< Title >

*NOTE: text, marked in grey, should be deleted as it is for explanatory purposes only.*

*- 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. This should also be completed in the footer.*

*- Some studies 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.*

*- Sections, marked in yellow, should be completed according to the specifics of the study.*

Acronym / Protocol code < >

Protocol version and date < >

Phase < >

EudraCT n° < >

*Number will be provided by HIRUZ CTU, in case your study is considered a drug study*

Sponsor < >

*Institutions (corporations, governments, etc) that provide any type of support should not be listed as sponsor, but should be mentioned below.*

Financial/Material Support: < >

Coordinating Investigator: < >

*Please add name and contact details.*

< Title >

Protocol Coordinating Investigator signature page

*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 study in compliance with the protocol, any amendments, GCP and the declaration of Helsinki, and all applicable regulatory requirements.

**Investigator:**

 Name:

 Function:

 Institution:

**Date: Signature:**

< Title >

Protocol Site Principal Investigator signature page

I certify that I will conduct the study in compliance with the protocol, any amendments, GCP and the declaration of Helsinki, and all applicable regulatory requirements.

**Investigator:**

 Name:

 Function:

 Institution:

**Date: Signature:**

**Protocol Amendment History:**

*Please list all amendments (substantial and non-substantial) to the protocol and describe the changes. Protocol version number of an amendment should be 2.0, 3.0 etc…*

*Do NOT list draft versions, only versions that are (to be) submitted to the Ethics Committee/FAMHP.*

*Example:*

|  |  |  |
| --- | --- | --- |
| ***Version*** | ***Date*** | ***Description of amendment*** |
| ***2.0*** | ***18/OCT/2019*** |  ***- Page 8 and 11: 1 inclusion criterion added:***  ***Systolic blood pressure must be < 140***  ***mmHg during screening*** ***- throughout the protocol: correction of***  ***spelling errors*** |

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Description of amendment** |
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# LIST OF ABBREVIATIONS

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

AE = Adverse Event

CA = Competent Authority

CI = Coordinating Investigator

CT = Clinical Trial Unit

DIBD = Development International Birth Date

DSMB = Data Safety Monitoring Board

DSUR = Development Safety Update Report

EC = Ethics Committee

eCRF = electronic Case Report Form

EDC = Electronic Data Capture

EPD = Electronic Patient Dossier

FAMHP = Federal Agency for Medicines and Health Products

FPI = First Patient In

GCP = Good Clinical Practice

GDPR = General Data Protection Regulation

GMP = Good Manufacturing Practice

HIRUZ = Health, Innovation and Research Institute UZ Ghent

IB = Investigator’s Brochure

ICF = Informed Consent Form

ICH = International Council for Harmonisation

IMP = Investigational Medicinal Product

IMPD = Investigational Medicinal Product Dossier

LVLS = Last Visit, Last Subject

PI = Principal Investigator

SAE = Seriouse Adverse Event

SAR = Serious Adverse Reaction

SmPC = Summary of Product Characteristics

SOP = Standard Operating Procedure

SUSAR = Suspected Unexpected Serious Adverse Reaction

TERENA = Trans-European Research and Education Networking Association

TLS = Transport Layer Security

# Protocol Summary

*All information in this protocol summary should be found in this protocol, no new information should be described in this summary.*

## Title

< Title of the study >

## Protocol specifics

< EudraCT number >

< Sponsor>

## Study Type and Study Phase

## Aim of the study (including primary endpoints)

## Subjects

### Number of subjects

### Target group

*Describe here which type of subjects/patients are targeted to be included in this study (e.g. patients who are suffering from a certain disease/symptoms)*

## Inclusion and exclusion criteria

## Study Interventions

### IMPs and dosage

### Schematic overview of the data collection & interventions

## Study duration

### For an individual subject

### For the whole study

# Rationale and background

## Rationale

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

## Background

*This section should include:*

*• A summary of findings from nonclinical in vitro or in vivo studies that have potential 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 study and that provide background for the study*

*• Applicable clinical, epidemiological, or public health background or context of the clinical study*

*• Importance of the clinical study and any relevant treatment issues or controversies*

## Risk/Benefit Assessment

*Include an assessment of known 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 study design*

*• Justification as to why the risks of participation in the study outweigh the value of the information to be gained*

A study-specific risk assessment plan (separate document) will be available to address, in detail, the most relevant potential risks and to specify the mitigation of those risks. Risks will be scaled into low, medium and high risks.

## Limitations

*Describe the limitations that are applicable to your study; e.g. limitations in available therapy, sample size, patient subgroups, etc...*

# Objectives

## Primary Objectives

*Provide a description of the study objectives, as well as a justification for selecting the particular objectives*. *Data points collected in the study should support an objective.*

*An objective is the purpose for performing the study 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, or health behavior).*

*The aim is to define the primary research question, to 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)*

*A useful guide to use in the development of a specific research question are the PICOT criteria:*

 *P Population (patients) - What specific patient 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*

## 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)*

# End Points + Time Points

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

## Primary End Points + Time Points

*The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective. Often Phase 2 and 3 studies include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective.*

*The primary endpoint/outcome 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 endpoint/outcome is 28 day survival.” It may be pertinent to list the time point at which endpoint/outcome will be measured if it is possible to be measured more than once during the study.*

## Secondary End Points + Time Points

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

## Tertiary/Exploratory End Points

*To identify any other endpoints/outcomes which are not well established.*

# Study design

## Description of study design

*The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design. A description of the study design should be consistent with the Protocol Summary and should contain following information:*

* *A description of the type/design of study 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 or non-inferiority design)*
* *Phase of the study*
* *Indicate mono- or multicentric*
* *Also, give a short description of the number of study groups/arms and study intervention (duration)*

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

*Also provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the study intervention(s) and control product(s).*

## Start of Study Definition

*Describe here what the first action of recruitment involves (e.g. date of first screening in electronic patient file, hanging posters or providing flyers in the waiting room, first meeting with the first potential patient…)*

*Also describe that the first included patient, the so-called ‘first-patient-in’ (FPI)will be reported to the EC. In addition to this, it should be clearly described what is considered an inclusion (e.g. first subject randomized, first signed ICF…)*

The study is considered started upon the first act of recruitment. For this trial this is considered as …..

The inclusion of the first subject (i.e. …) will be notified to the Central Ethical Committee.

## End of Study Definition

*Adapt the definitions below, in case this is not compliant to your specific protocol*

### For an individual subject

The subject has completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedures, as described in this protocol (see section “9. Study Specific Procedures”).

### For the whole study

Overall, the end of the study is reached when the last study procedure for the last subject has occurred: last subject, last visit (LSLV).

As soon as the whole study has ended (cfr the definition above), the Coordinating Investigator shall notify the HIRUZ Clinical Trial Unit, so that the Competent Authority and the Ethics Committee can be informed in a timely manner according to the regulatory requirements (within 90 days after end of the study, or if the study had to be terminated early, this period must be reduced to 15 days and the reasons should clearly explained).

The end of study report will be submitted to the Competent Authority and the Ethics Committee, no later than 1 year after the end of the study.

## Estimated duration of the study

### For an individual subject

*Describe the estimated time that will be needed for an individual form his first visit up to the last vist.*

### For the whole study

*Describe the estimated time that will be needed to complete the study, i.e. from ‘First Patient in’ (FPI) up to ‘Last Subject Last Visit’ (LSLV).*

# 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.*

• *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old 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, e.g., those criteria that every potential subject must satisfy, to qualify for study entry. Individuals must meet all of the inclusion criteria in order to be eligible to participate in the study. Please list all inclusion criteria below:*

## 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 devices, 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 study:

1. Current use of < specify disallowed concomitant medications*>*
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Treatment with another investigational drug or other intervention within *<*specify time frame*>*
6. Current smoker or tobacco use within *<*specify timeframe*>*
7. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>]

### Screen failures

*Subjects who consent to participate in the clinical study, who do not meet one or more criteria required for participation in the study during the screening procedures, are considered screen failures. Indicate how screen failures will be handled in the study, including conditions and criteria upon which re-screening is acceptable, when applicable.*

*Example text provided as a guide:*

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.

Individuals who do not meet the criteria for participation in this study (screen failure) because of a <specify > may be rescreened.

OR

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

# Target Population

## Subjects

### Number of subjects and planned recruitment rate

*Please determine the number of subjects (and describe the sub-groups if applicable) that you wish to include in your study.*

*Include a sufficient number of subjects if you would like to replace all those who do not complete the study.*

*Realistic estimates of expected accrual rate and duration of subject entry based on estimated sample size should be provided. This section may also include information such as the number of recruiting centres, the size / percentage of the population that is captured by the eligibility criteria, the expected consent rate, and the expected screen failure rate. This information will help sites to determine whether they are likely to be able to recruit their target number of subjects.*

The number of subjects that will be included in this study is: < >. Drop-outs will (not) be replaced

These are divided into following sub-groups:

It is expected that overall an accrual rate of … subjects per month is realistic in the whole study.

### Withdrawal and replacement of subjects

*Describe stopping criteria and reasons for excluding subjects that are already enrolled in the study. Also answer the question if subjects will be replaced if they do not complete the study.*

*Subjects may withdraw voluntarily from the study or the PI may discontinue a subject from the study. This section should state which adverse events would result in discontinuation of study intervention or subject discontinuation/withdrawal.*

Subjects are free to withdraw from participation in the study at any time upon request. A subject must be discontinued from the study if the subject (or legal representative) withdraws consent.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

* Pregnancy
* Significant study intervention non-compliance
* If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
* Disease progression which requires discontinuation of the study intervention
* If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
* Subject unable to receive <study intervention> for [x] days/weeks.
* …

In all cases, the reason why subjects are withdrawn must be recorded in detail in the eCRF and in the subject’s medical records. Prematurely discontinued subjects are not to be replaced automatically. The gathered subject data should be taken into account in the analyses of the study data.

Regardless of the withdrawal reason, the PI must consider the following:

* Procedures for safe discontinuation of participation;
* Retention and use of the data already collected;

A subject will be considered lost to follow-up if he or she fails to return for <specify number of visits> 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 to the clinic for a required study visit:

* The site will attempt to contact the subject and reschedule the missed visit <specify time frame> 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 study.
* Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, 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 study with a primary reason of lost to follow-up.

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

*e.g. Withdrawn subjects will be replaced until ‘x’ subjects have completed the study. If following data is available and/or procedures are completed, the subject will not be replaced:*

*In case of withdrawal, 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 study subject)..*

## Method of recruitment

*Describe:*

• *Source of subjects (e.g., inpatient hospital setting, outpatient clinics, student health service, or 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 study 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 make sure this covers all participating centers and not only the method of the coordinating center!*

## Screening

*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 (but not limited to):*

* *ECG*
* *laboratory tests*
* *scans*

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

# Investigational Medicinal Product (IMP)

*Please describe this for each IMP that will be used in the study. Please copy-paste section 8.1 for each IMP that you have to describe.*

*The protocol should detail if a Summary of Product Characteristics (SmPC) or Investigator Brochure (IB)/ Investigational Medicinal Product Dossier (IMPD) is going to be used.*

## <Name of the IMP>

*The official name as described on the SmPC (if applicable)*

### Composition and active substance of the IMP

*Describe the composition of the IMP, also add if treatment is defined by active substance only (or by brand) and define the active substance.*

### Manufacturer and Distributor of the IMP

*Please add both if these are different entities. Also, describe here who is responsible for the batch release of the IMP.*

### Preparation + Dosage + administration of the IMP

*Describe the preparation process, dosages used and way of administration. 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 GMP requirements (if applicable). Also mention if the IMP will be modified or not (e.g. repackaging or restitution).*

### Permitted dose adjustments and interruption of treatment

*Please include the allowed time window in which the IMP’s 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 patients 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 per IMP; also include the maximal duration of the treatment for a single subject.*

### Packaging and Labeling of the IMP

*Packaging/labeling of the IMP should be in accordance with the relevant GMP guidelines (if applicable).*

*Please add an example of the label that will be used. The hospital pharmacy of Ghent University Hospital can provide a template of the label that can be used (compliant to EudraLex volume 4, Annex 13).*

*Please explain how and by whom the labeling of the IMPs will be performed. (please make sure the description covers all participating centers)*

### Storage conditions of the IMP

*Describe the procedures and conditions for shipment, receipt, distribution, storage, return and destruction of the investigational medicinal product. This should be available for all participating centers.*

*Please describe how temperature deviations during storage should be handled. For details of this procedure, you can refer to an SOP (existing, or created, specifically for this study).*

### Known side effects of the medication

*Describe the most relevant side effects that are mentioned in the SmPC (if applicable) or list the side effects that are previously found in the investigator’s brochure.*

## Concomitant / Rescue Medication

*Concomitant Medication:*

*This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe the data that will be recorded related to permitted concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. Include details about when the information will be collected (e.g., screening, all study visits). Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints) and how the independent effects of concomitant and study 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 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 amendments at a later stage.*

*Rescue Medication:*

*List all medications, treatments, and/or procedures that may be provided during the study for “rescue therapy” and relevant instructions about administration of rescue medications.*

*Example text provided as a guide, customize as needed:*

The study site <will/will not> supply <specify type> rescue medication that will be <provided by the sponsor/obtained locally>. The following rescue medication may be used <specify name(s)>.

Although the use of rescue medication is allowable <at any time during the study>, the use of rescue medication should be delayed, if possible, for at least <insert timeframe> following the administration of <study intervention>. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

# Study Specific Procedures

## Informed Consent

*Please include the informed consent process, as this has to be performed prior to any study-related procedure (including screening).*

## Randomisation/blinding

*If applicable, please describe the randomisation or blinding process. Who is responsible for the randomisation/blinding, how the randomisation will be performed, which software/system will be used (also: see section 12), and where the randomisation codes are to be found… .*

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

### Deblinding procedures

*The timing and procedures for planned and unplanned breaking of randomization codes should be included. 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 HIRUZ and subsequently the EC).*

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

*If the study 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 study are held [please add relevant department]; in the event a code is required to be unblinded a formal request for unblinding will be made by the local Principal Investigator to the Coordinating Investigator.

The CI/PI documents the breaking of the code and the reasons for doing so on the CRF/study documents, in the site file and medical notes. It will also be documented at the end of the study 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 4.3) the coding system in blinded studies should include a mechanism that permits rapid un-blinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

## 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 undertaken.
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 pre-defined time point of the intervention) should be added if applicable. Also add drug compliance checks.*

*For screening details, you can refer to section 7.3*

*You can add the interventions that are performed as standard of care, and not performed on the premise of being included in the study. 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 study.*

*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 AEs/SAEs.*

## 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 study requires a 12 lead EGC this will need to be made clear to avoid potential errors*

*- if specialist, non-standardised assessments are required, care should be taken to detail exactly what needs to happen during the assessment*

*- It is an offence under the data protection act to process data that is irrelevant or excessive for the purpose for which it was collected. CRFs must therefore collect only the information directly relevant to the objectives and outcome measures detailed in the protocol. Collecting additional data not so specified is not permissible.*

## Schematic overview of the data collection & interventions

*Please provide a chronological overview with a timeline (including the allowed time windows – see 9.2)*

*It is important to give a clear view of the procedures per visit (including screening)*

*Example of a table:*

|  |  |
| --- | --- |
| **Procedures** | **Visits** *(insert visit numbers and adapt table as appropriate)* |
| **Screening** | **Baseline** | **Treatment Phase** | **Follow Up** |
| Informed consent |  |  |  |  |  |
| Inclusion/exclusion criteria check |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Add all study specific interventions\* |  |  |  |  |  |
| Drug Compliance |  |  |  |  |  |
| Adverse event check |  |  |  |  |  |
|  |  |  |  |  |  |

*Put an asterisk with all the interventions that are standard of care, so that it remains clear which interventions are study specific and which are not.*

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

## Restrictions for subjects during the study

*Add all relevant restrictions that are in place for subjects participating in the study 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…)*

# Sampling

## Types and number of samples

*List all separate types of samples + the amount and volume of samples that you would like to collect.*

## Timepoints of sampling

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

## Sample Handling & Analysis

*How will the samples be taken and which methods will be used for analyzing them + explain where analysis will be performed?*

## Sample Storage and/or shipping

*Describe the specific storage conditions and locations + the way they will be shipped and in what conditions (if applicable) + in which biobank will they be stored + who will be the medical guardian of the biobank?*

## Future use of stored samples

*Will all samples be destroyed or will you store them after the end of the study? And for which purpose + where and under which conditions will they be stored?*

# Statistical Considerations

## Sample size calculation

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

The outcome(s) on which the sample size calculation is based upon, is/are <outcome name>.

 *Please also provide description (include point in time, method of assessment)*

The calculation of the sample size below used the tool xxxxx and included the following parameters *…. (make sure it can easily be reproduced by a 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, or 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 approach used and provide references to the relevant literature. Please also explain the choice of this approach, and how it achieves the aim of a sample size calculation in terms of i) reassuring about the additional value of the new study, and ii), guide clinical practice in a meaningful way and influence 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/tools that will be used for analyzing the respective data sets. If possible/applicable, split up the methods for primary and secondary outcome measures.*

## Statistical analysis team

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

## Interim analysis

*Will you perform an interim analysis, and for which purpose? If yes, when will this analysis be scheduled (e.g. after a certain number of patients, or after a certain phase in the study)?*

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

# Data handling

*If a data management plan is to be produced separately, state this here and condense the most relevant information below.*

## Method of data collection

*First sentence only if ‘randomisation’ is in RedCap.*

Subjects that are included in the study, will be assigned a unique study number upon their registration in REDCap. On all documents submitted to the coordinating centre, sponsor or CI, patients will only be identified by their study number. The subject identification list will be safeguarded by the site. The name and any other directly identifying details will not be included in the study database.

### Case Report Form

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

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection. 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.

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 Coordinating Investigator.

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

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.

The study site staff is responsible for data entry in REDCap.

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

*Please list data that cannot be traced back to the source documents + motivation*

## Data storage

*During the study and analysis: Is data stored cfr GDPR, which safety measures are in place (e.g. secured servers)?*

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the UZ Gent 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 TERENA (Trans-European Research and Education Networking Association). All study sites will have access to REDCap. Site access is controlled with IP restriction.

## Archiving of data

*Please specify the locations and conditions of archiving.*

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 requirement(s).

## Access to data

*Describe who will have access to the study files, during and after the study.*

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

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 and log files.

# Safety

## Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| **Unexpected Adverse Event** | An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved 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)** | A serious adverse event is any untoward medical occurrence that:* results in death;
* is life-threatening;
* requires inpatient hospitalisation or prolongation of existing hospitalisation;
* results in persistent or significant disability/incapacity; *or*
* consists of a congenital anomaly or birth defect.

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. |
| **Serious Adverse Reaction (SAR)** | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:* in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product;
* in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the study in question.
 |

Attribution definitions

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

*Not related*

An adverse event which is not related to the use of the drug.

*Unlikely*

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.

*Possible*

An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

*Probable*

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), concomitant disease(s).

*Definitely*

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), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

## Reporting requirements

### AE reporting

*Please complete the time period of recording the AE’s. This can be until the end of the study, as described below; but can be changed at the discretion of the investigator.*

AE’s per subject will be recorded from the first drug administration until the end of the study for the subject, as defined in section 5.2.

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

### SAE reporting

*Please complete the number of days at the discretion of the coordinating investigator.*

SAE’s occurring within a period of xx days following the last intake of study medication will be reported as below.

All serious adverse events (initial and follow up information) and pregnancies occurring during this study must be reported by the local Principal Investigator within 24 hours after becoming aware of the SAE to:

* The local ethics committee (it is the responsibility of the local PI to report the local SAE’s to the local EC)
* HIRUZ CTU of the University Hospital Ghent
* The (National) Coordinating Investigator (in case of multicenter studies)
* The company that provides the IMP (as stipulated in the agreement)

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

### SUSAR reporting

In case the Coordinating Investigator, in consultation with HIRUZ CTU, decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), HIRUZ CTU will report the SUSAR to the Central EC and the CA within the timelines as defined in national legislation. The Coordinating Investigator reports the SUSAR to all local PI’s.

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.

### Other reporting requirements

*e.g. 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 IMP’s, according to the agreement)*

HIRUZ CTU: e-mail: hiruz.ctu@uzgent.be

 Tel: +3293320500

Coordinating Investigator: e-mail:

 Tel:

Marketing Authorisation Holder: Name

 e-mail:

 Tel:

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-patients, volunteers), they (or their designee, if appropriate) must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name and a 24-hour emergency contact number.

## Flowchart Reporting

|  |  |
| --- | --- |
| *Type of Adverse Event* | *Action to be taken* |
| AE | List all AE’s per subject in the patient’s file and add this information to the CRF. |
| SAE | Notify to HIRUZ CTU within 24 hours after becoming aware of the SAE + add the SAE to a list that will be reported yearly (see section 13.8). |
| SAR | Notify to HIRUZ CTU within 24 hours after becoming aware of the SAE.🡪 HIRUZ CTU will submit to the central EC🡪 study team informs company that provides the IMP |
| SUSAR | Notify to HIRUZ CTU within 24 hours after becoming aware of the SUSAR.🡪 HIRUZ CTU will submit to the central EC🡪 HIRUZ CTU will submit to the CA🡪 study team informs company that provides the IMP |

In case the (SU)SAR occurs at a local participating site, the local PI or study team should also contact:

* The local Ethics Committee
* The (National) Coordinating Investigator

## Events, excluded from reporting

*Please describe here events/symptoms/… which are excluded from reporting, since these are inherent to the studied patient group.*

## Data Safety Monitoring Board (DSMB)

*Please adjust and complete if this is not the case nor a correct reflection of the current study.
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).*

All study medication is registered and used in current practice. Considering the known safety profile of the study medications and study design, a DSMB is not foreseen.

## Development Safety Update Report

The Coordinating Investigator will provide a DSUR once a year throughout the entire duration of the clinical study, or on request, to the CA, Central Ethics Committee and Sponsor. This DSUR will include all SAE’s (who were not categorized as SAR’s and were not immediately reported to the EC).

The report will be submitted 1 year (+ maximum 60 days) after the ‘Development International Birth Date (DIBD)’ , and will subsequently be submitted each year until the study is declared ended. This DIBD is the date of the sponsor’s first overall authorisation to conduct the clinical trial in any country worldwide.

HIRUZ CTU can provide a template that can be used to complete this DSUR.

# Monitoring/Auditing/Inspection

## Monitoring

### General

Monitoring of the study will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained during an initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) ‘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 ‘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 GCP compatibility
* check on safety reporting compliance
* IMP handling and storage
* review of study data

## Inspection

This study can be inspected at any time by regulatory agencies during or after completion of the study. 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 GDPR, GCP and all other applicable local regulations.

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

## Protocol Deviation policy

Sponsor and all investigators agree to take any reasonable actions to correct protocol deviations/violations noted during monitoring/inspection, in consultation with the monitoring team. All deviations must be documented on a protocol deviation log by the study team that is kept available at any time for monitoring/inspection purposes. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC.

## Serious breach to GCP and/or the protocol

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be clearly documented and will be communicated with the Coordinating Investigator, HIRUZ CTU and possibly both the applicable Ethics Committee(s) and Competent authority.

Please contact HIRUZ CTU asap in case of a serious breach: hiruz.ctu@uzgent.be and/or +3293320500.

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

# Ethical and legal aspects

## Good Clinical Practice

The study will be conducted cfr the latest version of the ICH E6 (R2) GCP 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

*Here you can add specifics regarding the informed consent process, in case this has not been described in section 7.*

Eligible subjects may only be included in the study after providing written (witnessed, if needed)

Ethics Committee-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 study, the investigator must explain to potential subjects or their legal representatives the study and the implication of participation. 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 study, 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 study, 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 study
* which investigator obtained ICF with the date of signature
* if a copy was provided to the patient
* start and end of participation in the study

## Approval of the study protocol

### General

The protocol has been reviewed and approved by the Ethics Committee of the Ghent University (Hospital), designated as the central Ethics Committee, after consultation with the local Ethics Committees, and by the Competent Authority (CA) (FAMHP in Belgium). This study cannot start before both approvals have been obtained, a trial initiation visit has been performed by the monitor and, if applicable, all necessary agreements are finalized.

### Protocol amendments

Any significant change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Central Ethics Committee (and the CA if applicable).

Only amendments that are intended to eliminate an apparent immediate safety threat to patients may be implemented immediately.

Notwithstanding the need for approval of formal protocol amendments, the investigators are expected to take any immediate action, required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor.

## Confidentiality and Data Protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules (in Belgium: 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 study will be limited to those data that are necessary to fulfill the objectives of the study. 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.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

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 pseudonymized OR anonymized throughout the sample storage and analysis process and will not be labeled with personal identifiers.

## Liability and Insurance

The sponsor has taken a no fault insurance for this study (applicable in Belgium), in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2004).

Sponsor: Ghent University OR Ghent University Hospital

Insurance Details: Allianz Global Corporate & Specialty, Uitbreidingstraat 86, 2600 Berchem, Belgium, tel: +32 33 04 16 00

Policy number: BEL000862

## End of Study Notification

If all subjects have completed the study, a notification of the end of the study should be submitted to the (Central) Ethics Committee and the CA. This notification should be made within 90 days of the end of the clinical study. In case of early termination (definition in CT-1, 4.2), this is reduced to 15 days.

# Publication policy

*Do all investigators have a certain role in publication and 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 study 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 study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

# Reference List

*List the literature and data that are relevant to the study, and that provide background for the study. Please ensure the text contains appropriate cross references to this list. Please list all references according to Vancouver-style, Harvard-style or APA-style.*

# Appendices

*Please list all appendices and add them chronologically below.*

## Appendix 1: <name>

…

## Appendix 2: <name>

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