Opinion of SÚKL's Department of Clinical Trials on Medicinal Products on Ongoing Clinical Trials in Light of the COVID-19 Epidemiological Situation of 5th August 2022

In view of the coronavirus epidemiological situation that can affect ongoing clinical trials, SÚKL hereby releases statement regarding emergency measures that can apply for the conduct of these clinical trials.

It is recommended to always ascertain the trial subject's situation in advance by phone

- Whether the patient is in quarantine because he/she visited a risk region (or whether he/she has not been in contact with a person with confirmed coronavirus infection or weather he/she doesn´t wait for test result
- Whether coronavirus infection has not been confirmed for him/her (this information should be written into the medical records and CRF)
- Whether he/she does not share household with a quarantined person
- Whether he/she agrees to the proposed course of action (a telephone visit, sending of study medication by a courier or collection by a family member with confirmed receipt of shipment by phone and verification of data accuracy, control laboratory sampling…)
- Add the coronavirus medical history both to source documentation and the CRFs
    - Vaccination with COVID-19 vaccine (which vaccine, how many doses, when last dose)
    - Evidenced COVID-19 disease (in such a case, add also other details regarding hospitalisation/home care/treatment…, its duration, recovery…)
    - Reasons for quarantine
    - COVID-19 evidenced in another member of the patient's household

Recommendations for ongoing or authorised clinical trials

Control visits

1) It is possible to change, in justified cases, physical follow-up visit of a trial subject in order to ensure the subject's safety to a telephone visit. The phone visit has to be documented with a rationale referring to the current situation. In case a follow-up visit is completely omitted in order to ensure trial subject safety, it has to be documented and thereafter evaluated in terms of its impact upon the validity and quality of data from the clinical trial.

Investigational Medicinal Products (IMP) – study medication (including AMP-auxiliary medicinal product required by the Protocol and supplied by the sponsor) – the below-listed ways of providing the study medication to trial subjects:

1) **Investigational Medicinal Products (hereinafter referred to as the "IMPs") – stored at room temperature, any pharmaceutical forms except for parenterally administered IMPs (e.g. tablets, capsules, etc.)**:
    - Possibility to provide the supply of study medication to patients during the upcoming visit for a longer period of time than originally planned.
    - In case it is not practicable to supply the study medication directly to the patient during the upcoming visit, it is possible, as an emergency situation, to send the study medication by courier service. The courier service would collect the medicinal products at the trial site, from the investigator who is responsible for the investigational medicinal products and this fact would be recorded by the investigator in the trial subject's documentation. The

courier service would deliver the study medication to the patient's (= trial subject's) home, i.e. to the address provided by the investigator to the courier service. Thereafter, the investigator would make sure by phone that the patient has received the study medication and would record this fact to the trial subject's documentation.

- In case the courier service is to carry several medicinal products at one time, the investigator must also make sure that the trial subject received the correct medicinal product (by the IMP code or trial subject code), as in blinded clinical trials there are several medicinal products; the major purpose of the telephone check is to avoid confusion of medicinal products. The patient should start taking the therapy only after the investigator endorses the correctness of the shipment.
- The courier service should be organised by the sponsor, or, after an agreement with the sponsor, it may be organised by a study team member. The engagement of a courier service has to be covered by a contract which shall form part of the clinical trial documentation. The costs of courier service shall be covered by the sponsor.
- When sending investigational medicinal products containing narcotic or psychotropic substances by a courier service, it is recommended to pack each shipment for the trial subject into a box or another container that will be sealed by a study team member with an adhesive tape bearing a stamp or signature of the study team member. On confirmation of shipment take-over by the trial subject, the courier shall ask the trial subject to confirm that the shipment was delivered sealed and its integrity was not compromised.
- Another option is to have the IMP delivered to the trial subject by his/her family member, who has been previously appointed by the trial subject in phone conversation with the investigator. The investigator shall record this change of IMP dispensing in source data and CRF.

2) <u>IMPs – sterile pharmaceutical forms (except for intravenously administered IMPs) such as parenteral administration, subcutaneous administration, eye drops, etc. self-applied by trial subjects at home:</u>

- Procedures outlined under Section 1) shall apply.
- In this case, it is necessary to respect also the requirements for the storage of the study medication; mostly, this concerns products to be stored at temperatures between 2–8° C. In such a case it is essential to arrange for transportation of the products in cooler boxes meeting this requirement. For the duration of transport, continuous temperature monitoring has to be ensured and documented in the clinical trial documentation. The courier service should be organised – and paid for – by the sponsor who is responsible for the quality of the IMP. It is, however, necessary, that the investigator who is fully responsible for the trial subjects from the respective trial site, agree to this course of action.

- The courier service should be organised by the sponsor, or, after an agreement with the sponsor, it may be arranged for by a study team member. The engagement of a courier service has to be covered by a contract which shall form part of the clinical trial documentation. The costs of courier service shall be covered by the sponsor.
- When sending investigational medicinal products containing narcotic or psychotropic substances by a courier service, it is recommended to pack each shipment for the trial subject into a box or another container that will be sealed by a study team member with an adhesive tape bearing a stamp or signature of the study team member. On confirmation of shipment take-over by the trial subject, the courier shall ask the trial subject to confirm that the shipment was delivered sealed and its integrity was not compromised.

3) **<u>IMP – parenteral administration – i.v. – in the form of bolus or infusion, applied by the doctor at the trial site:</u>**
    - If permissible with a view to the protocol and the patient's condition of health, SÚKL recommends to postpone the visit as well as the application of the IMP. Protocols typically offer the possibility to postpone the administration of products by 14 days.
    - If the product administration cannot be postponed or it has already been postponed by the maximum period permissible, the following may be arranged for:
        - Administration at the trial site while observing the aforementioned safety hygienic rules.
        - In emergencies, if necessary, administration of the IMP at the patient's home; such administration shall be carried out by adequately qualified healthcare staff trained for this purpose.
        - Should the sponsor consider using the services of a specialised company licensed for the conduct of medical home care within the territory of the Czech Republic via qualified and properly trained paramedical staff, it is necessary to obtain the approval of the investigator from the respective trial site for this course of action, as the investigator is fully responsible for the trial subject and organisation of treatment for him/her. This course of action should be approved by the provider of healthcare services of the respective trial site. The question is how the clinical trial insurance covers this service, how compensation for injury to health caused by a procedure conducted by "medical home care" staff would be handled. In such a case, the IMP has to be dispensed by the study staff at the trial site. Where infusions requiring preparation by pharmacy are concerned, they would be dispensed to an employee of the trial site on a request form and thereafter dispensed by the investigator or appointed trial site employee to the medical home care employee.
        - Injections that may be reconstituted prior to administration: proceed as per manufacturer's instructions and, if permissible, reconstitute immediately prior to administration at the patient's, observing all of the procedures prescribed by the pharmaceutical manual.
        - Infusions that were prepared by the pharmacy have to be transported under strictly observed storage conditions for the reconstituted product – i.e. under continuous temperature monitoring during transport and in compliance with other conditions prescribed by the Protocol or Pharmaceutical Manual, and the total time between preparation and administration of the IMP must not exceed the in-use shelf life of the product after reconstitution, in accordance with the data specified in the Pharmaceutical Manual, as applicable.
        - In case of administration of IMPs presenting the risk of anaphylactic reaction, these IMPs should be administered exclusively at the trial site where intensive and resuscitation care may be arranged for.

4) Sending of study medication directly from the sponsor, albeit via third party, is not acceptable (the sponsor must not know trial subject's identification, his/her address….).

<u>The administration of study medication that influences the immune system is not possible/is contraindicated for trial subjects with confirmed coronavirus infection</u>. This shall not apply to COVID-19 clinical trials and clinical trials where the sponsor evaluates the risk/benefit ratio as favourable for the administration of study medication (e.g. medication for cancer patients…).

Control laboratory sampling:

If the trial subjects need to complete necessary control laboratory assessments prior to the IMP administration – such as blood count, biochemistry, urinalysis – and the IMP administration cannot be postponed, it is necessary to:

a. Arrange the date (as well as the time) of the visit to the trial site and completion of the control sampling beforehand over the phone.
b. Arrange for the conduct of the control sampling at trial subject's home either by contract laboratory staff or contract medical home care service availing of appropriately qualified and trained staff and means, proceeding in compliance with any other aforementioned safety measures (respirators for healthcare staff, masks for trial subjects, …) and exclude those trial subjects who have been quarantined or share a household with a person who has been quarantined or in whom coronavirus infection has been confirmed.
c. Arrange for sampling in a nearby local laboratory or with the general practitioner, if they agree to this. In such a case, the costs of the assessment shall be borne by the sponsor and they cannot be reported to the health insurance company.

Safety reporting

The sponsor shall safeguard the submission of the Suspected Unexpected Serious Adverse Reaction (hereinafter referred to as "SUSAR") reports to the EudraVigilance database. Clinical Trials (hereinafter "CT") that are approved and conducted according to the Clinical Trial Directive 2001/20/EC (hereinafter "CTD"), safety reports are made according to the guideline KLH-21, both in relation to SÚKL and in relation to Ethics Committees and Investigators.
CTs that are approved and maintained according to the Clinical Trial Regulation No. 536/2014 (hereinafter "CTR"), safety reports are made according to this CTR. More information can be found on: https://www.sukl.cz/leciva/bezpecnostni-hlaseni-v-kh
The investigator shall also report adverse drug reactions as per the original plan.
Safety reports should also include information pertaining to coronavirus and COVID-19. As of 4 May 2020, new codes have been established in the MedDRA terminology that may be used for SAE reporting – new codes (*The list of codes is given below the article in separate annexes*). The coronavirus history should be added for all enrolled trial subjects in ongoing CTs and it should also form part of the baseline assessment for newly enrolled trial subjects (patients as well as healthy volunteers).

Informed Consent Form / Patient Information Sheet

In case that the trial subject should be informed, it is possible to deliver the information also through ways other than "personal contact", e.g.:

- Communicating the information by phone and documenting it in the source documentation and in the CRF;
- In the form of written email information, with trial subject's acknowledgment of the email and a record thereof made to the source documentation and CRF.
- We recommend that patients should be informed about COVID-19 measures in the form of a separate supplement to the ICF. SÚKL will then only acknowledge this document, as the validity of such a document is only for the period of validity of this SÚKL's opinion.
- In case an amendment to the Patient Information Sheet/Informed Consent Form (hereinafter referred to as the "PIS/ICF amendment") or an **updated version of the Patient Information Sheet/Informed Consent Form** (hereinafter referred to as the "PIS/ICF") with information other than related to COVID-19 is issued, it is necessary to submit this PIS/ICF amendment or updated version of the PIS/ICF to SÚKL and to the ethics committee for approval prior to its

use in the clinical trial. An exception to this rule shall be PIS/ICF amendments or PIS/ICF updated versions containing safety information that need to be communicated to trial subjects as soon as practicable. In such a case, PIS/ICF amendments or PIS/ICF updated versions shall be presented to trial subjects as soon as possible and thereafter shall be notified to SÚKL and to the ethics committee.

- A PIS/ICF amendment or updated version may be sent to the trial subject by e-mail or post, but it is not possible to require that a document delivered in this manner be signed and the signed document be returned by post or a scan of the signed document be returned by e-mail. In case e-mail is used, the investigator/study team member shall ask the trial subject to acknowledge the receipt of the document and shall enter this fact to the CRF, and shall add the e-mail to source documentation. If the document is sent by post, the investigator/study team member shall check the receipt of the document by phone and shall enter this fact into the CRF and source documentation. During the next visit, the trial subject shall sign the PIS/ICF amendment or updated version, date it with the study visit date, and confirm that he/she was familiarised with this document.

Should you have any further questions, please contact MUDr. Alice Němcová, Director of Department of Clinical Trials on Medicinal Products (272 185 817, alice.nemcova@sukl.cz) or MUDr. Eva Hrušková Reinová, Head of Clinical Trials on Pharmaceuticals Unit (272 185 317, eva.hruskovareinova@sukl.cz).

Department of Clinical Trials on Medicinal Products
Date: 5th August 2022