**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 : PDF
1. 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
* 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. Title page 2](#_Toc106381959)

[2. Signature page 5](#_Toc106381960)

[3. Protocol synopsis 6](#_Toc106381961)

[4. Schedule of activities 7](#_Toc106381962)

[5. List of abbreviations and definitions 10](#_Toc106381963)

[6. Ethics 11](#_Toc106381964)

[7. Objectives 12](#_Toc106381965)

[7.1. Primary 12](#_Toc106381966)

[7.2. Secondary 12](#_Toc106381967)

[7.3. Endpoints 12](#_Toc106381968)

[8. Background Information and Scientific Rationale 13](#_Toc106381969)

[8.1. Medical Background 13](#_Toc106381970)

[8.2. Drug Profile 13](#_Toc106381971)

[8.3. Rationale 13](#_Toc106381972)

[9. Investigational plan 14](#_Toc106381973)

[9.1. Design 14](#_Toc106381974)

[9.2. Description of population 14](#_Toc106381975)

[9.3. Strategies for participant recruitment 14](#_Toc106381976)

[9.4. Participants eligibility 15](#_Toc106381977)

[9.4.1. Inclusion criteria 15](#_Toc106381978)

[9.4.2. Exclusion criteria 15](#_Toc106381979)

[9.4.3. Withdrawal 15](#_Toc106381980)

[9.5. Treatments 15](#_Toc106381981)

[9.5.1. Treatments Administered 16](#_Toc106381982)

[9.5.2. Identity of Investigational Products(s) 16](#_Toc106381983)

[9.5.3. Method of Assigning Participant to Treatment Groups 16](#_Toc106381984)

[9.5.4. Selection of Doses in the Study 16](#_Toc106381985)

[9.5.5. Selection and Timing of Dose for Each Patient 16](#_Toc106381986)

[9.5.6. Blinding 16](#_Toc106381987)

[9.5.7. Prior and concomitant therapy 16](#_Toc106381988)

[9.5.8. Treatment Compliance 16](#_Toc106381989)

[9.5.9. Investigational product management 16](#_Toc106381990)

[9.6. Study Procedures 17](#_Toc106381991)

[9.6.1. Sample lab collection 17](#_Toc106381992)

[9.7. Efficacy and Safety Variables 17](#_Toc106381993)

[9.7.1. Efficacy and Safety Measurements Assessed and Flow Chart 17](#_Toc106381994)

[9.7.2. Appropriateness of Measurements 17](#_Toc106381995)

[9.7.3. Primary Efficacy Variable(s) 17](#_Toc106381996)

[9.7.4. Drug Concentration Measurements 17](#_Toc106381997)

[9.8. Safety Reporting 18](#_Toc106381998)

[9.8.1. Definitions and reporting process 18](#_Toc106381999)

[9.8.2. Assessing, Recording, and Analyzing Safety Parameters 19](#_Toc106382000)

[9.9. Site Monitoring Plan 22](#_Toc106382001)

[9.10. Data Quality Assurance 22](#_Toc106382002)

[9.11. Statistical Analysis 22](#_Toc106382003)

[9.12. Changes in the Conduct of the Study or Planned Analyses 22](#_Toc106382004)

[9.13. Protocol Amendements 22](#_Toc106382005)

[10. Study patients 23](#_Toc106382006)

[10.1. Disposition of patient 23](#_Toc106382007)

[10.2. Patient follow-up 23](#_Toc106382008)

[10.3. Protocol Deviations 23](#_Toc106382009)

[10.4. Data Management Responsibilities 23](#_Toc106382010)

[10.5. Data breach 23](#_Toc106382011)

[11. Finance and Insurance 24](#_Toc106382012)

[12. End of trial 25](#_Toc106382013)

[13. Dissemination of Results and Publication Policy 25](#_Toc106382014)

[14. Archiving 25](#_Toc106382015)

[15. Study Report 25](#_Toc106382016)

[16. Literature References 25](#_Toc106382017)

[17. Appendix 26](#_Toc106382018)

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

Consider where subjects will be recruited and how (consultation, advertising,…); detailed description of the recruitment and informed consent process, particularly in cases where participants are unable to give informed consent

* 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

*Remark*: *specific exclusion criterion for* ***phase 1 studies***: the Belgian law of May 7, 2004 on human experiment ensures special protections for participants enrolled in phase I trials by requiring that individuals **cannot simultaneously participate in more than one phase 1.** Therefore:

* The protocol must specify that the investigators will check whether the enrolled individual already participates in another phase I trial ;
* The protocol must determine an **exclusion period** in which the participant cannot participate in another phase I trial. The length of period differs according to the nature of the research.
	+ 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. 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

Complete the document *AAHRPP-DOE-023 Risk assessment form* to determine the risk of the trial

* Based on the risk profile of the study product.
* For adverse event reporting, the protocol specifies the adverse events or abnormal laboratory test results that are critical to the safety assessments and that the investigator should report to the sponsor
* For adverse event reporting, the protocol specifies serious adverse events that the investigator does not need to report immediately to the sponsor.
* Describe how decisions will be made regarding determining relatedness and grading severity
* **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 xxx) 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

Complete the document *AAHRPP-DSQ-023 Monitoring Plan* to plan the site 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.

General description of site monitoring: who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

* 1. Data Quality Assurance
* Quality assurance and quality control systems implemented to assure the quality of the data (If none were used, this should be stated).
* Documentation of methods used in Appendix (e.g. monitoring, …)
* Audit procedure if any
	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

E.g. removal of a treatment group, changing entry criteria, changing dose

* Give timing and reason for the change
* Give implications for result interpretation
	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. Study patients
	1. Disposition of patient
* Clear accounting of all patients who entered the study (e.g. randomized, completed the study, screened, discontinued, …)
* Give reasons for discontinuation
* State whether blind was broken for discontinued subject
	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. Protocol Deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described

* 1. Data Management Responsibilities

Complete the document *AAHRPP-DSQ-021 Data Management Plan*

The protocol should provide information on how the data will be managed, including data handling and coding for computer analysis, monitoring and verification.

Instructions concerning the recording of study data on case report forms (CRF) :

* Name of used CRF – REDCap is required for clinical trials sponsored by CUSL
* Describe how data will be collected
* Refer to the CRF user manual

A description of the procedures for identifying data that are considered source data and are to be entered directly into the case report forms

Procedures for collecting data on participants who have withdrawn from treatment or the clinical trial, and for replacing and following up on these participants;

* 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.

1. Finance and Insurance

Describe financing and insurance arrangements:

* Insurance without fault (Law of 7 May 2004)
* Financial agreement between the Sponsor, the investigator and the Institution to which it belongs :
	+ Specific information to trials without direct individual benefit
	+ Data protection
	+ Conflict of interests

Details of the research funding and any cost which will be incurred should be detailed in the protocol, along with any per-participant or per-site payments.

Information about legal responsibilities and insurance must also be outlined.

The experimentation is covered under the Belgian Law of May 7, 2004 by a no-fault insurance (type of coverage: liability insurance).

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

1. End of trial

A clear and unambiguous definition of the end of the trial concerned and, if it is not the date of the last visit of the last participant, an indication of the estimated date of the end of the clinical trial and a justification for this

A description of the criteria for stopping parts or all of the clinical trial

1. Dissemination of Results and Publication Policy

The protocol should specify not only dissemination of results in the scientific media, but also to the community and/ or the participants, and consider dissemination to the policy makers where relevant. Publication policy should be clearly discussed- for example who will take the lead in publication and who will be acknowledged in publications, etc.

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

Secure archiving of all documentation of the experiment (CRF, Informed Consent, Source document,…) during at least 20 years. Specify who archives, where and access conditions.

Data to be kept at least 20 years after the trial termination according to the Belgian legislation: RD 18 May 2006 art.24

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
* Patient information and consent form
* Laboratory values and agreement
* Laboratory technics
* CRF / questionnaires
* CIOMS SAE form
* Other

**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)