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	Sweden (SE)
(b)	Notification number	B/SE/06/ EU-2006-000985-34
(c)	Date of acknowledgement of notification	2006-03-24
(d)	Title of the project	A Phase I-IIa Study of Dose-escalating Intravesical AdCD40L instillation in Urinary Bladder Carcinoma
(e)	Proposed period of release	From August 1, 2006 until December 31, 2008

2. Notifier

Name of institution or company: Uppsala University, Division of Clinical Immunology, Uppsala, Sweden.

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

specify phylum, class …

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

AdCD40L is consisting of a recombinant adenovirus group C serotype 5 E1E3 deleted vector expressing the human CD40L (CD154) gene under controll of a promoter derived from Rous

Sarcoma Virus (RSV) (Leimig et al Human Gene Ther 7:1233-1239, 1996; Takahashi et al Hum Gene Ther 12:659-670, 2001).

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

Recombinant AdCD40L was subjected to sequential passages (from pre-master seed to production level) in human embryonic kidney (HEK) 293 cells with the E1 replication genes in trans. CD40L expression was evaluated by flow cytometry and was transiently expressed as expected.

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.

Adenovirus is a common cold virus that infects humans giving rise to mild nonchronic disease. Individuals with a normally functioning immune system are not endangered by this virus. Most people have been exposed to adenovirus serotype 5 and have developed immunity for this pathogen.

The adenovirus serotype 5 virus used in this study is not capable for replication since the E1 and E3 regions are deleted from the genome. The vector will be locally instilled into the urinary bladder. Spreading of this vector outside the targeted bladder cancer patients is therefore extremely unlikely. The vector will be handled as a biohazardous agent in closed systems to avoid exposure to personnel and environment. The wash-outs will be collected in sealed bags pre-filled with Vircon® for inactivation of any remaining viral vector particles.
The urine will be collected and the vector elimination time will be evaluated using a vector specific quantitative PCR technique. Patients will stay at the clinic until virus particles no longer can be detected in the urine. Hence, the exposure of this vector outside the patients will be limited. Based on the character of this vector system it is our judgment that upon unwanted exposure to the environment this vector would not cause any potential harm to humans, animals or plants.

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		(X)
bacterium		(.)
fungus		(.)
animal		
-	mammals	(.)
-	insect	(.)
-	fish	(.)
-	other animal	(.)
	(specify phylum, class)	…

other, specify …

2. Name

(i)	order and/or higher taxon (for animals)	Adenoviridae
(ii)	genus	Mastadenovirus
(iii)	species	human Adenovirus
(iv)	subspecies	subgroup C
(v)	strain	serotype 5
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	Ad5

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)

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

Atlantic	x
Mediteranean	x

	Boreal	x
	Alpine	x
	Continental	x
	Macaronesian	x
(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	man

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

5. (a) Detection techniques
Quantitative PCR

(b) Identification techniques
Quantitative PCR

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
Adenoviral vectors are categorized as a GMM, level II, by the Swedish Work Environment Authority. The applicable guidelines for handling, protection, labeling and destruction of Ad will be followed and the study personnel will be trained to handle GMM. Handling of the Ad5 vector in pre-specified, restricted areas at the Pharmacy and at the clinic must be approved by the Swedish Work Environment Authority and by the Swedish Medical Products Agency before start of the study.

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (X) No (.) Not known (.)

If yes:

(a) to which of the following organisms:

humans	(X)
animals	(.)
plants	(.)
other	(.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

Adenovirus is a common cold virus that infects humans giving rise to mild non-chronic disease. Individuals with a normally functioning immune system are not endangered by this virus. Most people have been exposed to adenovirus serotype 5 and have developed immunity for this pathogen.

The parental wild type of Ad5, subgroup C, usually give rise to a mild transient upper respiratory infections ,"common cold", in man. Individuals with a normally functioning immune system develop life-long immunity for this pathogen and are not endangered by this virus. Infections in animals, caused by human Ad, have been observed only under experimental in laboratory environment. In these circumstances, adenoviruses can infect murine cells but they are not able to replicate.

The replication deficient Ad5 with E1 and E3 deleted is a laboratory product which is not found in the natural environment. Ad5 E1E3 deleted vector may cause serious immunogenic reactions if administered systemically and in high titers. In 1999 a patient died after injection of high-dose vector was injected directly into the hepatic artery. However, these kinds of vectors have been used without toxicity in a variety of other gene therapy programs. Even if the Ad5, E1E3 deleted vector itself may be well tolerated when used in the bladder cavity, local inflammation caused by the transgene CD40L is expected since it will be used to evoke the immune system to eradicate tumor cells. CD40L therapy could potentially lead to the development of autoimmune disease since CD40L is an immunostimulating molecule. In this study the CD40L expression is expected to be transient and confined to the bladder epithelium. Due to powerful peripheral tolerance against autologous antigens, no systemic autoimmunity is anticipated. However, patients with a strong autoimmune anamnesis will be excluded from this trial. No signs of systemic or local autoimmunity have been observed in animal studies performed in murine experimental models of bladder cancer. CD40L in soluble form has been injected into cancer patients without severe toxicity (Vonderheide et al J Clin Oncol 19:3280-3287, 2001). AdCD40L ex vivo transduced cells have been injected into cancer patients without severe toxicity (Biagi et al Clin Cancer Res 11:6916-6923, 2005).

8. Information concerning reproduction

(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:
Adenoviruses replicate in the human host.

There is no replication of Ad5 with E1E3 deletion, in any known, natural ecosystem. The viral vectors are produced in permissive cell lines expressing E1 region in trans such as the HEK 293 cells.

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 …	

(b) relevant factors affecting survivability: storage in buffer -80°C to +4°C.allows survival of viral particles outside host.

10. (a) Ways of dissemination
Direct contact or aerosol formation

(b) Factors affecting dissemination

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)
…, B/../../…

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(X)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
E1 and E3 regions have been deleted from the virus to make it replication incompetent. The adenoviral backbone is contained in the plasmid Addl327 (Leimig et al Human Gene Ther 7:1233-1239, 1996) A cassette with the human CD40L gene has been inserted into the

pAVs6A plasmid to create pAVs6AhCD40L (Takahashi et al Hum Gene Ther 12:659-670, 2001). The viral vector containing CD40L was constructed by recombination of the ClaI fragment of Addl327 with the pAVs6AhCD40L plasmid (Takahashi et al Hum Gene Ther 12:659-670, 2001). AdCD40L vector will be instilled in the urinary bladder of bladder cancer patients to deliver the human gene for CD40L to the surface epithelium of the bladder wall. CD40L is an immunostimulatory gene normally expressed on activated immune cells, especially T helper cells. CD40L interacts with CD40 expressed on other immune cells such as antigen presenting cells. Upon ligation the antigen presenting cells become activated and initiate immune responses of Th1 type. In cancer patients, the immune system is normally suppressed by the tumor. This impedes the immune systems capability of detecting and eradicating the tumor cells. Upon immunostimulating gene therapy the aim is to restore the immune systems anti-tumor capacity.

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

(b) Identity of the vector

1. pAVs6ahCD40L plasmid described in C2.
2. Ad-dl327 described in C2.

(c) Host range of the vector

Escherichia coli

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

Yes (x) No (.)

antibiotic resistance (x)
other, specify :

Indication of which antibiotic resistance gene is inserted: ampicillin
Note that the ampicillin gene is not present in the final viral vector particles of AdCD40L (see C2).

(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	(.)
other, specify		Homologous recombination

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
human CD40L cDNA
RSV promoter

(b) Source of each constituent part of the insert
CD40L cDNA was obtained from ATCC (Manassas, VA, USA)
RSV promoter has been obtained from Rous Sarcoma Virus and inserted into the pAVs6a plasmid.

(c) Intended function of each constituent part of the insert in the GMO
The human gene for CD40L will be translated into CD40L protein. CD40L is an immunostimulatory molecule normally expressed on activated immune cells such as T helper cells.
The RSV promoter will drive expression of the CD40L transgene in mammalian cells (human urinary bladder cancer cells in this study).

(d) Location of the insert in the host organism

-	on a free plasmid	(.)
-	integrated in the chromosome	(.)
-	other, specify	The insert is integrated into the viral vector genome.

(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)		
- 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	Homo
(iv)	species	Homosapiens
(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 (x) No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
Overexpression of CD40L will cause a local inflammation at the site of expression. In this study, we are attempting to alert the immune system to react to the tumor growing in the urinary bladder of the patients (see C7b).

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 (x) No (.) Unknown (.)

Specify The GMO is replication incompetent

(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 (x) No (.) Not known (.)

Specify Since it is not replication competent, it does not replicate and spread. This makes the GMO less pathogenic than its wild type counterpart. The CD40L expression will stimulate the immune system to destroy the cell infected by the virus vector. This will even further prevent spreading of the vector. It may also evoke a transient autoimmune reaction. However, this has not been seen in other studies using soluble CD40L or ex vivo transduced tumor cells injected into cancer patients (see C7b).

2. Genetic stability of the genetically modified organism

The AdCD40L virus vector is not integrated into the host genome and will only transiently survive in the host cell. For viral vector production see A3c.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (X?) No (.) Unknown (.)

(a) to which of the following organisms?

humans	(x)
animals	(.)
plants	(.)
other	…

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

AdCD40L is not capable for replication since the E1 and E3 regions are deleted from the genome. These replication-defective adenoviral vectors have no mechanism for long-term maintenance in cells and cannot form new vector particles and therefore not spread or cause viral infection. The vector DNA do not integrate into the host cell genome and the expression of the transgene – CD40L – is therefore limited to a short time period (days). The vector will be locally installed into the urinary bladder. Animal experiments confirm that the bladder is well isolated from other organs and no spreading has been seen in ovaries, kidneys, spleen, liver, heart or brain. Spreading of this vector outside the targeted urine bladder is therefore extremely unlikely.
A local inflammation caused by the transgene CD40L is expected. CD40L expression is expected to be transient and confined to the bladder epithelium. CD40L is a type II transmembrane protein which belongs to the tumour necrosis factor (TNF) gene superfamily. CD40L expression is restricted to activated or stimulated cells under pathological conditions such as inflammation. CD40L is crucial for the initiation of CD8+ T cell mediated immune responses mainly indirect via activation of immature DCs. Activation of immune cells leads to production and release of cytokines, chemokines, adhesion molecules, matrix metalloproteinases, procoagulant activities etc. In contrast, stimulation of CD40+ cancer cells with CD40L leads to induction of apoptosis by mechanisms not fully understood.

4. Description of identification and detection methods

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

(b) Techniques used to identify the GMO
Quantitative PCR

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The initiative for this study is based on extensive basic research in experimental human and animal models of urinary bladder cancer. Bladder cancer is an attractive target for immunostimulating gene therapy because it is sensitive for immunotherapy as demonstrated by the life-prolonging effect of bacillus Calmette-Guérin (BCG) instillations. Further, the tumor is localized in the bladder cavity which enables gene vector delivery into the tumor area without targeting other organs.

CD40L is one of the most potent stimulators of the immune system. CD40L is normally expressed on immune cells during inflammation. It is involved in the activation of cytolytic T killer cells that can target and destroy tumor cells. By inserting the gene for CD40L into the tumour area via gene therapy, the tumour will send activation signals to the immune system. In animal models, AdCD40L therapy cures aggressively growing tumors. The gained immune activation generates cytotolytic T cells that specifically recognize and kill tumor cells.

The immunological status will be thoroughly investigated before, during and after the treatments in all patients and the treatment effect on the tumor will be examined by transurethral inspection as well as histopathological evaluation.

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 (x) No (.)

The GMO will be instilled in the urinary bladder.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
AdCD40L will be diluted to patient doses at the hospital Pharmacy in Uppsala and administered at the Dept of Urology at Uppsala University hospital. The vector will be transported in sealed containers. AdCD40L will be handled only in pre-specified, restricted areas approved by the Swedish Work Environment Authority and the Swedish Medical Products Agency.

(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
The patients will be kept in the restricted area (hospital room) until virus particles no longer can be detected in urine.

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Urin is collected in containers and Virkon inactivated before disposal as biohazard waste.

(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:
$1 \times 10^{10} – 1 \times 10^{12}$ diluted in 50 ml PBS will be instilled at each treatment occasion. Up to 30 patients will undergo 3 treatments.

(b) Duration of the operation:
The GMO will be kept in the bladder for 30-60 minutes.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Transfer of the GMO will be done in sealed containers. The hospital personnel will wear protective clothes, eye-wear, face mask and gloves. Detailed procedures for all steps in handling the GMO is described the biohazard instructions.

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

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.
Not applicable

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)

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

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 patients will not leave the clinic until virus particles are no longer detectable in urine.

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:
   Not expected

   (b) from other organisms to the GMO:
   Not expected

   (c) likely consequences of gene transfer:
   Local inflammation, activation of immune system, possible stabilization or regress of the cancer disease.

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.):
   This will be the first time AdCD40L is used for in situ treatment of patients. The toxicity studies in rodents conclude that AdCD40L caused a slight increase of mild non-suppurative cystitis. The way of administration per se cause an occasional severe chronic suppurative cystitis associated with a pyelonephritis.

   However, patients with B-CLL have received tumor cells transduced in vitro with AdCD40L vector in two separate studies in the US. In the first study 11 patients received cells intravenously. The patients demonstrated flu-like symptoms and a few patients showed transient elevation of liver transaminases. Less commonly, symptoms such as headache, edema, dehydration and diarrhea were seen (Wierda et al Blood 96:2917-2924, 2000). In the second study, 9 patients received subcutaneous injections of cells. Local pain, redness and swelling were seen at the injection site. A few patients demonstrated a transient muscle ache and low-grade fever (Biagi et al Clin Cancer Res 11:6916-6923, 2005).

   Soluble CD40L protein has been injected intravenously (5 injections weekly) into 32 patients with various cancers in a clinical trial performed at the Harvard Medical School in the US. No severe side effects were seen except in one patient that demonstrated grade 4 elevation of liver transaminases post high-dose injection. Symptoms reported were some cases of hemoglobin reduction (not dose dependent), neutropenia, lymphopenia and pain. Dyspnea, asthenia, dyspepsia and pneumonia were seen in one patient each at the MTD level (decided by high transaminase in one patient) (Vonderheide et al J Clin Oncol 19:3280-3287, 2001).

   No impact on the environment has been observed in any of the studies referred to above.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
   Not expected

H. Information relating to monitoring

1. Methods for monitoring the GMOs
The GMO will be monitored in blood and urine by quantitative PCR? Serum will be analyzed for development of anti-adenovirus antibodies.

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 since there is no risk of transfer of donated genetic material form the patient to other organisms. The batch of AdCD40L to be used in the trial is tested to confirm that no replication competent viruses are present.

4. Size of the monitoring area (m^2)
Monitoring of treated patients.

5. Duration of the monitoring
According to protocol, i.e. until the vector is no longer detectable.

6. Frequency of the monitoring
According to protocol, i.e. until the vector is no longer detectable.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
1% Virkon will be used to disinfect working area and to inactivate eventual spillage.

2. Post-release treatment of the GMOs
The vector solution post instillation will be collected into a container with 1% Virkon solution. Also the wash-out fluid from the patient will be collected in the same Virkon containing container. The container will be sealed and disposed of as biohazardous material according to the hospital routines.

All vector containing materials will be inactivated in 1% Virkon solution for at least 10 minutes before disposing them in the biohazard waste box.

3. (a) Type and amount of waste generated
Vials of stock solution, syringes, tubing set, instillation catheter, wash-out fluid, and other material that may come in contact with the vector, as gloves etc.
A maximum of 2 patients per week and a total of 30 patients will be treated with the vector ($\leq 1x10^{12}$ particles).

3. (b) Treatment of waste
All waste material will be placed in sealed containers and inactivated with 1% Virkon before disposal as biohazardous material according to the hospital routines.

J. Information on emergency response plans

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

Vector suspension leakage: Inactivate vector solution with 1% Virkon for at least 10 minutes before cleaning with paper. Dispose the paper in boxes for biohazardous waste.

Vector suspension on clothes: Small (1-2 mL) volumes: Rinse with water and clean the clothes according to hospital routine. If large amount of vector contaminates clothes, pour 1% virkon solution on the contaminated area and dispose the clothes in a biohazard waste box.

Vector suspension on skin: Rinse with water. Wash with soap and rinse with water. Contact medical care if inflammation or irritation develops.

Vector suspension in the eyes: Rinse with eye-wash. Contact medical care if inflammation or irritation develops.

The supervisor and the GMM manager at the Clinic will be informed about any accidents that occurs when using GMM such as AdCD40L.

2. Methods for removal of the GMO(s) of the areas potentially affected
   See section J1.

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
   Patients will be monitored according to protocol and any clinically adverse events will be evaluated, followed-up and reported according to the procedures described in the protocol.