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/19/11**
(c) Date of acknowledgement of notification: 4th of June 2019
(d) Title of the project: *Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, alone or in combination with other agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors*

(e) Proposed period of release: August 2019 (FSFV) to December 2025 (LSLV) (76 months)

2. Notifier

Name of institution or company: GlaxoSmithKline R&D

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

other, specify (kingdom, phylum and class)

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

The investigational product, also called GSK3377794, is comprised of autologous T cells that have been transduced with GSK3988862A, a self-inactivating lentiviral vector

encoding a T cell receptor (TCR) targeted to recognize NY-ESO-1/LAGE1.

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

The lentiviral vector is replication incompetent. The TCR transgene is stably integrated into the genome of the target T cells after *ex vivo* transduction with the lentivirus vector. The transduced T cells cannot survive outside of the human body or *ex vivo* cell culture

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): **DE, FR, IT, NL, UK**

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:

ES

- Notification number: B/ES/19/04

ES, FR *(Please note that previous GMO submissions were made by the previous sponsor, Adaptimmune. GSK assumed sponsorship of these NYESO-1 clinical studies in July 2018.)*

- Notification number: B/ES/17/07 (ES), TG2867 & TG3702 (FR)

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 (**X**) No (.)

If yes:

- Member State of notification:

US & Canada

- Notification number:

NSN-19849 (Canada), N/A for US

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

The investigational product is patient-specific autologous T cells and is for intravenous infusion directly into the same patient that donated the cells. In the unlikely event that the cells should be exposed to the environment e.g. accidentally released from their container, they would rapidly lose viability and the vector sequences would be lost. This is because genetically manipulated T-lymphocytes can only survive ex-vivo under special cell culture conditions. Therefore, outside of this environment, the cells will not remain viable nor retain functionality. Thus the environmental risk conferred by inappropriate disposal of waste or unused product, or the accidental dissemination during product handling, is considered to be negligible.

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) Human Patients**
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

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

3. Geographical distribution of the organism: **Not applicable**

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

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

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

Atlantic ..
Mediteranean ..
Boreal ..
Alpine ..
Continental ..
Macaronesian ..

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

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

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

4. Natural habitat of the organism: **Not applicable**

(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:

5. (a) Detection techniques : **Not applicable**

(b) Identification techniques : **Not applicable**

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: **Not applicable**

8. Information concerning reproduction: **Not applicable**

(a) Generation time in natural ecosystems:

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

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

(c) Factors affecting reproduction:

9. Survivability: **Not applicable**

(a) ability to form structures enhancing survival or dormancy:

(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: **Not applicable**

10. (a) Ways of dissemination: **Not applicable**

(b) Factors affecting dissemination: **Not applicable**

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)

Not applicable.

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

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a patient's own T lymphocytes, obtained by leukapheresis, engineered to express a tumor-specific T-cell receptor (TCR), expanded *in vitro*, and re-infused into the participant, with the aim of generating an anti-tumor T-cell immune response. The New York esophageal squamous cell carcinoma 1 (NY-ESO-1) antigen is tumor-associated protein that has been found in several tumor types, including NSCLC. Previous clinical trials using ACT with T-cells directed against NY-ESO-1 have shown objective responses between 40-60% in participants with synovial sarcoma, metastatic melanoma, and multiple myeloma [Robbins, 2011; Robbins, 2015; Rapoport, 2015].

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	(**X**)
cosmid	(.)
transposable element	(.)
other, specify	

(b) Identity of the vector

GSK3988862A is a self-inactivating (SIN), replication incompetent lentiviral vector. GSK3988862A is produced by transient transfection of Human Embryonic Kidney (HEK) 293T cells followed by purification and concentration of harvested supernatant. GSK3988862A is a critical starting material required to manufacture GSK3377794.

(c) Host range of the vector
Mammalian cells

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (**X**) No ()

antibiotic resistance (.)
other, specify

The viral vector encodes the TCR transgene, which is stably integrated into the genome of target T cells. Transduced T cells are identified by flow cytometry, which uses a Dextramer reagent with a fluorescent label to measure expression of the recombinant TCR on the surface of transduced T cells. In addition, the number of copies of the vector in transduced T cells is measured using a qPCR method.

(e) Constituent fragments of the vector

GSK3988862A is an HIV-derived self-inactivating (SIN) lentiviral vector that comprises a 5' LTR and a 3' U3 deleted LTR. Transgene transcription is driven from the mammalian EF-1α promoter. To ensure equivalent expression of both chains the transgene is composed of the TCR α and β chains joined by the picornavirus 2A ribosome skipping factor. The vector also contains the central poly-purine tract (cPPT) and central termination sequence (CTS) for improved transduction efficiency, the rev response element (RRE) for RNA transport, and the psi packaging sequence.

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

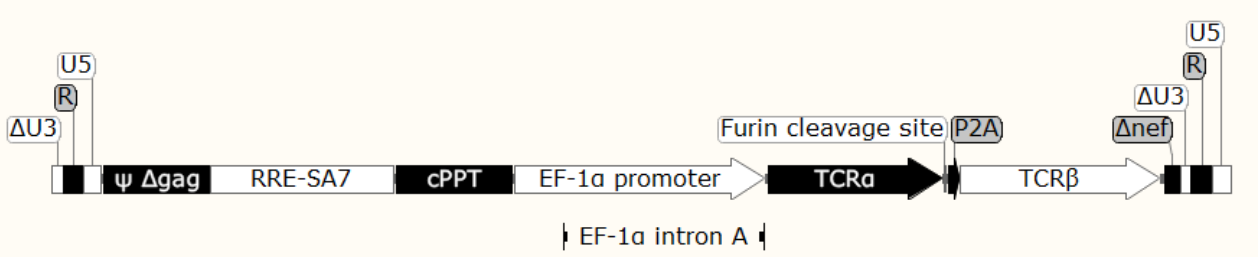
(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	**(X) Transduction (Ex-vivo)**

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



GSK3988862A provirus

(b) Source of each constituent part of the insert

The plasmid ADB934 contains the NY-ESO-1c259 TCR transgene for expression in target T cells and is schematically depicted in the figure above. The transfer vector is an HIV-1 derived self-inactivating (SIN) vector that comprises a 5' LTR and a 3' U3 deleted LTR. The entire ADB934 plasmid was chemically synthesised using published sequences and the TCR transgene. The EF-1α promoter sequence was obtained from the commercially available pTracer-CMV2 plasmid. The α and β TCR genes were were generated from human T cell clone 1G4 (Li et al. 2005) then affinity enhanced and codon optimised.

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

The EF-1α promoter is used to drive the expression of the NY-ESO-1c259 TCR transgene in target T cells. The NY-ESO-1c259 TCR transgene enables transduced T cells to recognize NY-ESO-1/LAGE1 expressing tumor cells.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify **(X): The host organism is patient-derived human T cells. Following *ex vivo* transduction, the insert integrates into the patient's T cells, which are then infused back into the patient. Integration is not site-specific.**

(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): Human**
- insect (.)
- fish (.)
- other animal (.)
(specify ph*y*lum, class)

other, specify

2. Complete name

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

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (**X**) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

humans (.)
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 (.) No (**X**)
If yes, specify

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 viral vector is replication incompetent and the TCR transgene is stably integrated into the genome of target T cells, which cannot survive outside of the human body.

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)

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

Transduced cells will not survive outside of the host, so there is no possibility to detect them in the environment.

(b) Techniques used to identify the GMO

Transduced T cells are identified using flow cytometry, which detects expression of recombinant TCR on the cell surface, and PCR, which detects vector integrated into T cells.

F. Information relating to the release

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

The purpose of the release is to evaluate the safety, tolerability, and antitumor activity of autologous genetically modified T cells (NY-ESO-1^{c259}T) in eligible patients with advanced non-small cell lung cancer (NSCLC). No benefit or harm to the environment is expected.

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:

Study will be carried out in the following sites:

- START Madrid Group, HM CIOCC, Hospital Universitario HM Sanchinarro, Madrid, Spain
- START MADRID-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain
- Clinica Universidad de Navarra, Pamplona, Spain
- Hospital Univeritario Vall d'Hebron, Barcelona, Spain
- Hospital Clínico Virgen de la Victoria, Málaga, Spain.

(a) Geographical location (administrative region and where appropriate grid reference):

See above sites.

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

(i) actual release site (m^2):

(ii) wider release site (m^2):

The release will be inside the hospital which is not required to be of a certain size for the clinical trial.

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

Not applicable

(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:

Patients will receive a dose in the range of 1×10^9- 8×10^9 by single intravenous infusion on Day 1 of the study. A total of approximately 8 patients are expected from the 4 Spanish sites.

(b) Duration of the operation:

It is estimated that the clinical trial will start in Spain around July of 2019 and planned enrolment to be completed by mid 2021. It is not possible to provide the exact time of administration of the investigational product, but dosing may be finished in late 2022.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release

T cells from the patient's peripheral blood are transduced *ex vivo* with the lentiviral vector in contract manufacturing facilities outside of Spain. No patient or staff member will come in direct contact with the lentiviral vector.

The Sponsor will provide all centres with study training, including training on receiving, storage, and manipulation of the T cell product. They will also receive training on how to prevent contamination, on proper waste disposal, and wearing appropriate personal protective equipment (PPE).

The cell product is transduced with a self-inactivating lentiviral vector. RCL testing will be performed by, or under the direction of, the manufacturing facility responsible for the manufacturing and release of the vector.

Once manufactured T-cell product arrives on-site, it must immediately be stored at ≤ - 130°C in the vapor phase of a liquid nitrogen or a mechanical freezer until the date of infusion. The T-cell product must not be thawed until immediately prior to infusion. The cells should be thawed either in a water bath at 37ºC at the patient's bedside or in a centralized facility. The product must be checked visually to confirm that it is fully thawed and to assess any visual aggregates. The cell product must not be washed or otherwise processed. The cells must be infused without delay and, if thawed centrally, must be transported to the patient by appropriately trained clinical staff, to preserve the chain of custody.

No additional hazards are expected in addition to those encountered when administering blood cell products or when handling the patient's blood sample. PPE should be used following standard local procedures for handling of cellular products or frozen blood.

All of the materials that come in contact with the product (e.g., plastics, needles, gloves, gauze, cotton, etc.) will be treated as clinical waste and incinerated/disposed of according to local procedures (hospital).

The cleanliness of the room will follow the standard procedures of the hospital for blood products. It requires no special measure cleaning or disinfection.

5. Short description of average environmental conditions (weather, temperature, etc.):

Not applicable.

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.

As of 27 January 2019, 100 patients have been exposed to GSK3377794 for the treatment of multiple myeloma, melanoma, synovial sarcoma, myxoid/round cell liposarcoma, ovarian cancer, and non-small cell lung cancer. GSK3377794 cells cannot survive outside the human body and are not infectious; therefore, they do not represent a risk to the environment or human life. To date, there have been no incidents of release of GSK3377794 into the environment or exposure to humans other than the patients that were infused with GSK3377794. Also, there have been no cases of RCL reported.

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): **Not applicable.**
   (i) order and/or higher taxon (for animals) …
   (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)

   The therapeutic approach underpinning NY-ESO-1^{c259}T, known as Adoptive T cell therapy (ACT), is a treatment that uses a cancer patient's own T lymphocytes genetically altered to enhance anti-tumor activity, expanded *in vitro* and re-infused back into the patient. The ultimate objective of the process is the stimulation and expansion of potent and antigen-specific T cell immunity.

3. Any other potentially significant interactions with other organisms in the environment.

   Not applicable.

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

   Not applicable.

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: **Not applicable**.

   (i) order and/or higher taxon (for animals) …

(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:

Vector is tested for Replication competent lentivirus (RCL) and is confirmed RCL negative at release. Also, vector is washed out during the T-cell manufacturing processes multiples times and cells are maintained at 37^0C for 12-14 days. Therefore, presence of free viral particles in the final product is unlikely

(b) from other organisms to the GMO:

The product is genetically modified autologous T cells, derived from an individual human patient for use in that individual only. The transduced T cells cannot survive outside the human body and are not infectious; therefore, they do not represent a risk to the wider environment, and the release does not pose a risk of potential transfer of genes to and from other species.

(c) likely consequences of gene transfer:

Please see response (b) above.

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.):

Not applicable.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

Not applicable.

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Upon administration of NY-ESO-1c259T to the patients, a PCR approach will be used to monitor persistence of the genetically modified autologous T cells. Additionally, RCL will be monitored using a PCR-based assay that detects and measures copies of the gene coding for the vector's envelope protein, namely Vesicular Stomatitis Virus G protein (VSV-G), that is necessary for the assembly of pseudotyped infectious lentiviral particles but absent from the vector's backbone.

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

All patients will be followed for 15 years from time of their last T cell infusion for observation of delayed Adverse Events (AE) in accordance with FDA and EMA requirements for gene therapy clinical trials (FDA, 2006a; FDA, 2010; EMEA, 2009). These assessments will be collected in the Interventional Phase of the study until disease progression, as defined by iRECIST and thereafter in the LTFU protocol 208750.

6. Frequency of the monitoring

RCL testing and monitoring will be performed on:

- **the cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for the manufacturing and release of the vector**
- **patient PBMCs which will be collected prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. If these tests are negative at all time points during the first year, PBMC samples will be collected and archived for up to 15 years post infusion; however, if VSV-G DNA copies are detected at any time point during the first 12 months after infusion, then patient samples will be tested until lentiviral gene copies are no longer detected in the patient.**

I. Information on post-release and waste treatment:

1. Post-release treatment of the site

Room cleaning post T cell infusion will follow hospital standard procedures for blood products. No special cleaning or disinfection measures are required.

2. Post-release treatment of the GMOs

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been detected *in vitro* or *in vivo*. Blood samples to test for RCL testing will be collected and tested as described above.

3. (a) Type and amount of waste generated

All of the materials that come in contact with the product (e.g., plastics, needles, gloves, gauze, cotton, etc.) will be treated as clinical waste.

3. (b) Treatment of waste

All materials that come into contact with the T cell product will be incinerated / disposed of according to local procedures (hospital). Any T cell product which requires destruction should be disposed in clinical waste bags for autoclaving, according to local safety rules for biological waste.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

No additional hazards are expected in addition to those encountered when administering blood cell products or when handling a patient's blood sample. Thus, proper PPE, methods, and procedures should be used following standard local procedures for the handling of cell products or frozen blood.

In the event of a spill, after taking the necessary immediate steps and precautions as suggested above, the Sponsor must be contacted with information on the cause of the spill (e.g., packaging malfunction) and an estimate of the volume or proportion of the T-cell product lost. If the spill is due to a failure in the product bag or packaging material these should be retained for investigation if possible.

As the volume of the T-cell product is small (approximately 200 mL), any spill is unlikely to require special handling; however if the T-cell product is spilled in combination with larger volumes of bodily fluid it may be appropriate to escalate cleaning of the area to an appropriate decontamination team. An appropriate decontaminiation team would be the hospital decontamination team responsible for handling potentially biohazardous materials.

2. Methods for removal of the GMO(s) of the areas potentially affected

The following guideline can be used as a minimum level to clean up spillage of T-cell product. If local procedures or SOPs require enhanced measures, then those should be followed. Note that spilled T-cell product should not be allowed to dry as this increases the potential for aerosol production.

Materials

- **Gloves (non-sterile, disposable medical examination gloves)**
- **Disposable apron**
- **Eye protection**
- **Chlorine release granules (if available)**
- **Disinfectant solution suitable for decontamination (preferably hypochlorite solution e.g. HYPO-CHLOR solution or 10,000 ppm sodium hypochlorite bleach; 6% hydrogen peroxide is a suitable alternative for surfaces that may be damaged by hypochlorite)**
- **Detergent solution or water for rinsing**
- **Paper towels or other suitable absorbent material**
- **Disposable forceps or scoop**
- **Sharps container for sharps disposal or broken glass, if applicable**
- **Medical waste bag suitable for potentially infectious elements, to dispose of non-sharp material**
- **Facilities for washing of hands with soap and hand sanitizer**

Procedure

- **Put on gloves and apron. If the spill is sufficient that there is a risk of splashing, wear eye protection.**
- **If a product bag is broken, place the bag (and cassette or overwrap if applicable) in a double bag of medical waste bag with absorbent material in the bottom and, retain for investigation, if possible.**
- **If the spill is onto clothing, it should be removed carefully avoiding further contamination. Contaminated clothing will require disinfection in accordance with current local institutional policy, or may require disposal if heavily contaminated.**

• Wash any potentially contaminated skin with soap and hand disinfectant.
• If the spill is on the floor, apply to chlorine release granules directly on the spill if available.
• Follow the granules manufacturer's instructions on contact time or leave for 15 minutes; clean with paper towels
• If you do not have granules, place disposable paper towels twice on the area of the spill to absorb and contain it, and then pour disinfectant solution on the spill to soak the towels
• Follow the instructions of the manufacturer of the disinfectant on contact time or leave for 15 minutes. Clean up with paper towels.
• If granules are not available, place disposable paper towels over twice the area of the spillage to absorb and contain it, then pour disinfectant solution on the spill to soak the towels. Follow disinfectant manufacturer's instructions on contact time or leave for 15 minutes.
• If broken glass or sharps are present, first place apply disinfectant solution to the spillage, then carefully remove the pieces of glass with disposable forceps or scroop to a sharps bin before cleaning as described above.
• Discard used absorbent material, contaminated waste and used gloves and apron into a healthcare waste bag.
• Wash the affected area with detergent and water.
• Hands must be washed with soap and hand disinfectant after cleaning.

If during the course of the spill or clean up any T-cell product comes into contact with broken skin, has been involved in a sharps or needle stick injury, or has been splashed into the eyes, nose or mouth, the local policy for inoculation incidents should be followed.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

All materials that come into contact with the product (e.g. plastic-ware, needles, gloves, gauze, cotton wool, etc.) will be treated as clinical waste and incinerated / disposed of consistent with local site (hospital) procedures.

4. Plans for protecting human health and the environment in the event of an undesirable effect

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a patient (FDA 2000). However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place. Nevertheless, it is agreed that the patient must be isolated until an understanding of how to manage the patient becomes clear.

Approaches that have been discussed for managing the patient are the following:

- **Provide targeted antiretroviral therapies based on genotyping of the RCL**
- **Intensive follow up of patient in consultation with gene therapy experts, study investigators, HIV physicians, Spanish Agency of Medicines and Sanitary Products (AEMPs) and Ethics Committees**
- **Inform local public health officials**
- **Identify sexual partners and provide appropriate counseling and intervention**