Master file records at the Clinical site were verified. It was observed that haemolysed samples had been identified and recorded.

At the BA site, the logbook for usage of HPLC instrument was reviewed for the usage of the instrument at the time of the study. It was observed that the lab had only one Mass spectrometer to be used in a facility with a capacity to perform 4-5 studies per year.

Issues raised during the inspection with regard to data processing and documentation were sufficiently resolved in the sites' CAPA.

20. Good laboratory practices

The deep freezer room used for storage of bio-samples was visited.

All information was logged in various logbooks:

- Room temperature log
- Freezer temperature log (Manual record)
- Print-outs of data-logger

There were two freezers at -20 and -70°C in the room.
Temperature of both freezers was monitored digitally. External digital thermometers were installed, in addition to the incorporated thermometer for -70°C freezer. The external thermometer was connected to the printer by a USB connection to keep a temperature log with defined intervals.

The BA-site's record of the temperature mapping for the freezers and refrigerators were available, during the inspection.

The temperature log of deep freezer for the study period was reviewed.

The laboratory was equipped with six micropipettes, with five in use during the inspection. The pipettes were calibrated by SE "Kharkivstandardmetrology" once a year, in addition to the calibration prior to the study by responsible personnel. The calibration was demonstrated adequately.

Labelling of chemicals was done properly.

The weighing room was visited to verify the existence and process of the calibration of balances. In-house calibration was demonstrated. The annual calibration of microbalances was conducted by the service provider.

The temperature of the refrigerator for the storage of working standards was monitored by an incorporated digital thermometer.

Issues raised during the inspection with regard to data processing and documentation were sufficiently resolved in the sites' CAPA.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The Randomization list was provided by the Sponsor in the initial package sent to the site.

Observations made regarding the randomization list was addressed properly.

22. Study report

In accordance with the allocation of duties, the analytical and statistical report was drafted by the study manager at the BA site. The report was finalized and authorized by the Head of Laboratory and the QA person.

All the established tables and charts and concentration of serums and analytes were sent to the Sponsor and to the PI, prior to the submission of the analytical report to the Sponsor and other applicable parties.

23. Miscellaneous

Samples taken	Not applicable
Assessment of the CRO master file	CRO Master File was present
Annexes attached	Not applicable

Discussions took place on how to generate and process the source data and logbooks used during a study, to ensure data integrity of source documentation throughout their life cycle.

The sites were guided to keep the raw data secured, accurate and re-constructible.

It was suggested to keep the record of sites' GPS coordinates in the CRO Master Files for identification purposes.

It was recommended to improve the administration of study products, improve controls to prevent subject samples being collected in the wrong container, and generally ensure the equal/same handling of subjects and their blood samples, including limiting the occurrence of haemolysis, to ensure that each subject was in fact their own control.

Part 3	**Conclusion**

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

Clinical site:
Clinical Diagnostic Centre of National University of Pharmacy (NUPh CDC)
27, Pushkinskaia Str.
Kharkov – 61057
Ukraine

Bioanalytical site (BA-site):
Laboratory of Pharmacokinetics (Kharkov) SE "State Expert Centre of the Ministry of Health of Ukraine"
33, Astronomicheskaia Str.
Kharkov – 61085
Ukraine

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 3 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
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report*. World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO multisource guidance
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf

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
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
   Short name: WHO TRS No. 996, Annex 5 WHO GDRMP guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
5. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP".
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1
http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1

9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

10. US FDA Code of Federal Regulations Part 11
http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

12. 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 TRS No. 961, Annex 9
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

13. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
Short name: WHO TRS No. 957, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf

14. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

15. WHO Good Clinical Laboratory Practices (GCLP)
http://www.who.int/tdr/publications/documents/gclp-web.pdf