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	Hungary
(b)	Notification number	B/HU/17/02
(c)	Date of acknowledgement of notification	24/10/2016
(d)	Title of the project	TK008: Randomized phase III. trial of haploidentical HCT with or without an add back strategy of HSV-Tk donor lymphocytes in patients with high risk acut leukemia
(e)	Proposed period of release	From 01/03/2017 until 31/12/2019

2. Notifier

Name of institution or company: **MolMed S.p.A.**

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 **human T lymphocytes**

(b) Identity of the GMO (genus and species)
Homo, homo sapiens

(c) Genetic stability – according to Annex IIIa, II, A(10)
Please refer to the ERA document, section 2.2.4.

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) **PT, PL, LT, HR**

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 **BE, DE, ES, FR, GR, IT**
- Notification number B/../../…

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 B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.
The risk for human health is absent or negligible. Please refer to the ERA document

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) **human T lymphocytes**

other, specify …

2. Name

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

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 (.)

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 **X**

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

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 **human T lymphocytes belong to the stem cell donors who donate for the patients included in the clinical trial**

(b) If the organism is an animal: natural habitat or usual agroecosystem:
N/A

5. (a) Detection techniques
Flow cytometry, molecular biology techniques

(b) Identification techniques
Flow cytometry, molecular biology techniques

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?

Yes **X** No (.)

If yes, specify
Declaration of Helsinki

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

8. Information concerning reproduction

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

9. Survivability

(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	**human T lymphocytes do not survive in the environmental**

(b) relevant factors affecting survivability:
replication/differentiation

10. (a) Ways of dissemination
None outside of the human body

(b) Factors affecting dissemination
None outside of the human body

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)
None

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
To make human T lymphocytes sensitive to (val)ganciclovir and detectable *in vivo*

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
SFCMM-3 Mut2 #48 retroviral vector

(c) Host range of the vector
Moloney Murine Leukaemia Virus

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

Yes **X** No (.)

antibiotic resistance	(.)
other, specify	**expression of the surface marker, ΔLNGFR**

Indication of which antibiotic resistance gene is inserted
None

(e) Constituent fragments of the vector
Please refer to the figure 1c of the submitted document, showing the vector map

(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?

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

6. Composition of the insert

(a) Composition of the insert
Gene for encoding the HSV thymidine kinase
Gene for encoding the truncated form of the NGFR

(b) Source of each constituent part of the insert
Herpesvirus Simplex 1
Human

(c) Intended function of each constituent part of the insert in the GMO
Suicide gene
Surface marker

(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
(N.B.: only information on the thymidine kinase insert are filled here below)

1. Indicate whether it is a:

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

other, specify …

2. Complete name

(i)	order and/or higher taxon (for animals)	**Herpesviridae**
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	**Herpes Simplex Virus 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: **HSV-1 infection in humans**

(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 (.) No **X**
If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?
Yes **X** No (.) 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
Please refer to the ERA document, section 2.2.4.

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
N/A

(b) Techniques used to identify the GMO
Flow cytometry and/or molecular biology techniques in patients' blood

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
Improvement of prognosis of patients affected by leukemia

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): Budapest, IX district, Albert Flórián str. 2-4.

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): 20 m^2
(ii) wider release site (m^2): 60 m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected: no

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO: no

4. Method and amount of release

(a) Quantities of GMOs to be released:
1 +/- 0.2 x 10e7 CD3+/kg of the receiving patient

(b) Duration of the operation:
Up to 4 months

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Contained use, from the shipping to the administration of the patients and waste management

5. Short description of average environmental conditions (weather, temperature, etc.)
N/A

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.
The GMO is being used from several years and has been granted for approval by the European Medicine Agency in June 2016 (CMA) for clinical use. A full Environmental Risk Assessment document exists (version 05, June 2016)

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)	…
(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 GMO is expected to allow for turning off of the GvHD (a complication occurring after hematopoietic stem cell transplantation) with the administration of antiviral agent, thus preventing the toxicities associated with the conventional immune suppressive treatment of GvHD

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

None

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. The GMO lives within the patients' organism

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)	…
(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:
Please refer to the ERA document, section 3.1.3.

(b) from other organisms to the GMO:
N/A

(c) likely consequences of gene transfer:
N/A

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.):
N/A

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

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Please refer to the ERA document, section 3.1

2. Methods for monitoring ecosystem effects
Please refer to the ERA document, section 3.2

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Please refer to the ERA document, section 1.3.7.1.

4. Size of the monitoring area (m^2)
20 m^2

5. Duration of the monitoring
8 hours/ occasion

6. Frequency of the monitoring
6 weekly

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Please refer to the ERA document, sections 3.2 and 3.3

2. Post-release treatment of the GMOs
N/A

3. (a) Type and amount of waste generated
Please refer to the ERA document, section 3.3

3. (b) Treatment of waste
Please refer to the ERA document, section 3.3

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Please refer to the ERA document, section 3.4 and Annex 8a of the same document

2. Methods for removal of the GMO(s) of the areas potentially affected
Please refer to the ERA document, section 3.4 and Annex 8a of the same document

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
Please refer to the ERA document, section 3.4 and Annex 8a of the same document

4. Plans for protecting human health and the environment in the event of an undesirable effect
Please refer to the ERA document, section 3.4 and Annex 8a of the same document