|  |
| --- |
| <Official Title>  Clinical Study Protocol  <Version number and date> |

*Instructions on how to fill in this document have an orange color or are described in comment bubbles and should be removed once the protocol is completed. Text placed between <> indicates that something must be filled in at that place in the document. Ensure to remove the <> symbols once the correct item is filled in.*

*If a section is not applicable, please state ‘N.A.’ in the section (no sections or headers should be deleted)*

*All draft versions should be numbered 0.1, 0.2, etc. The final version for initial submission should be numbered 1.0.*

*Some trials will not fit easily into this template protocol, because they have a very unusual design or organization. In this case you may need to significantly deviate from the template. We advise prior discussion with HIRUZ CTU in these situations;*

*For clarity: this template was created for mono-national trials that will only be conducted in Belgium. We advise prior discussion with HIRUZ CTU if you want to conduct an international trial with participating sites in other countries (as well).*

# General Study Information

|  |  |
| --- | --- |
| Short Title |  |
| Acronym / Protocol code |  |
| EU reference number | *The European Union (EU) reference number will be provided by HIRUZ CTU, if applicable* |
| Phase of the trial |  |
| Sponsor |  |
| Financial/Material support | *Institutions (corporations, governments, etc.) that provide any type of support should not be listed as sponsor, but should be mentioned here.* |
| Coordinating Investigator |  |

<Official Title>

Protocol Coordinating Investigator signature page

*Note: The coordinating investigator is the leading investigator of the trial to whom all local principal investigators (of each participating center) should report, regarding the trial. He/she can also be the principal investigator in his/her own site.*

I certify that I will conduct the trial in compliance with the protocol, any modifications, GCP and the declaration of Helsinki, the CTR and all other applicable regulatory requirements.

**Investigator:**

|  |  |
| --- | --- |
| Name: |  |
| Function: |  |
| Institution: |  |

|  |  |
| --- | --- |
| **Date:** |  |
| **Signature:** |  |

<Official Title>

Protocol Site Principal Investigator signature page

I certify that I will conduct the trial in compliance with the protocol, any modifications, GCP and the declaration of Helsinki, the CTR and all other applicable regulatory requirements.

|  |  |
| --- | --- |
| Name: |  |
| Function: |  |
| Institution: |  |

|  |  |
| --- | --- |
| **Date:** |  |
| **Signature:** |  |

# Protocol Modification History

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Description of modification** |
| 1.0 |  | Initial version to Regulatory Authorities (RA). |
|  |  |  |

*Please list all modifications to the protocol and describe the changes.*

*This means that all of the following need to be listed in the table:*

* *Substantial modifications;*
* *Non-substantial modifications but changes which are relevant for the supervision of the clinical trial by the Member State Concerned (MSC) (Clinical Trial Regulation (CTR) art. 81.9); as well as*
* *Non-substantial modifications;*

*Protocol version number of a substantial modification should be 2.0, 3.0, etc. Protocol version number of a not substantial modification should be 2.1, 2.2, 2.3, etc.*

*Do not list draft versions, only versions that are (to be) submitted to the RA.*

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# Introduction

## Rationale

*State the problem or question (e.g. describe the population, disease, current standard of care and limitations of knowledge or available therapy) and the reason for conducting the clinical trial.*

***Specify the hypothesis of the trial.***

## Background

*This section should include:*

* *A summary of findings from non-clinical studies that potentially have clinical significance;*
* *A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies;*
* *Discussion of important literature and data that are relevant to the trial and that provide background for the clinical trial;*
* *Applicable clinical, epidemiological, or public health background or context of the clinical trial;*
* *Relevance of the clinical trial and any relevant treatment issues or controversies;*
* *Ethical considerations relating to the clinical trial.*

## Risk/Benefit assessment

*Include an assessment of the known and potential risks and benefits, addressing each of the following:*

* *Rationale for the necessity of exposing subjects to risks and a summary of the ways that risks to subjects were minimized in the trial design;*
* *Justification as to why the risks of participation in the trial outweigh the value of the information to be gained.*

## Patient participation in trial design

*Describe if patients were involved in the design of the clinical trial, and if so, a description of their involvement.*

# Objectives

*An objective is the purpose for performing the trial in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g. to assess, to determine, to compare, to evaluate) and include the general purpose (e.g. efficacy, effectiveness, safety) and/or specific purpose (e.g. dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, health behavior).*

*Define the primary research question; address a specific hypothesis:*

* *the hypothesis which should be stated in quantifiable terms; e.g. “the experimental treatment will result in 12 months of additional survival compared to the control treatment”;*
* *the null and the alternative hypotheses;*
* *for multi-arm studies, the objectives should clarify the way in which all the intervention groups will be compared (e.g. A versus B, A versus C).*

*The PICOT criteria are a useful guide in the development of a specific research question:*

* *P – Population (subjects)*
  + *What specific subject population are you interested in?*
* *I – Intervention*
  + *What is your investigational intervention?*
* *C – Comparison Group*
  + *What is the main alternative to compare with the intervention?*
* *O – Outcome of interest*
  + *What do you intend to accomplish, measure, improve or affect?*
* *T – Time*
  + *What is the appropriate follow-up time to assess outcome?*

## Main objectives

*Provide a description of the main study objective(s), as well as a justification for selecting the particular objective(s). Data points collected in the trial should support an objective.*

## Secondary objectives

*The secondary objective(s) are goals that will provide further information on the use of the intervention.*

*The protocol should describe the secondary objectives which:*

* *may or may not be hypothesis-driven;*
* *may include secondary outcomes;*
* *may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data).*

## Exploratory objectives

*Other objectives that haven’t been mentioned above.*

# End points

*A study end point is a specific measurement or observation to assess the effect of the trial variable (study intervention). Study end points should be prioritized and should correspond to the study objectives and hypotheses being tested.*

*Always specify the timepoint (of measurement) along with the end point concerned, especially when it is possible to be measured more than once during the trial.*

## Primary end points

*The primary end point(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary end point is the basis for concluding that the trial met its objective. Often phase II and III studies include primary objectives, and therefore primary end points, to demonstrate effectiveness. Generally, there should be just one primary end point that will provide a clinically relevant, valid, and reliable measure of the primary objective.*

*The primary end point should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size. Less is more, e.g. “the primary end point is the two-year survival rate”.*

## Secondary end points

*Secondary end points are those that may provide supportive information about the study intervention’s effect on the primary end point or demonstrate additional effects on the disease or condition.*

## Exploratory end points

*Other end points that haven’t been mentioned above*.

# Trial design

## Overall design

### Design description

*The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should contain following information:*

* *A description of the type/design of trial to be conducted (e.g. randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority design, non-inferiority design…);*
* *Phase of the trial;*
* *Indicate mono- or multicentric;*
* *Indicate national or international;*
* *Also, give a short description of the number of study groups/arms and study intervention (duration).*

### Design rationale

*Describe the rationale for the type and selection of control (e.g. placebo, active drug, dose-response, historical) and trial design (e.g. non-inferiority as opposed to superiority).*

### Flowchart

*Include a schematic diagram/timeline of trial design, procedures and stages, without going into the specifics per trial visit. (Specifics per trial visit need to be described in section 9.7.)*

## Start of the trial

The trial is considered started upon the first act of recruitment of a potential subject. For this trial this is considered as <XX>.

The start of the trial shall be notified to the RA within 15 calendar days.

The first visit of the first subject (i.e. when the first subject or his/her legally designated representative signs his/her first informed consent to participate in the trial) (FSFV) will also be notified to the RA within 15 calendar days.

## End of the trial

*Adjust the definitions below if they do not fit the content of your protocol.*

### For an individual subject

The subject has completed the trial when <XX>.

### For the whole trial

The end of the recruitment of subjects shall be notified to the RA within 15 calendar days.

Overall, the end of the trial is reached when <XX>.

As soon as the whole trial has ended (cfr. the definition above), the RA shall be notified within 15 calendar days.

A summary of the results of the trial will be submitted to the RA within 1 year from the end of the trial, irrespective of the outcome of the trial.

## Trial duration

### For an individual subject

*Describe the estimated time that will be needed for an individual from his first visit/procedure up to the last visit/procedure (including follow-up, if relevant).*

### For the whole trial

*Describe the estimated time that will be needed to complete the whole trial, i.e. from start until end (as described above in the protocol – usually from first act of recruitment until Last Subject Last Visit (LSLV)).*

# Trial population

## Number of subjects and planned recruitment rate

*<XX>* subjects will be included in this trial, taking into account possible screen failures/drop-outs.

*<XX>* eligible subjects are necessary for analysis.

It is expected that overall an accrual rate of *<XX>* subjects per *<XX>* is realistic in the whole trial.

## Inclusion and exclusion criteria

*Use the following guidelines when developing subject eligibility criteria to be listed:*

* *The eligibility criteria should provide a definition of subject characteristics required for study entry/enrollment;*
* *If subjects require screening, distinguish between screening subjects vs enrolling subjects (subject eligibility screening can also be found as a topic infra);*
* *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g. do not state age ≥ 18 years as an inclusion criterion and age < 18 years as an exclusion criterion);*
* *Identify specific laboratory test results or clinical characteristics that will be used as criteria for enrollment or exclusion;*
* *If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g. licensed hormonal or barrier methods);*
* *If you have more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.*

### Inclusion criteria

*Inclusion criteria are characteristics that define the population under study. Individuals must meet all of the inclusion criteria in order to be eligible to participate in the trial.*

### Exclusion criteria

*Exclusion criteria are characteristics that make an individual ineligible for study participation. All individuals meeting any of the exclusion criteria at baseline will be excluded from study participation.*

*Some criteria to consider for exclusion are: pre-existing conditions or concurrent diagnoses, concomitant use of other medication(s) or device(s), known allergies, other factors that would cause harm or increased risk to the subject.*

*E.g., An individual who meets any of the following criteria will be excluded from participation in this trial:*

* *Current use of <Specify disallowed concomitant medications>;*
* *Presence of <Specific medical devices (e.g. cardiac pacemaker)>;*
* *Pregnancy and/or lactation;*
* *Known allergic reactions to components of the <IMP>, i.e. <Specify components/allergens>*
* *Treatment with another investigational drug or other intervention within <Specify time frame>;*
* *Current smoker or tobacco use within <Specify timeframe>;*
* *<Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>.*

### Justification of in- and exclusion criteria

*If applicable, please justify the inclusion of subjects who are incapable of giving informed consent or other special populations, such as minors.*

*Also add a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trial, an explanation of the reasons and justification for these exclusion criteria.*

## Withdrawal and replacement of subjects

### Withdrawal of subjects

*Describe stopping criteria and reasons for excluding subjects that are already enrolled in the trial. Subjects may withdraw voluntarily from the trial or the Principal Investigator (PI) may discontinue a subject from the trial. This section should also state which adverse events would result in discontinuation of study intervention or subject discontinuation/withdrawal.*

*If applicable, make a clear distinction between the criteria/reasons for withdrawing a subject from trial treatment and the criteria/reasons for withdrawing a subject from the clinical trial. Also describe the procedure for the collection of data regarding withdrawn subjects (if applicable).*

Subjects are free to withdraw from participation in the trial at any time. A subject must be discontinued from the trial if *<XX>* withdraws consent. The reason why a subject withdraws consent, if given, must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject’s medical records. The already gathered subject data should remain in the trial database.

However, subjects can choose to discontinue trial treatment or interventions, but remain in the trial for other assessments or data collection, if applicable. The reasons for a subject to withdraw from trial treatment, if given, must be recorded in detail in the eCRF and in the subject’s medical records. The subject data should be collected in the eCRF.

An investigator may discontinue trial treatment for a subject for the following reasons:

*Adjust the reasons below if they do not fit the design of your trial. You can also add other reasons.*

* Pregnancy;
* Significant trial intervention non-compliance;
* If any clinical Adverse Event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject;
* Disease progression which requires discontinuation of the trial intervention;
* If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further trial participation;
* Subject unable to receive *<XX>* for *<XX>* *<XX>*;
* *...*

The reasons for withdrawing a subject from trial treatment must be recorded in detail in the eCRF and in the subject’s medical records. However, even if trial treatment is discontinued, the subject will remain in the trial and other assessments or data collection should be done, if applicable. The subject data should be collected in the eCRF.

*Adjust the text below if it does not fit the design of your trial. You can also add other actions.*

A subject will be considered lost to follow-up if he or she fails to return for *<XX>* scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required trial visit:

* The site will attempt to contact the subject and reschedule the missed visit within *<XX>* and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the trial;
* Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (i.e. three telephone calls and a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record or study file;
* Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.
* *...*

### Replacement of subjects

*Specify the corresponding procedures for the replacement of subjects. Replacement of subjects is protocol-specific and needs to be tailored to the trial.*

*e.g. “Drop-outs will not be replaced.”*

*e.g. “Drop-outs will be replaced until <XX (amount)> subjects have completed the trial. If following data is available and/or procedures are completed, the subject will not be replaced:*

*<List up the situations when the subject will not be replaced >.”*

### Follow-up of withdrawn subjects

Regardless of the reason for withdrawal, the Principal Investigator (PI) must consider the following:

* Procedures for safe discontinuation of trial treatment;
* Retention and use of the data already collected;
* In case of withdrawing from trial treatment, continue other assessments or data collection, if applicable.

*Describe (1) if the investigator may use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the investigator; and (2) whether the investigator can continue to obtain data about the subject and if so, under what circumstances (after explicit consent of the discontinued trial subject).*

*Also describe how the withdrawn subjects will be followed up after trial participation (e.g. standard of care).*

## Method of recruitment and compensation for subjects

*Describe:*

* *Source of subjects (e.g. inpatient hospital setting, outpatient clinics, student health service, general public…);*
* *Recruitment venues;*
* *How potential subjects will be identified and approached;*
* *Types of recruitment strategies planned (e.g. patient groups, national newspaper, local flyers, social media…);*
* *If the trial requires long-term participation, describe procedures that will be used to enhance subject retention (e.g. multiple methods for contacting subjects, visit reminders, incentives for visit attendance);*
* *If subjects will be compensated or provided any incentives (e.g. vouchers, gift cards…) for study participation, describe amount, form and timing of such compensation in relation to study activities (include financial and non-financial incentives). Please note that any incentive/compensation needs to be explicitly evaluated and approved by the Independent Ethics Committee (IEC).*

*Please make sure this covers all participating centers and not only the method of the coordinating center.*

## Subject eligibility screening

Screen failures are subjects who were checked to participate in the trial but do not meet one or more criteria required for participation in the trial during the screening procedures. Screen failures will not be enrolled in the trial. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.

Screen failures *<XX>*.

## Subject follow-up after trial participation

*Please describe 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.*

# Investigational Medicinal Product (IMP)

*Please describe each IMP that will be used in the trial. Repeat the subsection(s) for each IMP that you have to describe.*

***Note that test products, reference products, comparators and placebos are all IMPs.***

## <Name of the IMP>

### General information

***A lot of the information below can be found in the*** *Summary of Product Characteristics (****SmPC****)****,*** *Investigational Medicinal Product Dossier (****IMPD****)* ***or*** *Investigator’s Brochure**(****IB****)****.***

|  |  |
| --- | --- |
| Also refer to | *<XX>* |
| Name of the IMP |  |
| Qualitative and quantitative composition |  |
| Pharmaceutical form |  |
| Method of administration |  |
| Authorized in the European Union (EU)  *(If the IMP is not authorized in the EU, but it is authorized elsewhere: please elaborate.)* | *<XX>* |
| Used within scope  *(If not: please explain / If the IMP is not authorized (worldwide): choose ‘N.A.’.)* | *<XX>* |
| Marketing authorization holder |  |
| Marketing authorization number(s) |  |
| EU substance number  *(Any substance(s) in the product must be registered in the database of the Substance Management System from the European Medicines Agency (EMA SMS).)* | SUB*<XXXXXX>* |
| Manufacturer |  |
| Distributor |  |
| Responsible for batch release |  |

### IMP rationale

*Please explain why you will be investigating this IMP.*

### Preparation of the IMP

*Describe the preparation process. Important to note is that it should be mentioned what is according to the SmPC of the IMP (if this is available) and what is experimental. Preparation of the IMP should be in accordance with the relevant Good Manufacturing Practices (GMP) requirements (if applicable). Also mention if the IMP will be modified or not (e.g. repackaging or restitution).*

### Administration, dosage and dose frequency of the IMP

*Describe the route of administration and the dosages to be used in the trial. It should be mentioned whether aforementioned matters are according to the SmPC of the IMP (if this is available) or not (i.e. if the IMP is used out of scope).*

*Also provide a justification for the route and mode of administration, planned dosage and dosage regime for the IMP.*

### Permitted dose adjustments and interruption of treatment

*Please include the allowed time window in which the IMP may be administered to the subject without creating a protocol deviation in doing so. Also describe whether the dosage will be modified in accordance with the subject’s results (e.g. lab results – and what the results should be), or in case of certain adverse events. Specify the exact dose modifications and/or accepted ranges.*

### Duration of treatment

*Describe the foreseen duration of the treatment of the IMP; also include the maximal duration of the treatment for a single subject.*

*Also provide a justification for the treatment period for the IMP.*

### Packaging and labeling of the IMP

*Packaging/labeling of the IMP should be in accordance with the relevant GMP guidelines (if applicable). Please explain how and by whom the packaging and labeling of the IMP will be performed. Please make sure the description covers all participating centers.*

*Please add an example of the label that will be used. Only the text that is labelled on the IMP, suffices (a mock-up does not need to be included in the protocol).*

*NOTE: in Belgium, the label has to be drawn up at least in the three national languages (Dutch, French, German). Exceptions on this rule:*

* *IMP is administered at the clinical trial site and the subjects do not handle the product: the label can be in one national language or in English;*
* *IMP is authorized: see the CTR art. 67, § 1, b), and the Belgian law on medicines for human use (25 March 1964) art. 6, §1quinquies and art. 6septies, §1.*

*NOTE: labeling of the IMP is not necessary1 in case of low-intervention trials. This means:*

* *the treatment is given according to the leaflet and the standard of care; and*
* *delivery takes place in accordance with the marketing authorization (and thus without any changes to the medicinal product).*

*Please discuss labeling in advance with pharmacy clinical trials/radio pharmacy Ghent University Hospital.*

*1https://www.famhp.be/en/news/derogation\_for\_sponsors\_of\_non\_commercial\_clinical\_trials\_to\_adapt\_packaginglabelling\_of\_an*

### Traceability, storage, return and destruction of the IMP

*Describe the procedures and conditions for shipment, receipt, distribution, storage, traceability, return and destruction of the investigational medicinal product. Also describe who will take care of the IMP supply. Please make sure the description covers all participating centers.*

*Also describe how temperature deviations during storage should be handled. For details of this procedure, if applicable, you can refer to a SOP (existing or created specifically for this trial).*

# Auxiliary Medicinal Product (AxMP)

*An AxMP is a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (CTR 536/2014).*

*Examples are medicinal products used as rescue medication, challenge agents, to assess end points in the clinical trial, or background treatment (but not concomitant medication).*

*More information can be found on:* https://health.ec.europa.eu/system/files/2017-08/2017\_06\_28\_recommendation\_on\_axmps\_0.pdf

*Please describe each AxMP that will be used in the trial. Repeat the subsection(s) for each AxMP that you have to describe.*

*NOTE: some sections need more information for unauthorized AxMPs than for authorized AxMPs. Please read the instructions carefully.*

## <Name of the AxMP>

### General information

*A lot of the information below can be found in the SmPC, Auxiliary Medicinal Product Dossier (AMPD) or IB.*

|  |  |
| --- | --- |
| Also refer to | *<XX>* |
| Name of the AxMP |  |
| Qualitative and quantitative composition |  |
| Pharmaceutical form |  |
| Method of administration |  |
| Authorized in the EU  *(If the AxMP is not authorized in the EU, but it is authorized elsewhere: please elaborate.)* | *<XX>* |
| Used within scope  *(If not: please explain / If the AxMP is not authorized (worldwide): choose ‘N.A.’.)* | *<XX>* |
| Marketing authorization holder |  |
| Marketing authorization number(s) |  |
| EU substance number  *(Any substance(s) in the product must be registered in the EMA SMS database.)* | SUB*<XXXXXX>* |
| Manufacturer |  |
| Distributor |  |
| Responsible for batch release |  |

### AxMP rationale

*Please explain why you will be administering this AxMP to the subjects of the trial.*

*If the AxMP is not authorized: please justify the use of non-authorized auxiliary medicinal products in the trial.*

### Preparation of the AxMP

*Describe the preparation process. Important to note is that it should be mentioned what is according to the SmPC of the AxMP (if this is available) and what is experimental. Preparation of the AxMP should be in accordance with the relevant GMP requirements (if applicable).*

*Also mention if the AxMP will be modified or not (e.g. repackaging or restitution).*

### Administration, dosage and dose frequency of the AxMP

*Describe the route of administration and the dosages to be used in the trial. It should be mentioned whether aforementioned matters are according to the SmPC of the AxMP (if this is available) or not (i.e. if the AxMP is used out of scope).*

*Also provide a justification for the route and mode of administration, planned dosage and dosage regime for the AxMP.*

### Permitted dose adjustments and interruption of treatment

*Please include the allowed time window in which the AxMP may be administered to the subject without creating a protocol deviation in doing so.*

*Also describe whether the dosage will be modified in accordance with the subject’s results (e.g. lab results – and what the results should be), or in case of certain adverse events.*

*Specify the exact dose modifications and/or accepted ranges.*

### Duration of treatment

*Describe the foreseen duration of the treatment of the AxMP; also include the maximal duration of the treatment for a single subject.*

*Also provide a justification for the treatment period for the AxMP.*

### Packaging and labeling of the AxMP

*Packaging/labeling of the AxMP should be in accordance with the relevant GMP guidelines (if applicable). Please explain how and by whom the packaging and labeling of the AxMP will be performed. Please make sure the description covers all participating centers.*

*Please add an example of the label that will be used. Only the text that is labelled on the AxMP, suffices (a mock-up does not need to be included in the protocol).*

*Labeling: Only to be completed if it concerns an unauthorized AxMP. Otherwise, write ‘According to routine practice.’*

*NOTE: in Belgium, the label has to be drawn up at least in the three national languages (Dutch, French, German).*

*Exception on this rule: if the AxMP is administered at the clinical trial site and the participants do not handle the product, the label can be in one national language or in English.*

*Please discuss labeling in advance with pharmacy clinical trials / radiopharmacy Ghent University Hospital.*

### Traceability, storage, return and destruction of the AxMP

*If not applicable, write ‘According to routine practice.’.*

*Describe the procedures and conditions for shipment, receipt, distribution, storage, traceability, return and destruction of the investigational medicinal product. Also describe who will take care of the AxMP supply. Please make sure the description covers all participating centers.*

*Also describe how temperature deviations during storage should be handled. For details of this procedure, if applicable, you can refer to a SOP (existing or created specifically for this trial).*

# Concomitant medication and treatment

*Please describe the treatments (including medicinal products), which are specifically permitted or not permitted, before and/or during the clinical trial. This section should be consistent with the (medication) restrictions in the inclusion/exclusion criteria previously listed.*

*Concomitant medication is unrelated to the clinical trial and not relevant for the design of the*

*clinical trial (as opposed to AxMPs).*

*Describe the data that will be recorded related to permitted concomitant medications, supplements, complementary and alternative therapies, treatments and procedures. Include details about when the information will be collected (e.g. during the screening visit, during all trial visits).*

*Describe how allowed concomitant therapy might affect the outcome (e.g. drug-drug interaction or direct effects on the trial endpoints) and how the independent effects of concomitant and trial interventions could be ascertained.*

*Also clearly describe if concomitant vaccination of the subject is allowed during the trial (e.g. COVID-vaccination, flu vaccination...) and what the potential risks/benefits are as well as if it would potentially affect the trial’s outcome.*

*Please conduct a specific risk assessment for concomitant use of a COVID-19 vaccine for each IMP and with specific consideration for the trial population. Include the appropriate flexibilities in order to avoid the need for substantial modifications at a later stage.*

### Concomitant medication

### Concomitant treatment

# Study specific procedures

## Eligibility screening process

*This section should give details of the subject eligibility screening process for the project including information to be collected regarding subjects who are screened.*

*List any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria such as electrocardiogram (ECG), laboratory tests, scans, …*

*Any assessments and or procedures performed as part of routine care which will be used to screen subjects for eligibility will require defined timelines (e.g. X-rays within the last 6 months). Specify the maximum duration allowed between recruitment and screening (if applicable) and between screening and enrolment (if applicable).*

*Also refer to section 5.5.*

## Informed consent

*Refer to section 15.2.*

## Measures taken to minimize bias

### Randomization

*If applicable, please describe the randomization process. Who is responsible for the randomization, how will the randomization be performed, which software/system will be used (see further in the protocol as well), where are the randomization codes to be found, arrangements for the maintenance of clinical trial treatment randomization codes, timing and procedures for unplanned and planned breaking of the randomization codes (if relevant), …*

*This section should include a description how study subjects will be assigned to study groups, without being so specific that randomization might be compromised (e.g. the ratio between intervention and placebo groups may be stated).*

### Blinding

*If applicable, please describe the blinding process. Who is responsible for the blinding, how will the blinding be performed, which software/system will be used (see further in the protocol as well), where are the blinding codes to be found, arrangements for the maintenance of clinical trial treatment blinding codes, …*

*This section should include a description how study subjects will be assigned to study groups, without being so specific that blinding might be compromised (e.g. the ratio between intervention and placebo groups may be stated).*

*Unblinded information should be accessible only to persons who need to be involved in the safety reporting to the Agency, to Data Safety Monitoring Boards (‘DSMB’), or to persons performing ongoing safety evaluations during the clinical trial.*

### Unblinding procedures

*The timing and procedures for planned and unplanned breaking of study codes should be described. Include a statement regarding when unblinding may occur and who may unblind.*

*Provide the criteria for breaking the study blind or subject code. Discuss the circumstances in which the blind would be broken for an individual or for all subjects (e.g. for Suspected Unexpected Serious Adverse Reactions (SUSARs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported (to the sponsor and HIRUZ, and by them subsequently to the RA if applicable).*

*If the trial allows for some investigators to remain unblinded (e.g. to allow them to adjust medication), the means of shielding other investigators should be explained. Describe efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible.*

The study code should only be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the subject is receiving before he or she can be treated. If possible, other study team members should remain blinded.

The code breaks for the trial are kept at *<XX>* ; in the event a code is required to be unblinded a formal request for unblinding will be made by the local PI to the Coordinating Investigator (CI).

The CI/PI documents the breaking of the code and the reasons for doing so on the eCRF/study documents, in the site file and medical notes. It will also be documented at the end of the trial in any final study report and/or statistical report.

The study team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.

As the investigator is responsible for the medical care of the individual study subject (Declaration of Helsinki §3 and ICH-GCP E6(R2) 4.3) the coding system should include a mechanism that permits rapid unblinding (ICH-GCP E6(R2) 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

### Other measures taken to minimise bias

*Please describe other measures taken to minimize bias (if applicable), apart from randomization and blinding.*

## Study specific interventions

*Please describe the interventions in detail. The protocol should describe what the procedures/assessments are at each visit and where they will be performed.*

*Specify the time points of the visits. Also time windows (period of time in which the intervention can take place; i.e. an allowed deviation of the predefined time point of the intervention) should be added if applicable. Also add drug compliance checks.*

*For screening details, you can refer to section 5.5.*

*You can add the interventions that are performed as standard of care, and not performed on the premise of being included in the trial. It has to be clearly stated which interventions are standard (where the only study specific procedure is the data collection) and which are specifically performed for this trial.*

*Examples of interventions are (but not limited to):*

* *Physical examination (e.g. height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
* *Vital signs (e.g. temperature, pulse, respirations, blood pressure). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.*
* *Radiographic or other imaging assessments. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging.*
* *Biological specimen collection and laboratory evaluations. Include specific test components and estimated volume and type of specimens needed for each test (see section 10).*
* *Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.*
* *Assessment of adverse events. Describe provisions for follow-up of ongoing (Serious) AEs ((S)AEs).*
* *Administration of the IMP(s).*

Since the subjects are not under 24-hour supervision of the investigator or his/her staff, they will be provided with a study card indicating at least the name of the investigational medicinal product, the dosage, the PI’s name and a 24-hour emergency contact number.

## Restrictions for subjects during the trial

*Add all relevant restrictions that are in place for subjects participating in the trial and make sure to describe the duration of the restriction. (e.g. being sober for a period of time prior to IMP administration or blood sampling…)*

## Overview of collected data

*Please describe in detail all data that you wish to record (this should align with the information in section 12). Only data that forms part of the predefined data set essential for analysis should be collected.*

*The following should be considered:*

* *the relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable;*
* *do any of the procedures need to be undertaken in a certain order;*
* *are explanations needed? E.g. if 3 measurements are to be taken and averaged that should be explained;*
* *for particularly complex procedures or those that differ from routine standard practice, these should be detailed in full. E.g. if a 6 lead ECG is normal routine practice but the trial requires a 12 lead ECG, this will need to be made clear to avoid potential errors;*
* *if specialist, non-standardized assessments are required, care should be taken to detail exactly what needs to happen during the assessment.*

*It is an infringement of the data protection regulation to process data that is irrelevant or excessive for the purpose for which it was collected. Case Report Forms (CRFs) must therefore only collect the information directly relevant to the objectives and outcome measures detailed in the protocol. Collecting additional data not specified in that way is unacceptable.*

## Schematic overview of the data collection and interventions

*Please provide a chronological overview with a timeline (including the allowed time windows).It is important to give a clear view of the procedures per visit (including the screening visit). A simple example of a schematic overview (a table) has been added below.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***Screening visit***  ***(T-1)*** | ***Visit 1 / Baseline***  ***(T0)*** | ***Visit 2 (1 month)***  ***(T1)*** | ***Visit 3 (2 months)***  ***(T2)*** | ***Follow-up visit (6 months) (T3)*** |
| ***Informed consent*** | *X* |  |  |  |  |
| ***Inclusion/exclusion criteria check*** | *X* |  |  |  |  |
| ***Pregnancy test (urine stick)*** | *X* | *X* | *X* | *X* | *X* |
| ***Randomization*** | *X (between T-1 and T0)* | |  |  |  |
| ***Study specific intervention A*** |  |  | *X* | *X* |  |
| ***Study specific intervention B*** |  |  | *X* | *X* |  |
| ***Blood analysis***  ***(6 ml blood)*** | *X\** | *X* | *X* | *X* | *X\** |
| ***Study specific intervention D*** |  |  | *X* | *X* |  |
| ***Drug intake*** |  | *X (from T0 until T2, every day 3x 5mg)* | | |  |
| ***Questionnaire XYZ*** | *X (from T-1 until T3, once every week)* | | | | |
| ***Drug accountability*** |  |  | *X* | *X* |  |
| ***Adverse event check*** |  |  | *X* | *X* | *X* |

*\* Intervention is standard of care and is being performed regardless of inclusion in the trial.*

# Biological samples

*This section should contain a description of the arrangements for the collection, storage and future use of biological samples from the trial subjects.*

*List all separate types of biological samples and the amount and volume of samples that you will collect during the trial. Please make sure the necessary information is also recorded in section 9.*

*If the necessary information is already contained in a separate document (e.g. a specific sampling SOP), you can refer to that document instead. Please make sure all participating sites are covered.*

## Types and number of samples

## Timepoints of sample collection

*When should the samples be taken during the trial, and is there a time window that is allowed without creating a protocol deviation?*

## Sample handling and analysis

*How will the samples be taken and which methods will be used for analyzing them. Also explain where the analyses will be performed. Please make sure all participating centers are covered.*

## Sample storage and shipment

*Describe the specific storage conditions and locations. Describe the way the biological samples will be shipped and in what conditions (if applicable). Also mention in which biobank(s) they will be stored and who is the medical guardian of the biobank(s).*

*Please make sure all participating centers are covered.*

## Future use of stored samples

*Please describe what you will do with the biological samples after the trial has ended. Will all samples be destroyed or will you store them after the end of the trial?*

*If you will store them: for which purpose, where, for how long and under which conditions will the biological samples be stored?*

# Statistical considerations

*An appropriate level of statistical advice should be sought to ensure study validity.*

*If extra help is needed, you can contact the Biostatistics Unit (Cel Biostatistiek) from Ghent University. See https://www.ugent.be/ge/nl/diensten/biostatistiek/overzicht-en.htm*

*If applicable, reference can be made to a separate Statistical Plan.*

## Sample size calculation, power calculation, significance level

The *<XX>* on which the sample size calculation is based upon, *<XX>*.

The calculation of the sample size used the tool *<XX>* and included the following parameters: *<XX>*.

*Please also provide a description (include point in time, method of assessment). Make sure your calculation method(s) can easily be reproduced by another statistician.*

*Formal sample size calculations typically require the power to be specified and the following values with justification:*

* *The target difference: in a superiority study*
  + *This is the difference in the primary outcome that the study is designed to detect reliable.*
  + *This should be the smallest size of effect that would be of clinical interest. This is of critical importance in the sample size calculation, and should be justified in the form of appropriate references, pilot data or clinical arguments.*
  + *Expected effects in the intervention and comparison group should also be mentioned (thus not only the expected difference between the groups).*
* *Significance level: what risk is acceptable of concluding the treatment is effective, when in reality the treatment is ineffective (usually 5%).*
* *The power of the study: the probability that the test will correctly reject the null hypothesis when the alternative hypothesis is true (usually minimum 80%).*
* *In studies with continuous outcomes, the standard deviation of the primary endpoint should be included:*
  + *if previous studies or literature are used to estimate or justify the assumptions made to determine this parameter any other parameters relevant to the design (e.g. dropout rate, noncompliance rates, median survival rate, response rate…), provide references.*

*If a Bayesian or an alternative statistical approach is used, please state the used approach and provide references to the relevant literature. Please explain the choice of this approach, and how it achieves the aim of a sample size calculation in terms of*

* *reassuring about the additional value of the new study; and*
* *guiding clinical practice in a meaningful way and influencing key stakeholders.*

*If the choice of the sample size was not based upon statistical consideration, then this should be explicitly stated along with a rationale for the intended sample size (e.g. exploratory nature of pilot studies, pragmatic considerations for studies in rare diseases…).*

## Type of statistical methods

*Please list and describe each method/tool that will be used for analyzing the respective data sets. If possible/applicable, split up the methods for primary and secondary outcome measures. Describe the selection of subjects to be included in the analyses.*

*Also determine criteria for the termination of the clinical trial.*

*Please describe the procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan.*

## Statistical analysis team

*Please list the team members or department that will be responsible for the statistical analysis and their contact details.*

## Interim analysis

*Describe the purpose of one or multiple interim analyses (if applicable). Describe the timing and conditions of the planned interim analysis (e.g. the number of subjects planned to be enrolled before interim analysis).*

*If one or more interim analyses are planned, it should be considered whether the sample size should be increased to account for multiple testing.*

# Data handling

*If applicable, reference can be made to a separate Data Management Plan.*

## Method of data collection

*Please adapt the text below as applicable to your trial.*

An Electronic Data Capture (EDC) system, i.e. REDCap, will be used for data collection. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

### Case Report Form (CRF)

*An Excel spreadsheet is not acceptable as CRF. Please provide details of the methods to be used to ensure validity and quality of data (e.g. double entry, cross validation…), which should be proportionate to the study.*

*If applicable, reference can be made to a separate Data Validation Plan.*

Only the data required by the protocol are captured in the eCRF. The eCRFs and the database will be developed, based on the protocol. The final eCRF design will be approved by the CI. The study site staff is responsible for data entry in REDCap.

Subjects that are included in the trial, will be assigned a unique study number upon their registration in REDCap. On all documents submitted to the sponsor or CI, subjects will *<XX>*. REDCap has built-in options for univariate alerts, such as valid-value, valid-range, and missing-value alerts.

Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.

All data entries and corrections will only be performed by study site staff, authorized by the Investigator. Data will be reviewed by trained personnel (monitor, data manager) and any errors or inconsistencies will be clarified.

### Data directly collected in the CRF (no source available)

*Please list data that cannot be traced back to the source documents, including a motivation. Describe the procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data.*

## Data storage

*During the trial and analysis: Is data stored in accordance with the General Data Protection Regulation (GDPR), which safety measures are in place (e.g. secured servers)?*

*Please adapt the text below as applicable to your trial.*

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements.

Privacy and data integrity between the user’s browser and the server is provided by mandatory use of Transport Layer Security (TLS), and a server certificate issued by the Trans-European Research and Education Networking Association (TERENA). All trial sites will have access to REDCap. Site access is controlled with IP restriction.

## Archiving of data

The investigator and sponsor specific essential documents will be retained for at least 25 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirements.

*Please specify the locations and conditions of archiving. Also adapt the text above as applicable to your trial.*

*Note: REDCap cannot be used as an archive. For example, it is possible that it will no longer exist within a few years. At the end of the study, study data should be extracted and archived.*

## Access to data

*Describe who will have access to the study files, during and after the trial. Please adapt the text below as applicable to your trial.*

The investigators and institutions involved in the trial will permit clinical trial-related monitoring, audits and regulatory inspections (including provision of direct access to source data and documents).

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Furthermore, users will only be able to see data of subjects of their own site. Any activity in the software is traced and transparent via the audit trail.

# Safety

## Definitions

|  |  |
| --- | --- |
| **Adverse Events and Adverse Reactions** | |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. |
| **Unexpected Adverse Event** | An adverse event of which the nature or severity is not consistent with the Reference Safety Information (RSI) of the product (i.e. the applicable information in the Investigator’s Brochure (IB) for an investigational medicinal product which is not authorized or in the Summary of Product Characteristics (SmPC) for an authorized investigational medicinal product). |
| **Adverse Reaction (AR)** | An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase “response to an investigational medicinal product” means that a causal relationship between a study medication and an AE 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. |
| **Serious Adverse Event (SAE)** | Any untoward medical occurrence that:   * requires inpatient hospitalisation or prolongation of existing hospitalisation; * results in persistent or significant disability/incapacity; * results in a congenital anomaly or birth defect; * is life-threatening; *or* * results in death.   Other important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences.  NOTE: The term “life-threatening” in the definition of “serious” 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. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature, severity or outcome of which is not consistent with the RSI. |

*NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.*

|  |  |
| --- | --- |
| **Attributions** | |
| **Term** | **Definition** |
| **Not related** | An adverse event which is not related to the use of the drug. |
| **Unlikely related** | An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely. |
| **Possibly related** | An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s) or concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded. |
| **Probably related** | An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s) or concomitant disease(s). |
| **Definitely related** | An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge). |

An adverse event is considered associated with the use of the drug if the attribution is ‘possibly’, ‘probably’ or ‘definitely related’.

## Reporting requirements

*Please adapt the text of section 13.2 as applicable to your trial.*

### AE reporting

All relevant AEs per subject will be recorded *<XX>*.

Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE. These AEs should be recorded in the patient’s file and in the CRF.

### SAE reporting

SAEs occurring within a period of *<XX>* *<XX>* following the last intake of study medication will be reported as below.

All serious adverse events (initial and follow up information – except for those, described in section 13.5) and events, described in section 13.2.4, occurring during this trial must be reported by the local PI within 24 hours after becoming aware of the event to:

* HIRUZ CTU of Ghent University Hospital;
* the CI;
* the company that provides the IMP (as stipulated in the agreement).

This reporting is done by using the appropriate electronic/paper SAE form. For the contact details, see below.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

### SUSAR reporting

In case the CI/sponsor, in consultation with HIRUZ CTU, decides the SAE is a SUSAR (considering the seriousness, probability of harmfulness and unexpectedness), HIRUZ CTU will report the SUSAR to the European Medicines Agency (EMA), through the Eudravigilance (EV) database within the timelines as defined in European legislation.

In case of a fatal or life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. In case of a non life-threatening SUSAR the reporting process must be completed within 15 calendar days.

Coordinating Investigator informs local PIs of safety profile changes, not of individual SUSAR reports. For example, information derived from SUSAR reports could be provided via investigators’ letters including both an updated benefit-risk evaluation and risk mitigation measures.

### Other reporting requirements

*e.g. AEs or lab abnormalities that are important for safety evaluations that need reporting from the investigator to the sponsor, reporting of pregnancies, other events of special interest…*

## List of contact details for safety reporting

*Also other relevant contact details can be added in this section (e.g. pharmacovigilance department of a company which provides the IMPs, according to the agreement).*

|  |  |  |
| --- | --- | --- |
| HIRUZ CTU | E | [hiruz.ctu@uzgent.be](https://zenya.uzgent.be/management/hyperlinkloader.aspx?hyperlinkid=3551af48-ffb3-4e03-b167-51e5e0cfda34) |
| T | +32 9 332 05 00 |
| Coordinating Investigator | N |  |
| E |  |
| T |  |
| Marketing Authorization Holder (MAH) | N |  |
| E |  |
| T |  |

## Flowchart reporting

*Please adapt the flowchart below as applicable to your trial.*

|  |  |
| --- | --- |
| **Type of Adverse Event** | **Action(s) be taken** |
| **AE** | List all relevant AEs per subject in the patient’s file and add this information to the CRF. |
| **SAE** | * Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SAE by completing the appropriate electronic/paper SAE form; * Add the SAE to a list that will be reported yearly (see section 13.7); * Add the SAE in the CRF (please take into account section 13.5). |
| **SUSAR** | * Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SAE by completing the appropriate electronic/paper SAE form; * The CI/sponsor will assess the causality and unexpectedness of the SAE to determine if it qualifies as a SUSAR; * HIRUZ CTU submits the SUSAR to the EMA (through EV database) after communication with the CI and within the mandatory timeframe; * Study team of CI informs company that provides the IMP (as stipulated in the agreement); * Coordinating Investigator informs local PIs of safety profile changes. |

Reporting to the local Ethics Committee (EC) of SAEs and SUSARs remains the responsibility of the PI and should be done in accordance with the requirements of the local institution’s procedure.

## Events excluded from reporting

*Please describe (serious) adverse events/symptoms/… which are excluded from immediate reporting (e.g. because these are inherent to the studied patient group).*

## Data Safety Monitoring Board (DSMB)

*Please adjust the text below if this is not a correct reflection of your trial.*

All investigational medicinal products are authorized and used in current practice. Considering the known safety profile of the investigational medicinal products and trial design, a DSMB is not foreseen.

*If a DSMB is foreseen, please describe how the board is installed, and which responsibilities are delegated to them. For details, you can refer to a separate safety charter (which can be added in the appendices).*

## Annual Safety Report (ASR)

*If the trial ends before the end of the ASR period, the summary of the results of the trial, which is submitted within one year after the end of the trial as defined in this protocol, acts as an ASR. This also applies to clinical trials lasting less than one year.*

The Coordinating Investigator will provide an ASR once a year throughout the entire duration of this clinical trial, or on request, to the EMA. This ASR will include all SAEs and relevant safety information regarding all investigational medicinal products, used in this trial.

The report will be submitted no later than 60 calendar days after the ASR Data Lock Point (DLP). The first DLP is 1 year after the first date of the sponsor’s authorization to conduct the clinical trial. Subsequently, the ASR will be submitted each year (+ maximum 60 days) until the trial is declared ended.

The Coordinating Investigator provides the ASR to all local PIs.

## Follow-up after an adverse reaction

*Please describe how follow-up will be organized for subjects that have encountered an adverse reaction (e.g. the type and duration of the follow-up).*

# Monitoring, audits and inspections

## Monitoring

### General

Monitoring of the trial will be performed in compliance with ICH-GCP E6(R2) and the applicable regulatory requirements. The study team will be trained during a site initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) ‘Clinical Trial Monitoring Plan’.

### Monitoring team

Monitoring services will be provided by HIRUZ CTU. All relevant contact details (e.g. primary contact person) can be found in the ‘Clinical Trial Monitoring Plan’.

### Scope

Monitoring services will consist of the following (non-exhaustive list):

* review of informed consents and the followed process;
* check on recruitment status;
* checking for protocol deviations/violations;
* checking Good Clinical Practice (GCP) compatibility;
* check on safety reporting compliance;
* IMP handling and storage;
* review of study data.

More information can be found in the Clinical Trial Monitoring Plan.

## Inspection

This trial can be inspected at any time by regulatory agencies during or after completion of the trial. Therefore access to all study records, including source documents, must be accessible to the inspection representatives. Subject privacy must be respected at all times, in accordance to the General Data Protection Regulation (GDPR), GCP and all other applicable local regulations.

The investigator/study team should immediately notify the sponsor if (s)he has been contacted by a regulatory agency concerning an upcoming inspection.

## Non-compliance policy

Sponsor and all investigators agree to take any reasonable actions to correct protocol or other non-compliances/violations noted during monitoring/inspection, in consultation with the monitoring team. All non-compliances must be documented on the correct deviation log by the study team that is kept available at any time for monitoring/inspection purposes.

Subject, site and sponsor non-compliances must be reported in the eCRF. In case a (potential) critical non-compliance is detected, the sponsor should be contacted within 1 business day of awareness and the escalation procedure should be started.

Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may take place without prior approval of the sponsor and the RA.

## Serious breach to GCP and/or the protocol

A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Any deviation of the approved protocol version or the CTR that has a major impact on the subject safety and/or rights, data integrity and/or study conduct should be clearly documented on the applicable deviation log and will be communicated with the Coordinating Investigator, HIRUZ CTU and possibly the RA.

Please contact HIRUZ CTU immediately in case of a potential serious breach: [hiruz.ctu@uzgent.be](https://zenya.uzgent.be/management/hyperlinkloader.aspx?hyperlinkid=03170ef6-583a-4f40-91cf-15e1d783a246) and/or +32 9 332 05 00.

The sponsor shall notify the RA about a serious breach of the CTR or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

Early termination of the trial (in a specific center or overall) may be necessary in case of major non-compliance.

# Ethical and legal aspects

*Please adapt the text of section 15 as applicable to your trial.*

## Good Clinical Practice

The trial will be conducted in accordance with the latest version of the ICH-GCP E6(R2) guidelines, creating a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical studies that provides assurance that the data and reported results are accurate and that the rights, integrity and confidentiality of study subjects are protected.

## Informed consent

*Please include a detailed description of the informed consent procedure, as this has to be performed prior to any study-related procedure (including screening). Adapt the proposed text according to the trial population (e.g. delete mention of pediatric subjects if the study population of the trial is ≥18y).*

*Please make sure this covers all participating centers and not only the method of the coordinating center! In particular:*

* *in clinical trials with minors or incapacitated subjects: the procedures to obtain informed consent from the legally designated representatives, and the involvement of the minor or incapacitated subject shall be described;*
* *if a procedure with consent witnessed by an impartial witness is to be used: relevant information on the reason for using an impartial witness, on the selection of the impartial witness and on the procedure for obtaining informed consent shall be provided;*
* *in the case of clinical trials in emergency situations: the procedure for obtaining the informed consent of the subject or the legally designated representative to continue the clinical trial shall be described; as well as the description of the procedures followed to identify the urgency of the situation and to document it;*
* *in the case of clinical trials where their methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products and where, as a consequence, simplified means for obtaining informed consent will be used: the simplified means shall be described.*

*And/or refer to section 9.2 if the necessary information has already been contained in that section.*

Eligible subjects may only be included in the trial after providing written (witnessed, if needed) Independent Ethics Committee (IEC) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. Informed consent must be obtained before conducting any study-specific procedures (as described in this protocol).

Prior to entry in the trial, the investigator must explain the trial and the implication(s) of participation to potential subjects and/or their legal representatives. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject’s or his/her legal representative’s dated signature or the signature of an independent witness who certifies the subject’s consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent. Subjects who are unable to comprehend the information provided or pediatric subjects can only be enrolled after consent of a legally acceptable representative.

The following information should be added to the Electronic Patient Dossier (EPD):

* which version of the ICF was obtained;
* who signed the ICF;
* if sufficient time has been given to consider participation into the trial;
* which investigator obtained ICF with the date of signature;
* if a copy was provided to the subject;
* start of participation in the trial.

## Approval of the study protocol

### General

The protocol has been reviewed and approved by the RA. This trial cannot start before their approval has been obtained, a site initiation visit has been performed by the monitor and, if applicable, all necessary agreements are finalized.

### Protocol modifications and urgent safety measures

Any substantial change or addition to the protocol can only be made in a written protocol modification that must be approved by the RA.

Only modifications that are intended to eliminate an apparent immediate safety threat to the participants may be implemented immediately.

Notwithstanding the need for approval of formal protocol modifications, the investigators are expected to take any immediate action, required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor without undue delay, in order for the sponsor to notify the RA.

## Confidentiality and data protection

All study data will be handled in accordance with the law on GDPR and institutional rules (i.e. in accordance with the Belgian laws dated on 30 July 2018 and 22 August 2002).

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives of the trial. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential. In case of data security breach, local institution’s procedures will be followed.

Site personnel informs the subject about the processing of personal data and direct access for the investigator/institution to his or her original medical records (source data/documents) for trial-related monitoring, audit, EC review and regulatory inspection. The subject is also informed about the transfer of the data to other entities, if applicable.

All data will be *<XX>*. *<XX>* is the responsibility of the PI. *<XX>* can be done by the PI or any other medical practitioner–investigator appointed by the PI and legally authorized to do so (therapeutic relationship with the participant). The key for encryption and decryption of pseudonymised data is kept by the PI and other investigators authorized by the PI. Data is processed in an electronic, secure database (REDCap), in accordance with the technical and organizational security measures of the Ghent University Hospital.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Stored samples will be *<XX>* throughout the sample storage and analysis process and will not be labeled with personal identifiers.

## Liability and insurance

This study protocol is without prejudice to national and European Union law on the civil and criminal liability of the Sponsor, Coordinating Investigator, Principal Investigator(s) and other parties concerned.

The sponsor has entered into a no-fault insurance policy for this trial, in accordance with the relevant legislation (article 12 of the Belgian Law of 7 May 2017 and article 76 of the EU Regulation 536/2014).

# Publication policy

*Do all investigators have a certain role in publication? Who will be first author, last author, etc.? Are there requirements for an investigator to be mentioned on the publication?*

*The publication and authorship policies should be described in this section. For example, for a trial with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues.*

*This section should detail:*

* *guidelines on authorship on the final study report;*
* *criteria for individually named authors or group authorship (The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication);*
* *if professional medical writers are going to be hired and how their employment and funding will be acknowledged in study reports.*

This trial will be registered at EU Clinical Trials (through the Clinical Trials Information System (CTIS)), and results information from this trial will be submitted to aforementioned website. In addition, every attempt will be made to publish results in peer-reviewed journals.

# List of abbreviations

*Please add all abbreviations that are used in the protocol.*

*Abbreviations in orange are only mentioned in instructions of this template and need to be removed when these are not mentioned in the final protocol version.*

AE = Adverse Event

AMPD = Auxiliary Medicinal Product Dossier

APA = American Psychological Association

AR = Adverse Reaction

ASR = Annual Safety Report

AxMP = Auxiliary Medicinal Product

CI = Coordinating Investigator

CRF = Case Report Form

CTIS = Clinical Trials Information System

CTR = Clinical Trial Regulation

CTU = Clinical Trial Unit

DLP = Data Lock Point

DSMB = Data Safety Monitoring Board

EC = Ethics Committee

ECG = Electrocardiogram

eCRF = electronic Case Report Form

EDC = Electronic Data Capture

EMA = European Medicines Agency

EMA SMS = Substance Management System from the European Medicines Agency

EPD = Electronic Patient Dossier

EU = European Union

EV = Eudravigilance

FSFV = First Subject First Visit

GCP = Good Clinical Practice

GDPR = General Data Protection Regulation

GMP = Good Manufacturing Practices

HIRUZ = Health, Innovation and Research Institute UZ Ghent

IB = Investigator’s Brochure

ICF = Informed Consent Form

ICH = International Conference on Harmonisation

IEC = Independent Ethics Committee

IMP = Investigational Medicinal Product

IP = Internet Protocol

LSLV = Last Subject Last Visit

MAH = Marketing Authorization Holder

MSC = Member State Concerned

PI = Principal Investigator

RA = Regulatory Authorities

REDCap = Research Electronic Data Capture

RSI = Reference Safety Information

SAE = Serious Adverse Event

SmPC = Summary of Product Characteristics

SMS = Substance Management System

SUSAR = Suspected Unexpected Serious Adverse Reaction

TERENA = Trans-European Research and Education Networking Association

TLS = Transport Layer Security

# List of references

*List the literature and data that are relevant to the trial, and that provide background for the trial. Please ensure the text contains appropriate cross references to this list. Please list all references according to the Vancouver-style, the Harvard-style or the American Psychological Association (APA) style. An easy way to do this is making use of the bibliography option in Microsoft Word.*

# Appendices

## Appendix 1: *<XX>*

## Appendix 2: *<XX>*