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To Whom it May Concern

Clinical trials in Ukraine: current state and perspectives

Information sheet

The Clinical Trials Subcommittee (Subcommittee) of the European Business Association (Association) conducted an assessment of current state of the clinical trials (CTs) industry in Ukraine and the results of work during martial law.

The full-scale war of the rf against Ukraine, which began on February 24, 2022, had a significant impact on every branch of Ukraine's economy, to include the processes of planning and conducting CTs, as well as the peculiarities of working in the legal regime of martial law.

According to the member-companies of the Association Subcommittee, all efforts of key stakeholders have been and still remain focused on ensuring the safety of patients and company personnel, as well as uninterrupted operations, in particular through the following:

- introduction by the companies of the Business Continuity Plan (BCP), in particular additional supply of investigational medicinal products (IMP) and other CT materials, setting up communication channels, etc.;
- temporary stop of recruitment of new subjects to active CTs and the start of new CTs;
- implementation of measures aimed at providing the subjects' safety and data integrity in active CTs, in particular, 24/7 "monitor-researcher-subject" communication and acting according to the plan;
- 24/7 communication between all stakeholders to identify issues and organize regulatory support of processes, in particular, preparation and publication of recommendations of regulatory bodies, improvement of the regulatory environment, etc.;
- united 24/7 work in CT sites, companies, regulatory bodies, etc.;
- relocation of the CT sites, transfer of subjects within Ukraine and abroad;
- relocation of the companies' personnel within Ukraine and abroad and ensuring remote work;
- solving logistical issues of supply and delivery of the IMPs and CT materials to the CT sites and to the CT subjects;
- solving issues of exporting bio-samples and involving local laboratories, if necessary;
- arranging for remote work, to include electronic submission/communication and direct electronic communication with regulatory bodies, etc.;
- implementation of measures to ensure uninterrupted power supply and access to the Internet network and cellular communication.

Based on the data of the State Enterprise "State Expert Centre of the Ministry of Health of Ukraine" (SEC and MoH, respectively) for 2022[1] and Q1 2023[2], the state with the CTs in Ukraine is outlined in the following major figures:

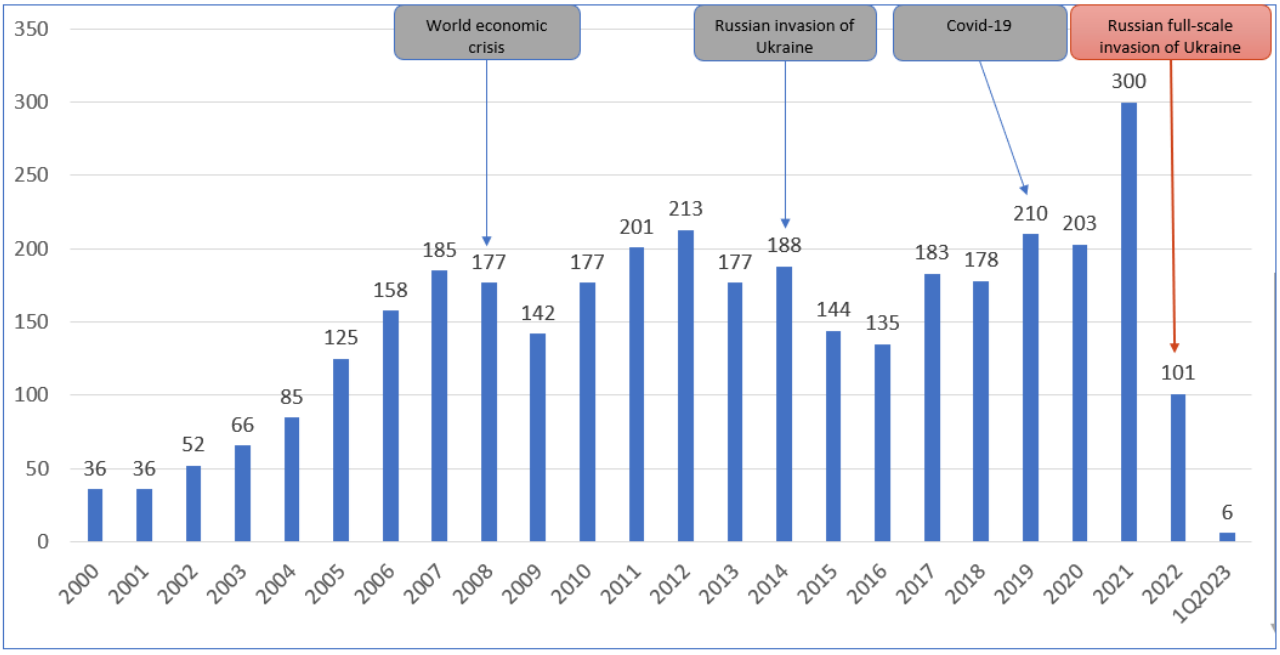
[1] https://www.dec.gov.ua/wp-content/uploads/2023/02/infodovidka-shhodo-stanu-provedennya-kv-za-2022-rikmm.pdf
[2] https://www.dec.gov.ua/wp-content/uploads/2023/05/infodovidka-shhodo-stanu-provedennya-kv-za-i-kvartal-2023m03.pdf

- in 2023, the total number of **started CTs** reduced by **16.6%** as compared to 2022;

- **18.5% of current started CTs** were early terminated **in 2022 due to the full-scale war;**
- it was announced that **472** subjects would be transferred to other approved clinical trial sites in Ukraine and abroad, for the period of 2022-2023;
- in the first year of the full-scale war, the recruitment of new patients and/or screening and/or randomization was suspended in **36.6%** of started CTs, and the start was suspended in **21.4%** of CTs approved by MoH.

It should be noted that due to the influence of external negative factors, during the last 10 years, some fluctuations in the number of CTs in Ukraine were observed, but the industry managed to recover its position quickly and proceeded to develop, in particular, due to the presence of significant unrealized potential. In detail, the state of fluctuations in the number of international multicentre CTs in Ukraine, depending on external factors, is shown in the diagram below.

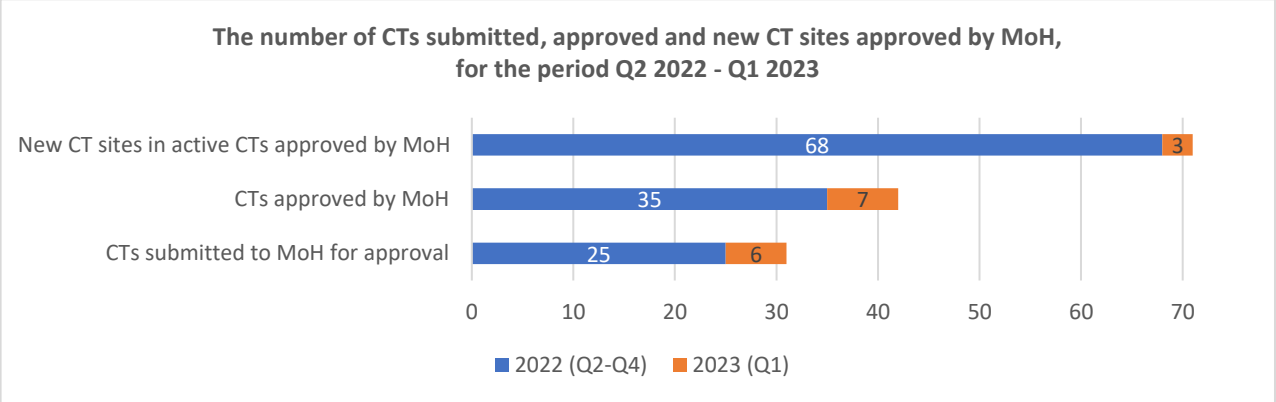
The history of CTs recovery in Ukraine



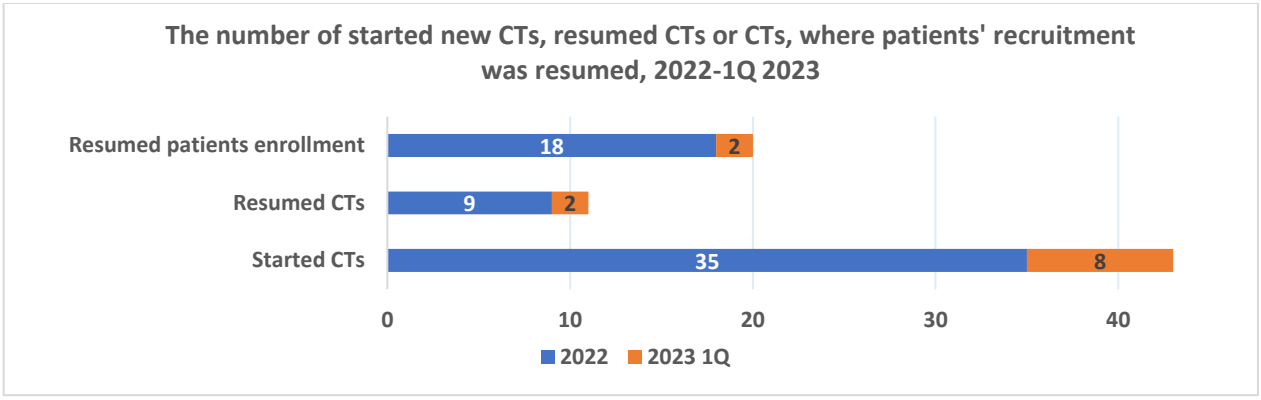
Approvals of international multicentre CTs in Ukraine in 2000-2023

Currently, there are certain signs of CTs recovery in Ukraine after the start of a full-scale war:

- **31 CTs were submitted for Regulatory Authority (RA) evaluation** o the MoH/SEC**;**
- **42 CTs** submitted after the start of a full-scale war **were approved for conduct;**
- **43 CTs were started;**
- **71 new CT sites** in active CTs **were approved** with substantial amendments, thereby the total number of approved CT sites for active CTs increased by **23%** and as on March 31, 2023, numbered **379 CT sites;**



- **11 CTs** were **resumed;**
- In **20 active CTs, the patients' recruitment was resumed;**



- in 2023, there were no notifications on any suspended patients' recruitment in CTs;
- **32 patients** returned from abroad to the CT sites in Ukraine;
- **1,550 substantial amendments (SA) were approved.**

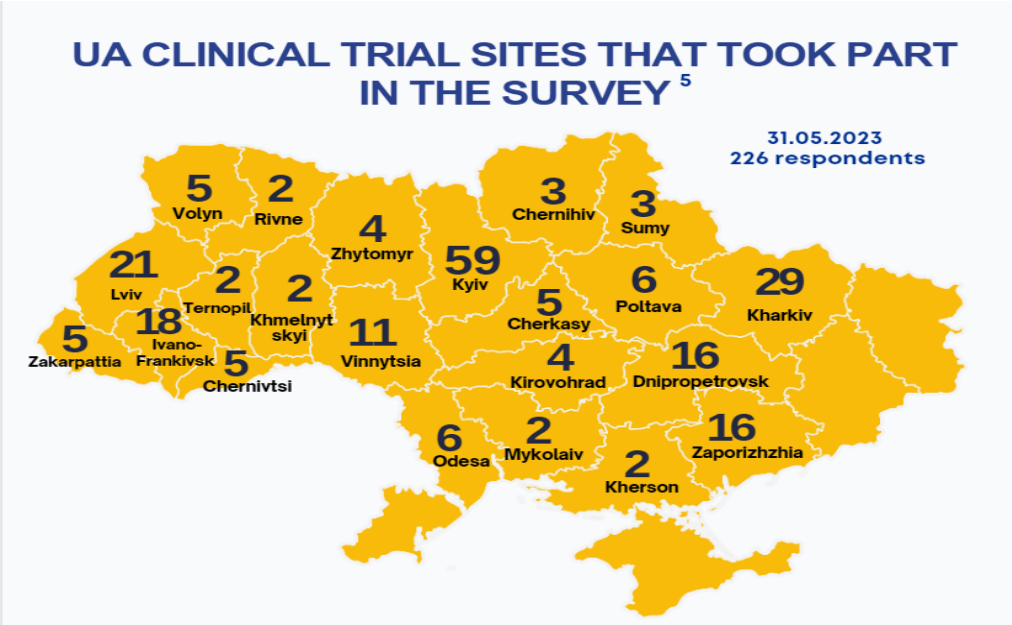
In this context, it should also be noted that the regulatory authorities, namely the MoH and SEC, proceed steadily evaluating and approving CT materials and performing regulatory supervision of CTs in Ukraine. During the period of 2022 and Q1 2023, the SEC/MoH processed 5,905 reports from applicants, including 1,702 applications for the conduct of CTs/SAs.

From May 2022, the conduct of clinical audits of CTs by the regulatory authority of Ukraine (RA audits) has been resumed, including the compliance with regulatory requirements when transferring subjects to other CT sites during the war. The number of RA audits conducted in 2022 exceeded the same in 2020 during the Covid-19 Pandemic (28 vs. 25, respectively), and in 2023 there is a tendency to their increase - in particular, in Q1 2023 8 RA audits were conducted, and in Q2 it is planned to conduct 14 RA audits. Conducting RA audits is an important aspect of guaranteeing the quality of CTs and protecting the rights, safety and well-being of subjects.

Training seminars on compliance with Good Clinical Practice (GCP) principles (including under martial law), have been resumed. In 2022 – Q1 2023, the SEC conducted **7 GCP trainings**, where more than 400 trainees (investigators, representatives of applicants, members of ethics commissions, etc.)[3] took part.

Local Ethics Commissions have adapted to current conditions[4], in particular with the use of remote access technologies, the transition to electronic document management based on the SEC recommendation.

CT sites proceed to operate in active CTs and in CTs that are starting. Thus, 92% of 226 active CT sites[5] that took part in the Association's survey have active CTs, and 99% reported that their sites are fully adapted to conducting CTs, have all the necessary base and resources for continuing and starting new CTs in Ukraine.



The SECs and sponsors did not receive information about the destruction of health care facilities, where CT sites with active CTs are located.

Hospitals, as objects of critical infrastructure, have uninterrupted power supply and access to the Internet. According to the MoH, all hospitals are equipped with alternative power sources[6] in case central power grid is down, and the installation of solar power plants has begun[7].

Clinical sites visited by the CT monitors have access to bomb shelters.

The patients visit hospitals within the framework of active CTs. 93% of the surveyed CT sites confirmed that the number of patients in their centres increased or remained at the previous level[8].

CT logistics support. After a partial logistical collapse in the first days and weeks of the full-scale war, the Association Subcommittee experts noted that the logistics chains have been gradually restored, all major local depots are working in full, and transportation across the territory of Ukraine is taking place in a standard mode. All supplies of the CT materials and equipment (export, import) have been switched from air supply to land transport. Most courier services are fully operational and are currently able to deliver to all active CT sites.

[3] https://www.dec.gov.ua/wp-content/uploads/2023/02/infodovidka-shhodo-stanu-provedennya-kv-za-2022-rikmm.pdf ; and https://www.dec.gov.ua/wp-content/uploads/2023/05/infodovidka-shhodo-stanu-provedennya-kv-za-i-kvartal-2023m03.pdf

[4] EBA Clinical Trials Subcommittee survey the "Analysis of the CTs state in Ukraine" dd. August 26, 2022, and the "Analysis of CT sites state in Ukraine" dd. May 31, 2023.

[5] EBA Clinical Trials Subcommittee survey the "Analysis of CT sites state in Ukraine" dd. May 31, 2023.

[6] https://www.ukrinform.ua/rubric-society/3644180-u-moz-zapevnili-so-vsi-likarni-zabezpeceni-generatorami.html

[7] https://interfax.com.ua/news/greendeal/899153.html

[8] EBA Clinical Trials Subcommittee survey the "Analysis of CT sites state in Ukraine" dd. May 31, 2023.

IMP supplies. The member-companies of the Association Subcommittee note that IMP delivery is possible in the usual way through a local depot, and then to the CT sites. There is a practice of the IMP delivery from abroad directly to the CT sites or directly to the patients (from abroad or from a local depot). According to the survey of the member-companies of the Association Subcommittee, at least half of the companies implemented this practice following the SEC recommendations. Some logistics companies organized and put into operation newly certified depots in the west of Ukraine, which improved CT logistics greatly.

According to the survey, 95% of the surveyed 226 CT sites with active CTs consider the provision of the IMP and all other necessary materials for conducting active CTs to be adequate.

Delivery of biological samples to the central laboratory abroad. Due to the closure of the airspace over the territory of Ukraine, there is currently no air service, and land transport is used to export biological samples. Business representatives note that carriers have confirmed <72 hours transit time for frozen and refrigerated bio-samples. Delivery of ambient biological samples in <48 hours is already in progress by logistics and courier companies, but the cost of such delivery is still quite high.

There is a practice of involving local laboratories, if necessary. According to information from member-companies of the Association Subcommittee, a full-fledged transition to the use of local laboratories for the analysis of certain biological samples is being considered. Business representatives report on the positive practice of certification of local laboratories for the purposes of CTs with the audit of equipment and relevant processes.

Companies providing transportation of CT patients are working as usual.

CTs monitoring. To confirm the reliability of the CT data, the companies have gained good experience in conducting remote monitoring and remote verification of primary data (remote SDV) during the Covid-19 Pandemic[9]. This experience is successfully used during a full-scale war as recommended by the SEC[10] and the European Medical Agency (EMA). Most of the companies resumed visits to the CT sites for CT monitoring (onsite). According to the survey of member-companies of the Association Subcommittee, their geography is also constantly expanding. Onsite monitoring of CTs in Kyiv, western and central regions of Ukraine in most companies is performed with minimal restrictions.

Most of the companies (sponsors, contract research organizations (CROs), logistics companies) provided their employees with powerful power stations and a stable Internet connection, which allowed them to work fully and be available during scheduled power outages, which were relevant at the end of 2022 and at the beginning 2023 and currently no longer observed.

CT sites audits conducted by sponsors/CROs. According to information from member-companies of the Association Subcommittee, there are examples of conducting audits not only online, but also offline with a visit to the CT sites.

During this time, significant steps were also taken by all stakeholders to improve the regulation of CTs and the conditions for CTs conducting in Ukraine.

The need to support CTs in Ukraine is reflected in applicable and developed strategic documents of the Government and the MoH, in particular, the "National Economic Strategy Until 2030"[11], the draft of the Health Care Sector Recovery Plan of Ukraine (Materials of the working group "Health Care System")[12], the draft of the Health Care Development Strategies Until 2030, etc., as well as in the Association proposals: "A Guide to Reforms. Business Vision for the Next Decade"[13], "Proposals of the European Business Association regarding the recovery of the economy of Ukraine, October 2022"[14].

[9] https://www.ema.europa.eu/en/news/advice-sponsors-managing-impact-war-ukraine-clinical-trials
[10] https://www.dec.gov.ua/announcement/do-uvagy-sponsoriv-klinichnyh-vyprobuvan-predstavnykiv-sponsoriv-doslidnykiv-kerivnykiv- pidpryvemstv-ustanov-ta-organizaczij-zadivanyh-u-provedenni-klinichnyh-vvprobuvan/
[11] Approved by the Resolution No. 179 of the Cabinet of Ministers of Ukraine dd. March 3, 2021/.
[12] https://www.kmu.gov.ua/storage/app/sites/1/recoveryrada/ua/health-care.pdf
[13] https://eba.com.ua/wp-content/uploads/2021/02/EBA-Strategy2030.pdf
[14] https://eba.com.ua/wp-content/uploads/2022/12/EBA VIDNOVLENNYA EKONOMIKY UKRAYINY.pdf

Despite the full-scale war, the Association Subcommittee, in close cooperation with the MoH/SEC/parliamentarians, proceeds to work on improving the legislation for the conduct of CTs in Ukraine and its harmonization with the legislation of the European Union (EU), in particular.

- There were several stages of implementation of **digitalization elements in CTs**, in particular electronic document management, electronic submission of CT/SA materials for study and approval, the possibility of using electronic informed consent, telemedicine, the possibility of using electronic source medical documentation (provided it is implemented by the MoH), etc[15].
  - Amendments initiated by the Association Subcommittee to the Procedure for conducting clinical trials of medicinal products and expert evaluation of clinical trial materials, approved by the MoH Order No. 690 dd. September 23, 2009, (the Procedure), are awaiting approval, which, according to the Association Subcommittee experts will contribute to **further CTs digitalization and harmonization of requirements with the EU regulation**, in particular in terms of reporting about IMP safety during CTs.
  - Work is ongoing with the MoH regarding the possibility of adapting the "patient's cabinet" in the eHealth electronic system for use in CTs.
- There was a significant reduction in the terms of CTs approval in Ukraine: RA evaluation - up to **30 days**, MoH approval - up to **5 days**[16].
- On the initiative and participation of the Association Subcommittee, the issue of providing patients with compassionate medicines in the **programs of access of CT subjects to the IMP after the CT completion** and the programs of extended access of patients to unregistered medicines (PTTA/CUP) was settled[17]. In May 2023, the MoH approved the first program for access of subjects to the IMP after the CT completion.
- **New edition of the Law of Ukraine "On Medicines"** No. 2469-IX adopted on July 28, 2022 subject to amendments proposed by the Association Subcommittee experts, once enforced, will significantly improve the regulatory environment for the conduct of clinical trials in Ukraine and will lead to the harmonization of requirements in Ukraine with the EU legislation, in particular Regulation of the European Parliament and the Council No. 536/2014 dd. April 16, 2014 regarding clinical trials of medicinal products intended for human use and the repeal of Directive 2001/20/EC (Regulation No. 536/2014).

Despite the full-scale war, business is also making efforts to improve the legal field to create favorable conditions for the CT in Ukraine, namely.

- It is expected to pass the draft Law "On Amendments to the Tax Code of Ukraine on the Settlement of the Issue of Providing Compassionate Medicines to Patient" No. 5737 dd. July 6, 2021, regarding **tax incentives for the importation of medicines within the scope of compassion programs**, in particular in programs of providing CT subjects (patients) with access to the IMP after the CT completion.
- Proposals for amending the Procedure for harmonization of the IMP labelling with the Regulation No. 536/2014 were submitted to the MoH.
- Work proceeds on the development of the draft Law "On Clinical Trials", which will make it possible to maximally harmonize the requirements for conducting CTs in Ukraine with the EU legislation.
- Preparation of proposals to amend, as follows, are in progress:

[15] MoH Order "On Amendments to the Procedure for Conducting Clinical Trials of Medicines and Expert Study of Clinical Trial Materials" No. 2609 dd. November 25, 2021 and MoH Order "On Approval of Amendments to the Procedure for Conducting Clinical Trials of Medicines and Expert Study of Clinical Trial Materials" No. 538 dd. March 28, 2022.

[16] MoH Order "On Approval of Amendments to the Procedure for Conducting Clinical Trials of Medicines and Expert Study of Clinical Trial Materials" No. 190 dd. January 31, 2023.

[17] The Law of Ukraine "On Amendments to Certain Legislative Acts of Ukraine Regarding the Settlement of the Issue of Providing Compassionate Medicines to Patients" No. 2054-IX dd. February 15, 2022 and the MoH Order "On Approving the Procedure for Approving and Conducting the Program of Extended Access for Patients to Unregistered Medicines and the Program of Access for the Subjects (Patients) to the IMP after the CT Completion and Amendments to the Procedure for Importing Unregistered Medicinal Products, Standard Samples, Reagents into the Territory of Ukraine" No. 1525 dd. August 24, 2022

- applicable Law of Ukraine "On Medicines" No. 123/96-BP dd. April 4, 1996, regarding the implementation of actual approaches and technologies for conducting CTs - decentralized CTs, etc.
- the Customs Code of Ukraine regarding the implementation of customs control in the priority order when exporting biospecimens for CTs.

The Association Subcommittee experts proceed to work together with the VRU, MoH, SEC, public organizations to **increase the awareness** of society, physicians, healthcare institutions and patients about CTs in Ukraine. The Association continues the informational project "Clinical Trials Truth"[18].

According to the Association Subcommittee experts, **all CT stakeholders demonstrated a high level of reliability in their work, ensuring the safety of patients and reliability of data received in extreme conditions, as well as the ability to effectively cooperate between the regulator, business and clinical sites, and to quickly adapt to a new reality**. The CT sites have confirmed their **readiness and ability to participate in new CTs**[19]. Active work to improve the regulatory environment for CTs development in Ukraine is in progress.

Business representatives note that all CT stakeholders have already **created the most favorable conditions for the rapid recovery of CTs in Ukraine** to renew and increase Ukraine's contribution to the development of innovative drugs in the world.

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Sincerely,

Anna Derevyanko,
Executive Director

[18] https://www.trialstruth.com.ua/

[19] EBA Clinical Trials Subcommittee survey the "Analysis of CT sites state in Ukraine" dd. May 31, 2023.