Approved by:

Dr. Stefan Dimitrov
Chairman of the ECI

Effective from: 05 -03- 2021 2020.

SAFETY MONITORING

1. **The goal** of the procedure is to determine the procedure for monitoring the safety of investigational medicinal products implemented in approved by the Ethics Committee for clinical trials (ECCT) of medicinal products.
2. **Covers** all safety data from clinical trials, which have received a favorable opinion from the ECCT.
3. **Responsible** for implementation shall be the chairman, vice-chairman, members and secretary of the ECCT.

4. **Legislative acts and documents used for the preparation of this SOP**
   4.1. Ordinance № 31 on determining the rules for Good Clinical Practice (promulgated, SG No. 67/2007);
   4.2. Appendix № 1 - the principles of Good Clinical Practice (GCP)

5. **Procedure (sections 5, 6, 7, 8 and 9)**

   5.1. **Individual reports of adverse reactions**

   5.2. The Sponsor shall notify the ECCT of any suspected unexpected serious adverse reaction that occurs in the course of the clinical trial on the territory of the Republic of Bulgaria, which leads to death or life-threatening condition, no later than 7 days from the receipt of information about it. The Sponsor shall provide the Commission with additional information on the case within 8 days of the date on which the notification is sent.

   5.3. The Sponsor shall notify the ECCT of all suspected unexpected serious adverse reactions that occurred during the clinical trial on the territory of the Republic of Bulgaria, which are not fatal or life-threatening, no later than 15 days from receipt of information about their occurrence.

   5.4. The Sponsor shall notify the ECCT of all suspected unexpected serious adverse reactions that occurred in the course of the clinical trial outside the territory of the Republic of Bulgaria at longer periods, but not less than once every six months.

   5.5. The decision on the reporting deadlines for suspected serious and unexpected adverse reactions shall be taken by the ECCT on a case-by-case basis, and the contracting authority shall be notified in writing of the reporting deadline requirement.

   5.6. The possibility to extend the reporting intervals is assessed at the initial review of the trial and is part of the Opinion on an application for a new clinical trial or when evaluating reports on the progress of the study, of which the Sponsor shall be notified

in writing of the reporting deadline.

5.7. Where the investigational medicinal product is not authorized for use, the sponsor shall notify the ECCT of any suspected serious and unexpected adverse reactions in the course of the use of the investigational medicinal product, regardless of their origin.

5.8. Reports of suspected serious and unexpected adverse reactions shall be submitted to the ECCT by electronic means and / or via official e-mail of ECCT.

5.9. The adverse reaction report shall also contain the following: title and code of the trial, sponsor, description of the event, outcome, disclosure or not of the code, relationship of the investigational product to the event (causal relationship) according to the principal investigator, reassessment opinion or not on the clinical trial authorization.

6. **Annual safety report**

6.1. Once a year, the sponsor shall provide ECCT with a list of all suspected serious adverse reactions that have occurred during the past period and a safety report of the study participants.

6.2. The form and content of the report are determined by Ordinance № 31 on Good Clinical Practice.

6.3. The annual safety report shall be submitted electronically and via the official e-mail to the ECCT.

6.4. The annual safety report shall summarize the safety data of the investigational medicinal product for the last one-year period from the date of the first authorization to conduct a clinical trial with the investigational product in the European Union.

6.5. When conducting more than one clinical trial with the same investigational product, the sponsor shall submit a general annual safety report. In these cases, the report shall contain data on the safety profile of the investigational product and the annual safety reports for each of the clinical trials conducted in Bulgaria.

6.6. The Sponsor shall submit the annual safety report within 60 calendar days after the end of the period covered by the report. For clinical trials lasting less than one year, an annual safety report shall be submitted within 90 days after the end of the trial, with the notification under Article 142, paragraph 2 of the LMPHM. At the request of the ECCT, the Sponsor shall provide an annual safety report outside that period.

6.7. The annual safety reports shall be examined by a member of the ECCT appointed by the Chairman of the ECCT and, if necessary (at the discretion of the reviewers), shall be presented at a meeting of the ECCT.

7. **Other safety data**

7.1. The Sponsor shall provide the ECCT with all safety data updates and periodic reports.

7.2. The Sponsor shall inform the ECCT of any other information that may pose a threat to the health and well-being of patients, affect the course of the study or change the ECCT's positive opinion on the continuation of the clinical trial.

7.3. The new data submitted shall be examined and evaluated by a Member of the ECCT

or an external expert appointed by the Chairman and submitted to the ECCT for an opinion on the necessary measures.

8. **Investigator's brochure update**

8.1. When updating an Investigator's brochure, the Sponsor shall provide it to the committee for information.

8.2. The addition of new information to the Investigator's brochure is not a significant change if it does not lead to changes in the protocol procedures or informed consent (to be formulated by the Sponsor).

8.3. The new information is presented as a summary, including a short summary in Bulgarian, and the pages of the documentation are marked, **with tracked changes**, comparing the current and proposed new texts (possibly as track changes), as well as a justification of the changes and an opinion from the Sponsor on the change of the benefit / risk ratio.

9. **Taking action by the ECCT**

9.1. The ECCT shall assess the information received (from individual adverse reaction reports, annual safety reports, other safety data and an updated Investigator's brochure) and its relevance to the trial conduct.

9.2. The ECCT shall record the decision on the status of the test in one of the following ways:

- confirms the positive opinion;
- requires additional information;
- requires a change in the protocol and / or informed consent to reflect the new information;
- issues a decision to terminate the positive opinion.

In case of a decision for necessity of change in the protocol, the statement shall be forwarded to BDA with a recommendation of BDA to request from the Sponsor a change in the protocol, according to the authority of the BDA under art. 127, para 1 of LMPHM.