Notification report

General information

Notification Number: B/BE/03/B3

Member State:*Belgium*

Date of Acknowledgement:*30/07/2003*

Title of the Project:
Study TG1024.01: "Phase I multicentre study of TG1024 (Adenovirus interleukin 2) in patients with metastatic melanoma or other advanced solid tumor cancers"

Proposed period of release From:*01/05/2004* **To:***31/05/2005*

Name of the Institute(s) or Company(ies): *Transgene S.A.*;

3. Is the same GMPt release planned elsewhere in the Community?
No

4 - Has the same GMPt been notified elsewhere by the same notifier?
No

GMO characterization

GMO is a:
DNA Virus

Identity of the GMO:
Non replicative, recombinant adenovirus of type 5 (group C) deleted in regions E1 and E3, named ADTG13383.

Information relating to the recipient or parental organisms from wich the GMO is derived

Indicate whether the recipient or parental organism is a:	Common Name	Genus	Species	Subspecies	Strain	Pathovar
DNA Virus	*Adenovirus human serotype 5 (Ad5)*	*Mastadenovirus*	*Human adenovirus type 5*	*subgroup C*		

Full dossier text

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

A. GENERAL INFORMATION

A.1 Details of notification

a) Member State of notification: BELGIUM
b) Notification number: B/BE/03/B3
c) Date of acknowledgment of notification: 30 July 2003
d) Title of the projectStudy TG1024.01: Phase I multicentre study of TG1024 (Adenovirus interleukin 2) in patients with metastatic melanoma or other advanced solid tumor cancers
e) Proposed period of release: Q4 2003 - Q4 2004

A.2 Notifier

Name of institution or company: Transgene S.A

A.3 GMO characterization

a) Indicate whether the GMO is a:
viroid
RNA virus

DNA virus x
bacterium:
- fungus
- animal
- mammals
- insect
- fish
- other animal, specify phylum, class
other, specify (kingdom, phylum and class)

b) Identity of the GMO: Non replicative, recombinant adenovirus of type 5 (group C) deleted in regions E1 and E3, named ADTG13383

c) Genetic stability - according to Annex IIIA, II, A (10)
Genetic stability of the genome of ADTG13383 was controlled after 7 passages at MOI 1 vp/cell on the complementation cell line PER.C6 and the ability of each clone to induce the synthesis of IL2 was verified. 100% of these clones had kept this ability. Moreover, at each passage, the genomic DNA was isolated from viral particles and analyzed by restriction enzymes. The resulting patterns are congruent with that of purified virus and consistent with theoretical pattern. Thus, according to these methods, no evidence of genetic instability was observed while the number of vector generations was pushed over the production passage of clinical lots.

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

Yes [If yes, insert the country code(s)]
No x

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

Yes (If yes: - Member State of notification: - Notification number:)
No x

A.6 Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes x
If yes: - Member State of notification: The same GMO is already used in Switzerland through the same clinical study.- Notification number: OFSP: GT2001004 ; OICM: 2001S01181
No

A.7 Summary of the potential environmental impact of the release of the GMOs

The adenovirus is localized in the nucleus of the infected cell, as an episomal form, without known risk of integration in the genome of the infected cell. Considering that the recombinant adenovirus has lost all replicative capability, at the death of the cell, the viral DNA is naturally eliminate. Based on its physiology, the injected tumor can be considered as a confined environment. From the site of intra tumoral injection, viral DNA is however detected in some organs like liver and lungs or spleen. As well, we cannot exclude a very limited presence, of viral DNA in biological fluids like urine, faeces or saliva. But considering the nature of this viral DNA, infectious or not, and the character non replicatif of Ad-IL2, the probability of a biological risk for public health or environment is very low. Otherwise, the appearance of a recombination event in situ, during a co-infection with a wild type adenovirus is extremely low, and would implicate a very low amount of viral particles, so that they would be rapidly eliminate by the immune system and consequently would have no consequence on health.

B. Information relating to the recipient or parental organism from which the GMO is derived

B.1 Recipient or parental organism characterization:

a) Indicate whether the recipient or parental organism is a:

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

B.2 Name

(i) order and/or higher taxon (for animals): Family: Adenoviridae
(ii) genus: Mastadenovirus
(iii) species: Human adenovirus C
(iv) subspecies: Serotype 5
(v) strain
(vi) pathovar (biotype, ecotype, race, etc.)
(vii) common name: Ad5 E1° E3° (Deleted in E1 and E3 genes)

B.3 Geographical distribution of the organism

a) Indigenous to, or otherwise established in, the country where the notification is made:

Yes
No Not applicable
Not known

b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes
If yes, indicate the type of ecosystem in which it is found:
Atlantic
Mediterranean
Boreal
Alpine
Continental
Macaronesian
(ii) No Not applicable
(iii) Not known

Not applicable for a) and b):
The strain Ad5 E1° and E3° is non replicative on normal cells, this virus need for its propagation, a complementation cell line which bring it up missing functions, that are, at minimum, proteins coded by E1A and E1B genes. This explains that Ad5 E1° and E3° cannot be found in the natural environment, it is only a strain which does not belong to any known ecosystem.

c) Is it frequently used in the country where the notification is made?

Yes
No x

d) Is it regularly kept in the country where the notification is made?

Yes
No x

B.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
in association with animals
other (specify): Ad5 E1° and E3° is a laboratory strain not replicative in a natural environment. The parental wild type strain is found in human and other mammals, it is moderately pathogen in human.

b) If the organism is an animal: natural habitat or usual agro ecosystem:

B.5 Techniques

a) Detection techniques

By infection of permissive cells in culture
By PCR assay

b)Identification techniques

PCR with specific primers for the deletions

B.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: The organism AdE1° E3° has been classified by the French authorities (CGG) and by the Swiss authorities (SKBS) in group II. In France when adenoviral particles amount is inferior to 1012 vp (viral particles) for each operation, the recombinant adenovirus must be manipulated in a L2 laboratory environment. If the amount is superior to 1012 vp, L3 environment is recommended.

B.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 x
plants
other
b) give the relevant information specified under Annex III A, point II. (A).(11).(d) of Directive 2001/18/EC
In animal and human, the Ad5 E1° E3° vectors have been reported to induce inflammatory reactions. The dose and the route of administration are major issues related to the pathogenicity of the organism. In 1999, fatal event was reported in one patient receiving more than 1013 pfu (plaques forming units) of an Ad5 E1° E3° by hepatic intra-arterial route.

B.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
d) Factors affecting reproduction: There is no replication of Ad5 E1° E3° in natural ecosystems. The probability that the missing E1 function, necessary for viral replication, is complemented, is extremely low in natural ecosystems.

B.9 Survivability

a) Ability to form structures enhancing survival or dormancy: Not applicable
(i) endospores
(ii) cysts
(iii) sclerotia
(iv) asexual spores (fungi)
(v) sexual spores (fungi)
(vi) eggs
(vii) pupae
(viii) larvae
(ix) other, please specify

b) Relevant factors affecting survivability: Not applicable

B.10 Dissemination

a) Ways of dissemination

The Ad5 E1° E3° needs to complement at minimum the E1 regions to be able to replicate and consequently to possibly disseminate. As mentioned above in 8, this probability is very low in the

natural ecosystems. In laboratory, the Ad5 E1° E3° can be propagated in a complementation cell line which bring up the required proteins. PER.C6 cell has been chosen as complementation cell line. The absence of homology between DNA sequences (PER.C6 genome and recombinant adenovirus described here after), prevent any recombination event between the cell and the virus during its replication.After infection of Ad5 E1° E3° in animal or in human, adenoviral DNA fragment can be found by PCR analysis in biological fluids like blood. The dissemination of the virus depend on the route of administration and on the dose.

b) Factors affecting dissemination

The propagation of Ad5 E1° E3° and the culture of PER.C6 cell need specific culture media and culture conditions that limit its propagation in a specialized laboratory.

B.11 Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

Not known

C. Information relating to the genetic modification

C.1 Type of the genetic modification

(i) insertion of genetic material x
(ii) deletion of genetic material
(iii) base substitution
(iv) cell fusion
(v) other, specify

C.2 Intended outcome of the genetic modification

Constitutive expression of human interleukin 2

C.3 (a) Has a vector been used in the process of modification?

Yes x
No
If no, go straight to question 5.

First of all, the recombinant adenovirus genome is entirely reconstituted in a plasmid vector, through different successive steps of homologous recombination.The purified plasmid DNA is digested with a restriction enzyme (PacI) that generates a linear fragment without the sequences used for bacterial replication (origin of replication and antibiotic resistance).This linear fragment is used for the transfection of the complementation cell line (PER.C6) and allows the generation of the first complete viral particle (encapsided viral genome).

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes x
No
If no, go straight to question 5.

C.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

C.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, please specify: Homologous recombination to generate the plasmid, then transfection of PER.C6 cell with the PacI fragment of linear DNA from pTG13383.The final GMO contains only viral genes.

C.6 Composition of the insert

a) Composition of the insert: See table on C.6 c)
b) Source of each constituent part of the insert: See table on C.6 c)
c) Intended function of each constituent part of the insert in the GMO: Element of the insert - Origin - Function

pCMV: immediate early enhancer/promotor region from human CMV
From pCI mammalian expression vector (U47119)
Promoter starting the transcription of the downstream gene

Int: synthetic intron: donor site from the human b-globin intron 1 - acceptor and branch point from a murine igG gene
From pCI mammalian expression vector (U47119)
Synthetic intron increasing the transcription of the downstream gene

IL2: human interleukin 2, cDNA
Positions 117-566 according to genbank (X01586)
Gene of interest

SV40 poly A: late poly A site from SV 40
From pCI (U47119)
Polyadenylation sequence ending the transcription

CMV : Cytomegalovirus

SV40: Sarcoma Virus 40

d) Location of the insert in the host organism
- on a free plasmid
- integrated in the chromosome x
Integrated in the vector genome, in place of E1 region (here vector means Ad5 deleted in E1 and E3)

- 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 (Donor)

D.1 Indicate whether it is a:

viroid
RNA virus
DNA virus
bacterium
fungus
animal: x
- mammals x
- insect
- fish
- other animal (specify phylum, class)
other, specify: Human origin for the gene of interest: Interleukin 2. The cDNA was synthesized from messenger RNA extracted from human PBL.See also table in paragraph C.6 c), for the origin of other fragments.

D.2 Complete name

(i) order and/or higher taxon (for animals): Primates
(ii) family name (for plants): Hominidae
(iii) genus: Homo
(iv) species: Homo sapiens
(v) subspecies
(vi) strain
(vii) cultivar/breeding line
(viii) pathovar
(ix) common name

D.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:
a) 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, point II (A) (11) (d):

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 related to exposure to biological agents at work?

Yes
No x
If yes, specify:

D.5 Do the donor and recipient organism exchange genetic material naturally?

Yes
No

Not known x

E. Information relating to the genetically modified organism

E.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: Receptor organism = Ad5 E1° E3°

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
Not known
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

E.2 Genetic stability of the genetically modified organism

See paragraph A.3 c)

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

Yes
No
Not known

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)The adenoviral vector being a virus whose few genes are still functional, surrounding DNA is expressed. It is clear from many early studies that AdE1°E3° vectors do express in vivo (experimental animals, rodents) residual viral genes {Yang, Jooss, et al. 1996 #39190} ; {Yang, Nunes, et al. 1994 #39000} ; {Yang, Su, et al. 1996 #39160}. We have shown in vitro (A549 cells), that AdE1°E3° vectors express early and late viral genes but much reduced compared to wild type Ad5 {Lusky, Christ, et al. 1998 #22910}. At our knowledge, there are no studies that has directly compared the level of transgene expression and the level of viral gene expression side by side in a preclinical study and clearly in humans this has never been done. It can be assumed however, that viral gene expression is supposed to be much lower than transgene expression (replication defective vector), since transgene expression is usually from a strong promoter (AdIL2 - CMV).Furthermore, although adenoviral gene therapies have been commonly associated with very good tolerance and minimal toxicity in most clinical studies, the occurrence of serious and fatal adverse events in a few of adenoviral gene therapy studies conducted to demonstrate that at high doses of adenoviral vectors, adenoviral capsid proteins can trigger an innate immune response mediated by antigen presenting cells and macrophages, featuring a massive release of cytokines (IL6). Host factors could be implicated because two patients treated with the same dose had very different outcomes {Liebert 2002 #22310}{Stephenson 2001 #33950}.

E.4 Description of identification and detection methods

a) Techniques used to detect the GMO in the environment: Specific PCR, culture on complementation cell line.
b) Techniques used to identify the GMO: Specific PCR

F. Information relating to the release

F.1 Purpose of the release (including any significant potential environmental benefits that may be expected)

Non specific immunotherapy by interleukin 2 expressed from a recombinant adenovirus.

F.2 Is the site of the release different from the natural habitat or from the ecosystem in which the recipient organism is regularly used, kept or found?

Yes
No x
If yes, specify:

F.3 Information concerning the release and the surrounding area

a) Geographical location (administrative region and where appropriate grid reference):
b) Size of the site (m2):(i) actual release site (m2):(ii) wider release area (m2):
c) Proximity to internationally recognized biotopes or protected areas (including drinking water reservoirs), which could be affected:
d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO:

Not relevant. The GMO is administered in human by the intra-tumoral route.

F.4 Method and amount of release

a) Quantities of GMOs to be released: one dose of 3x1011 vp per injection
b) Duration of the operation: a few minutes

c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release: All transfers of the preparation must be done using a closed container. During product manipulations, goggles and labcoat must be worn and gloves are recommended. Prior to the administration of the product, the suspension of vector particles must be prepared under condition compliant with injectable preparations.Patients can be maintained for observation. The analysis of GMO present in effluents allows to monitor the potential dissemination out of the organism which is expected to be low from the intra-tumoral injection site. Data obtained from previous studies in human with this GMO or similar GMO, showed the presence of adenoviral DNA fragments (PCR analysis) in blood of patients through a long administration cycles. No presence in urine has been reported.

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

Usual conditions for hospitalization.

F.6 Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human impacts from the release

The most commonly reported adverse events associated with the intra-tumoral injection of Ad-IL2 (TG1024) which have been reported by the patients of the on going phase I/II study are fatigue, injection site erythema, injection site pain, pyrexia, rigors, nausea, vomiting, anorexia, dizziness, headache and transient lymphopenia within 24 hours after injection.
One patient has experienced a reversible thrombocytopenia, in combination with Dacarbazine. Site redness, swelling and discomfort and fatigue were reported with previous generations of vector, TG1021 and TG1022.
Besides, the principal adverse events that are known to be related to the use of adenoviral vectors are flu-like symptoms such as fever, chills, elevated liver enzymes and thrombocytopenia.
Considering the nature of the vector, patients should be closely monitored for at least: transaminases, evidence of Disseminated Intravascular Coagulation, thrombocytopenia and blood IL6 levels.

G. Interactions of the GMO with the environment and potential impact on the environment if significantly different from the recipient or parent organism

G.1 Name of target organisms (if applicable)
(i) order and/or higher taxon (for animals): Primates
(ii) family name (for plants): Hominidae
(iii) genus: Homo
(iv) species: Homo sapiens
(v) subspecies
(vi) strain
(vii) cultivar
(viii) pathovar
(ix) common name

G.2 Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
At the injection site: Infection of cells by the recombinant AdenovirusIn infected cells: Expression of human interleukin 2In the injected tumor: immune and inflammatory reactions against tumorIn the organism: distant effects of the immune anti-tumoral response in other tumors present in the patients.

G.3 Other potentially significant interactions with other organisms in the environment
One cannot exclude that the missing E1 function, necessary for viral replication, could be complemented during co-infection of the vector with a wild type (Ad5) adenovirus. However, our assessment of this risk concludes that this event is not likely to cause any significant harm in patients, for the following reasons:
- This complementation will not extend beyond the viremia of Ad5, which is known to be limited. The vector will be complemented only as long as the parental virus propagates.
- This complementation will be limited to areas where both types of viral particles are numerous enough to simultaneously infect the same cell. Consequently, only a fraction of the dose of vector administered will be amplified, and this amplification will be less efficient than the amplification of the wild type parental virus (Ad5).
- Since adenoviruses are not known to naturally propagate in places like the site of administration, a hypothetical complementation will occur only on vector particles that have disseminated from this site. Again, these particles will represent only a fraction of the dose administered.
- A fraction of the administered dose of vector particles being partially amplified for a limited time will add only a fraction of the dose of IL2 that is expected with the treatment.In addition, the absence of sequence homology between the vector and the PER.C6 complementation cell line genomes should eliminate the occurrence of Replication Competent Adenovirus (RCA), during the production process. Furthermore, a control test for the detection of RCA is performed for each released clinical lot.

G.4 Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes No Not known x
Give details:As mentioned above, the propagation and the replication of the vector needs the use of complementation cells and a specific culture media (see above, paragraph G.3).

G.5 Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
It is not known whether the GMO could be disseminated from the animal or human injected with the GMO and could become transferred in one other mammals.

G.6 Complete name of non-target organisms which (taking into account the nature of 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
(viii) pathovar
(ix) common name
Not known x

G.7 Likelihood of genetic exchange in vivo
a) from the GMO to other organisms in the release ecosystem: Not known
b) from other organisms to the GMO: Not known
c) likely consequences of gene transfer: See paragraph G.3

G.8 Give references to relevant results (if available) from studies of the behavior and characteristic of the GMO and its ecological impact carried out in simulated natural environments (e.g. microcosms, etc.):
No data available.

G.9 Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism
Not expected. No difference with the parental organism.

H Information relating to monitoring
H.1 Methods for monitoring the GMOs
By specific PCR.Control of the presence of the GMO in blood, tonsils, urines, and feces from the human patients infected with the GMO.

H.2 Methods for monitoring ecosystem effects
Not applicable.

H.3 Methods for detecting transfer of the donated genetic material from the GMO to other organisms
As mentioned in paragraph G.3, if the GMO should complement its E1 region during co-infection with a wild type adenovirus, methods of PCR analysis and/or cell culture are set up to monitor specifically the presence of Replication Competent Adenovirus (RCA). Furthermore, a quality control test is performed to detect the presence of RCA in each clinical lot used in clinical study.

H.4 Size of the monitoring area (m2)
Monitoring of treated patients.

H.5 Duration of the monitoring
Monitoring of patients virology according to the protocol.

H.6 Frequency of the monitoring
See the protocol.

I - Information on post-release and waste treatment

I.1 Post-release treatment of the site
Decontamination:

Material(opened ampoules, tubes for dilution, syringe, needle, gauze dressing...):
Transgene procedure: Disinfection Protocol for Therapeutic Units (vials / cryotubes),OrPut in a specific container (i.e. sharpsafe) that is treated according to regular hospital procedure for infectious material.

Labcoat, goggles, patient gown, bedding:
If contaminated by the study drug:regular hospital procedure for infectious material.

Gloves(single usage):
Regular hospital procedure for infectious material.

Work area:
Regular hospital procedures (use of a disinfectant active on the handled product or bleach [= 1.6°Cl i.e. 5 g/l of active chlorine]).

Destruction:

Material(opened ampoules, tubes for dilution, syringe, needle, gauze dressing ...):
Regular procedure for hospital wastes.

Labcoat, goggles, patient gown, bedding:
Not applicable

Gloves(single usage):
Regular procedure for hospital wastes.

Work area:
Not applicable

I.2 Post-release treatment of the GMOs
See below treatment of wastes

I.3 (a) Type and amount of waste generated
See paragraph I.1The quantity of wastes per injection is limited. The administered volume is below 1 ml (corresponding to an administered dose of 3x1011 vp), the size of pipettes and syringes is adapted to this low volume.

(b) Treatment of waste
All material used for preparation and administration will be placed in a closed container, then decontaminated according to the regular hospital procedures for infectious material or according to the disinfection protocol for therapeutic units recommended by Transgene S.A. Decontaminated wastes will be then, discarded according to the regular way of destruction for hospital wastes.

J Information on emergency response plans
J.1 Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
In case of accidental shedding of the product (cracked or broken ampoules): Contaminated area must be cleaned with a disinfectant active on the study drug or bleach >= 1.6°Cl i.e. 5 g/l of active chlorine).In case of skin contamination with / without injury: Wash immediately under tap water. Then treat the area with a disinfectant solution containing iode or chlorehexidine (4%) for 5 minutes. Rinse. Then treat the area with bleach (1.4°Cl i.e. 4.5 g/l of active chlorine) for 5 minutes. Rinse again. Cover with a sterile gauze dressing, which should be appropriately discarded when removed. The injured person should receive counseling from investigator and should then be closely followed for a period of at least 2 weeks for the development of a flu-like syndrome or other symptoms.In case of eye contamination: Irrigate immediately the eye during 15 minutes with lukewarm water being careful not to contaminate the other eye. The injured person should receive counseling from an ophthalmologist.In case of ingestion: Do not make vomit and call the investigator immediately. The person should be closely followed for a period of at least 2 weeks for the development of a flu-like syndrome or other symptoms..

J.2 Methods for removal of the GMO(s) of the areas potentially affected
Bleach or any other antiviral product regularly used as a viral disinfectant at the hospital.

J.3 Methods for disposal or sanitation of plants, animals, soils etc. that were exposed during or after the spread
They will be decontaminated according to the standard procedures in place at hospital for contaminated wastes.

J.4 Plans for protecting human health and the environment in the event of an undesirable effect
Patients will be monitored for the occurrence of serious adverse events (SAE) according to the clinical protocol: each SAE will be registered and evaluated by the hospital staff and the sponsor of the study, and health authorities will be notified when relevant.