**DEFINITION**

Un protocole de recherche clinique est un **document** décrivant le(s) objectif(s), la conception, la méthodologie, les aspects statistiques et l’organisation de l’essai clinique(Art 2,22° Règlement européen 536/2014).

**INSTRUCTIONS D’UTILISATION**

* Ce document est un modèle de protocole basé sur les directives du règlement européen 536/2014[[1]](#footnote-1) (Annexe 1, D) et les bonnes pratiques cliniques de recherche (ICH GCP[[2]](#footnote-2)).
* Les parties proposées dans ce modèle doivent TOUTES figurer dans votre document final afin de répondre aux requis réglementaires.
* Certains renseignements peuvent également être fournis dans d'autres documents qui doivent être référencés dans le protocole en annexes (brochure d’investigateur, consentement éclairé, contrat de recherche, plan statistique, plan de gestion des risques, plan de monitoring, etc).
* Le texte en rouge qui correspond aux instructions d’utilisation doit être retiré, ainsi que cette première page.
* Le texte en noir doit être conservé.
* Vous pouvez modifier les styles de titres et de mise en page. N’oubliez pas de mettre à jour la table des matières.
* Chaque version de protocole doit être numérotée et datée en pied-de-page.
* Le protocole doit être écrit en anglais.
* Format final pour la soumission : PDF

Title page

The title page should contain the following information:

* Protocol title
* Clinical Development phase
* Acronym
* Protocol identification (code or number)
* Name of test drug/investigational product.
* EuCT Number = numéro européen d’identification généré lors de la création de l’étude sur le portail CTIS (voir guichet central académique)
* Sponsor
* If not apparent from the title, a brief (one to two sentences) description giving design (parallel, cross-over, blinding, randomized) comparison (placebo, active, dose/response), duration, dose, and patient population
* Name and affiliation of principal investigator (address and phone number)
* Name and affiliation of coordinating investigator(s) (address and phone number)
* Name of the Sponsor including the name of Responsible medical head and address and phone/fax numbers
* Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor or Institution (principal Investigator, sub investigators)
* Identification and full contact details of the centralized laboratory and/or any other centralized medico-technical service

The information contained in this document is the property of the Sponsor/Co-ordinating/Principal Investigator and may not be reproduced, published or disclosed to others without written authorization of the Sponsor/Co-ordinating Principal Investigator.

* Version and date of protocole

Version History

| **Version** | **Approval Date** |  | **Changes** |
| --- | --- | --- | --- |
| 1  |  | Original |  |
| 2 |  | Amendment  |  |
| 3 |  | Amendment |  |
| 4 |  | Amendment |  |

1. Signature page

**SPONSOR REPRESENTATIVE**

 Name Signature Date

**INVESTIGATOR (S)**

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects.

I agree to personally conduct or supervise this trial and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with the protocol, Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I will ensure that the requirements relating to Regulatory Authorities and Ethics Committee review and approval are met.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements including the provision of direct access to data and source documents.

I agree to promptly report to the Regulatory Authorities and EC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Regulatory Authorities approval, except where necessary to ensure the safety of study participants.

 Name Signature Date

 Name Signature Date

1. Protocol synopsis

|  |
| --- |
| Name of Sponsor/Company: |
| Name of Finished Product : |
| Name of Active Ingredient : |
| Title of Study |
| Indication |
| Study centre(s)  |
| Publication (reference) |
| Studied period (years): (date of first enrolment) (date of last completed)  | Clinical Phase:  |
| Objectives: - Primary - Secondary |
| Hypotheses |
| Study Design (Treatment Schema) |
| Number of patients (planned and analysed) |
| Endpoints : - Primary- Secondary |
| Diagnosis |
| Main criteria for inclusion (inclusion/exclusion criteria) |
| IP dosage and mode of administration :  |
| Procedures : Schedule of assessments – Study Flowchart |
| Duration of treatment :  |
| Statistical Considerations |

1. Schedule of activities

Insert the study flowchart

Table des matières à mettre à jour

Pour que vos titres soient repris dans la table des matières, vous devez utiliser des styles de titres configurés dans le document. Utilisez les titres proposés dans la barre d’outils du document Word ou créez vos propres styles de titres.

Table of contents

[1. Signature page 4](#_Toc142656994)

[2. Protocol synopsis 5](#_Toc142656995)

[3. Schedule of activities 6](#_Toc142656996)

[4. List of abbreviations and definitions 9](#_Toc142656997)

[5. Ethics 10](#_Toc142656998)

[6. Objectives 11](#_Toc142656999)

[6.1. Primary 11](#_Toc142657000)

[6.2. Secondary 11](#_Toc142657001)

[6.3. Endpoints 11](#_Toc142657002)

[7. Background Information and Scientific Rationale 12](#_Toc142657003)

[7.1. Medical Background 12](#_Toc142657004)

[7.2. Drug Profile 12](#_Toc142657005)

[7.3. Rationale 12](#_Toc142657006)

[8. Investigational plan 13](#_Toc142657007)

[8.1. Design 13](#_Toc142657008)

[8.2. Description of population 13](#_Toc142657009)

[8.3. Strategies for participant recruitment 13](#_Toc142657010)

[8.3.1. Recruitment process 13](#_Toc142657011)

[8.3.2. Informed consent process 14](#_Toc142657012)

[8.4. Participants eligibility 16](#_Toc142657013)

[8.4.1. Inclusion criteria 16](#_Toc142657014)

[8.4.2. Exclusion criteria 16](#_Toc142657015)

[8.4.3. Withdrawal 16](#_Toc142657016)

[8.4.4. Patient follow-up 16](#_Toc142657017)

[8.5. Treatments 16](#_Toc142657018)

[8.5.1. Treatments Administered 17](#_Toc142657019)

[8.5.2. Identity of Investigational Products(s) 17](#_Toc142657020)

[8.5.3. Method of Assigning Participant to Treatment Groups 17](#_Toc142657021)

[8.5.4. Selection of Doses in the Study 17](#_Toc142657022)

[8.5.5. Selection and Timing of Dose for Each Patient 17](#_Toc142657023)

[8.5.6. Blinding 17](#_Toc142657024)

[8.5.7. Prior and concomitant therapy 17](#_Toc142657025)

[8.5.8. Treatment Compliance 17](#_Toc142657026)

[8.5.9. Investigational product management 17](#_Toc142657027)

[8.6. Study Procedures 18](#_Toc142657028)

[8.6.1. Sample lab collection 18](#_Toc142657029)

[8.7. Efficacy and Safety Variables 18](#_Toc142657030)

[8.7.1. Efficacy and Safety Measurements Assessed and Flow Chart 18](#_Toc142657031)

[8.7.2. Appropriateness of Measurements 18](#_Toc142657032)

[8.7.3. Primary Efficacy Variable(s) 18](#_Toc142657033)

[8.7.4. Drug Concentration Measurements 18](#_Toc142657034)

[8.8. Safety Reporting 19](#_Toc142657035)

[8.8.1. Definitions and reporting process 19](#_Toc142657036)

[8.8.2. Assessing, Recording, and Analyzing Safety Parameters 20](#_Toc142657037)

[8.9. Site Monitoring Plan 23](#_Toc142657038)

[8.9.1. Monitoring team 23](#_Toc142657039)

[8.9.2. Scope 23](#_Toc142657040)

[8.10. Data Quality Assurance 23](#_Toc142657041)

[8.11. Statistical Analysis 24](#_Toc142657042)

[8.12. Changes in the Conduct of the Study or Planned Analyses 24](#_Toc142657043)

[8.13. Protocol Amendements 24](#_Toc142657044)

[9. Protocol Deviations 25](#_Toc142657045)

[10. Data Management Responsibilities 25](#_Toc142657046)

[10.1. Data handling and record keeping 25](#_Toc142657047)

[10.2. Case Report Form 26](#_Toc142657048)

[10.3. Data storage 26](#_Toc142657049)

[10.4. Access to data 26](#_Toc142657050)

[10.5. Data breach 26](#_Toc142657051)

[11. Finance and Insurance 27](#_Toc142657052)

[12. End of trial 27](#_Toc142657053)

[12.1. For an individual subject 27](#_Toc142657054)

[12.2. For the whole study 28](#_Toc142657055)

[13. Dissemination of Results and Publication Policy 28](#_Toc142657056)

[14. Archiving 28](#_Toc142657057)

[15. Study Report 28](#_Toc142657058)

[16. Literature References 28](#_Toc142657059)

[17. Appendix 28](#_Toc142657060)

1. List of abbreviations and definitions
2. Ethics
* *This protocol, any protocol amendments, informed consent form and other relevant documents (eg. recruitment advertisements) will be submitted to the Regulatory Authorities (RA) for formal approval to conduct the study. The decision of the RA concerning the conduct of the study will be made in writing to the sponsor via CTIS portal. All correspondence with the RA should be find in the portal.*
* *The study will be conducted in accordance with legal and regulatory requirements (European Regulatory 536/2014, Belgian law for clinical trials of 7 May 2017, Belgian law of 7 May 2004, Belgian law for Patient rights 22 August 2002, Private life GDPR 2018), as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the last version of Declaration of Helsinki (World Medical Association).*
* *All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC designed by the RA. The formal consent of a subject, using the EC-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The written informed consent document should be prepared in the language of the potential patient population.*
* *The identity of the participant will remain kept confidential according to the General Data Protection Regulation of 27 April 2016 (in application on 25 May 2018), to the Belgian law of 30 July 2018 on the protection of natural persons with regard to the processing of personal data and the Belgian patient’s right law (22 August 2002). Personal data will be coded. Subjects will not be identified by name or in any other recognizable way in any of the records, results or publications related to the experiment.*
1. Objectives

*Goals are broad statements of what the proposal hopes to accomplish. They create a setting for the proposal. Specific objectives are statements of the research question(s). Objectives should be simple (not complex), specific (not vague), and stated in advance (not after the research is done). After statement of the primary objective, secondary objectives may be mentioned.*

* 1. Primary
	2. Secondary
	3. Endpoints
1. Background Information and Scientific Rationale
	1. Medical Background

Literature Revue: (references listed)

* The name and description of the study intervention/investigational products(s)
* Scientific explanation to define the issue : Discussion of important literature and data that are relevant to the trial and that provide background for the trial
* Justification of the study considering the current knowledge: A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance, and a summary from relevant clinical trials
* Benefits expected for the research : Importance of the study and any relevant treatment issues or controversies
* Perspectives for the scientific community, the hospital, the public health.
	1. Drug Profile

Substance, toxicology, pharmacokinetics, clinical studies.

* 1. Rationale
* Description of the route of administration and justification, dosage, dosing regimen, intervention periods, and selection of study population
* Statement of the hypothesis
* Discussion of known risks and benefits, if any, to human subjects
* A summary of the known and potential risks and benefits, including an assessment of the expected benefits and risks; for participants in a clinical trial in an emergency situation, the scientific grounds for considering that their participation is likely to produce a direct clinically relevant benefit are documented;
* Where patients have been involved in the design of the clinical trial, a description of how they were involved;
* An analysis of the relevance of the clinical trial
1. Investigational plan
	1. Design

Definition of the characteristics of the biomedical research by standard terms

* Physio-(patho)logical experimentation, genetic, epidemiological, genetics, therapy,…
* Monocenter or multicenter (national or international) ; number of centers
* Clinical Phase
* With or without direct individual benefit
* Nature of control(s) (e.g., placebo, no treatment, active drug, dose-response)
* Method of assignment to treatment (randomization, stratification)
* Number of study groups/arms
* Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators, and unblinded patients and/or investigators)
* Prospective, retrospective
* Study configuration : parallel groups or cross-over
* Approximate time to complete study enrollment
* Expected duration of subject participation
* Description of the sequence and duration of all trial periods, including follow-up
* Methods for collecting data for assessment of study objectives
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)
* Interim analysis plans
	1. Description of population
* Patient population studied

a description of the groups and subgroups of participants in the clinical trial, including, if applicable, groups of participants with specific needs, e.g., age, gender, participation of healthy volunteers, participants with rare and ultra-rare diseases

* Number of patients planned
	1. Strategies for participant recruitment
		1. Recruitment process

Detailed description of the recruitment process :

* How will potential participants be identified?
* What resources will be used for recruitment? (Describe the format of the resources, e.g. paper or electronic and how these will be presented to potential participants e.g. via the post, in the clinic, through social media or on the radio)
* Provide a clear indication of what the first act of recruitment is
* Will identification of potential participants involve access to identifiable information? If yes, describe what measures will be in place to confirm that access to this information will be lawful
* Who will be approaching potential participants and who will be obtaining informed consent? (Describe the professional role and whether there is a prior clinical relationship with potential participants)
	+ 1. Informed consent process

Information related to the clinical trial and therapeutic alternatives is provided to patients or their legal representative by the investigator during the consultation, according to the requirements pertaining to consent covered by ICH-GCP (E6).

There are also informed they could withdraw their consent at any time during the study without any consequence. This point is written in the informed consent form.

Patients or their legal representative receive the patient information and consent form and have time to think about their participation to the trial (how many time ?). They have the opportunity to ask questions to the investigator (by email, phone or in consultation).

Patients or their legal representative come back after the reflection period. The investigator makes sure they have understood the information. They sign and date the informed consent form simultaneously with the investigator.

Patients or their legal representative receive a copy of the signed informed consent form.

If patients or their legal representative refuse the trial, they will receive the standard treatment.

Special requirements : keep the applicable text below

* participants with temporary or definitive disabilities to give consent (intensive care/emergency unit, cognitive disorders, participants deprived of their rights) : not applicable (delete the following text) or (delete “not applicable”) provide justification for recruiting incapacitated adults. The legal representative expresses in place of the participant who will be invited to sign an informed consent form as soon as he/she retrieves his/her ability to give his/her consent, at any moment during the clinical trial. In case of disability, the legal representative exercises the rights of the patient. The adult participant who is unable to give his consent in full knowledge is associated to the decision as much as possible and taking into account his ability of understanding (importance to provide an adapted oral information).
* emergency situations where an informed consent cannot be obtained prior the inclusion of the participant : not applicable (delete the following text) or (delete “not applicable”) describe why it would not be possible to obtain consent from potential participants or a legal representative prior to recruiting into the clinical trial. The investigator will document the approaches to have a contact with the legal representative of the participant. The investigator will verify if the patient has not expressed any previous objection to participate in the clinical trial. This information is written in the patient’s chart. The participant will be invited to sign an informed consent form as soon as he/she retrieves his/her ability to give his/her consent, at any moment during the clinical trial.
* participants unable to sign or read the inform consent form (because of a health issue) : not applicable (delete the following text) or (delete “not applicable”) an impartial witness should be present during the entire process of consent. The impartial witness will be identified (complete with description of how the witness is identified). After the written consent document and any other written information to be provided to participants have been read and explained to the participant or his legal representative, and after the participant or his legal representative has orally consented to his participation in the trial and, if capable of doing so, has personally signed and dated the consent document, the witness must personally sign and date the consent document. By signing the consent document, the witness attests that the information contained in the consent document and any other written information has been accurately explained and apparently understood by the participant or his/her legal representative, and that consent has been freely given by the participant or his/her legal representative.
* potential participants (or their legal representative) who do not speak the national language : not applicable (delete the following text) or (delete “not applicable”) the inform consent will be also given in different languages (Dutch, English and French). If necessary, an impartial translator should be present during the entire process of consent. Translator could be asked to our social department or could be a participant’s family member. After the written consent document and any other written information to be provided to participants have been read and explained to the participant or his legal representative, and after the participant or his legal representative has personally signed and dated the consent document, the translator must personally sign and date the consent document. By signing the consent document, the translator attests that the information contained in the consent document and any other written information has been accurately explained and apparently understood by the participant or his/her legal representative, and that consent has been freely given by the participant or his/her legal representative.
* Minors : not applicable (delete the following text) or (delete “not applicable”) provide justification for recruiting minors. Information would be given to the two parents, guardian or other mandated representative of the minor participant. The inform consent form would be signed by them. The minor should be involved in the process of informed consent, taking into account his age, his maturity degree (capacity of understanding) and his medical care if he is selected to participate. The deliberate objection of a minor to take part to the experiment should always be respected even if the parents gave their consent except if the child needs a treatment not yet available out of the experiment, if experimental intervention could be therapeutically beneficial or if no other therapies are possible. In this particular context, if the child is very young or immature, a parent or a guardian can skip this objection. If the child is older and closer to be able to give his consent, the investigator must try to get the express assent or the favorable opinion of the Ethics Committee to begin or continue the experimental treatment. After the age of 6 years, the minor should sign an information form adapted to his age and capacity of understanding.

The minor participant would sign an inform consent form when he reaches the age of legal competence. At this time, the participation will be rediscuss between the participant and the investigator.

Remarks : The participant’s legal representative is the person designated by a written mandate dated and signed by both parties to represent the rights and defend the interests of the participant. If there is no legally designated person, the legal representative would be, in order, the cohabitant (spouse, legal or effective), the adult child, the father or mother, the adult brother or sister.

* 1. Participants eligibility

Characteristics of the subjects to be included: age, sex, weight, size, race, medical history, biological parameters, definition of the pathology and the enumeration of its characteristics.

Rationale for gender and age distribution of participants

Justification for inclusion of participants unable to give informed consent or other special populations such as minors

* + 1. Inclusion criteria

Provide a statement that subjects must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion.

* + 1. Exclusion criteria

Provide a statement that all subjects meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

If individuals of a specific gender or age group are not included in clinical trials or are underrepresented in clinical trials, an explanation of the reasons and justification for these non-inclusion criteria

* + 1. Withdrawal

Provide a list of reasons for which subjects may be discontinued from the study. Also note that subjects may withdraw voluntarily from participation in the study at any time. Describe the efforts to follow subjects who withdraw from the study.

* + 1. Patient follow-up

A description of how participants will be cared for after their participation in the clinical trial, if additional care is required as a result of their participation in the clinical trial and if it differs from the care normally expected for their medical condition.

* 1. Treatments

A statement as to whether the investigational and ancillary medicinal products used in the clinical trial are authorised; if so, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations; and, if not authorised, a justification for the use of unauthorised ancillary medicinal products in the clinical trial is provided

Where a clinical trial is conducted with an active substance available in the Union under different trade names and present in a number of authorised medicinal products, the protocol may define the treatment only in terms of the active substance or the Anatomical Therapeutic Chemical (ATC) classification code (levels 3 to 5), without specifying the trade name of each product

* + 1. Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described.

Route and mode of administration, dose, and dosage schedule.

* + 1. Identity of Investigational Products(s)

Brief description of the test drug(s)/investigational product(s) (formulation, strength, storage, dose)

* + 1. Method of Assigning Participant to Treatment Groups

The specific methods used to assign patients to treatment groups, to screen and randomize eligible patient, perform subsequent assignment, manage initial/resupply ordering of drug supplies and handle emergency unblinding (e.g. IVRS, IWRS …) should be described.

* + 1. Selection of Doses in the Study

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

* + 1. Selection and Timing of Dose for Each Patient

Assignment of medication numbers to eligible patients should be described (e.g. IVRS, IWRS …).

Time of day, interval of dosing and the relation of dosing to meals should be described and, if timing was not specified, this should be noted.

* + 1. Blinding

Procedure for breaking the blinding or rationale for no blinding should be explained.

* + 1. Prior and concomitant therapy

Medication allowed before and during the trial

Drug-drug interactions and effect on trial endpoints

* + 1. Treatment Compliance

Description of measures taken to ensure and document treatment compliance (e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring).

* + 1. Investigational product management

A description of the procedures adopted for the traceability, retention, destruction and reshipment of investigational medicinal products and unauthorized ancillary medicinal products

Procedures for accountability for the provision and administration of drugs to participants, including the maintenance of the blinding procedure, if applicable

* 1. Study Procedures

Refer to the Schedule of activities (Study Flowchart)

The schedule must include clinic visits (screening, study period, follow-up visits), all contacts (e.g., telephone contacts) and all study procedures to be done during the protocol.

The protocol should specify the time that each phase of the project is likely to take, along with a detailed month by month timeline for each activity to be undertaken.

* + 1. Sample lab collection

A description of the arrangements for complying with applicable rules for the collection, storage and future use of biological samples from clinical trial participants, if applicable, unless provided in a separate document

* 1. Efficacy and Safety Variables
		1. Efficacy and Safety Measurements Assessed and Flow Chart

Schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration), methods for measurements and persons responsible, specific instructions, definitions used to characterize outcome, laboratory techniques.

Means of obtaining AE data.

AE rating (seriousness, severity).

* + 1. Appropriateness of Measurements

If any of the efficacy or safety assessments was not standard, its reliability, accuracy, and relevance should be documented.

* + 1. Primary Efficacy Variable(s)

The primary measurements and endpoints used to determine efficacy should be clearly specified.

* + 1. Drug Concentration Measurements
* Drug concentrations to be measured
* Sample collection times
* Periods in relation to the timing of drug administration
* Relation of drug administration and sampling to ingestion of food, posture, and the possible effects of concomitant medication/alcohol/ caffeine/nicotine
* Biological sample measured, handling of samples (storage, labeling …) and method of measurement used (referring to published and/or internal assay validation documentation for methodological details).
* Other (e.g. pharmacodynamics, pharmacogenomics, …)
* Samples shipment: frequency, address and contact information for laboratory personnel (Include days and times shipments are allowed, any labeling requirements for specimen shipping and any special instructions such as dry ice or wet ice or the completion of a specimen-tracking)
	1. Safety Reporting
		1. Definitions and reporting process

**ADVERSE EVENT (AE)**

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

**SERIOUS ADVERSE EVENT (SAE)**

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

* Results in death;
* Is life-threatening (immediate risk of death);
* Requires inpatient hospitalization or prolongation of existing hospitalization;
* Results in persistent or significant disability/incapacity;
* Results in congenital anomaly/birth defect.

**SUSARS**

For the purpose of regulatory reporting, SPONSOR will determine the expectedness of events suspected of being related to study drug based on the SmPC. Sponsor will report in an expedited manner to Regulatory Authorities and Ethics Committee concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with European Regulatory 536/2014 and in accordance with country-specific requirements. Sponsor shall notify the Investigator of any AE associated with the use of study drug in this study that is both serious and unexpected (ie, SUSAR).

**ANNUAL SAFETY REPORT (ASR):**

The sponsor writes a safety report annually. The sponsor sends the report about the safety of the trial medication to the regulatory authority.

The key date is the date of the first authorization of the clinical trial by the regulatory authority. All data obtained up to this date (each year) will be included in the ASR. Beginning with the key date, there is a time-limit of 60 days for the preparation and submission of the ASR.

Other definition if relevant :

**UNBLINDING PROCEDURE:**

In this double blind trial, the investigator assesses seriousness, causality and expectedness as if the patient was receiving the study medication.

As regards to the sponsor, if the event is considered as a SUSAR the blind will be broken only for that specific subject.

Only those events occurring among patients on active drugs will be considered to be SUSARs requiring reporting to the regulatory authority and ethics committee.

The investigator must notify the sponsor of each unblinding performed.

* + 1. Assessing, Recording, and Analyzing Safety Parameters

The evaluated risk for this trial is a xxx risk.

**Adapt the text below to the protocol-specific reporting procedures**

* + - 1. Time Period and Frequency for Collecting AE and SAE Information

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has signed the consent through last patient visit**.** Collect all non-serious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of xxx days following discontinuation of dosing.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, the severity and the seriousness of the adverse event.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

All SAEs must be collected and require immediate (within 24 hours) notification from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within xxx days following discontinuation of dosing. The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure.

In the event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For reported death of a subject, whatever the cause could be, the investigator shall supply the sponsor with any additional information requested.

The investigator uses the standard CIOMS SAE FORM (see Appendix) to submit the SAE to the sponsor. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

* + - 1. Method of Detecting AEs and SAEs

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant’s legally acceptable representative).

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

AEs including SAEs occurring during at home period should be collected during in-clinic visits or during call with participants, and reported as early as possible (In the case of SAE, within 24 hours of learning of the event).

* + - 1. Follow-up of AEs and SAEs

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious.

For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.

All identified non-serious AEs and/or laboratory abnormalities must be recorded and described on CRF.

* + - 1. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator’s Brochure.

The Sponsor or designee must report to regulatory authorities :

* Via CTIS portal :
	+ Unexpected events : Events that affect the benefit-risk balance of a [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) that were unforeseen, e.g. an unexpected increase in the incidence of expected [serious adverse reactions](https://www.ema.europa.eu/en/glossary/serious-adverse-reaction) that may be clinically important. Unexpected events do not include SUSARs.
	+ Urgent safety measures : Measures taken to protect [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) subjects due to an unexpected event that is likely to seriously affect the benefit-risk balance of the [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial)
	+ Annual safety reports : Yearly updates on the safety of each [investigational medicinal product](https://www.ema.europa.eu/en/glossary/investigational-medicinal-product) used in a [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial)
* Via EudraVigilance portal :
	+ Suspected unexpected [serious adverse reactions](https://www.ema.europa.eu/en/glossary/serious-adverse-reaction) (SUSARs) : as soon as possible and at the latest within 7 days for any event resulting in death or endangering the life of the participant; at the latest within 15 days for any other event.
		- 1. Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for xx months after study product administration, the investigator must immediately notify the sponsor.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported au sponsor. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

* + - 1. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the CRF :

* Any laboratory test result that is clinically significant or meets the definition of an SAE
* Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted
* Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

* 1. Site Monitoring Plan

The document *AAHRPP-DSQ-023 Monitoring Plan* will be completed by the CRA responsible to conduct the study monitoring.

Site monitoring is conducted to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH and regulatory guidelines.

Monitoring of the study will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained in an initiation visit. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) ‘Monitoring plan’ (see Appendix). The investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

* + 1. Monitoring team

Monitoring services will be provided in collaboration with the clinical trial centre of the Cliniques universitaires Saint-Luc. All relevant contact details (e.g. primary contact person) can be found in the ‘Monitoring plan’ (see Appendix).

* + 1. Scope

Quality control measures will be followed throughout the study. The clinical study monitor will observe the progress of the study. Contacts with the investigator and on-site visits for the purpose of data review will occur in collaboration with the clinical trial centre of the Hospital Saint-Luc. The monitor will ensure compliance of the study site with the protocol, applicable SOPs and guidelines as described in this protocol. The review of the subjects’ medical records will be performed in a manner to ensure that subject confidentiality is maintained. The investigator agrees to allow the monitor access to any or all of the study materials needed for the monitor to properly review the study progress. The investigator (or deputy) agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit.

* 1. Data Quality Assurance

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 20 July 2018 and 22 Aug. 2002].

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil 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. The investigator will ensure that the confidentiality of subjects' data will be preserved. On CRFs or any other documents, the subjects will not be identified by their names, but by their study number. Documents that identify the names of participants against their study number will be maintained by the investigator in strict confidence.

Monitors, auditors and other authorized agents will be granted direct access to study subject’s original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study at meetings or in publications, the subjects’ identity will remain confidential.

* 1. Statistical Analysis

Use the document *AAHRPP-DSQ-020 Statistical Analysis Plan (guideline)* to complete this section

* Reasons for the sample size selected, statistical power of the study, level of significance to be used
* Describe planned analyses, comparisons and statistical tests
* Reasons for excluding subject from an analysis
* Planned monitoring of the results
* Frequency and nature of interim analyses
	1. Changes in the Conduct of the Study or Planned Analyses

In the event that the Ethics Committee requires, as a condition of approval, substantial changes to the clinical protocol, or in the event of a decision to modify the previously accepted clinical protocol, the investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment describing any change to the clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be notified to the Ethics Committee(s).

* 1. Protocol Amendements

If amendments to the protocol (modifying sense or objectives or modifying the undergone constraints or the risks incurred by the subjects) turn out to be necessary, they will be subjected at first opinion of the promoter of the study. After agreement by the promoter, these amendments will then be submitted to the opinion of the Regulatory Authorities and Ethic Committee having examined the initial protocol.

1. Protocol Deviations

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.

1. Data Management Responsibilities

1) Data management plan : Complete the document *AAHRPP-DSQ-021 Data Management Plan* if the study has an high risk level. Place this document in appendix and refer to it. Remove all information below in this case.

2) no data management plan :

* 1. Data handling and record keeping

Subjects who are included in the study will be assigned a unique study number. On all documents submitted to the sponsor, 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.

An electronic case report form (eCRF) will be used in REDCap software. The eCRF will be completed for subjects who have signed the informed consent. This eCRF will include specific pages for inclusion and exclusion criteria, and for reporting each visit. Other specific pages will be dedicated to concomitant treatments and AEs (non-serious and serious). The investigator will review, approve and validate each completed eCRF; the investigator’s signature (validation) serving as attestation of the investigator’s responsibility for ensuring that all data entered on the eCRF are complete, accurate and authentic.

All data will be processed according to the principles that the new European General Data Protection Regulation (GDPR) imposes, which is in force since 25 May 2018.

1. Who will responsible for the processing of personal data?

complete

2. Who is Data Protection Officer for the processing?

The institutional DPO could be reached by this email address : rgpd@saintluc.uclouvain.be

3. The purpose of the processing:

* Scientific research

4. The legal basis of the processing:

* Consent, but this can be withdrawn

4. Who are potential recipients of the personal data?

* All researchers involved in this clinical trial or in research projects that use materials original from this clinical trial. Staff involved in monitoring and ethical evaluation and people from competent authorities. Subcontracted parties that perform analysis on study-related data or materials.

5. It is possible that the personal data will be viewed by people who are in countries that do not use the same standards as the EU in terms of legal protection of data. In that case, we guarantee that the conditions of European and Belgian legislation on the protection of personal data will be respected.

6. The storage period:

* Study-related documents will be stored for at least 25 years, data included in the medical file for 30 years.
	1. Case Report Form

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.

The eCRFs will be developed, based on the protocol. The final eCRF design will be approved by the Co-ordinating/Principal 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) and any errors or inconsistencies will be clarified. The investigator must verify that all data entries in the eCRF are accurate and correct.

REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the CUSL. REDCap is a web-based system.

* 1. Data storage

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Cliniques universitaires Saint-Luc campus and meets hospital level security and back-up requirements.

* 1. Access to data

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. Any activity in the software is traced and transparent via the audit trail and log files.

* 1. Data breach

A description of the measures taken to comply with the rules in force relating to the protection of personal data, and in particular the technical and organizational arrangements that will be applied to prevent unauthorized access, disclosure, dissemination, modification or loss of the information and personal data processed

A description of the measures that will be applied to guarantee the confidentiality of the information and personal data of the participants

A description of the measures that will be applied in the event of a data security breach, in order to mitigate the possible adverse effects

The Sponsor or designee must report to regulatory authorities, via CTIS portal, serious data breaches : transgressions against the [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) protocol or the [Clinical Trials](https://www.ema.europa.eu/en/glossary/clinical-trial) Regulation that are likely to significantly affect the safety and rights of a subject or the reliability and robustness of the data generated in the [clinical tria](https://www.ema.europa.eu/en/glossary/clinical-trial)l.

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, the sponsor and possibly both the applicable Ethics Committee(s) and Competent authority.

1. Finance and Insurance

The sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2017).

The subjects taking part in this study will be covered by the insurance taken by the sponsor, if they were to suffer any prejudice as a result of taking part in the study and according to ICH-GCP requirements, the institution has taken out personal liability insurance with an Insurance company following the Belgian regulations. This insurance was taken out with MS Amlin Insurance SE.

Policy holder:

Cliniques universitaires Saint-Luc

Avenue Hippocrate, 10

1200 Brussels

Issuer of the certificate of insurance:

MS Amlin Insurance SE

Boulevard du Roi Albert II, 37

1030 Brussels

N° de police : LXX00259

See details of the research funding and any cost which will be incurred in Appendix (déclaration financière).

No compensation is offered to trial participants. Participants will not pay for study drugs and procedures outside the scope of standard care (detailed in the financial statement).

1. End of trial
	1. For an individual subject

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

* 1. 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 co-ordinating/Principal Investigator shall notify the sponsor, 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 the 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).

1. Dissemination of Results and Publication Policy

This trial is registered on EU Clinical Trials portal (<https://euclinicaltrials.eu/home>) and is available to the public.

Study results will be published on EU Clinical Trials portal one year after the end of the study.

Duly justified reasons for submitting the summary of clinical trial results after more than one year

1. Archiving

Essential clinical trial documents are kept for 25 years after the end of the study, in accordance with the Art. 58 of the EU regulation 536/2014.

Source documentation are kept for 30 years, according to the Belgian legislation (Art 35 Belgian Law of 22 April 2019).

Specify who archives, where and access conditions.

1. Study Report

Deadline of writing final report, who will draft it and to whom it will be transmitted.

1. Literature References

List of bibliographic references related to the clinical investigation

1. Appendix
* Monitoring plan
* CIOMS SAE form

**CIOMS SAE FORM**

|  |  |
| --- | --- |
| **SERIOUS ADVERSE EVENT REPORT** |  **SUSAR** (Suspect Unexpected Serious Adverse Reaction): **⁯ YES ⁯NO** |
| PROTOCOL NAME: |
| ETHICS COMMITTEE REFERENCE NUMBER: | EUDRACT / SITE N° / PATIENT N° …. - …… - .. / … / ….  |

**I. REACTION INFORMATION**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1. PATIENT INITIALS  | 1a. COUNTRY  | 2. DATE OF BIRTH  | 2a. AGE  | 3. SEX  | 4-6 REACTION ONSET  | 9-12 CHECK ALL APPROPRIATE |
| (first, last)  |    | Day  | Month  | Year  | Years  |    | Day  | Month  | Year  | TO ADVERSEREACTION  |
| 7 DESCRIBE REACTION(S) (including relevant tests/lab data)  | PATIENT DIED INVOLVED ORPROLONGEDINPATIENTHOSPITALISATION INVOLVEDPERSISTENT ORSIGNIFICANTDISABILITY ORINCAPACITY LIFETHREATENINGCONGENITAL ANOMALYOTHER MEDICALLY IMPORTANT CONDITION |
| 8 MedDRA : SYSTEM ORGAN CLASS LOWEST LEVEL TERM  |
| 14: OUTCOME: DAY/MONTH/YEAR: …. / …. / ….RESOLVED: RESOLVED WITH SEQUELAEONGOING: UNKNOWN: FATAL (+date of death):  |

**II. SUSPECT DRUG(S) / DEVICE(S) INFORMATION**

|  |  |
| --- | --- |
| 15. SUSPECT DRUG(S) (include generic name)/ DEVICE(S) | 22. DID REACTIONABATE AFTERSTOPPING DRUG / REMOVING DEVICE? YES NO NA  |
| 16. CAUSALITY: CERTAIN: PROBABLE: POSSIBLE: UNLIKELY: CONDITIONAL: UNASSESSABLE: |
| 17. DAILY DOSE(S)  | 18. ROUTE(S) OF ADMINISTRATION  | 23. DID REACTIONREAPPEARAFTER REINTRODUCTION? YES NO NA  |
| 19. INDICATION(S) FOR USE  |
| 20. THERAPY DATES (from/to)  | 21. THERAPY DURATION |

**III. CONCOMITANT DRUG(S) AND HISTORY**

|  |
| --- |
| 24. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)    |
| 25. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)    |

**IV. INVESTIGATOR INFORMATION**

|  |  |
| --- | --- |
| 26a. NAME OF REPORTER  | 28-28a. NAME AND ADDRESS OF INVESTIGATOR |
| 26b. MFR CONTROL NO. |  26c. DATE RECEIVEDBY MANUFACTURER |
| 26d. REPORT SOURCESTUDY LITERATUREHEALTH PROFESSIONAL REGULATORY AUTHORITY OTHER | SPONSOR USE: REPORT NO. |
| DATE OF THIS REPORT  | 27a. REPORT TYPEINITIAL FOLLOW-UP  | INVESTIGATOR / REPORTER SIGNATURE |

1. [Règlement 536/2014 du parlement européen et du conseil du 16 avril 2014 relatif aux essais cliniques de médicaments à usage humain](https://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32014R0536&from=FR) [↑](#footnote-ref-1)
2. [ICH GCP E6 (R2) Guide de bonnes pratiques cliniques](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf) [↑](#footnote-ref-2)