

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/17/11**
- (c) Date of acknowledgement of notification: **16/05/2017**
- (d) Title of the project: **A Phase Open Label, Clinical Trial Evaluating the Safety and Anti-tumor Activity of Autologous T Cells Expressing Enhanced TCRs Specific for Alpha-fetoprotein (AFP^{c332}T) in HLA-A2 Positive Subjects with Advanced Hepatocellular Carcinoma (HCC)**
- (e) Proposed period of release: **01/09/2017-31/12/2018**

2. Notifier

Name of institution or company: **Adaptimmune LLC**

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 is defined as AFP^{c332}T transduced patient-specific autologous T cells that have been transduced with a self-inactivating (SIN) lentiviral vector (LV) encoding a high affinity AFP tumour antigen specific T-cell receptor (TCR).

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

The viral vector is replication incompetent and the TCR transgene is stably integrated in transduced T cells which cannot survive outside of the human body.

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

Yes ☒ No ☐

If yes, insert the country code(s): **DE, FR and GB**

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

Yes ☒ No ☐

If yes:

- Member State of notification : **DE and FR**
- Notification number: **not yet available**

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 ☐

If yes:

- Member State of notification: **US**
- Notification number: **N/A**

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 characterization:

- (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 ..
 Mediterranean ..
 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

The intended outcome of the genetic modification is that a patient's T lymphocytes express an enhanced affinity T cell receptor (TCR). As part of the natural immune surveillance system, subject's T lymphocytes carry TCRs which recognize peptides derived from intracellular protein presented on HLA. To guard against autoimmune disease, natural TCRs have a low affinity for peptides derived from self-proteins and therefore respond poorly to cancer antigens. The genetic modification introduces an

enhanced affinity TCR into the T lymphocyte so that it will recognize and respond to a peptide specifically produced by a cancer cell.

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

The transfer vector is a self-inactivating (SIN), replication incompetent lentiviral vector.

- (c) Host range of the vector

Mammalian cells

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

antibiotic resistance (.)
other, specify

Indication of which antibiotic resistance gene is inserted

- (e) Constituent fragments of the vector

The transfer vector is an HIV-derived self-inactivating (SIN) vector that comprises a 5' LTR and a 3' U3 deleted LTR. A long form of the cppt/CTS sequence (546 bases) was amplified from the NL4-3 molecular clone and incorporated into the vector backbone where indicated. The EF1 α promoter was derived from the commercially available pTracer-CMV2 plasmid (Invitrogen Corporation, Carlsbad, CA) (Kim, 1990). The α and β TCR genes, were provided

by Adaptimmune separated by the picornavirus 2A “cleavage” factor which is derived from the published sequence with an added Gly-Ser-Gly linker between the NH2 terminal protein and the 2A peptide to improve cleavage efficiency (Szymczak, 2004) The 2A peptide bond skipping sequence ensures equivalent expression of both chains (note; 2A sequence is not shown in the restriction map). The vector also contains the central polypurine tract and central termination sequence (cppt/CTS) (Sirven, 2000) 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

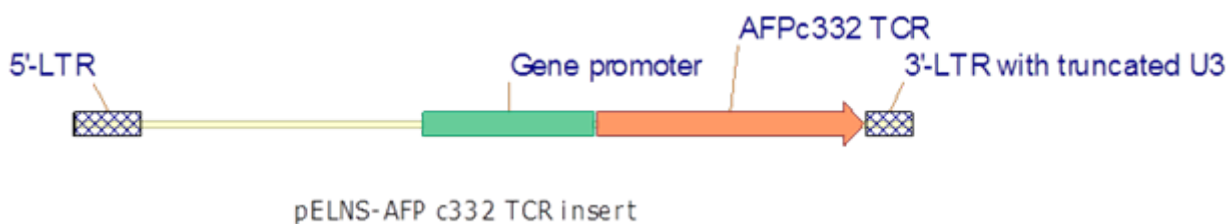
- | | | |
|-------|-----------------|----------------------------|
| (i) | transformation | (.) |
| (ii) | electroporation | (.) |
| (iii) | macroinjection | (.) |
| (iv) | microinjection | (.) |
| (v) | infection | (.) |
| (vi) | other, specify | (X) Transduction (Ex-vivo) |

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



(b) Source of each constituent part of the insert

The plasmid pELNS-AFP-c332 contains the AFP c332 TCR transgene for expression in target T cells and is schematically depicted in the figure above.

It is designed to be a self-inactivating (SIN) vector that comprises a 5' LTR and a 3' U3 deleted LTR. Within the LTRs, the transgene is composed of the α and β chains of the AFP specific TCR and the TCR gene expression is driven by a gene promoter.

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

The gene promoter is for driving the expression of the AFP c332 TCR transgene in target T cells. The AFP c332 TCR transgene is a high affinity AFP specific TCR for the therapy.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (X)
- other, specify (X): **The host organism is human T**

cells (patient's T cells). The insert integrates into the patient's T cells, ex vivo, which are infused back into the patient.

(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 (.)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (X): **Human**

- 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 ...

(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 in transduced 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 cells are identified using flow cytometry detecting the expression of recombinant T-cell Receptor (TCR) on the cell surface.

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 and tolerability of autologous genetically modified T cells (AFP^{c332}T) in HLA-A2 positive subjects with advanced hepatocellular carcinoma (HCC). The host organism is human, the insert integrates into the hosts' T cells, ex vivo, which are infused back into the patient. No direct benefit 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:

Site: Hospital Universidad de Navarra

Principal Investigator: Dr. Bruno Sangro

Site address: Av. de Pío XII, 36, 31008 Pamplona, Navarra

Site: Hospital Clínic Barcelona

Principal Investigator: Dr. Jordi Bruix

Site address: Villarroel, 170 - 08036 Barcelona

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

- (b) Size of the site (m²):

(i) actual release site (m²):

(ii) wider release site (m²):

- (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:

This is a dose escalation trial that will evaluate 3 doses of transduced cells administered after a lymphodepleting chemotherapy regimen using a 3+3 dose escalation design. The doses for each cell dose group are as follows.

Group 1a and 1b: 0.1×10^9 (range: 0.08×10^9 to 0.12×10^9) transduced cells (3-6 patients per group).

Group 2: 1×10^9 (range: 0.8×10^9 to 1.2×10^9) transduced cells (3-6 patients).

Group 3: 5×10^9 (range: 1×10^9 to 6×10^9) transduced cells (3-6 patients)

Recruitment for the study is competitive, approximately 2 subjects are expected in the 2 Spanish sites, but it is not possible to predict which doses the patients will receive.

A second infusion of AFP^{c332}Tcells may be given to certain eligible subjects who have documented progression of disease following response to the initial infusion and whose tumor continues to express the appropriate antigen target.

(b) Duration of the operation:

The clinical trial is estimated to start in Spain around September 2017 and complete towards the end of 2018. It is not possible to provide the exact timing of administration of the investigational product as this is dependent upon identification of eligible patients and their clinical condition. 1 subject per site are expected to be eligible to receive the investigational product during this period.

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

The Sponsor will provide all sites with training on study including receipt, storage and handling of the T cell product. The Sponsor will also provide the site with an Apheresis and T-Cell Product Manual.

The T cell product is designed using self-inactivating lentivirus. As part of the release testing before the T cell product is shipped from the manufacturer to the site RCL must be negative.

Frozen T cell product is shipped to the responsible person at the site by a specialist courier in validated cryoshippers. The product is frozen in bags that are coated an overwrap bag to aid any potential safety handling aspects. The product is removed from the cryoshipper and transferred to liquid nitrogen storage until required for infusion.

When the patient is ready for the infusion, the frozen T cell product will be removed from liquid nitrogen storage and transferred frozen in a sealed container to the patient's bedside. The frozen T cell product must be transported to the patient by appropriately trained clinical staff, to preserve the chain of custody.

The T cell product will be thawed in a water bath at the patient's bedside, according to institutional standard procedures for frozen blood products. Once thawed the T cell product will be infused into the patient.

No additional hazards besides those encountered when administering cellular blood products and handling patient blood sample are expected. Gloves and aprons should be worn following standard local procedures for handling frozen cellular or blood products.

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

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

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.

AFP^{c332}T has not been tested previously, this is the first in human trial. There is no information of previous releases.

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 AFP^{c332}T, known as Adoptive T cell therapy (ACT), is a treatment that uses a cancer subject's own T lymphocytes genetically altered to enhance anti-tumor activity, expanded in vitro and re-infused into the subject. 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 37⁰C for 12-14 days. Therefore, presence of free viral particles in the final product is unlikely as lentiviruses are not stable at 37⁰C for more than 48 hours.

- (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

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. RCL will be monitored in patient who have received the T cells 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. RCL testing and monitoring will take place on:

- **The cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for vector manufacturing and release of the vector.**
- **Subject PBMC samples 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 annually until assessments for persistence have discontinued or until Year 15, whichever comes first.**

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 (m²)

Not applicable

5. Duration of the monitoring

All subjects will be followed for 15 years from time of their last T cell infusion for observation of delayed Adverse Events in accordance with FDA and EMA requirements for gene therapy clinical trials (FDA, 2006a; FDA, 2006b; FDA Briefing Document, 2010; EMEA guidelines, 2009).

6. Frequency of the monitoring

Subjects will be seen and laboratory analysis conducted at Months 3, 6, and 12 in the first year post-infusion. Subjects will then be seen in the clinic and samples taken every 6 months in Years 2-5, and annually from Years 6-15 (medical history, physical exam, adverse events, exposure to mutagenic agents, anti-tumor agents and other medicinal products). If a subject receives a second T cell infusion, the clock restarts with the second infusion. These assessments will be collected in the Interventional Phase of the study until disease progression and thereafter in a long term follow up (LTFU) phase.

Upon completion of the Interventional Phase, subjects will transition into the LTFU phase.

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 from patients prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. The RCL test looks for a specific the gene coding for the vector's envelope protein. If these tests are negative at all time points during the first year, samples will be collected and archived for up to 15 years post infusion; however, if a positive test is obtained, the Investigator will be informed and the patient scheduled for a retest as soon as possible. A review by the Sponsor's Safety Review Team and Safety Governance Board will take place. If the second test is positive, infusions for all subjects receiving cells modified with the same vector lot will be postponed. The subject with the confirmed positive test will be scheduled for leukapheresis and a biological RCL performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product. If the biological RCL is positive, all AFP^{c332}T cell infusions will be halted. An action plan will be discussed with all Regulatory Authorities and experts as appropriate. Additional subjects will not be treated until such time as a plan is agreed upon, completed, and reviewed.

3. (a) Type and amount of waste generated

Waste will include plastic-ware including intravenous infusion sets, empty infusion bags, needles, gloves, aprons, gauze, cotton wool and any other disposable materials used to infuse the T cell product to each individual patient.

3. (b) Treatment of waste

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

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

The Sponsor will provide all sites with training on study including receipt, storage and handling of the T cell product. The Sponsor will also provide the site with an Apheresis and T-Cell Product Manual.

In the event of accidental spillage, the study 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 (approx. 200mLs) 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.

The following guideline should 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 releasing 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 bin for disposal of sharps or broken glass if present**
- **Medical waste bags suitable for potentially infectious items, for disposal of non-sharp material**
- **Hand wash facilities including soap and hand disinfectant**

Procedure

- **Put on gloves and apron. If spill is sufficient that there is a risk of splashing, put on eye protection**
- **If a product bag is broken, place 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 per the 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 chlorine releasing granules directly to the spill if available.**

- Follow granule manufacturer's instructions 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 apply disinfectant solution to the spillage, then carefully remove the pieces of glass with disposable forceps or scoop to a sharps bin, before wiping up as 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 following cleaning up

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.

Monitoring for the presence & persistence of genetically modified T cells applies to all individuals who receive the gene modified T cells (and would also be similarly applied to individuals in the unlikely event of accidental or unintended administration).

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

All used infusion materials and /or TCR-transduced T cells which require destruction should be disposed in clinical waste bags for autoclaving, according to local safety rules for biological waste.

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

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject (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 subject are the following:

- Provide targeted antiretroviral therapies based on genotyping of the RCL
- Intensive follow up of subject 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**