Additional Opinion of SÚKL's Department of Clinical Trials on Medicinal Products on Ongoing Clinical Trials in Light of the COVID-19 Epidemiological Situation of 16 March 2020

With reference to the previous SÚKL recommendations of 13 March 2020, please find below additional SÚKL's position on ongoing clinical trials:

Always ascertain the trial subject's situation in advance by phone

- Whether the patient is not in quarantine because he/she visited a risk region (for an updated list of risk regions, please refer to: https://koronavirus.mzcr.cz/staty-sveta-s-vysokym-rizikem-prenosu-nakazy/) or whether he/she has not been in contact with a person with confirmed coronavirus infection
- Whether coronavirus infection has not been confirmed for him/her
- 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 with confirmed receipt of shipment by phone and verification of data accuracy, control laboratory sampling…)

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 – this should apply only to visits that are necessary and cannot be handled "online".
- 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).

The administration of study medication that influences the immune system is not possible/is contraindicated for trial subjects with confirmed coronavirus infection.

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.

2) **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:**
   - 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, agrees to this course of action.

3) **IMP – parenteral administration – i.v. – in the form of bolus or infusion, applied by the doctor at the trial site:**
   - If permissible with a view to the protocol, 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) Where trial subjects need to complete necessary control assessments prior to the IMP administration – such as blood count, biochemistry, urinalysis – and the IMP administration cannot be postponed, the following course of action must be applied:
   - Arrange the date (as well as the time) of the visit to the trial site and completion of the draws beforehand by phone.
   - Arrange for the conduct of draws 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 patients who have been quarantined or share household with a person who has been quarantined or in whom coronavirus infection has been confirmed.

5) As for the return of study medication by the patient to the investigator at the trial site by courier service: in this case, SÚKL considers the sending of unused study medication by courier service inappropriate and requires 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.

6) SÚKL STRONGLY DISCOURAGES the commencement of newly authorised clinical trials and the enrolment of new patients in ongoing clinical trials!

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.

The SÚKL will not approve the method of securing the evaluated products (IPMs) to subjects; the sponsor is only obliged to inform us (see citations of the Act on Pharmaceuticals above)

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. Ondřej Palán, Head of Clinical Trials on Pharmaceuticals Unit (272 185 327, ondrej.palan@sukl.cz).

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