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	**Netherlands**
(b)	Notification number	**B/NL/08/003**
(c)	Date of acknowledgement of notification	**20/08/2008**
(d)	Title of the project	

Intradermal vaccination with naked DNA encoding the fusion protein domain1 of tetanus toxin fragment C and MART-1(aa 26-35) for the induction of MART-1-specific T cell immunity in stage IV melanoma patients

(e)	Proposed period of release	**From 01/11/2008 until 01/11/2018**

2. Notifier

Name of institution or company:

Stichting Het Nederlands Kanker Instituut
Plesmanlaan 121
1066 CX Amsterdam
PO Box 90203
1006 BE Amsterdam
The Netherlands

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

specify phylum, class

The medicinal product is not a GMO per se. It is an investigational gene therapy medicinal product consisting of a purified plasmid DNA (pDNA) drug substance.

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

Not relevant. The plasmid DNA does not have a taxonomic classification.

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

Annex IIIa, II, A(10): Verification of the genetic stability of the organisms and factors affecting it. **Available data indicates the prokaryotic and eukaryotic sequence elements of the pDNA are genetically stable under the controlled conditions used for plasmid manufacture, and will not become unstable via integration of plasmid sequences in trial subjects treated with the pDNA.**

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

Yes (.) No (**x**)

If yes, insert the country code(s) …

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/../../…

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 plasmid pDERMATT is a DNA molecule which has no properties of a living organism or virus and cannot be considered as a GMO. After administering to a patient it is possible that the plasmid will enter body cells. As a result of this the patient will carry some genetically modified cells. These cells cannot survive outside the patient in the environment.
Theoretically an interaction of the plasmid with a virus or viral sequences in the cell is possible. The chance is however negligible small. Also the chance that there will be an

uptake of the plasmid pDERMATT by bacteria which will facilitate the replication of the plasmid is negligible small.
Finally is the chance that vertical transmission will occur negligible small

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

other, specify

pDERMATT is a pDNA derived from the commercially available pVAX1 vector which is specially designed for use in the development of DNA vaccines. This artificial bacterial plasmid does not exist in the natural environment and does not have a taxonomic classification.

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 **pVAX1**

3. Geographical distribution of the organism

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

The pVAX1 vector is used in research laboratories worldwide.

(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 (.)

(used in research laboratories)

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

(used in research laboratories)

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

(used in research laboratories)

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 …

The pVAX1 pDNA is not known to exist in the natural environment.

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

5. (a) Detection techniques

Polymerase Chain Reaction (PCR) assays

(b) Identification techniques

Polymerase Chain Reaction (PCR) assays

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

…

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

The pVAX1 pDNA is not known to exist in the natural environment, so the generation time of pVAX1 in natural ecosystems is not known.

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

Plasmids such as pVAX1 and pDERMATT will not undergo episomal replications in mammalian cells.

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

(c) Factors affecting reproduction:

Both the recipient pVAX1 pDNA and the pDERMATT pDNA are capable of reproduction (replication) in bacteria. Because the plasmids have a ColE1 ori only bacteria of the family *Enterobacteriaceae* are capable to facilitate the replication of the plasmid DNA. These bacteria are not common on the human skin where the pDNA will be injected. In the unlikely case the plasmid will be in contact with bacteria from the intestine the uptake of the plasmid in the absence of kanamycin will have no advantage for growth and will lead to loss of the plasmid.

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	

The pVAX1 or pDERMATT pDNAs are not known to form any of the structures listed above. Instances of inadvertent environmental release would generally be expected to lead to rapid degradation of the pDNA due to the abundance of deoxyribonucleases in the natural environment.

(b) relevant factors affecting survivability:

Because the plasmids pVAX1 pDNA and the pDERMATT pDNA have a ColE1 ori, only bacteria of the family *Enterobacteriaceae* are capable to facilitate the replication of the plasmid DNA. The chance that the plasmid will be taken up by bacteria and will be persistent is negligibly small.

10. (a) Ways of dissemination

Theoretically an interaction of the plasmid with a virus or viral sequences in human cell is possible. The chance is however negligible small. Also the chance that there will be an uptake of the plasmid pVAX1 or pDERMATT by bacteria which will facilitate the replication of the plasmid is negligible small.
Finally is the chance that vertical transmission will occur negligible small

(b) Factors affecting dissemination

A CMV promoter from the CMV virus is present in the plasmids pVAX1 and pDERMATT. CMV is a herpes virus and infection with these viruses occur mainly by oral and sexual transmission where epithelia cell will be infected. CMV has no tropism for keratinocytes and therefore will not be present on the skin where the plasmid will be administered by injection with a tattoo device.

Because the plasmid has a ColE1 ori only bacteria of the family *Enterobacteriaceae* are capable to facilitate the replication of the plasmid DNA. These bacteria are not common on the human skin where the pDNA will be injected.

The plasmid will be injected with a tattoo device in the epidermis. The chance that the injected pDNA will be transported to the germinal cell is negligible small.

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

The plasmid backbone is a commercially available plasmid (pVAX1) with a CMV promoter sequence, a T7 bacteriophage promoter/priming site, a multiple cloning site, a bovine growth hormone (BGH) polyadenolation signal, a kanamycin resistance gene and a pUC origin of replication site for propagation of the plasmid in E. coli.
In the multiple cloning site the genetic sequence for a fusion protein will be cloned. This protein consists of the codon optimalised sequence of the non toxic domain of tetanus toxine fragment C (TTFC) and the sequence of a 9 amino acid peptide (aa. 26-35, ELAGIGILTV) from the MART-1 protein, with the ability to bind to HLA-A*0201 molecules with high affinity.

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

If no, go straight to question 5.

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

If no, go straight to question 5.

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

(a) Type of vector

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

(b) Identity of the vector
…

(c) Host range of the vector
…

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

antibiotic resistance (.)
other, specify …

Indication of which antibiotic resistance gene is inserted
…

(e) Constituent fragments of the vector
…

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

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(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

pDERMATT was constructed using standard recombinant DNA cloning methods.

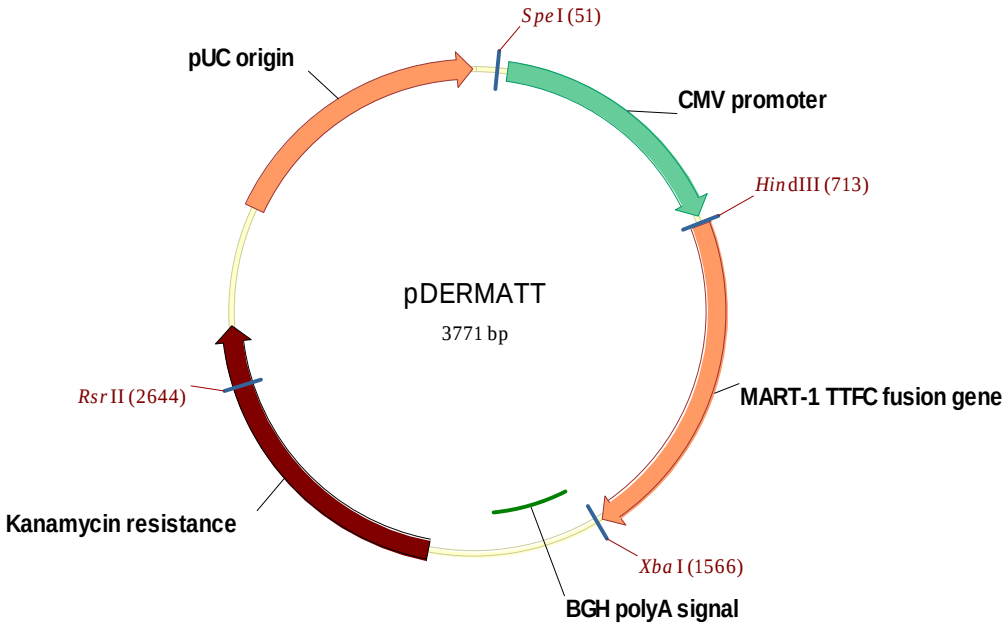
6. Composition of the insert

(a) Composition of the insert

In the multiple cloning site the genetic sequence for a fusion protein will be cloned. This protein consists of:

- **The codon optimalised sequence of the non toxic domain of tetanus toxine fragment C (TTFC). Only domain-1 or jelly roll motive (aa. 865-1120) with a lectine look-a-like protein structure from TTFC is used.**
- **The sequence of a 9 amino acid peptide (aa. 26-35, ELAGIGILTV) from the MART-1 protein, with the ability to bind to HLA-A*0201 molecules with high affinity.**

A plasmid map of pDERMATT is provided in the figure below.



(b) Source of each constituent part of the insert

Domain-1 or jelly roll motive (aa. 865-1120) from tetanus toxine fragment C. The sequence of a 9 amino acid peptide (aa. 26-35, ELAGIGILTV) from the MART-1 protein.

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

Domain-1 from tetanus toxine fragment C contains helper epitopes which are important for inducing a helper T cell response. This response is necessary to get a strong cytotoxic T cell response.
The sequence of a 9 amino acid peptide (aa. 26-35, ELAGIGILTV) from the MART-1 protein has the ability to bind to HLA-A*0201 molecules with high affinity.

(d) Location of the insert in the host organism

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

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No **(x)**
If yes, specify …

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

1. Indicate whether it is a:

viroid		(.)	
RNA virus		(.)	
DNA virus		(.)	
bacterium		(**x**)	**Domain-1 from tetanus toxine fragment C**
fungus		(.)	
animal			
-	mammals	(**x**)	**9 amino acid peptide from the MART-1 protein (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	…

Domain-1 from tetanus toxine fragment C:
Kingdom: Bacteria
Phylum: Firmicutes
Class: Clostridia
Order: Clostridiales
Family: Clostridiaceae
Genus: Clostridium
Species: Clostridium tetani

9 amino acid peptide from the MART-1 protein:
- **Kingdom: Animalia**
- **Phylum: Chordata**
- **Class: Mammalia**
- **Order: Primates**
- **Family: Hominidae**
- **Genus: Homo**
- **Species: H. sapiens**

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 (.)

Only the tetanus toxine is significantly pathogenic. The domain-1 from tetanus toxine fragment C is not pathogenic.

If yes, specify the following:

(b) to which of the following organisms:

humans	(**x**)	**Full length tetanus toxine, not domain-1 of TTFC**
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 (.) Not known (**x**)
Specify

pVAX1 or pDERMATT are not GMO.
Survival of pVAX1 or the pDERMATT pDNA in the natural environment has not been studied. Based on the data and considerations provided under B(8) and B(9) above, the potential for survival of the pDERMATT pDNA in the natural environment as a consequence of the intended use is considered remote.

(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

pVAX1 or pDERMATT are not GMO.The bacterial origin of DNA replication of pDERMATT is derived from pVAX1
and confers the ability to replicate in E. coli. Because the pDERMATT pDNA has a ColE1 ori only bacteria of the family *Enterobacteriaceae* are capable to facilitate the replication of the plasmid DNA.

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (**.**) No (**x**) Not known (.)
Specify

pVAX1 or pDERMATT are not GMO. Dissemination of pVAX1 or the pDERMATT pDNA in the natural environment
has not been studied. Based on the data and considerations provided under B(8) and B(9) above, the potential for dissemination of the pDERMATT pDNA in the natural environment as a consequence of the intended use is considered remote, and no greater than that of pVAX1.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (**x**) Not known (.)
Specify

The plasmids pVAX1 and pDERMATT are not GMO and not pathogens in humans.

2. Genetic stability of the genetically modified organism
Not relevant.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
Yes (.) No (**x**) Unknown (.)
pVAX1 or pDERMATT are not GMO.

(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

Polymerase Chain Reaction (PCR) assays

(b) Techniques used to identify the GMO

Polymerase Chain Reaction (PCR) assays

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 a phase 1 clinical trial in stage IV melanoma patients.

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 (.)

   If yes, specify …

   Not relevant. There is no natural habitat or ecosystem for the pDERMATT pDNA.

3. Information concerning the release and the surrounding area

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

   Nederlands Kanker Instituut/Antoni van Leeuwenhoek Hospital (NKI-AVL)
   Plesmanlaan 121
   1066 CX Amsterdam
   PO Box 90203
   1006 BE Amsterdam
   The Netherlands

   (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

   Not relevant (see below)

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

   Not relevant (see below)

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

   Sections (b)-(d) above are not considered relevant. Environmental release of pDERMATT is not intended beyond the treatment of trial subjects.
   Subjects will be administered the product by injection with a tattoo device into the skin of arms or legs. Treatment will be given at the NKI-AVL, but on an outpatient basis.
   Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs) cannot be specified under these circumstances as the movement of treated subjects will not be restricted. Flora and fauna including crops, livestock and migratory species which may potentially interact with pDERMATT pDNA under these circumstances include bacteria present on or in human subjects as detailed under B(8)(d) above. pDERMATT is not a GMO.

4. Method and amount of release

(a) Quantities of GMOs to be released:

Patients treated at the Nederlands Kanker Instituut will receive multiple injections of the plasmid (not a GMO) with a tattoo vaccination device. Vaccination will be done at day 0, 3 and 6. The dose will be maximal 4 mg plasmid DNA. Four weeks after the initial vaccination a booster vaccination will be given with the same dose.

(b) Duration of the operation:

The duration of the clinical trial will not exceed ten years.

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

Safety containment measures for handling of the pDERMATT pDNA will follow institutional guidelines. Patients will not be isolated or subjected to containment following treatment. pDERMATT is not a GMO.

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

The product (not a GMO) will be administered to trial subjects (patients) at the NKI-AVL in an enclosed facility at ambient temperature.

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.

No data available because no previous releases have been carried out with the same plasmid (not a GMO).

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	…

Human:

- **Kingdom: Animalia**
- **Phylum: Chordata**
- **Class: Mammalia**
- **Order: Primates**
- **Family: Hominidae**
- **Genus: Homo**
- **Species: H. sapiens**

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

The pDNA will be injected into the epidermis and top layer of dermis. Keratinocytes are the major cell type to be transfected, although resident antigen-presenting cells, such as Langerhans cells and dermal dendritic cells may be transfected as well. Based on extensive in vivo and in vitro pre-clinical data gene expression by transfected cells will be transient and most likely short (several days). Despite the short duration of gene expression, preclinical data have revealed that this pDNA vaccination strategy is potent and fast in the induction of cellular immune responses against the MART-1 epitope. Since keratinocytes are the prime cell type to be transfected, the gene products will be produced and through the process of cross-presentation (via antigen-presenting cells) be presented to cytotoxic T–lymphocytes in the draining lymph node.

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

Other potentially significant interactions with other organisms in the environment are not expected for the reasons given under B(8) and B(10) above.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes (.) No (**x**) Not known (.)

Give details

See B(8) and B(10) above.

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

The pDERMATT pDNA (not a GMO) could potentially disseminate into soils and waste water through accidents in transport or improper handling and disposal at the clinical site. The possibility of dissemination and establishment in soil or wastewater ecosystems (e.g., uptake and replication in permissive bacteria) in these cases is considered remote based on the considerations provided above under B(8) and B(10).

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	…

No significant harm to non-target organisms is anticipated.

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:

The likelihood of genetic exchange between pDERMATT and bacteria present on or in treated human subjects is considered remote for the reasons stated under B(8).

(b) from other organisms to the GMO:

Not relevant, because the plasmid is not a GMO.

(c) likely consequences of gene transfer:

Because the plasmid pDERMATT has a ColE1 ori only bacteria of the family *Enterobacteriaceae* are capable to facilitate the replication of the plasmid DNA. The chance that the plasmid will be taken up by these bacteria and will be persistent is negligibly small. In the unlikely case the plasmid will be in contact with these bacteria the uptake of the plasmid in the absence of kanamycin will have no advantage for growth and will lead to loss of the plasmid.

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.):

No studies of pDERMATT have been performed in simulated natural environments.

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

No significant interactions with biogeochemical processes are anticipated.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
   …

2. Methods for monitoring ecosystem effects
   …

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

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

5. Duration of the monitoring
   …

6. Frequency of the monitoring

   Methods for monitoring include PCR assays utilizing primers specific for pDERMATT pDNA sequences that have previously been developed for detection of the pDNA in mouse tissue samples. However, based on the non clinical safety experience with pDERMATT, no monitoring is planned.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

No post-release treatment of the site is planned. A post-injection clinical evaluation of trial subjects (vital signs and symptom-directed exam) will be performed after each administration. The subject may leave the clinic once the investigator deems the subject to be clinically stable. Periodic evaluations will be performed at scheduled visits throughout the duration of treatment. All subjects are required to have a follow-up safety assessment four weeks after their termination visit.

2. Post-release treatment of the GMOs

Disposal of used syringes, gloves or other items that may potentially contain residual amounts of the medicinal product will be performed in accordance with legal and institutional procedures of the NKI-AVL.

3. (a) Type and amount of waste generated

The type of waste will be used syringes, vials, gloves or other disposables that may potentially contain residual amounts of the medicinal product. The amount of medical waste generated on a daily basis will not exceed 5 mg pDNA.

3. (b) Treatment of waste

Treatment of medical waste will be performed in accordance with legal and institutional procedures of the NKI-AVL.

J. Information on emergency response plans

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

   Instructions on spill response procedures will be provided to the clinical site. Site personnel responsible for spill cleanup will be instructed to wear proper personal protective equipment (protective gloves, safety glasses, and clothing).

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

   Spilled liquids will be absorbed with common absorbent materials and placed in appropriate containers for disposal.

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

   Disposal of spilled liquids will be performed in accordance with institutional procedures. Disposal or sanitation of plants, animals, soils, etc. exposed to the product is not mandated due to the low risk of resultant harm.

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

   Because the medicinal product does not appear to pose a significant risk to human health or the environment, specific plans for protection have not been prepared.