Clinical Trial Protocol (model)

information on clinical trial MODEL protocol

This protocol model has been designed mainly for non-commercial clinical trials which are subject to Regulation 536/2014 of the European Parliament and of the Council (Clinical trials on medicinal products for human use), the Clinical Trials Regulation (CTR). The model is available for use by all investigators who are carrying out clinical trials if they so wish, however there is no requirement to use it.

Advisory text and quotations from GCP and the CTR are in parentheses *i.e.* < >. All of these should be deleted before finalising the document.

All sample text is in ‘*Italic’* style. This text should be altered or deleted as required while the draft is being developed.

The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.

study title

<Insert the title of the study>

Reference numbers

*EU trial number:*

*Sponsor’s protocol code number:*

*Date and version number:*

study sponsor

<Insert the name of the sponsor (=coordinating or principal investigator in non-commercial studies)>

compliance Statement

*This trial is to be conducted in compliance with this protocol, with the Regulation 536/2014 of the European Parliament and of the Council and with the principles of Good Clinical Practice.*

confidentiality statement

*This document contains confidential information that must not be disclosed to anyone other than the sponsor, the study team, regulatory authorities, and members of the Ethics Committee.*

contact details

|  |
| --- |
| Contact detailsChief investigator/ Co-ordinating investigatorName/title: Contact details: Principal Investigators Name(s)/ titles: Contact details:Sponsor Name: Contact details:Funder(s) :Name:Contact details: |
| Signatures<The sponsor and the principal investigator(s) responsible for conducting the trial should sign the protocol. Site-specific information may be provided on separate protocol page(s).><Name and title and position in the company of the person(s) authorised to sign the protocol and the protocol modification(s) for the sponsor should be included.> |
| Other relevant information<Include other important information as necessary (e.g. name, title, address, and telephone and fax number(s) of the sponsor's medical expert for the trial; name, contact details of contract research organisation/study monitor; name and contact details of medical/safety monitor if other than the sponsor; name and contact details of central laboratories and/or technical departments, statistical and data management etc.)> |

document history

<Details of all protocol amendments should be included in this section whenever a new version of the protocol is created.>

|  |  |  |
| --- | --- | --- |
| **Document** | **Date of Issue** | **Summary of Change** |
|  |  |  |
| Protocol version no. | <Insert date> | <Describe changes> |
| Original protocol | <Insert date> | Not applicable |

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1. synopsis

<A brief synopsis (usually limited to 3 pages) that summarises the study should be provided. An example is presented below.>

|  |  |
| --- | --- |
| Title of study |  |
| Name of sponsor/company |  |
| Phase of development |  |
| Objectives |  |
| Trial design |  |
| Key inclusion criteria |  |
| Key exclusion criteria |  |
| Number of subjects |  |
| Test product, dose and mode of administration |  |
| Duration of treatment |  |
| Statistical methods |  |
| Sample size |  |

1. abbreviations and definition of terms

<A list of the abbreviations should be provided. Examples of abbreviations are listed below, amend as appropriate.>

<An excessive use of abbreviations may be counterproductive.>

AxMP Auxiliary medicinal product

CA Competent authority

CRF Case report form

CRO Contract research organisation

GCP Good Clinical Practice

IB Investigators brochure

ICF Informed consent form

IMP Investigational medicinal product

RSI Reference Safety Information

SAE Serious adverse event

SAR Serious adverse reaction

SmPC Summary of product characteristics

SOP Standard operating procedure

SUSAR Suspected unexpected serious adverse reaction

<Explain non-standard terminology>

1. introduction

<The introduction should be concise. It should provide background information sufficiently to allow reasoning if the prospective trial and methodology therein are justified. An excessive review of literature is best avoided.>

* 1. Background information

<Briefly describe the main characteristics of the disease being studied and currently available treatment.>

<Include a summary of results from nonclinical studies that have potential clinical significance.>

<Include a summary from relevant clinical trials.>

<Describe the population to be studied.>

<Provide discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference list to be inserted later).>

* 1. Rationale for the study

<Identify the problem to be studied (e.g., justify unmet medical need, describe limitations of knowledge). Describe your hypothesis. Justify and discuss the selection of control.>

<Include a name, description and characteristics of the investigational medical product(s) to be studied in this clinical trial.>

<Include a discussion of known risks and benefits, if any, to human subjects.>

<Description of and justification for the route of administration, dose, dosage regimen, and treatment period(s) of the investigational and the auxiliary medicinal products>

<Where patients were involved in the design of the clinical trial, describe their involvement>

1. study objective

<Include a description of the objectives and the purpose of the trial.>

<The objectives of the study are the questions that the study is intended to answer and are based on the hypothesis formulated.>

<Usually there is only one primary objective and a few secondary objectives.>

* 1. Primary objective

<The primary objective is the main question to be answered by the study.>

<Example: to quantify the efficacy of X compared with placebo in subjects with <insert condition>>

* 1. Secondary objective

<Secondary objectives are additional questions to be addressed.>

<Example: to identify safety issues of treatment X in subjects with <insert condition>>

* 1. Exploratory objectives

< Include exploratory objectives, if needed>

* 1. Primary and secondary/exploratory endpoints/outcome measures

<Give a general description the endpoints/outcome measures and how/when they will be measured during the trial. Examples:

* the change in blood pressure (mmHg) measured from upper extremity from baseline to month X
* time (days) to first onset>

<Primary endpoints should be capable of measuring the primary objective of the study. Choice of primary endpoint must be justified. Primary endpoint is used in calculation of sample size and will be used to decide the overall results or ‘success’ of the trial. Secondary endpoints provide supportive data only.>

<Assessments of endpoints/outcome measures (for example efficacy and safety assessment) should be described in detail in section 8.5>

1. trial design
	1. General considerations

<The overall study plan and design of the study e.g., multicentre, randomised, double-blind, placebo-controlled, parallel design or cross-over, open labelled, phase I, II, III, IV etc should be included. List the countries in which the trial will take place.>

<It is usually helpful to display the design of the study graphically.>

Figure 1: Study Schema

**Follow up**

**Investigational Arm**

RANDOMISATION

EN

ROLMENT

**Control Arm**

**Follow up**

<Include a description of the sequence and duration of all trial periods, e.g. screening period, treatment period, post-treatment follow-up period and provide the expected duration of subjects’ participation and the number of visits. Describe the dose and mode of administration of investigational medicinal products and comparator.>

<Discussion of the trial design>

* 1. Selection of study population
		1. Overall description of trial subjects

<Give an overall description of the trial subjects. Justify the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, explain the reasons and justify these exclusion criteria. Describe the presence or absence of a medical condition/disease of subjects.>

<Provide a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors>

* + 1. Inclusion criteria

<Include an introductory clause – e.g, that subjects meeting all the criteria below may be included in the study.>

*To be eligible for inclusion, each subject must meet each of the following criteria at Screening and must continue to fulfil these criteria at Baseline (Visit 1).*

<List as many criteria as necessary to clearly define your study population.>

<If men and women of reproductive capability will be enrolled, indicate whether contraception is required. If yes, include details of allowable contraception methods for the trial (see CTFG Recommendations related to contraception and pregnancy testing in clinical trials).>

<Example criteria, amend as appropriate:>

* *Written informed consent*
* *Aged 18 years or older at screening*
* *Diagnosed with* <disease of a particular severity or duration>
* <if healthy volunteers> *Good general health based upon the results of the medical history, laboratory tests, physical examination, and 12-lead ECG as assessed by the investigator*
* *not of childbearing potential or willing use effective contraception during the study and for* <\_\_> *months thereafter*

<Add additional study specific criteria as required.>

* + 1. Exclusion criteria

<Include a statement that all candidates meeting any of the exclusion criteria at screening/ baseline will be excluded from study participation and then list each criterion.>

*Subjects are excluded from the study if any of the following criteria is met at Screening or at Baseline:*

<Example criteria, amend as appropriate:>

* *Allergy or hypersensitivity to study medications or their ingredients*
* *Pregnancy or breast-feeding, aim of becoming pregnant during the study.*
* *Participation in another study and receipt of any other investigational agent within <*include time frame*>*
* *Inability to provide written informed consent*
* *Any significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk by participation in the study, or may influence the result of the study.*
* *A history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements.*
* *Known history of, or documented positive hepatitis B or C or HIV infection*
* *Prior or concurrent malignancy*
* *Aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3 x upper-limit of normal*
* *Creatinine clearance (CrCl) < 60 ml/min measured by 24-hour urine collection or estimated from the Cockcroft and Gault formula*
* *Clinically significant ECG findings as judged by the investigator*

<Add additional criteria as required.>

* + 1. Restrictions during the trial

<Describe possible restrictions (e.g. those regarding diet or strenuous physical activity) that apply during the trial.>

*Concomitant medication and therapy are discussed in section 6.7.*

* + 1. Withdrawal of subjects from treatment

<Criteria for withdrawing individuals from treatment or the trial>

* 1. Randomisation and blinding
		1. Randomisation

<Include a detailed description of the randomisation method to be used in the study, how randomisation is going to be carried out, and who will provide the randomisation codes.>

<If not randomised, describe the methods used to assign subjects to treatment groups.>

* + 1. Blinding

<Describe the specific procedures used to carry out blinding.>

<Include arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant.>

<Include a statement that the study will be conducted in a double-blind fashion. Study treatment assignment will be blinded for both the investigators and the subject.>

<Include the circumstances in which the blind would be broken for an individual or for all subjects, e.g., for serious adverse events>

<Any intentional or unintentional breaking of the blind will be recorded and reported to the sponsor as soon as possible.>

* 1. Study assessments and procedures

*The schedule of assessments in the trial is summarised in Table 1.*

<Describe all study assessments and procedures in detail. Include detailed schedule of assessments. Provide an outline of all the study visits, procedures to be done during the study, follow-up after the study and discontinuation visit.>

<In the study procedures and assessments, if applicable, windows should be defined outside of which the occurrence of the procedure/assessment would constitute a protocol violation.>

<Include a statement that informed consent will be obtained prior to any study-related procedures being undertaken>

<Estimate the duration of participation in the trial and, when applicable, duration of various trial periods>

Table 1. Schedule of events <amend as applicable>

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedures | Screen | Visit 1Baseline | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6End of Treatment | Visit 7Follow up |
| Day |  | D1 | Dxx±y d | Dxx±y d | Dxx±y d | Dxx±y d | Dxx±y d | Dxx±y d |
| Eligibility Criteria | ● | ● |  |  |  |  |  |  |
| Informed consent | ● |  |  |  |  |  |  |  |
| Medical history | ● | ● |  |  |  |  |  |  |
| Physical examination  | ● | ●a | ●a | ●a | ●a | ●a | ●a | ● |
| Vital signs | ● | ● |  |  |  |  | ● | ● |
| Viral serology | ● |  |  |  |  |  |  |  |
| Haematology and chemistry | ● | ● |  |  |  |  | ● | ● |
| Electrocardiogram | ● |  |  |  |  |  |  |  |
| Pregnancy testb | ● | ● |  |  |  |  |  |  |
| Randomisation |  | ● |  |  |  |  |  |  |
| Dispensing of study medications  |  | ● |  | ● |  | ● |  |  |
| Concomitant medications | ● | ● | ● | ● | ● | ● | ● | ● |
| <Assessment (describe)> |  | ● | ● | ● | ● | ● | ● | ● |
| <Assessment (describe)> |  | ● | ● | ● | ● | ● | ● | ● |
| <Assessment (describe)> |  | ● | ● | ● | ● | ● | ● | ● |
| Adverse events  |  | ● | ● | ● | ● | ● | ● | ● |
| Medication compliance  |  |  | ● | ● | ● | ● | ● |  |

aper investigator’s discretion bin females of childbearing potential

* + 1. Description of Study Assessments

<Provide details as appropriate.>

<Demographics: Age, gender and ethnicity will be recorded.

Physical Examination: The physical examination will include the evaluation of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems. Height, weight and axillary temperature will be recorded.

ECG: One ECG including a 12-lead examination will be performed at Screening. Abnormal findings will be noted for clinical significance. The report will be signed by the investigator.>

* + 1. Endpoints assessments

<Describe the end-points assessments briefly.>

Efficacy Assessment

<Describe how the efficacy assessments/outcome measures are measured, in detail. Examples:

* Take blood pressure (mmHg) twice with at least 3 minutes apart after at least 10 min rest from non-dominant upper extremity in a subject in supine position
* Ask if the subject has had <event> since last visit and document details <describe which details> and time (date), duration>

Safety Assessment

<Describe the safety parameters/assessments and their timing>

<The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, and laboratory assessments.>

* 1. Study visit structure
		1. Screening procedure

<Describe in detail the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent>

<Include a statement that informed consent will be obtained prior to any study related procedures being undertaken>

<Describe pre-screening procedures. Discuss the sequence of events that should occur during Screening and the decision points regarding eligibility. List the framework prior to recruitment within which screening tests and visits must be done, e.g. what the maximum duration allowed between screening and randomisation is. Describe all procedures that must be completed before the subject can be included into the study.>

<Consider including that during the screening period, subjects will be evaluated for eligibility. Date of screening, subject age, gender and reason for ineligibility (if subject is not eligible) will be recorded. The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to continue in the study.>

* + 1. Baseline assessments (Visit 1)

 <Specify and describe all baseline assessments and interventions at baseline visit>

* + 1. Visit 2 (3, 4, 5…)

<Describe all the visits and procedures that must be performed during the study treatment phase. Specify if they are clinic visits or telephone assessments. Add visit numbers and window periods if applicable.>

<For each visit, consider:

* eligibility check
* assessment of efficacy outcome measures
* assessments of safety (adverse event monitoring, vital signs, laboratory assessments)
* dispensing of study medications
* recording of concomitant medications
* assessment of compliance with study medications

A detailed description of each of the assessments, if not covered anywhere else in the protocol should be included here.>

* + 1. End-of-Treatment visit

<Specify and describe all assessments and procedures at end-of-treatment visit>

* + 1. Follow-up visit

<Specify and describe all assessments and procedures at follow-up visit>

* 1. End-of-trial
		1. Definition

<A clear and unambiguous definition of the end of the clinical trial in question and, if it is not the date of the last visit of the last subject, a specification of the estimated end date and a justification thereof>

<The Sponsors and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.>

<The end-of-trial is the date of the last visit/telephone follow-up/ home visit of the last subject. The end of study visit form should include:

* assessment of endpoints/outcome measures
* assessments of safety
* assessment of compliance with study treatment(s)
* recording of concomitant medications>
	+ 1. Premature termination of the study

<Describe the criteria for terminating the study prematurely and the procedures that will take place if the study is terminated prematurely.>

<Include a statement of the reasons that the study or a part of the study may be stopped e.g. new information about safety or efficacy, unsatisfactory progress of the study or other (specify).>

<Include all procedures and assessments related to the end-of-study visit.>

* + 1. Reporting the end of trial

<The end of the study in the member state concerned shall be reported through the EU portal within 15 days from the end of the clinical trial in relation to that Member State. The end of the study in all the member states concerned shall be reported in the CTIS within 15 days from the end of the clinical trial in the last Member State concerned.>

* 1. Discontinuation/withdrawal of subjects from study protocol

*Participants have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The participant is not obliged to disclose the reason for discontinuation. The investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study at any time if it is in the best interest of the subject.*

*Subjects must discontinue the investigational medicinal product(s) and be withdrawn from the study for any of the following reasons* <amend as required>*:*

* *withdrawal of consent by the subject*
* *any medical condition that the investigator or sponsor determines may jeopardize the subject’s safety if she or he continues receiving the study treatment*
* *pregnancy*
* *ineligibility (either arising during the study or retrospectively having been overlooked at screening)*
* *an adverse event which requires discontinuation of the study medication*
* *treatment failure and disease progression*
* *lack of compliance with the study or study procedures (e.g., dosing, study visits)*
* *lost to follow-up <*include a statement that at least 3 documented attempts must be made to contact any subject lost to follow-up*.>*

<Describe procedures relating to the withdrawal of subjects from treatment or from the clinical trial including procedures for the collection of data regarding withdrawn subjects, and the follow-up of subjects that have withdrawn from treatment or from the clinical trial>

*If a subject is withdrawn before completing the study, the reason for withdrawal shall be entered on the appropriate case report form (CRF) page.*

*If a subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised.*

<Describe if withdrawn subjects will be replaced and the procedures for replacement of subjects.>

* 1. Participant care after the trial

<Include a description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question.>

<Comment the possibility of continued access to trial medication>

1. treatment of trial subjects
	1. Description of study treatment(s)

<Describe the study treatment(s) including placebo and comparator if used plus all the auxiliary medicinal products.>

<Detail the full name, generic name and trade name of the study treatments if appropriate and the dosage form *e.g.* tablet, capsule etc.>

<Describe the marketing authorisation status of the medications and whether they are used per the terms of marketing authorisation>

<Describe the dosage and administration of study medications. Include the rationale for the dosage. Mention, whether the IMP should be taken in fasting or in fed conditions >

* 1. Formulation, packaging and handling

<Describe the dosage form, packaging, and labelling of the study treatment(s).>

<Detail the name and address of the company that will supply the study treatment(s).>

<Detail the name and address of the company or pharmacy performing any additional packaging that may be necessary and study labelling (if appropriate).>

<For labelling requirements, refer to Annex 13 (EU Guidelines to Good Manufacturing Practice, Investigational Medicinal Products).>

* 1. Storage and disposition of study treatment(s)

<Describe the storage conditions and the storage arrangements of the study treatment.>

<Storage conditions prior to and, if necessary, after product preparation or reconstitution must be precise. The time to administration after preparation/reconstitution must be specified>

<Describe the procedures for checking that appropriate temperatures are maintained.>

*The study treatments will be stored and locked in a secure place until they are dispensed for subject use or are returned to the sponsor.*

*The investigational products are for investigational use only and are to be used only within the context of this study.*

* 1. Accountability of the study treatment(s)

<Describe how medication, including the placebo/comparator will be accounted for. Usually, a table of distributed and returned number of *e.g.* tablets, with dates and package identification number, per each subject is sufficient for documenting the accountability.>

<Describe the procedures for the shipment, receipt, disposition, return and destruction of the investigational medicinal products.>

<Describe the arrangements for tracing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product>

<Describe how study treatment accountability/compliance will be monitored.>

*The study medication will be supplied to pharmacy by* <provide details of the company> *and retrieved at the end of the study.*

*The investigator is responsible for the control of the treatment(s) under investigation. Adequate records for the receipt and disposition of the IMP must be maintained.*

*The investigator will use a standard prescription manner of the institution and the investigator/research nurse will collect the medication from the pharmacy.*

*Accountability and subject compliance with study treatments will be assessed by maintaining dispensing and return records*.

* 1. Assessment of compliance

<Describe how compliance is assessed. Will the subjects be asked to bring all unused or part-used medication/vials and packaging from used medication at each visit? >

<Define significant non-compliance and what procedures will be taken if there is significant non-compliance.>

*The investigator is responsible for ensuring that the study treatment is administered in compliance with the protocol. Subject compliance will be assessed by maintaining dispensing records*.

* 1. Overdose of study treatment

<Describe how the overdose of a study treatment will be handled.>

* 1. Prior and concomitant treatment

*Any non-study medication during the trial will be recorded on the CRF.*

<Consider therapies other than medication, to be recorded>

<Describe the timelines for documenting medications and other therapy (*e.g.* from the date the subject signs informed consent to the last visit).>

* + 1. Permitted medications

<Describe other medications and other therapies which will be allowed before and during the study.>

* + 1. Prohibited medications

<List any contraindicated medications and therapies and check that they correspond with the exclusion and withdrawal criteria. Comment on what will happen if a prohibited medication is taken during the study. Can subjects participate in any investigational treatment studies while participating in this study?>

1. safety reporting

<Include a statement that the safety and tolerability will be evaluated throughout the study based on adverse events, laboratory values, vital signs and physical exam findings *etc.*>

<Refer to the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) or an updated guidance while preparing this section.>

* 1. Definitions
		1. Adverse event

Adverse event is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, even if not considered related to the medicinal product.

* + 1. Adverse reaction

All untoward and unintended responses to a medicinal product related to any dose count as adverse reactions. The phrase ‘responses to a medicinal product’ means that a causal relationship between a study medication and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

* + 1. Serious adverse event (SAE)

*Any untoward medical occurrence or affect that at any dose:*

* *results in death,*
* *is life-threatening\*,*
* *requires hospitalisation or prolongation of existing hospitalisation,*
* *results in persistent or significant disability or incapacity,*
* *is a congenital anomaly or birth defect*
* *counts as an important medical event\*\**

\*Regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

\*\*Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition

* + 1. Suspected unexpected serious adverse reactions (SUSARs)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised medicinal product.

* 1. Evaluation of adverse events and SAEs
		1. Assessment of seriousness

The investigator should assess seriousness as defined in section 7.1.3.

* + 1. Assessment of causality

*All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor.*

*All adverse events judged as being related to an interaction between the study medication and another medication will also be considered adverse reactions.*

*Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.*

* + 1. Assessment of intensity

<A generally acceptable grading of severity should be used. In oncology, Common Terminology Criteria for Adverse Events (CTCAE) should be followed.>

*The investigator will assess severity for each adverse event and record this on the CRF according to one of the following categories:*

*Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.*

*Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.*

*Severe: An event that prevents normal everyday activities.*

<Note: the term ‘severe’, should not be confused with ‘serious’ which is a regulatory definition based on subject/event outcome or action criteria>

* + 1. Assessment of expectedness

<The expectedness of an adverse reaction will be determined by the sponsor according to the reference safety information *e.g.* a dedicated chapter in investigator's brochure for a non-authorised investigational medicinal product, or the summary of product characteristics, chapter 4.8 for an authorised medicinal product which is used according to the terms and conditions of the marketing authorisation.>

* + 1. Emergency unblinding procedures

<If the study is blinded, detail the procedures for the breaking of the study blind, who can perform this, where details of contacts for unblinding can be found etc.>

* 1. Reporting procedures for all adverse events

*All adverse events occurring during the study observed by the investigator or reported by the subject will be recorded on the CRF.*

*The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken. Follow-up information should be provided as necessary.*

*Adverse events considered related to the study medication as judged by an investigator or the sponsor will be followed until resolution or until the event is considered stable. All related adverse events that result in a subject’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.*

*It will be left to the investigator’s clinical judgment whether an adverse event is of sufficient severity to require the subject’s removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.*

Any pregnancy occurring during the clinical study and the outcome (e.g., delivery of healthy child at term, spontaneous abortion) of the pregnancy should be recorded and followed-up.

* 1. Reporting procedures for serious adverse events

*The investigator will report all serious adverse events immediately to the sponsor except for* <those that the protocol or investigator’s brochure identifies as not requiring immediate reporting>. *The immediate report will be followed by detailed, written reports. The immediate and follow-up reports will identify subjects by unique code numbers assigned to the latter. The immediate report will be made by the investigator to the sponsor within 24 h following knowledge of the serious adverse event.*

*All SAE information must be recorded on an SAE form and sent expeditiously to the sponsor. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and sent expeditiously to the sponsor.*

*The sponsor will keep detailed records of all adverse events reported by the investigator or investigators.*

*In cases where reporting is not required immediately the investigator will report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the investigator’s brochure.*

<The academic sponsors will report all SUSARs to the competent authorities concerned, *i.e.* to Fimea, using CIOMS-I template. Commercial sponsors report SUSARs directly to EudraVigilance database. Fatal or life-threatening SUSARs must be reported within 7 days. SUSARs which are not fatal and not life-threatening are to be reported within 15 days. The sponsor will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.>

*If the initial report is incomplete, e.g. if the sponsor has not provided all the information within seven days, the sponsor will submit a completed report based on the initial information within an additional eight days.*

*If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information will be reported as a follow-up report within 15 days.*

<For further information regarding reporting requirements refer to detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’).>

*In addition to the expedited reporting above, the sponsor shall submit once a year throughout the clinical trial or on request, a safety report to the competent authority and ethics committees. The annual safety report will be presented in the DSUR format as per ICH guideline E2F - Note for guidance on development safety update reports.*

<If a study specific safety monitoring committee is to be used, describe arrangements for SAE reporting here. Include emergency reporting contact details.>

* 1. Data safety monitoring board

<The composition of the data safety monitoring board (DSMB) should be described, and it should be clear that no member has a conflict of interest with the sponsor or company involved in the study. Criteria on which the DSMB may recommend terminating the trial prematurely should be clearly defined before the trial has started.>

<See the EMA Guideline on Data Monitoring Committees for assessing the need for a DSMB and for information on the establishment of a DSMB and their working procedures.>

<If other committees, for example, Steering Committees or Endpoint Adjudication Committees are established describe the role, composition and responsibilities of these committees.>

* 1. Pregnancy

<Pregnancy is not considered an adverse event or SAE. However, the investigator shall collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study.>

<The investigator should record the information on a Pregnancy Notification Form and submit this to the sponsor.>

<Any pregnancy that occurs in a trial subject or a trial subject’s partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery.>

1. statistics

<Refer to the ICH E9 (Statistical principles for clinical trials) and ICH E9 (R1) (Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials) guidelines>

* 1. Description of statistical methods

<Describe the statistical methods to be employed, including timing of any planned interim analysis(es). Describe the level of confidence to be used (e.g. 95% confidence interval (CI)). Describe also possible data transformations (e.g. log transformation of PK parameters).>

*Continuous variables will be summarised by number of patients, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by counts and percentages.*

* 1. Determination of sample size subjects

<State the approximate number of subjects required to complete. The number of subjects required for the study should be justified.>

<The number of subjects should always be large enough to provide a reliable answer to questions addressed and is usually determined by the primary objective of the trial.>

<If the sample size is determined on some other basis, this should be made clear and justified.>

<There are many formulae to calculate the size of the study population. It should be clear which method is used and the reasons why this method has been chosen. Also, the calculation itself should be given with a predefined p-value (usually 5%) and power.>

* 1. Analysis sets

<The set of subjects whose data are to be included in the analyses should be defined in the statistical section of the protocol, e.g. intention-to-treat, per protocol, safety >

* 1. Demographic and baseline disease characteristics

<Describe how the demographic and baseline disease characteristics will be analysed.>

*Demographic and baseline disease characteristics will be summarised descriptively by treatment group (treatment sequence).*

* 1. Efficacy analysis
		1. Primary efficacy endpoint

<Describe how the primary efficacy endpoint is derived and describe the planned analysis. Describe also possible subgroup and sensitivity analyses. Include information regarding an interim analysis, when necessary.>

* + 1. Secondary efficacy endpoints

<Describe how the secondary efficacy endpoints are derived and describe the planned analyses.>

* 1. Safety analysis

<Describe how the safety endpoints are analysed (descriptively or using a statistical model). Include for example: adverse events, vital signs, physical examination, clinical laboratory analysis.>

* 1. The level of statistical significance

<State the level of significance to be used. Describe handling of potential multiplicity issues>

* 1. Criteria for the termination of the trial

<Describe>

* 1. Procedure for accounting for missing, unused and spurious data

<Describe>

* 1. Procedure for reporting any deviation(s) from the original statistical plan

<Procedures for reporting any deviations from the original statistical plan should be described and justified>

1. direct access to source data/documents

*Direct access to study documents and source data will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.*

1. data handling and record keeping
	1. Data collection, source documents and case report forms

<Briefly discuss where data will be entered stored and handled>.

<Define what will comprise source documents.>

<Describe the procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data>

*Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. All data entered on CRFs must be entered legibly. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the investigator.*

*Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.*

*All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.*

* 1. Data reporting

<Describe method of data entry/management. Identify any data that is recorded directly on the CRF, *i.e.*, there is no prior written or electronic record of data that would be considered ‘source data’.>

<Include that the participants will be identified by a study specific subject number or code in the database. The name or any other identifying detail will not be included in any study data file.>

1. retention of essential documents

<Essential documents should be retained for at least 25 years from study end. The investigator and institution should agree to retain the trial-related essential documents as required by the applicable regulatory requirements and until the sponsor informs the investigator or institution these documents are no longer necessary>.

1. quality control and quality assurance procedures

<Discuss the measures undertaken to ensure that the data obtained from this research are accurate, complete, and reliable.>

<Describe measures in data management to ensure the data frozen will be free of errors. These may include *e.g.* double data entry and automated plausibility checks.>

<Describe arrangements for GCP monitoring.>

1. audits and inspections

*<This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.>*

1. ethical considerations

<Note: ethics committee requirements should be considered in preparing this section>

* 1. Declaration of Helsinki

*The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.*

* 1. Good Clinical Practice

*This study will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and set out in directive 2005/28/EC as well as in accordance with the ethical principles underlying European Union Regulation (EU) No 536/2014.*

* 1. Approvals

*Required documents including the protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other required documents will be submitted to* <a recognised research ethics committee> *and the competent authority for written approval.*

*The sponsor will submit and obtain approval from the above parties for substantial modifications to the original approved documents.*

<Describe organisational approval procedures of study sites for studies.>

* 1. Informed consent

<Specify who will take informed consent, how and when it will be taken. Informed consent should be obtained prior to any study related procedures being undertaken.>

<Include a statement that the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent form.>

<A representative subject information leaflet and a sample subject consent form can be attached as a separate document.>

* 1. Benefits and risks assessment

<Give a justification of the proposed study.>

<For studies with capacitated adults and therapeutic research with minors and incapacitated subjects, it should be explained why the risk to and burden for the subject will be in proportion to the potential value of the research and, if applicable, it should be stated to what extent the research may be beneficial to the subject.>

<In case of non-therapeutic research with minors and incapacitated subjects it should be stated why the risks and the burden associated with participation can be considered minimal.>

* 1. Subject confidentiality

<A description of the arrangements to comply with the applicable rules on the protection of personal data. In particular, organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed should be described.>

<A description of measures that will be implemented to ensure confidentiality of records and personal data of subjects. A description of measures that will be implemented in case of data security breach to mitigate the possible adverse effects.>

*The trial staff will ensure that the subjects’ anonymity is maintained. The subjects will be identified only by initials and a subject’s identification number on the CRF and any database. All documents will be stored securely. The study will comply with the EU General Data Protection Regulation 2016/679.*

*The sponsor shall be notified immediately upon a data security breach observed. The sponsor will promptly analyse the case and notify regulatory bodies as indicated.*

* 1. Retention of biological samples

<A description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document>

* 1. Other ethical considerations

<Include any other ethical considerations specific to the study, such as frequency and duration of visits and assessments, volume and frequency of blood draws, restrictions.>

1. financing and insurance

<Describe financing and insurance arrangements. >

<*Xx holds an insurance (‘potilasvahinkovakuutus’) and the (commercial) sponsor has taken a specific Clinical Trial insurance which apply to this trial.*>

<Y is funding this trial.>

1. clinical study report and publication policy

<Include who will sign the study report. Describe the publication policy.>

*A summary report of the study will be provided to the CTIS portal within a year after the end of the trial.*

1. references

<Insert references used in text.>