Opinion of SÚKL's Department of Clinical Trials on Medicinal Products on Ongoing Clinical Trials and To-Be-Commenced Clinical Trials in Light of the COVID-19 Epidemiological Situation of 22 November 2021, added 25 November 2021

In view of the current serious and still worsening coronavirus epidemiological situation that can affect ongoing and newly initiated 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

Applications for new clinical trials

Applications for authorisation/notification of clinical trials on COVID-19 shall be assessed as a priority in abbreviated timelines (approximately during 30 days).

Any other applications for clinical trial authorisation/notification are assessed as usual.

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.

2) In case of a trial subject's visit to the trial site it is necessary to:

- Arrange for the visit beforehand by phone, so as to prevent any patient accumulation; dedicate specific time for healthcare staff to conduct follow-up visits. Furthermore, a COVID-19 questionnaire should be completed with the trial subject (in the form of a questionnaire or an affidavit regarding the trial subject's condition of health in the last 14 days and his/her COVID-19 history), and on the basis thereof, select a date and time for the visit.
- Provide personal protective equipment for healthcare staff as well as for trial subjects; this is essential for immunosuppressed patients (such as patients on long-term corticosteroid therapy or on any immunosuppressive therapy, i.e. especially cancer patients and any post-

transplantation patients), patients with comorbidities, and elderly patients (over 65 years of age). Protective equipment should be safeguarded by the sponsor.

3) Initiation visits for trial subjects newly enrolled in ongoing clinical trials
   - Where the sponsor evaluates the risk/benefit ratio for newly enrolled patients as favourable for enrolment in the study and the situation in the trial site is also favourable (sufficient study staff capacity), the initiation visit has to be organised at the trial site, taking into account all of the aforementioned conditions (COVID-19 medical history, phone arrangements for the time of the visit, provision of protective equipment to the patient and healthcare staff…). There is possibility to shorten the duration of initiation visit by sending Patient Information Leaflet/Informed Consent form to patients in advance by e-mail. Such patient will be prepared for the discussion with investigator on following initiation visit. During the initiation visit to the trial site, the investigator, in an interview with the patient, shall explain everything regarding the clinical trial and shall obtained a signed informed consent from the patient.

4) The initiation of COVID-19 clinical trials and the enrolment of new trial subjects to such clinical trials shall be conducted in compliance with the approved documentation without further limitations. The initiation of clinical trials in serious indications when the treatment of such illness is not possible to postpone (oncological, neurological and other indications) and enrollment of new subjects in such clinical trials can be conducted also in compliance with the approved documentation without further limitations.

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, 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….).

5) As for the return of study medication by the patient to the investigator at the trial site by courier service: SÚKL prefers that the patient keep the unused study medication and return all medication, i.e. for control purposes, used and unused medication, only after safety measures are lifted; the medication is to be returned directly to the investigator during the trial subject's next personal visit to the trial site, when the investigator shall record everything in the trial subject's documentation. In justified cases it is possible that unused medication will be collected by courier and will be transferred to the study center for evidence and disposal.
   If a trial subject's participation in a clinical trial is terminated (early termination or regular completion) and the patient is not to come to the trial site anymore, it is possible to organise the collection of unused study medication from the trial subject by a courier service. Everything has to be properly recorded in the clinical trial documentation.

The administration of study medication that influences the immune system is not possible/is contraindicated for trial subjects with confirmed coronavirus infection. 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 and of the Development Safety Update Report (hereinafter referred to as "DSUR") to SÚKL on an ongoing basis as per the original plan, in compliance with guideline KHL-21 and guideline CT-3. Furthermore, the sponsor shall report to SÚKL any death of a trial subject not meeting the SUSAR definition.
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 clinical trials 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.
- 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") 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.

Investigators - changes of investigators

In the case of investigator´s /principal investigator´s illness his duties may be temporarily taken over by his representative (co-investigator). If the investigator's representative cannot take over the investigator's responsibilities, either, his duties and activities may be delegated to and coordinated by an investigator from another trial site. Another option could be the approval of a new investigator by the local Ethics Committee (EC).

Closure of the trial site / opening of a new substitute trial site

In case of a closure of a trial site in relation to the current emergency (all staff in quarantine etc.) it is possible to proceed as follows:

- suspend the activities of this trial site for the required time. Temporarily transfer the trial subjects to another trial site, if agreed both with the sponsor and the investigator. The trial subject has to agree with this change;
- or, if possible, with regard to the design of the clinical trial, temporarily suspend the clinical trial;
- or, if there is no other option, end the clinical trial at the trial site and transfer the trial subjects from this trial site to another trial site or to stop their participation in this clinical trial. In this case, where a chronic or continued condition is concerned, the investigator should inform trial subjects about their further treatment.

If necessary, a new, substitute trial site may be opened; all GCP requirements and requirements stipulated by effective legislation must be met (such as approval by the local ethics committee, agreement concluded by and between the sponsor and the healthcare service provider, etc.). For SÚKL and MEC (multicentric ethics committee), only notification is required (CTA form update); it is not classified as substantial amendment and reimbursement of costs for SÚKL is not required.

Clinical Trial Monitoring

Changes to the monitoring plan involving a change of a site visit to remote monitoring or change of dates of monitoring do not have to be reported to SÚKL or to the ethics committee by the sponsor, yet everything has to be documented and justified in the clinical trial dossier. SÚKL does not provide its opinion on the organisation of monitoring when authorising clinical trials, either, and it does not have to be included in the annual progress report for the clinical trial.

In response to frequent questions regarding the possibility of alternative ensuring of monitoring, please find below the position of SÚKL (Department of Clinical Trials and GCP inspectors):

1. Centralised monitoring is permitted.
2. Remote monitoring – source data are currently in paper form. **Remote monitoring** using **copying or scanning of reports or medical documentation, making and use of de-identified certified copies or certified copies of de-identified source documents is not acceptable.**

SÚKL's position, i.e. the position of the Department of Clinical Trials as well as that of GCP inspectors is unanimous; SÚKL would consider monitoring organized as described above a breach of GCP and legal regulations.

3. In case the reduced frequency of monitoring posed a hazard in respect of a particular CT, SÚKL would accept an alternative approach, such as central monitoring + teleconference monitoring, if feasible with regard to the workload of healthcare staff at the trial site, i.e. an appointed study team member would read the source data and the monitor would check them against the CRFs within the scope of the TC. Nevertheless, after the emergency situation passes, data obtained in this manner would have to be verified by standard process, and for this reason, this alternative approach should only be employed in justified cases identified by risk analysis.
4. A combination of centralised + teleconference monitoring is permissible.
5. In case of videoconference monitoring, the representatives of the sponsor/CRO must not make any photocopies of the documents (pictures, printscreens etc.). Videoconference monitoring must be ensured by secured transmission. Furthermore, it must be verifiably ensured that only the monitor (authorized person) may consult the documentation and that no unauthorized person shall be allowed to attend the videoconference. The sponsor has to establish a standard procedure for such type of monitoring. It is necessary to follow GDPR requirements as well as those of Act No 110/2019 on personal data processing.

Initiation of newly authorised clinical trials / recruitment of new trial subjects (patients)

Always ascertain the current situation at the concerned trial site with the principal investigator/investigator (by phone, e-mail):

- What is the current situation at the given healthcare facility, whether any limiting measures have been imposed therein in relation to the COVID-19 situation;
- What is the personnel situation in the study team conducting the clinical trial or appointed to conduct the clinical trial in question.

The commencement of newly authorised clinical trials and the enrolment of new trial subjects (patients) in ongoing clinical trials must be considered by the sponsor very carefully, always reviewing the risk/benefit ratio. When evaluating the risk/benefit ratio, the current epidemiological situation in the concerned location, the situation at the trial site (staffing and team member capacity), and the grounds for initiation of such clinical trial with regard to the patient safety shall be taken into account.

To protect the safety of the trial subjects:

- When commencing new clinical trials or enrolling new patients/trial subjects in ongoing clinical trials, it is necessary to assess the epidemiological situation at the particular healthcare facility (the condition of health of the CT team members, their capacity available for the conduct of the clinical trial, and, if applicable, imposed restrictions in the particular healthcare facility).
- The sponsor shall forthwith notify SÚKL and the ethics committees of the commencement of a new clinical trial by means of a letter (Section 55(6) of Act No 378/2007 Coll., on Pharmaceuticals, as amended; Section 15(1) of Decree No 226/2008 Coll., on Good Clinical Practice). The letter may be sent to SÚKL electronically, always with the clinical trial identification by the EudraCT Number of SÚKL's file number “sp. zn. sukls”. (Via data mailbox or e-mail: posta@sukl.cz).
- Where the enrolment of new patients to clinical trials is resumed, the sponsor shall be obliged to send this information to SÚKL and to the ethics committee together. The notification is not

subject to reimbursement for expert activities. SÚKL shall confirm (take note of) the receipt of this information.

- Conduct clinical trials involving healthy volunteers or "healthy patients", i.e. such clinical trials that do not provide therapeutic benefit to the enrolled trial subjects, such as bioequivalence or pharmacokinetic studies, shall be possible providing safety measures are in place; at present.
- Recommended safety measures in the commencement of clinical trials with healthy volunteers or clinical trials without therapeutic benefit for the enrolled trial subjects:
    - Take COVID history of the prospective trial subject no more than 4 days prior to invitation to the trial site.
    - Perform an RT-PCR test for the presence of SARS-CoV-2 and evaluate its result prior to the trial subject's enrolment.
    - Take COVID history of all study team members, including laboratory staff who are not in contact with the enrolled trial subjects but who will process biological material taken from trial subject, no more than 34 days prior to invitation to the trial site.
    - Perform an RT-PCR test for the presence of SARS-CoV-2 and evaluate its result for all study team members who are in contact with trial subjects, with the exception of study team members who submit a valid certificate of:
        - Up to 180 days after a laboratory-confirmed positive COVID-19 test
        - Complete COVID-19 vaccination, at least 14 days from receiving the second shot of two-dose vaccine or the first shot of a single-dose vaccine).
    - Safety measures during the conduct of the clinical trial
        - Maximum isolation of individual persons in the course of the study.
        - During hospitalisation, reduce the number of trial subjects in one room to the minimum practicable, no more than 4 persons.
        - Provide protective aids for the staff – single-use masks; for sampling purposes: single-use gowns, respirators or single-use masks + face shields, gloves to be changed by the staff after each trial subject sampling.
        - Minimise the free movement of trial subjects at the trial site, obligatory wearing of masks.
        - For the purposes of catering, define trial subject groups that will remain unchanged throughout the clinical trial (e.g. by rooms). One table shall be occupied by trial subjects from the same room.
        - Provide disinfection at corridors and in rooms.
        - Tighter hygienic and disinfection rules, particularly at sanitary rooms and common areas
        - The included healthy volunteers and study team members are obliged to wear a respirator without an exhalation valve, at least class FFP2 (KN95/N95) in the situation where 2 or more people come into contact at a time. The exception of time for food.

Sponsors are notified to check the validity of SÚKL's authorisation/approval for to-date not initiated clinical trials. In case the expiry of the authorisation/approval of a notified clinical trial is approaching (i.e. 1 year of the date of issue of the authorisation/approval of the clinical trial), it is necessary to re-apply for the issue of the authorisation/approval of a notified clinical trial with SÚKL prior to the expiry date of the application. The handling of such application shall be considered a substantial amendment and is subject to fee.

In case an authorisation/approval of notified clinical trial expires, SÚKL shall not re-issue a backdated authorisation/approval of notified clinical trial and the sponsor will have to submit an application for the issue of a new authorisation/approval of notified clinical trial (resubmission) and cover the full fee for expert activities.

Due to the variability of clinical trials, it is not feasible to cover all potential situations. **Trial subject safety in ensuring data validity, and hence the quality of the clinical trial conduct, is the responsibility of the sponsor; trial subject safety at the trial site is the responsibility of the investigator or principal investigator who is also responsible for the entire study team.**

Act No 378/2007 Coll., on Pharmaceuticals
Section 56(3):
Where any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product arises which may affect the safety of the trial subjects, the sponsor and the investigator shall be obliged to take urgent measures to protect the trial subjects against any immediate hazard. Provisions of paragraphs 1 and 2 shall not be prejudiced hereby. The sponsor shall forthwith inform the Institute and the concerned ethics committees of these new facts and of the measures taken.

SÚKL will not approve or acknowledge the method of securing the investigational medicinal products (IPMs) for trial subjects; the sponsor is only obliged to inform SÚKL and ECs (see citations of the Act on Pharmaceuticals above). Sponsors are asked to notify SÚKL and ECs of all emergency measures concerning ongoing and approved but non-initiated clinical trials in the Czech Republic. SÚKL records all of these measures and enters them in CT documentation. SÚKL will not consider notification of emergency measures as a substantial amendment and will not require the reimbursement of costs.

In case the sponsor needs SÚKL's acknowledgment of the emergency measures notified to SÚKL, we will provide it electronically upon request.
Emergency measures cannot be effective indefinitely; SÚKL hereby defines that the date of termination of the possibility to apply such emergency measures will be announced minimum 14 days in advance.

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
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