PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) Member State of notification SPAIN
(b) Notification number B/ES/22/10
(c) Date of acknowledgement of notification 16 Mayo 2022
(d) Title of the project: Phase II clinical trial of autologous hematopoietic stem cell gene therapy for the treatment of severe combined immunodeficiency due to RAG1 gene deficiency. "PHASE I/II CLINICAL TRIAL OF AUTOLOGOUS HEMATOPOIETIC STEM CELL GENE THERAPY FOR RAG1-DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY" (EudraCT: 2019-002343-14).
(e) Proposed period of release: The study will begin with the inclusion of the first patient after the approval of this GMO release application for clinical trials and will end three years after the inclusion of the last patient

2. Notifier

Name of institution or company: Leiden University Medical Center, Netherlands

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid		(.)	
RNA virus		(.)	
DNA virus		(.)	
bacterium		(.)	
fungus		(.)	
animal			
-	mammals	(X)	
-	insect	(.)	
-	fish	(.)	
-	other animal	(.)	specify phylum, class

other, specify (kingdom, phylum and class)

(b) Identity of the GMO (genus and species)

Autologous CD34+ human hematopoietic stem cell transduced with HIV-1-derived lentiviral vector self-inactivating non-replicative (SIN) to transcribe and translate the RAG1 gene into the correct protein in the nucleus of the transduced cells.

(c) Genetic stability – according to Annex IIIa, II, A(10) YES

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes (X) No (.)

If yes, insert the country code(s): Possibly in AT, BE, DE, DK, ES, FI, FR, GB, GR, IE, IS, IT, LU, NO, PT, SE

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes (X) No (.)

If yes:

- Member State of notification: Netherlands
- Notification number: B/NL/18/014

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (.) No (X)

If yes:

- Member State of notification
- Notification number

7. Summary of the potential environmental impact of the release of the GMOs.

No environmental impact is expected because the release of the investigational medicinal product, transduced autologous CD34+ cells (RAG1 LV CD34+ cells), is limited to administration to the patient in the hospital. According to the environmental risk analysis, the therapeutic product will not reach the environment.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid (.)
RNA virus (.)
DNA virus (.)

bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

2. Name
(i) order and/or higher taxon (for animals): Animal
(ii) genus: Homo
(iii) species: Homo spiens
(iv) subspecies
(v) strain
(vi) pathovar (biotype, ecotype, race, etc.)
(vii) common name: Human

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (X) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (X)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	X
Mediteranean	X
Boreal	X
Alpine	X
Continental	X
Macaronesian	X

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (X) No (.)

(d) Is it frequently kept in the country where the notification is made?
Yes (X) No (.)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water (.)
soil, free-living (.)
soil in association with plant-root systems (.)
in association with plant leaf/stem systems (.)
other, specify

(b) If the organism is an animal: natural habitat or usual agroecosystem:
natural habitat or usual agroecosystem: Human

5. (a) Detection techniques : Blood análisis techniques

(b) Identification techniques : Blood análisis techniques

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (.) No (X)
If yes, specify
…

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)
animals (.)
plants ()
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

The donor of the autologous CD34+ hematopoietic stem cells used as source material will be tested for infection by adventitious viral agents. The donor will be tested for HIV-1&2, HTLV I&II, HBV, and HCV prior to donating blood and bone marrow. If the result is positive for HIV-1&2 and/or HTLV I&II, the donor will be excluded from the study.

8. Information concerning reproduction

(a) Generation time in natural ecosystems: NOT APPLICABLE for human CD34+ hematopoietic stem cells

(b) Generation time in the ecosystem where the release will take place:

(c) Way of reproduction: Sexual .. Asexual ..

(c) Factors affecting reproduction:

9. Survivability

(a) ability to form structures enhancing survival or dormancy: NOT APPLICABLE for human CD34+ hematopoietic stem cells

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	

(b) relevant factors affecting survivability: The survival of human CD34+ hematopoietic stem cells (=blood stem cells) requires the combination of several factors: appropriate medium, appropriate temperature and CO2 level. The environmental conditions outside the host are substantially different and not appropriate for its survival (temperature, pH, ultraviolet radiation, as well as the change in biophysical and biochemical conditions)

10. (a) Ways of dissemination

Blood Blood stem cells can only be transmitted between individuals through injection or other routes of direct blood contact between individuals. Dissemination in the environment is not possible due to rapid inactivation.

b) Factors affecting dissemination

In the event that it is transmitted by direct blood contact with another individual (recipient), the recipient's immune system will eliminate them.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify	

2. Intended outcome of the genetic modification
RAG1 LV CD34+ cells is a medicinal product under investigation for gene therapy, by which CD34+ hematopoietic stem cells from a patient with severe combined immunodeficiency (SCID) due to RAG1 gene deficiency are genetically modified ex vivo, through transduction, to transcribe and correctly translate the RAG1 protein in its nucleus. Following administration of autologous modified CD34+ cells (RAG1 LV CD34+ cells) to the patient, they are expected to engraft in the bone marrow and generate blood cells of all lineages, including B lymphocytes and T lymphocytes. As a result, the The development of T and B lymphocytes would be unblocked by the presence of the correct copy of the RAG1 gene, allowing the functions of the immune system to be reconstituted, improving immune protection and patient survival.

3. (a) Has a vector been used in the process of modification?
Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes (X) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(.)
bacteriophage	(.)
virus	(.)
cosmid	(X)
transposable element	(.)
other, specify	

(b) Identity of the vector: Third-generation replication-deficient HIV-1-derived viral vector.

(c) Host range of the vector: Pseudotyped VSV-G capable of transducing many different non-dividing human and animal cells

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (X) No (.)

antibiotic resistance (.)
other, specify: Detection of copies of WPRE/coRAG1 in the DNA of blood cells by quantitative PCR (qPCR) analysis

Indication of which antibiotic resistance gene is inserted

(e) Constituent fragments of the vector: Replication deficient self-inactivating (SIN) lentiviral vector that includes an expression cassette for expression of the enzyme RAG1.

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify: Transduction

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify (.)

6. Composition of the insert

(a) Composition of the insert

The transfer plasmid pCCL-MND-coRAG1 contains part of the cytomegalovirus (CMV) promoter, minimal lentiviral sequences (see below) and the transgene expression cassette composed of the myeloproliferative sarcoma virus (MND) promoter enhancer, transgem variant. Codon-optimized RAG1 and the woodchuck hepatitis B virus modified regulatory element (WPRE) post-transcriptional element.
The transfer plasmid vector is a fully synthetic, HIV-1 derived, self-inactivating (SIN) and replication-defective containing the following lentiviral sequences: the Long Terminal Repeat (LTR) 5'U3 sequence and the Long Terminal Repeat (LTR) 3'U3 sequence. Deleted LTR U3, a packaging signal, the Rev response element (RPE), and the polypurine tract (PPT)

(b) Source of each constituent part of the insert

HIV-1, cytomegalovirus (CMV), woodchuck hepatitis B virus (Woodchuck HBV) as listed in question a). The RAG1 insert is DNA completely synthesized to include the codon optimized version of the native RAG1 gene that does not change the protein/amino acid sequence.

(c) Intended function of each constituent part of the insert in the GMO

CMV promoter. The CMV promoter in the transfer plasmid pCCL-MND-coRAG1 is used to transcribe the vector genome in HEK293T cells during lentiviral vector production. However, the CMV promoter itself is not part of the single-stranded messenger RNA vector genome transcribed by the transfer plasmid and incorporated into the lentiviral particles.
Transgenic expression cassette.
MND promoter. Controls transgene transcription

RAG1 transgene. Transcription and translation of the human RAG1 gene sequence will lead to the formation of the RAG1 protein in the nucleus, which plays a key role in the rearrangement and recombination of immunoglobulin genes and T cell receptor molecules. The RAG1 protein, in dimer with the RAG2 protein, is essential for the formation of B lymphocytes and thymocytes, which are two key cell types of the adaptive immune system. The immune system of SCID patients does not work. The RAG1 sequence used in this lentiviral vector system is a codon optimized version of the RAG1 sequence present in people who do not have SCID. The optimized codon contained in CD34+ hematopoietic stem cells leads to changes that improve the expression of the protein required for the proper functioning of T lymphocytes and B lymphocytes. However, it does not affect the actual RAG1 amino acid sequence, therefore, the protein itself.
WPRE. The modified WPRE enhances the expression of the transgene cassette.

Lentiviral sequences:
The vector genome contains the minimal viral cis-activation sequences that are required for vector packaging, reverse transcription, and integration of the vector genome into the host cell genome. All this entails the following:

- The LTR ends contain repeated sequences at the terminal end of the RNA required for reverse transcription and target recognition for integration. The LTRs have been modified to self-inactivating (SIN) LTRs, which means that not the entire vector genome is transcribed.

- The packaging signal (Ψ) overlaps the 5'LTR end and a small portion of the gag gene. This is a complex structural feature with hairpin loop structure necessary for packing; that is, for incorporation of the virus RNA genome into the particle as it assembles within the cytoplasm.

- The RRE (Rev response element) is a structural element recognized by the Rev protein, which exports RNA from the nucleus to the cytoplasm where the viral particles are assembled. The RRE is part of the env gene.

- The polypurine tract (PPT) is a region at the 3' end of the genome that is required for second-strand DNA synthesis. The core PPT (cPTT) is conserved among lentiviruses and is required to generate the lentiviral vector, although its precise function is not well understood.

d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (X)
- other, specify

e) Does the insert contain parts whose product or function are not known?

Yes (.) No (X)

If yes, specify

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (X)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)
- fish (.)
- other animal (.)

(specify phylum, class)

other, specify

2. Complete name

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	Retrovirus
(iv)	species	Human Immunodeficiency Virus type 1 (HIV-1)
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	Human Immunodeficiency Virus type 1 (HIV-1)

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (X) No (.) Not known (.)

If yes, specify the following:

(b) to which of the following organisms:

humans (X)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (X) No (.)

If yes, specify : Wild HIV is classified as a group 3 organism. However, the replication defect of the lentiviral vector used for CD34+ stem cells is not pathogenic. No viral particle can be produced after transduction, as only 15% of the original HIV-1 sequence remains.

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (.) No (X) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

Yes (.) No (X) Not known (.)

Specify

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?

Yes (.) No (X) Unknown (.)

Specify

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (.) No (X) Not known (.)

Specify

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (X) Not known (.)

Specify

2. Genetic stability of the genetically modified organism: The RAG1 transgene is introduced into CD34+ stem cells by lentiviral gene transfer. After integration of the SIN vector into the genome of the CD34+ cell, the modified gene of the CD34+ cells is genetically stable and the genetic information encoding the RAG1 protein forms an integral part of the DNA of the host CD34+ cell.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i): The replication deficient genome of the lentiviral vector is integrated as provirus into the genome of the transduced CD34+ cells. No new viral particle can be packaged into the host cell since the gag gene cannot be transcribed because it lacks the plasmid that codes for gag. Furthermore, the pol gene and the rest of the accessory elements are absent in the viral vector. The transgene inserted into the lentiviral vector does not code for pathogenicity factors, cytokine coding sequences, oncogenes, antibiotic resistance genes or dangerous inserts.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment: Following administration, the persistence of RAG1-engineered cells in patients will be monitored by quantitative qPCR analysis for the detection of the RAG1 transgene.

(b) Techniques used to identify the GMO

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected):
2.

Reason:
Severe Combined Immune Deficiency (SCID) is a rare disease in which specific cells of the immune system do not develop properly. All patients with SCID have reduced T-lymphocyte number or function, and clinical symptoms appear in childhood. Patients suffer from persistent diarrhoea, opportunistic infections and stunted growth and it becomes a medical emergency.
SCID can arise from a number of genetic defects that affect lymphocyte development and function. The treatment of choice is hematopoietic stem cell transplantation (HSCT). RAG1 and RAG2 gene therapy products could be a treatment option for RAG1-deficient SCID patients and RAG2-deficient

SCID patients, respectively, when the patient lacks a human leukocyte antigen (HLA)-matched donor to donate the hematopoietic stem cells for transplantation

Expected clinical activity:

Autologous transduced CD34+ stem cells (RAG1 LV CD34+ cells) are expected to engraft into the patient's bone marrow and give rise to blood cell lineages, including B cells and T cells. Blocking T cell development and B should be mitigated by the presence of the correct copy of the RAG1 gene (and therefore, the release of the RAG1 protein in the nucleus of the transduced cell), allowing the restoration of immune function and improving protection and survival.

Mechanism of action:

1) Provide the correct copy of the RAG1 genes in the genome of B and T lymphocytes during their developmental stages.
2) Consequently, restore the development of T and B lymphocytes in the thymus and bone marrow, respectively.
3) Leading to the restoration of the number of T and B lymphocytes in the peripheral blood and lymphoid organs, and the functional restoration of immunity.

Treatment with RAG1 gene therapy products is not expected to have long-term, positive or negative environmental effects.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (.) No (X)

If yes, specify

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Hospital Universitari Vall d'Hebron (HUVH), Barcelona España

(b) Size of the site (m^2):

(i) actual release site (m^2): The drug is administered to the patient intravenously in a hospital clinical setting of the HUVH

(ii) wider release site (m^2): NOT APPLICABLE

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

It will not affect any environmental zones outside of the HUVH room. Containment measures during the administration of the RAG1 LV CD34+ cells (=OMG) gene therapy investigational medicinal product to patients exclude the release of RAG1 LV CD34+ cells into the environment. Healthcare personnel involved in the administration of the product will use personal protective equipment to avoid exposure to the RAG1 LV CD34+ cells product.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO: NOT APPLICABLE

4. Method and amount of release

   (a) Quantities of GMOs to be released: Treatment with the investigational medicinal product RAG1 LV CD34+ cells consists of a single infusion. However, it is not ruled out that it could be extended to 5 infusions. The maximum dose a patient could receive is 5x107 RAG1 LV CD34+ cells per dose.

   (b) Duration of the operation: The administration of RAG1 LV CD34+ cells will last 30 minutes.

   (c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release: The HUVH will follow the standard procedures established by the Biological Safety Committee (CSB_HUVH) for the safe handling of the GMO, measures in case of accidental spillage, personal protection equipment, first aid, decontamination and disposal. These measures will be taken to avoid any release of the RAG1 LV CD34+ cells product into the environment.

5. Short description of average environmental conditions (weather, temperature, etc.): The HUVH has rooms that meet the hygiene conditions required for the treatment of immunocompromised patients.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release: NOT APPLICABLE. The medicinal product RAG1 LV CD34+ cells of gene therapy has not been administered in humans before.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	Human
(ii)	family name for plants	…
(iii)	genus	...
(iv)	species	...
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable): Autologous transduced CD34+ hematopoietic stem cells (RAG1 LV CD34+ cells) are expected to engraft into the patient's bone marrow and, in turn, give rise to blood cell lineages, including T cells and B cells. T and B lymphocytes should be palliated by the presence of the correct copy of the RAG1 gene (and therefore, the release of the RAG1 protein in the nucleus of the transduced cell), allowing the restoration of immune

function and improving protection and survival of patients suffering from SCID due to RAG1 deficiency.

3. Any other potentially significant interactions with other organisms in the environment: They are not expected

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (X) Not known (.)
Give details

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established: None, except patients receiving transduced autologous CD34+ stem cell product (RAG1 LV CD34+ cells). Exposure requires direct injection of autologous RAG1 LV CD34+ cells. Immuno-suppressed individuals other than patients are advised not to participate in the administration of the autologous RAG1 LV CD34+ cells medicinal product. People with a functional immune system would eliminate the RAG1 LV CD34+ cells product in the event of accidental injection. Mere contact exposure to the blood of treated patients will not result in transmission of RAG1 genetically modified cells, as such cells are rapidly inactivated under environmental conditions.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i)	order and/or higher taxon (for animals)	NOT APPLICABLE
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem: NONE

(b) from other organisms to the GMO: NONE

(c) likely consequences of gene transfer: NOT APPLICABLE

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.): Simulations have not been performed.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism): NONE

H. Information relating to monitoring

1. Methods for monitoring the GMOs: Patients will continue to be followed for at least 15 years from the infusion of the autologous RAG1 LV CD34+ cells investigational medicinal product by pharmacovigilance authorities. Patients who have received the autologous RAG1 LV CD34+ cells product will undergo semiannual and annual evaluations during follow-up per protocol. If the patient leaves the study prematurely, the 15-year follow-up period will continue. If the patient is lost to follow-up after receiving treatment, no additional specific measures will be applied. Patients will be seen once or twice at HUVH for a physical examination and medical history (including concomitant medication and adverse events), with particular attention to features possibly related to lentivirus-associated events. In addition, the patient will have blood samples, and possibly other samples, drawn to assess the safety and persistence of the RAG1 vector.

2. Methods for monitoring ecosystem effects NOT APPLICABLE

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms NOT APPLICABLE

4. Size of the monitoring area (m^2) NOT APPLICABLE

5. Duration of the monitoring See section H1

6. Frequency of the monitoring See section H1

I. Information on post-release and waste treatment

1. Post-release treatment of the site: Standard decontamination and waste disposal procedures will be performed to prevent any release of the RAG1 LV CD34+ cells product into the environment. See section 4c

2. Post-release treatment of the GMOs: NONE

3. (a) Type and amount of waste generated: Contaminated material used for administration of the RAG1 LV CD34+ cells product, including cryopreservation bags and infusion lines that will be in contact with the RAG1 LV CD34+ cells product.

3. (b) Treatment of waste: All material will be disposed of safely and in the same manner as other blood products in accordance with the HUVH Intra-Hospital Waste Management Guideline HUVH Waste Disposal Practices for Biological Material and GMOs.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread: The HUVH will take the procedures for the safe handling of GMOs (CBS-HUVH), measures in case of accidental spillage, personal protection equipment, first aid, decontamination and elimination. These measures will be taken to avoid any release of the RAG1 LV CD34+ cells product into the environment.

2. Methods for removal of the GMO(s) of the areas potentially affected: All disposable materials used during the preparation of the investigational product in the room where the infusion is administered or in the preparation laboratory (including gloves, masks, syringes, needles, catheters and tubes) and that come into contact with The product will be disposed of as biological risk materials (class III medical or biomedical waste) in group II and III containers, according to the HUVH intra-hospital waste management guide

In the event of an accidental spill, surfaces will be decontaminated with broad-spectrum disinfectants following the procedures established in the CSB_HUVH biosafety manual.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread: NOT APPLICABLE

4. Plans for protecting human health and the environment in the event of an undesirable effect: NOT APPLICABLE, except for the emergency response in the event of accidental injection by medical personnel, which consists of disinfection of the injection site and follow-up in the event of symptoms related to the immune reaction against the RAG1 LV CD34+ cells product.