Guide: Clinical study protocol for ATMP

Introduction:
In the absence of detailed guidance or a template for the content of the Clinical study protocol for Advanced therapeutic medicinal product (ATMP) quality, this document has been created as an authoring guide.
This document may be used as a guide. However, the content should be adjusted to the nature of the product/process.
The guide should preferably be used together with the Regulatory guide, with useful links to different documents important to consider in the creation of the Clinical study protocol.
In the guide, instructions are shown in <*italic*> while text suggestions are displayed as plain text.
In development of an ATMP a risk-based approach needs to be taken during the whole process. Typical risks are associated with off-target activity/mutagenicity, micro-contamination, viral and non-viral adventitious agents, immunogenicity, origin of the cells, method used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable.
For guidance; EMA/CAT Reflection paper on risk-based approach.
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-products_en.pdf

This guide was created by:
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Final version of this guide was reviewed by the Swedish Medical Products Agency (MPA).

Disclaimer:
The following guide are produced and designed as a support for users within the ATMP-field.
The project group aims to ensure that the guide available on the website are up to date but cannot provide any guarantees. Users themselves are therefore responsible for checking that the content is correct and current with applicable regulations.

Document History:

Version number	Date	Revision description
1.0	2019-05-09	First version
2.0	2020-03-31	Minor revision

<Title>

EudraCT number:	*<X>*
Version number:	*<X>*
Development phase:	*<X>*
Release date:	*<X>*
Clinical Study Sponsor:	*<X>*

Emergency information

	Name, title, phone number e-mail address
Sponsor/First line of contact	*<X>*
24h hotline	*<X>*
xxx	*<X>*

Administrative information

	Name, title, address, and e-mail address
Sponsor	*<X>*
Coordinating Investigator	*<X>*
Investigators	*<X>*
Project Manager/ Monitor	*<X>*
Steering committee	*<X> If applicable*
Independent Data Monitoring Board (IDMB)	IDMB Chair: *<X>* IDMB Members: *<X>*
Clinical sites	*<X>*

Protocol Synopsis

PROTOCOL IDENTITY AND OBJECTIVES	
EudraCT-number:	*<X>*
Study Code:	*<X>*
Title:	*<X>*
Short Title:	*<X>*
Version:	*<X>*
Release date:	*<X>*
Type of study	*<X>*
Clinical phase:	*<X>*
Objectives:	Primary Objective(s) • Secondary Objective(s) •
INVESTIGATIONAL PRODUCT (iATMP) AND COMPARATOR DRUG: • *<Name or Code of iATMP>* • *<X>* (Comparator Drug) • Administration: • Dosage:	
METHODOLOGY	
Purpose and rationale:	*<X>*
Study Design:	*<X>*
Primary Endpoint/Variable:	*1. <X>*
Secondary Endpoints/Variables:	*1. <X>* *2. <X>*
POPULATION OF STUDY SUBJECTS	
Description and Number of Study Subjects:	*<X>*
Inclusion Criteria:	1. *<X>* 2. *<X>*
Exclusion Criteria:	1. *<X>* 2. *<X>*
Data analysis:	*< short description of the statistical analysis plan>*
STUDY TIMETABLE	
First subject in:	Q*<X>* 20*<XX>*

Duration of investigation per subject:	Q<*X*> 20<*XX*>
Last Subject Out:	Q<*X*> 20<*XX*>
End of Study:	Q<*X*> 20<*XX*>

Signature page

Investigator's Statement

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study.

I, the undersigned, agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki; version no:*XX* and that are consistent with ICH-GCP; version no: *XX* and the applicable national laws and regulations.

The information contained in this document is the property of the sponsor of this study and provided in confidence. It is understood that this information will not be disclosed to others, except to the extent necessary to obtain informed consent from study subjects.

Coordinating Investigator:

_____ _____

Signature Date

Sponsor:

_____ _____

Signature Date

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Table 1

Abbreviation/Term	Definition
AE	Adverse Event
ATMP	Advanced Therapy Medicinal Product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GCP	GCP
iATMP	Investigational Advanced therapy Medicinal Product
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
MTD	Medicine technical device
PI	Principal Investigator
SAE	Serious Adverse Event

1. Introduction

<The following subsections should provide a brief overview of the relevant background information and rationale for the clinical study.>

1.1 Disease Background and Current Standard Treatment

<Describe the study population, disease (incl. grading/stages with special focus on the target stage), current standard of care, if one exists, and limitations of knowledge or available therapy.>

1.2 The ATMP-Investigational Medicinal Product: Background Information

<Describe the background of the Investigational Advanced therapy Medicinal Product (iATMP).>

1.3 Pre-clinical Studies

*<Provide a summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance eg. pharmacology, pharmacokinetics (distribution, cell survival), pharmacodynamic, proof-of-principle, toxicology (*favourably with clear references to IB and/or IMPD sections*).>*

1.4 Clinical Studies

<Provide a summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other indications, countries or as hospital exemption, named patient basis, compassionate use program.>

1.5 Rationale for Conducting the Study

<State the reason for conducting the clinical trial.>

1.6 Rationale for Study Design, Doses and Control Groups

<Justify the study design, especially when there is discrepancy between the optimal design and what is proposed (eg.randomized double-blinded placebo-controlled design), if rare disease and small numbers available patients, how statistic methodology is adjusted to cover the limitation, justification if historical controls proposed, discussion on gender if not both allowed in patient selection criteria, discussion on age limitation, favourably in general on clinical development plan to explain how central regulatory requirements will be fulfilled (eg. contact with Paediatric committee/PDCO for agreement on Paediatric development plan /PIP; contact with Orphan Committee/COMP, in general, how statistic methodology is implemented to cover limitations, etc.

** Justify the endpoints selected and proposed variables for endpoint evaluation (including how to evaluate to avoid bias and when to evaluate to be purposeful in relation to expected outcome of the IMP). Data points collected in the study should support the objectives or have a regulatory purpose. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study's objectives.*

Provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the study intervention(s). It is acknowledged that in the case of some ATMPs (eg. autologous products or patient specific allogeneic donor products) it may not be possible to perform formal dose finding studies, but the dose selected must be justified and explained how risks are mitigated.

Describe the rationale for the type and selection of control (e.g. placebo, active drug, standard of care, dose-response, historic data) and study design. Discuss known or potential problems associated with the control group chosen considering the specific disease and intervention(s) being studied. A control group is not always applicable. In such cases, justification for the absence of a control group should be given.>

1.7 Risk/Benefit Considerations

<Discuss known and assessed potential risks (*) and benefits from clinical or nonclinical studies, and from relevant published literature. Describe any risks and benefits to participants by participating in the study that the Sponsor foresees, addressing each of the following:

- *Immediate risks and benefits*
- *Long-range risks and benefits*

(*) Discuss separate to the IMP, indication/disease, patient's other co-morbidity factors and trial environment (including IMP administration and if applicable special medicine technical devices (MTD)/instruments needed for the use of the final product) related risks and to the risks associated risk factors.
If the ATMP is a combined ATMP including an integrated MTD, discuss separate to the MTD related risk factors and risks.

If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered and explain why alternative procedures are not included.>

In the assessment include the rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design.

In case of ATMPs involving viral vector-based gene therapy, present the virus, virus vector construct and possible other relevant to the product related elements and discuss the risk for vector integration, viral shedding, product's distribution (local, systemic) and duration as the background to any precautions required that should be implemented, where applicable.

2. Study objectives and endpoints

<Provide a description of the study objectives and endpoints, eg. in a table format as shown below>

OBJECTIVES	ENDPOINTS
Primary *<The primary objective is the main question and generally drives statistical planning for the trial>*	*<The primary endpoint(s) is the basis for concluding that the study has met its objective. The variable(s) proposed to evaluate the primary endpoint(s) should be clearly specified in terms of method and time(s) of assessment. >*
Secondary *<The secondary objective(s) are goals that will provide further information on the use of the intervention>*	*<Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both>*
Exploratory *<Exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research>*	*<Exploratory endpoints may include clinically important events that are expected to increase knowledge on the effect of treatment or disease condition>*

2.1 Study Population

<Provide a description of the study population and participant recruitment>

2.2 Inclusion Criteria

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

2.3 Exclusion Criteria

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

2.4 Screening and Subject Logs

<Describe that a log of all subjects screened for inclusion into the study will be set up. Define the information to be included in the log.
Describe that a log of all subjects included into the study will be set up. Define the information to be included in the log.>

2.5 Informed consent

<Describe the procedures for retrieving the informed consent.>

2.6 Lifestyle Considerations/Restrictions

<Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, timing of meals relative to dosing, intake of caffeine, alcohol, or tobacco, or limits on activity).>

2.7 Subject Enrolment and Randomization

<This section should contain a description of randomization procedures (if applicable to the study design). Include justification, especially when not equal sized groups.
Describe possibly implemented stratification and justification for that. >

2.8 Methods for Blinding and Unblinding

<This section should contain a description of blinding procedures (if applicable to the study design. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind.>

2.9 Screen Failures and Procedures for Handling Incorrectly Enrolled or Randomized Subjects

<Indicate how screen failures and incorrectly enrolled or randomized subjects will be handled in the trial, including conditions and criteria upon which re-screening is acceptable, if applicable. Include information if a subject may be replaced with another one and how many replaced subjects are allowed)>

2.9 Criteria for Subject Discontinuation

<This section should state which adverse events would result in discontinuation of study intervention or participant discontinuation/withdrawal. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable).>

2.9.1 Follow Up after Subject Discontinuation

<Describe the subsequent therapy and follow-up after subject discontinuation in the study.>

3. Study Design

3.1 Overall Study Design

<Describe:

- *Phase of the study*
- *Indicate if single site or multi-site/multi-national*
- *A description of the type/design of study to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation)*
- *The number of study groups/arms*
- *Study intervention duration (incl. safety and efficacy follow-up time period)*
- *Name of study intervention(s) alt. study without intervention*
- *Note if the study includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose)*
- Long-term follow-up 5 years (10 years for GTMP)
- *Name of sub-studies, if any, included in this protocol>*

Figure 1 Study Design

<Include a schematic figure of the study design.>

Table 2 Schedule of Assessments

<Include a table listing all of the study assessments to be performed at the different study visits.

For biosampling, include the total volume to be collected and specify the analytes to be determined.>

3.2 Study Visits

<Describe the different visits, when they occur and study procedures and evaluations to be done as part of the study to support the determination of safety and/or efficacy, as per the primary and secondary objectives outlined in this protocol.>
Think: When? What? How? Who?
Justify each proposed element of the visits
<It's recommended to include a table with all the visits and the procedures and examinations to be performed at the individual visits.>

3.2.1 Run-In Phase

<Describe if a run-in phase is applicable. Details and rational to be outlined in section 5.1.>

3.2.2 Study Visit(s)

<Describe the study visits and the procedures to be undertaken including visits for follow up.>

3.2.2.1Drop-Out Visit or Early Discontinuation

<Define what is meant by 'Subject discontinuation' (eg. safety concerns defined by the investigator, patient withdraws his/her informed consent, no compliance, etc)
Describe the visit and procedures to be undertaken for follow up of a participant who discontinues participation in the study for any reasons, whenever the subject agrees to perform such a visit.

Describe in short terms how a patient is referred to the health care system, i.e. communication with the responsible treating physician and whether any to the ATMP related safety aspects are to be followed (eg. patient dosed with GMO product) >

3.2.2.2Lost to Follow-Up
<Define when a subject is considered lost to follow up and the number and type of actions to be taken.>

3.3 Study Assessments
3.3.1 Demographic and Other Baseline Characteristics

3.3.1.1 Demographics
<Describe the demographics.>

3.1.1.2 Medical History
<Describe the medical history and other baseline characteristics.>

3.1.1.3 Prior and Concomitant Medications
<Describe the data that will be recorded related to permitted prior and concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. Include details about when the information will be collected (e.g., screening, all study visits).>

3.1.2 Physical Examination, Vital Signs and Performance Status
<Describe the data that will be recorded related to physical examination, vital signs and performance status.>

3.1.3 Efficacy Measurements and Endpoints

3.1.3.1 X <Efficacy Endpoint #1>
<List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy, as per the primary and secondary objectives outlined in this protocol.>

3.1.3.2 X <Efficacy Endpoint #2>
<x>

3.1.4 Safety Measurements and Endpoints

3.1.4.1 X <Safety Endpoint #1>
<List and describe all study procedures and evaluations to be done as part of the study to support the determination of safety.>

3.1.4.2 X <Safety Endpoint #2>
<x>

3.1.5 Exploratory assessments/Other Safety Measurements and Variables
<List and describe all study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention's safety or that are done for other purposes (e.g., screening, eligibility, enrollment).>

3.2 Long-Term Follow-Up

<If the ATMP has the potential for prolonged biological activity after a single/early repeated administration, long-term follow-up of subjects should be envisaged. The follow up strategy should be based on a risk-assessment having regard to all information available to the sponsor. This strategy may need to go beyond the end of the trial. For example, in the case of gene therapy medicinal products using integrating vectors, a follow-up of 15 years after administration is expected. Follow up to subjects treated should be ensured also in cases of early termination of the clinical trials (see 3.2.2.1).>

3.2.1 Additional Care of Subjects After the Study

<Describe the subsequent therapy and follow-up of subjects after the study (see 3.2.2.1).>

3.3 End of Study

<State that the clinical study is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.>

3.4 Study Discontinuation

<List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, sponsor/funder decision, regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, and sponsor and provide the reason(s) for the termination or temporary suspension.
Describe if and under what circumstances study participants will be replaced.>

3.4.1 Follow Up after Study Discontinuation

<Describe the subsequent therapy and follow-up after study discontinuation (see 3.2.2.1.>

4. Study treatments

4.1 Pre-Treatment Phase

<If applicable, describe any wash-out or pre-treatment (conditioning) procedures including dosing regimen and cell/tissue acquisition method.>

4.1.1 Rationale for Conditioning Therapy (if applicable)

<Describe the rationale for the conditioning therapy, if applicable.>

4.1.2 Acquisition of Cells [or Tissue] (if applicable)

<Describe the procedures for the acquisition of cells/tissues, if applicable i.e. surgical procedures or apheresis including screening of donor/patient or refer to specific acquisition instructions.>

4.2 iATMP

<The following subsections should describe the study intervention that is being tested for safety and effectiveness in the clinical trial, and any control product being used in the trial.
Where an ATMP incorporates a medical device as a combined ATMP or MTD is used for ATMP administration procedure), the protocol should also contain information on:

- *the characteristics, performance and intended use of the device;*
- *whether the medical device part(s) comply with the relevant general safety and performance requirements provided for under the EU legislation on medical devices for the intended use. When this is not the case, a justification should be provided and compliance of the medical device component of the combination product with the relevant general safety and performance requirements set out in Annex 1 of the Medical Regulation 2017/457 must be documented in the protocol.>*

4.2.1 Product, Dose and Mode of Administration

<Describe the IATMP and procedures for selecting each participant's dose of iATMP. For drugs include the timing of dosing (e.g., time of day, interval), the duration (e.g., the length of time study participants will be administered the study intervention), the planned route of administration (e.g., oral, nasal, intramuscular), and the relation of dosing to meals.

Detailed information on the administration of the iATMP should be provided when the administration requires specific concomitant therapy and/or involves surgical procedures that could have an impact on the safety or efficacy of the product. This includes information on the standardisation and optimisation of the processes involved, including -where applicable- the surgical procedures.>*

*A separate manual can be included the protocol concerning the specific ATMP administration related procedures. The document must be referred as a part of the parent protocol (reference to EudraCT number, protocol version and date). Favourably systematically collected data is planned for example by implementing specific forms to be filled at each ATMP dosing time point(s). This type of data has been requested at the time point of marketing authorization application (MAA); this type raw data is the basis for specific sections in the final SmPC.

4.2.2 Product accountability

<Describe how to handle remaining product>

4.2.3 Packaging, Labelling, Storage and Handling

<State the name of the manufacturer who will perform the packaging and labelling. Include a figure of the label proposed.
Describe the storage conditions and where the product will be stored.
Describe any preparations needed prior to administration of the iATMP and disposal.>

4.3 Control/Comparator Product(s)

4.3.1 Product, Dose and Mode of Administration

<Describe the control product and procedures for selecting each participant's dose of control/comparator product. For drugs, that includes the timing of dosing (e.g., time of day, interval), the duration (e.g., the length of time study participants will be administered the study intervention), the planned route of administration (e.g., oral, nasal, intramuscular), and the relation of dosing to meals.>

4.3.2 Packaging, Labelling, Storage and Handling

<State the name of the manufacturer who will perform the packaging and labelling, if applicable. Include a figure of the label proposed.
Describe the storage conditions and where the product will be stored.
Describe any preparations needed prior to administration of the product.>

4.4 Rescue Therapy

<List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions about administration of rescue medications, as applicable.>

4.5 Concomitant medication

<Describe allowed concomitant medication, whether IMP or NIMP>

4.6 Excluded Medications

<This section should be consistent with the medication restrictions in the inclusion/exclusion criteria listed previously.>

4.7 Treatment Compliance and Accountability

<Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).>

5. Safety reporting

5.1 Definitions

5.1.1 Adverse Event

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The degree (i.e. mild-moderate-severe) of all AE shall be evaluated

5.1.2 Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any phase of the study (ie, run-in, treatment, wash-out or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the Investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?”
<If applicable, please include that an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.>

5.1.3 Suspected Unexpected Serious Adverse Reactions

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

5.2 Assessment of Adverse Events

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

5.3 Reporting Procedures

5.3.1 Reporting of Adverse Events

<Describe how Adverse Events will be reported to the local monitor or other Sponsor representative.>

5.3.2 Reporting of Serious Adverse Events

When the Investigator becomes aware of a SAE during the course of the study, the SAE must be reported to the local monitor or other Sponsor representative within one (1) day and a completed written SAE report must be sent as soon as possible.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The Investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

5.3.3 Reporting of Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions (SUSARs) that are life-threatening or result in death will be reported by the Sponsor to the EU common Eudravigilance data base and Independent Ethics Committee (IEC)

within 7 days, and if necessary the follow up report should be completed within the following 8 days. Other SUSARs should be reported within 15 days.

5.4 Follow-up of AEs, SAEs and SUSARs

<Describe how AEs, SAEs and SUSARs will be followed until resolved or considered stable. Include duration of follow-up after appearance of events (eg, 1 week, 2 months).>

5.5 Annual Safety Update

As long as the study is ongoing, the Sponsor will annually send a summary of all SAEs to the Medical Product Agency (MPA) in Sweden and the IEC in a Development Safety Update Report (DSUR). The report will also summarize the safety and the risk for the subjects still ongoing in the study. Furthermore, the global published literature on safety information of same/similar type of products is to be included.

5.6 Pregnancy

<Include content in this section if applicable. Pregnancy is not an AE, but some studies will require unique considerations if pregnancy was to occur during the study. State the study's pregnancy-related policy and procedure. Provide appropriate modifications to study procedures, if applicable (eg discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome). Include information of the procedures of both genders being the subject dosed with the ATMP or partner of the dosed subject.>

5.7 Data Safety Monitoring Board (DSMB)

<Describe the composition of the DSMB, frequency of interim data review, final data analysis and method of reviews as well as communication strategy. A separate DSMB charter shall provide further detail of DSMB membership, responsibilities and administration of the DSMB.>

6. Data Management and Statistical Analysis

6.1 Hypothesis

<State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (eg, superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.>

6.2 Determination of Sample Size

<Describe the sample size determination, include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study.>

6.3 Statistical Analysis Plan (SAP)

<Describe the plan and methods for the statistical analyses including handling of missing data and incomplete subject data-sets (e.g. data for subject withdrawn).>

6.4 Interim Analyses

<The describe the planned interim analyses to be performed, if applicable.>

6.5 Data Safety Monitoring Board

<Describe the work performed by the Data Safety Monitoring Board (DSMB) or refer to a DSMB charter.>

6.6 Interim Analyses

<The describe the planned interim analyses to be performed, if applicable.>

7. Quality Control and Quality Assurance

7.1 Training of Study Staff at Site(s)

Before the first subject is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the study staff at site(s) and also train them in any study specific procedures and web-based data capture system(s) utilised. The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

7.2 Monitoring of the Study

During the study, a Sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The Sponsor representative will be available between visits if the Investigator(s) or other staff at the centre need information and advice about the study conduct.

8. Ethical and Regulatory requirements

8.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the Sponsor policy on Bioethics and Human Biological Samples.

8.3 Subject Data Protection

Should any data processing be transferred to any other organization, within or outside of EU, appropriate agreements and/or and other documentation to ensure that the processing is carried out in accordance with all the provisions of the General Data Protection Regulation and other relevant legislations will be completed before any data transfer is performed.

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will be fully informed about the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.
The Informed Consent Form will explain how study data will be stored to maintain confidentiality in accordance with national data legislation. All data computer processed by the sponsor will be pseudonymized and identified by <<Study Code/Subject ID/Initials>>.
The Informed Consent Form will also explain that for data verification purposes, authorized representatives of the sponsor, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

8.4 Ethics and Regulatory Review
An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

8.5 Changes to the Clinical Study Protocol and Informed Consent Form
Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator and Sponsor.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

Sponsor will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s).

8.6 Audits and Inspections
Authorised representatives of Sponsor, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact Sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

9. Financing and Insurance

9.1 Financing of the study
<Describe the financing of the study.>

9.2 Insurance
<Describe the insurance of the investigational medicinal product defining whether it is covered by the "Läkemedelsförsäkringen" or if a separate insurance policy has been signed.>

10. Publication Policy
<Describe the plans for making the study results available to the public domain.>

11. References

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