Q & A from workshop of 11 November 2019

1)

Q*: Is it acceptable for the sponsor to submit, as part of application for phase 2 CT authorisation, to-date obtained safety data* for a non-authorised IMP arising mostly from clinical trials in patients with another indication than the one that is the subject of the planned CT?

A: Phase II of clinical trials (hereinafter referred to as "CT") – first-in-man administration in the new indication.

It is necessary to submit data from phase I CTs on the safety and tolerability of the medicinal product that do not have to be linked to the disease, providing it is the same medicinal product (the same manufacturer, the same manufacturing process, the same pharmaceutical form, the same route of administration).

2)

Q: *Is it acceptable to plan the initiation of a phase III CT for tumour diseases with a non-authorised investigational medicinal product (hereinafter referred to as "IMP") practically in parallel with the conduct with its phase II CT (separate protocol rather than an adaptive design including several phases under a single protocol)? At the time of submission of the application for the CT (CTA), only results from phase I studies could be available.*

A: **NO** – we will not authorise a CT for phase III without phase II data; the only exception being CTs on biosimilars, where phase Ii is not required.

3)

Q*: Is the sponsor obliged to reimburse an AMP (auxiliary, non-investigational medicinal product) that is prescribed by the protocol, if taken from the market in the Czech Republic, concerns a commonly available therapy, but in practice other alternative medicines also exist?*

A: In case of an AMP authorised in the Czech Republic and taken from the market in the Czech Republic, the sponsor is not obliged to reimburse this AMP, although prescribed by the protocol. The provision of and payment for medicinal products in the CT should, *inter alia*, be stipulated by the contract concluded between the sponsor/healthcare service provider.

4)

Q:

If the Protocol states that the comparator treatment is to be chosen by the Principle investigator (concerning e.g. corticosteroids), does this need to be specified in Annex 1? If so and there is no specific drug substance defined, how should it be specified? Is it sufficient to state that the drug product will be supplied from the local market in the cover letter?

A:

It is insufficient to include the information (that the medicines will be taken from the local market) only in the cover letter. Even if specific medicinal products are not defined, the Sponsor must specify the active substance(s) in the CTA form. If the possible use of a number of active substances is referred to, each such substance needs to be listed in the CTA form. Furthermore, for each group of products with the same active substance, one of them has to be selected and its Summary of the

Product Characteristics (SmPC) which will be used by the investigators as a guideline for adverse drug reaction reporting has to be presented.

5)

Q: *If sites suddenly run out of the study medication (a centrally supplied authorised drug product) and it is necessary to replace it immediately from the local market, is it necessary to report this forthwith to SÚKL and the EC, or is it sufficient to include the information in the progress report?*

A: At all times, SÚKL must have current information on what drug product is used in the CT.

Required procedure:

- A medicinal product authorised via the centralised procedure, newly supplied from the market within the Czech Republic – notification
- Alternative product from the market within the Czech Republic – substantial amendment, SmPC

6)

Q: *Pursuant to Czech legislation, the investigational medicinal product (IMP) is to be dispensed by the doctor or pharmacist delegated for the "IMP Dispensing" role in the Delegation log, and hence they are the individuals who dispense the IMP to patients/trial subjects. They complete the Dispensing log and the doctor makes an entry in the patient´s card.*

Can this "IMP Dispensing" role be assigned also to a nurse or the study coordinator, if s/he dispenses the medicine on the basis of instructions provided by the investigator? Can a nurse/coordinator complete and sign the Dispensing log (on the basis of information from the investigator) as an administrative act "IMP management (receipt, storage, return, destruction)", if the basic information on the dispensing and return of the medication, patient instruction and compliance are recorded in the patient card by the doctor?

A: Investigational medicinal products (IMP) – may be dispensed only by a pharmacist or provided to the trial subject by the doctor. These are the only persons who may instruct the patient as to how the medicine is to be taken, stored, etc.

Leftover, unused medication – may be received also by the nurse, if the nurse has been appropriately trained to do so, a record of his/her training exists, and the Delegation log states that this activity will be conducted by the nurse and that the nurse is responsible for it.

Records made into Dispensing log – a person appointed by the doctor/investigator, trained + a record of the person´s training.

A CT coordinator without healthcare education may not handle medicines (*dispensing*, *patient instruction*, *etc.*).

7)

Q: *Can the implementation of the CT Regulation bring also the possibility of an electronic informed consent?*

A: Yes, SÚKL, together with the representatives of multicentric ethics committees (MEC) and lawyers, has been drafting a guideline that would allow for electronic informed consent or electronic signature of the informed consent even before the Regulation takes effect.

8)

Q: *Requirements for document approval by MEC, LEC (local ethics committee):*

Is a mere MEC approval of amendments to protocol and updates to the ICF (patient information/informed consent form) without LEC approval sufficient? If so, is there any legal basis to this?

A: Yes, this is sufficient. The multicentric ethics committee (MEC) assesses and approves any documentation and source materials of the CT, except for the centre/trial site and investigator, which are approved by the local ethics committee (LEC). LEC does not approve these documents, but in case of disagreement with an amendment or the ICF, it may revoke its approval of the site or investigator authorisation.

References
Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended,
Section 53. Ethics Committee

(7) In preparing its opinion, the ethics committee shall consider:
a) the relevance of the clinical trial and the trial design;
b) whether the evaluation of the anticipated benefits and risks as per Section 52, paragraph 3 (a) is satisfactory and whether the conclusions are justified;
c) the protocol;
d) the suitability of the investigator and supporting staff;
e) the investigator's brochure;
f) the adequacy of the healthcare facility;
g) the adequacy and completeness of the written information for trial subjects and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research of persons incapable of giving informed consent as regards the specific restrictions laid down in Section 52, paragraphs 2 to 5;
h) provision for compensation or indemnity in the event of death or injury attributable to the clinical trial;
i) any insurance or indemnity to cover the liability of the investigator and sponsor which shall also cover the damages for the event of a death of the trial subject or an injury of the trial subject arising from the conduct of the clinical trial;
j) the amount and, where appropriate, the arrangements for remunerating or compensating investigators and trial subjects and the relevant aspects of any agreement concluded by the sponsor and the trial site;
k) the method of recruiting trial subjects.

Section 54 Opinions of ethics committees on multi-centric clinical trials

(1) Where multi-centric clinical trials to be conducted in the Czech Republic are concerned, the sponsor shall submit the application for an opinion to a single ethics committee for multicentric trials; concurrently, the sponsor shall submit an application for an opinion to the ethics committees established by the healthcare service providers which are the planned trial sites (hereinafter referred to as the "local ethics committee") and shall inform these ethics committees about the ethics committee for multi-centric clinical trials with which the application for an opinion on the relevant clinical trial has been lodged. The application for an opinion must contain details of the sponsor, details specifying the subject-matter of the application, and its rationale. The scope of particulars regarding the application for an opinion and related documentation which are submitted to the ethics committees, details of their evaluation, hand-over of reports and opinions, mutual co-

operation among ethics committees and with the Institute shall be stipulated by an implementing legal regulation.

(2) In its opinion, the ethics committee for multi-centric trials shall assess the facts referred to in Section 53, paragraph 7 (a) to (c), (e), (g) to (k).
(3) The local ethics committee shall provide the sponsor with its opinion on the facts pursuant to Section 53, paragraph 7 (d) and (f) and shall express its final opinion on the conduct of the clinical trial at the given trial site. The local ethics committee shall not be entitled to request changes to the design of the clinical trial and relevant documentation, for which the ethics committee for multi-centric trials has issued its favourable opinion; it shall, however, be entitled to express its rejection of the conduct of the clinical trial at the given site which shall be final. A favourable opinion on the clinical trial issued by a local ethics committee shall be effective only if the ethics committee for multi-centric trials issues its favourable opinion.

9)

Q: *Separate informed consents for sub-studies (such as optional biopsies, post-progression treatment):*
from your point of view, is it acceptable to have the patient sign a consent at the beginning of the study, although the procedure as such takes place sometimes in the future, in the course of the study? Or is a signature granted only immediately before the procedure in questions acceptable, so that it is obvious that it is the patient´s free will and choice at the time of the procedure?

A: Optional informed consents are approved only by ethics committees and so it depends on them what requirements they establish.

10)

Q: *GCP stipulates that patients should be informed about new information in the study "in a timely manner"; does that mean that they should sign the informed consent in the course of the study at the beginning of the visit as the first procedure? Or could this be done any time during the visit, if the information is not essential or does not concern safety and is rather of an informative nature? If patients do not sign the informed consent in the course of the study at the first visit after SÚKL´s and ethics committee´s approval, is that considered a deviation from GCP, or does it depend on how this is defined by the sponsor?*

A: If the patient information sheet/informed consent form (hereinafter referred to as "PIS/ICF") contains safety information, the investigator should provide it as soon as possible.

If the PIS/ICF contains information that could change the patient´s opinion regarding his/her participation in the CT, the trial subject should sign it prior to any procedure during the nearest visit.

If it concerns new information, but only of supplementary nature, it does not matter whether the patient signs at the beginning of the visit or in its course.

11)

Q: *Should the substantial amendment concerning a change to the CT sponsor be lodged by the representative of the existing sponsor, or of the new sponsor? Which documents need to be submitted immediately and which may be updated only upon the next change?*

A: The application is to be lodged by the original sponsor, they are the proprietor of the CT, the application cannot be lodged by anyone else. The application (substantial amendment) has to be submitted prior to the change of the sponsor. A change of the sponsor is governed by Section 59 of

Act No 378/2007 Coll., on Pharmaceuticals, as amended; together with the application, it is necessary to submit an updated application form (CTA form in the PDF + xml. format), powers of attorney and authorisations, and a list of documentation, including versions and dates of origin (*all of the documents handed over to the new sponsor)*.

12)

Q: *Is there any local regulation/provision stipulating that the Sponsor keep the CVs of team members other than the Principle Investigator on file?*

A: Yes, this requirement is stipulated by Annex 3 to Decree No 226/2008 Coll.; equally, this should be stipulated in GCP ICH E6 (R2); it always applies only to the CVs of investigators or sub-investigators, not the other team members.

Annex 3 to Decree No 226/2008 Coll.

Basic documents serving for the purposes of evidencing compliance with the principles of good clinical practice and requirements stipulated by legal regulations

No.	Document title	Purpose of document storage	Stored at the investigator´s or healthcare facility	Stored at the sponsor ´s
I/ 10.	CVs and data on the qualification of the investigator(s) and sub-investigators, if applicable.	To evidence the qualification and competence to conduct the clinical trial	X	X

13)

Q: *Is it possible for a healthcare facility to refuse monitors access to the facility´s electronic system, giving the reason that the system is intended solely for the purposes of the healthcare facility? The monitor therefore cannot access data in the electronic system.*

A: Yes, a healthcare facility may refuse to grant permission to view a computer record, unless the computer record constitutes the source data and the source data are available as printed out, signed and dated sheets. It is therefore advisable to keep this in mind when drafting the contract between the Sponsor and the healthcare provider so that such situations may be prevented.

Clinical trials of Pharmaceuticals Unit 6.3.2020