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	The Netherlands
(b)	Notification number	B/NL/16/011
(c)	Date of acknowledgement of notification	2*/11/16*
(d)	Title of the project	*TEGs – T cells retrovirally engineered to express a defined γδT cell receptor*
(e)	Proposed period of release	*From 01/01/2016 until 01/01/2040*

2. Notifier

Name of institution or company: *Universitair Medisch Centrum Utrecht (UMCU), Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*

3. GMO characterization

(a) Indicate whether the GMO is a:

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

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

Allogeneic or autologous human T cells retrovirally transduced with a replication-deficient derived viral vector (pMP71, isolated from a murine Moloney Murine Leukemia Virus) to express a yδTCR of human origin

(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) *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 (.) No (X)
If yes:
- Member State of notification …
- Notification number B/../../…

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 B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.
An environmental impact is not expected as the release of TEGs is limited to patient administration in hospital settings. According to the environmental risk assessment, TEGs dissemination to the environment is 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:

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

2. Name

(i)	order and/or higher taxon (for animals)	*primata*
(ii)	genus	*homo*
(iii)	species	*sapiens*
(iv)	subspecies	*n/a*
(v)	strain	*n/a*
(vi)	pathovar (biotype, ecotype, race, etc.)	*n/a*
(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),
following information not applicable to humans

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

Atlantic	*n/a*
Mediteranean	*n/a*
Boreal	*n/a*
Alpine	*n/a*
Continental	*n/a*
Macaronesian	*n/a*

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

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

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

4. Natural habitat of the organism: *n/a*

(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
Standard techniques of blood cell analysis

(b) Identification techniques
Standard techniques of blood cell analysis

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 recipient cells from which the GMO is derived, do not survive outside the host. The cells are not pathogenic and do not persist or replicate in the environment or other organisms.

Donors will be controlled for viral adventitious agents as per country specific guidance. Patients will at least be tested for HIV, HTLV, HBV and HCV prior to blood donation and excluded from the clinical study if tested positive.

8. Information concerning reproduction: *n/a for human T cells*

(a) Generation time in natural ecosystems:
(b) Generation time in the ecosystem where the release will take place:
(c) Way of reproduction: Sexual Asexual
(d) Factors affecting reproduction:

9. Survivability

(a) ability to form structures enhancing survival or dormancy: *n/a for human T 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 blood cells requires a complex combination of sufficient media, temperature and CO2. The environmental conditions (such as temperature, pH, UV, and a change in the biophysical and biochemical conditions) outside the host are substantially different and not appropriate for its survival. The GMO has a short survival out of the host.

10. (a) Ways of dissemination

The cells can only enter the environment via blood or lymph e.g. when samples are taken during the clinical trial or when an injury occurs. The chance for these 'spilled transduced cells' to be transferred into another person than the patient is very unlikely.

(b) Factors affecting dissemination
In the unlikely event that transduced T cells transfer from patient to the blood of another person, the GMO will be cleared by the recipient because of the allogeneic mismatch and cleared by the immune system of the recipient. Furthermore, outside a human host, the GMO cannot survive.

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)
n/a

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
Peripheral blood T cells derived from either patients or donors are ex vivo retrovirally transduced, expanded and purified to provide a T cell engineered to express a defined γδTCR (TEG).

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?*
Partially, 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
Replication deficient MoMLV vector.

(c) Host range of the vector
Pseudo typed with a xenotropic RD114 derived envelop and infectious for human, baboon, chimpanzee, gorilla, rhesus monkey, bat, dog, mink and rabbit derived 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
Replication deficient retroviral vector including an expression cassette for the expression of a defined γδT cell receptor.

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

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

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

(i)	transformation	(.)
(ii)	microinjection	(.)

(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify

6. Composition of the insert

(a) Composition of the insert

The MP71 vector is derived from the SF1 vector (GenBank accession no. AJ224005). SF1 consists of a 5' LTR leader derived from MESV (Murine Embryonic Stem cell Virus) and a 3' LTR including enhancer/promotor (EP) derived from SFFV (Spleen Focus Forming Virus). The Long Terminal Repeats (LTRs) of the retroviral vector are non-Self-INactivating Long Terminal Repeats (non-SIN LTRs).

To obtain the MP71 vector the LTRs are partly replaced by LTRs based on MPSV (Myeloproliferative Sarcoma Virus) and SFFV. The remaining leader sequence is derived from MESV.

Therefore, this vector contains sequences from MoMLV, SFFV, MESV and MPSV. All these viruses belong to the gamma-retrovirus genus of the Retroviridae family.

(b) Source of each constituent part of the insert
See above

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

(e) Location of the insert in the host organism

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

(f) 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 (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify *human γδTCR sequence*

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 γδT cell receptor is introduced in the T cells via retroviral transduction and integrated in the genome of the donor T cells. T cells are genetically stable.

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)
In the MP71 vector, the gag, pol and env genes are absent. This renders the vector replication deficient and it no longer has pathogenic properties. In addition, all deviating start codons are removed from the leader sequence of MP71 which prevents potential translation of unknown proteins. Furthermore, all viral sequences that can potentially recombine are removed resulting in minimalisation of the chance of homologous recombination with endogenous viruses (and therefore the chance that replication competent viruses develop) occurring.

4. Description of identification and detection methods

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

Post-administration monitoring of patients for persistence of TEG will take place using flowcytometry and molecular techniques.

(b) Techniques used to identify the GMO
Identity of TEGs is determined by flow cytometry with an antibody specific for γδ T cell receptor protein expression.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
Potential tumour control in patients with a malignancy who have a poor prognosis. This therapy is deemed applicable to a broad patient population by its mode of action. Therefore, in the future, TEG treatment is believed to be able to serve as a curative treatment in various haematological and solid malignancies.

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):
The clinical trials will take place initially in UMC Utrecht, the Netherlands and may in future extent to other hospitals in the Community.

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
No environmental sites outside the hospital room will be affected. The clinical study will be performed in a manner that mitigates the risk of contamination in accordance with the requirements for gene therapeutic medicinal products.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
n/a

4. Method and amount of release

(a) Quantities of GMOs to be released:
TEGs are intended to be used in various indications concerning malignancies. The dose level, dose frequency, route of administration, treatment period will be optimized to obtain a safe and effective dose regimen. For this application a maximum of 20 dosages up to 1x10E12 TEG cells/kg body weight are proposed.

(b) Duration of the operation:
Duration of TEG cell suspension administration.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
The methods and procedures in place in the hospitals involved in the clinical studies are dedicated for mitigation the risk of contamination in accordance with the requirements for gen therapeutic medicinal products.

5. Short description of average environmental conditions (weather, temperature, etc.)
The GMO is applied in hospital setting.

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.
n/a

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)	*primata*
(ii)	family name for plants	*n/a*
(iii)	genus	*homo*
(iv)	species	*sapiens*
(v)	subspecies	*n/a*
(vi)	strain	*n/a*
(vii)	cultivar/breeding line	*n/a*
(viii)	pathovar	*n/a*
(ix)	common name	*human*

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
Tumour cells display an altered metabolic state, which causes specific surface molecules (i.e. the extracellular region of BTN3A1) to undergo a conformational change rendering it recognizable to γδTCRs. This is expected to provide tumour control in patients with malignancies and thereby prolonging overall survival.

3. Any other potentially significant interactions with other organisms in the environment
None 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

The cells can only enter the environment via blood or lymph e.g. when samples are taken during the clinical trial or when an injury occurs. The chance for these 'spilled transduced cells' to be transferred into another person than the patient is very unlikely. Moreover, in the unlikely event that transduced T cells transfer from patient to the blood of another person, the GMO will be cleared by the recipient because of the allogeneic mismatch and cleared by the immune system of the recipient. Furthermore, outside a human host, the GMO cannot survive and all recipients of the GMO will be excluded from donating blood or blood products.

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
n/a

(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:
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.):
To date, no clinical trials have been performed with the GMO.

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 after TEG administration for the term as stipulated by the health authority guidance.

2. Methods for monitoring ecosystem effects
n/a

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
n/a

4. Size of the monitoring area (m^2)
n/a

5. Duration of the monitoring
See H1

6. Frequency of the monitoring
See H1

I. Information on post-release and waste treatment

1. Post-release treatment of the site
The methods and procedures in place in the hospitals involved in the clinical studies are dedicated to mitigate the risk of contamination in accordance with the requirements for gene therapeutic medicinal products.

2. Post-release treatment of the GMOs
none

3. (a) Type and amount of waste generated
Contaminated material used in production, administration of the patient, sampling of the patient and processing of patient samples.

3. (b) Treatment of waste
All (potentially) GMO contaminated waste from production, administration of the patient, sampling of the patient and processing of patient samples will be stored in special containers for contaminated waste. These containers are air tight and leak proof and will be removed according to local applicable guidance for gene therapy medicinal products.

J. Information on emergency response plans

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

The methods and procedures in place in the hospitals involved in the clinical studies are dedicated to mitigate the risk of contamination in accordance with the requirements for gene therapeutic medicinal products.

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

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

4. Plans for protecting human health and the environment in the event of an undesirable effect
None other than the standard emergency care given in case of accidental injection of medical personnel, which consists of disinfection of the injection site and follow-up if symptoms occur.