SNIF: GMOB-2023-18438

Domain:
GMO

Authorisation type:
Deliberate release of GMO or a combination of GMOs for any other purpose than for placing on the market

Application type:
Summary notification for the release of genetically modified higher organisms other than higher plants in line with Decision 2002/813/EC Annex, Part 1.

Recipient Member State:
Hungary

Competent Authority:
Ministry of Agricture/ Department for Biodiveristy and Gene Conservation

Notification number:
B/HU/23/02

Acknowledgement date:
2023-10-03

A- General information

Details of notification

Details of notification
A Randomized, Partially Masked, Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD (ASCENT)
Member State of notification
Hungary
Title of the project
A Randomized, Partially Masked, Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD (ASCENT)
Proposed period of release
Starting date
2023-11-30
Finishing date
2025-11-30

Notifier

Name of institute or company
AbbVie Inc.
Email
Not provided
Phone number
Not provided
Website
Not provided
Address
Not provided
Post code
Not provided
Country
Hungary

GMO characterisation

(a) Indicate whether the GMO is a:

Viroid
No
RNA virus
No
DNA virus
Yes
Bacterium
No
Fungus
No
Animal

No
Other
No

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

Family: Parvoviridae Genus: Dependoparvovirus Species: Adeno-associated virus (recombinant AAV-derived-replication-deficient viral vector)

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

The GMO is an AAV8 viral vector carrying an anti-VEGF Fab transgene expression cassette. The AAV8 vector is a DNA viral vector. Generally, DNA viruses are genetically stable due to intrinsic thermodynamic stability of the DNA molecule. The frequency of errors during the replication of DNA is relatively low; and host cells have molecular mechanisms that can repair replication errors made by DNA polymerases. The GMO was constructed by DNA recombinant technology which allowed the replacement of all viral genes by the transgene expression cassette. Deletion of all viral DNA, except for inverted terminal repeats, rendered the GMO replication incompetent and, therefore, genetically stable since no further genetic modifications or rounds of replications are possible even in the presence of a helper virus. The manufacturing process further supports genetic stability of the produced GMO by using characterised and fully sequenced DNA plasmids released following GMP requirements. Also, the vector-delivered DNA is maintained in the host cells without genome integration as episomal concatemers.

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

Yes
Country
Hungary

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

No

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

Yes
Country
US
Insert the notification number(s) (if exist)
17280/SN0000
Country
CA
Insert the notification number(s) (if exist)
NSN-21105
Country
JP
Insert the notification number(s) (if exist)
MHLW/PSEHB Notification No. 0603-49 MOE/NCB Notification No. 2106031

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

The GMO is an adeno-associated viral vector of serotype 8 carrying an anti-VEGF Fab transgene expression cassette inserted by recombinant DNA technology. This GMO is completely devoid of all viral genetic material (except for inverted terminal repeats) and, therefore, the GMO is replication incompetent. The vector genome is a single stranded DNA genome with AAV2-derived inverted terminal repeats (ITRs) flanking the anti VEGF Fab expression cassette. Expression from the transgene cassette is driven by a CB7 promoter, a hybrid between a CMV immediate early enhancer and the chicken actin promoter, while transcription from this promoter is enhanced by the presence of the chicken actin intron (CI). The polyadenylation signal for the expression cassette is the RBG polyA. The GMO is planned to be administered in study RGX-314-3101, a phase 3 clinical trial; the planned number of participants is 660 The GMO will be administered subretinally as a single dose. Participants who receive ABBV-RGX-314 will be followed for approximately 1 year in study RGX-314-3101 (for participants randomized to one of the two ABBV-RGX-314 arms or during the second year for control participants who crossover to receive ABBV-RGX-314 at Week 56). All participants with nAMD who receive subretinal ABBV-RGX-314 will be strongly encouraged to enroll in a long term follow up study (RGX-314-5101) to be monitored for at least 5 years post-ABBV-RGX-314 administration. Potential GMO release to the environment will be analysed in serum, urine and tears obtained from participants in the US only study RGX-314-2103 (who received the same doses as those being evaluated in RGX-314-3101). The samples will be analysed for GMO detection and quantification based on a specific qPCR. Given the transient and minimal vector shedding of ABBV-RGX-314 following subretinal administration observed in the Phase 1/2a Study RGX-314-001, vector shedding in humans is not further evaluated in the ongoing pivotal trials (RGX-314-2104 and RGX-314-3101). In the pivotal studies, participants will be monitored clinically. Once released, the GMO cannot confer any selective advantage to bacteria or other microorganisms because the GMO does not contain prokaryotic promoters, antibiotic or other types of resistance genes, which would enhance or constrain their growth. For humans other than the clinical trial subjects, the infection likelihood with this GMO is negligible; shedding is expected to occur at very low levels for a limited time, if at all. In the unlikely scenario that the GMO is transmitted from a participant to other humans, the severity of potential adverse effects is negligible because a transgene expression cassette contained in the GMO encodes a humanized anti-VEGF Fab, designed to bind and inhibit human VEGF. The dissemination of the GMO in the environment is severely restricted since the GMO is rendered replication-incompetent by removing from the GMOs genome rep and cap genes required for replication and packaging. Altogether, the risk for people, animals, microorganisms and the environment exposed to the GMO is negligible.

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

1. Recipient or parental organism characterisation

Indicate whether the recipient or parental organism is a:

Viroid
No
RNA virus
No
DNA virus
Yes
Bacterium
No
Fungus
No
Animal
No
Other
No

2. Name

(i) Order and/or higher taxon (for animals)
Parvoviridae
(ii) Genus
Dependoparvovirus
(iii) Species
Adeno-associated dependoparvovirus
(iv) Subspecies
N/A
(v) Strain
N/A
(vi) Pathovar (biotype, ecotype, race, etc.)
AAV2 (ITRs) /AAV8 (capsid)

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
yes
(b) Indigenous to, or otherwise established in, other EC countries:
yes
Indicate the type of ecosystem in which it is found:
atlantic
mediterranean
boreal
alpine
continental
macaronesian

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

4. Natural habitat of the organism

(a) Is the organism a microorganism ?
Yes
Water
No
Soil, free-living
No
Soil in association with plant-root systems
No
In association with plant leaf/stem systems
No
In association with animals
No
Other
Yes
Specify
Human and non-human primates
(b) Is the organism an animal?
Yes
Natural habitat or usual agroecosystem
Not applicable

5(a) Detection Techniques

Detection Techniques
Quantitative polymerase chain reaction (qPCR)

5(b) Identification Techniques

Identification Techniques
Quantitative polymerase chain reaction (qPCR)

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

Yes
Specify
AAVs are not known to be a pathogenic virus in humans. AAVs are not assigned an Advisory Committee on Dangerous Pathogens (ACDP) category and are also classified biosafety Group/Class 1 or 2 depending on the European member state.

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

no

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
After entry into the host cell nucleus, wild-type AAV can follow either one of two distinct and interchangeable pathways of its life cycle: the lytic or the latent phase. For entry into a lytic phase, a latently infected cell needs to be co-infected with a helper virus, inducing genome rescue of the provirus DNA followed by replication and packaging of the viral genome. Finally, upon helper virus-induced cell lysis, the newly assembled virions are released.
(b) Generation time in the ecosystem where the release will take place:
The GMO will remain in the transduced cell and only the transgene protein expressed will have an effect in the surrounding cells. The GMO is a recombinant vector incapable of replication due to lack of all its viral genetic material.
(c) Way of reproduction
Asexual
(d) Factors affecting reproduction:
Wild type AAV requires a helper virus (adenovirus or herpesvirus) for effective replication.

9. Survivability

(a) Ability to form structures enhancing survival or dormancy:

(i) endospores
No
(ii) cysts
No
(iii) sclerotia
No
(iv) asexual spores (fungi)
No
(v) sexual spores (fungi)
No
(vi) eggs
No
(vii) pupae
No
(viii) larvae
No
Other
Yes
Specify
Not applicable
(b) Relevant factors affecting survivability
The survival of GMO outside of the host is expected to be the same as wild-type AAV8. AAV does not form survival structures but can remain infectious for at least a month at room temperature following simple desiccation or lyophilisation. Wild-type AAV and GMOs based on AAV vectors are susceptible to appropriate virucidal disinfectants with activity for non-enveloped viruses, such as Softa-Man acute for disinfecting the hands and Incidin PLUS, alkaline solutions at pH >9, 5% phenol, heat (>80C for 60 minutes), UV radiation and extreme pH (<2 and >12). Effective disinfectants require a minimum of 20 minutes contact time to be effective.

10(a) Ways of dissemination

Dispersal (dissemination) of adeno-associated viruses is not documented definitively, but is likely through inhalation of aerosolised droplets, mucous membrane contact, parenteral injection, or ingestion.

10(b) Factors affecting dissemination

The GMO is a replication-incompetent virus derived from AAV2 (ITRs) and AAV8 (capsid). The genetic modifications do not affect its survival outside the host or probable mode of dissemination. It is unable to replicate even in the presence of a helper virus.

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

Insertion of genetic material
Yes
Deletion of genetic material
Yes
Base substitution
No
Cell fusion
No
Other
No

2. Intended outcome of the genetic modification

The intended outcome is a GMO, which is a recombinant adeno-associated virus (AAV) serotype 8 (AAV8) vector encoding humanized anti-VEGF Fab transgene protein. Other than the AAV serotype 2 inverted terminal repeat sequences (ITR) at each end of the single-stranded DNA virus genome, all other viral sequences have been removed and replaced with the humanized anti-VEGF Fab expression cassette and control elements necessary to drive transgene expression. The viral genome is packaged in an AAV8 capsid, resulting in a recombinant viral vector that can drive expression of the anti-VEGF Fab in transduced human cells, but is not able to replicate in host cells in the absence of a helper virus and wild type AAV.

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

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

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

(a) Type of vector

Plasmid
Yes
Bacteriophage
No
Virus
No
Cosmid
No
Transposable element
No
Other
No
(b) Identity of the vector
A schematic representation of the transgene vector is shown in the figure below:
(c) Host range of the vector

The vectors (plasmids) replicate in E.coli

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

Yes

Antibiotic resistance

Yes

Indication of which antibiotic resistance gene is inserted

The kanamycin resistance gene is inserted in the vectors (plasmids). This gene confers kanamycin resistance to bacterial cells used for plasmid production.

Other

No

(e) Constituent fragments of the vector

Only the transgene expression cassette from the transgene vector is inserted into the genome of the GMO, clinical vector. Other vectors (plasmids) used in the manufacture of the GMO do not supply any genetic material to the final product, the GMO. In addition to the transgene expression cassette, the transgene vector carries a bacterial origin of replication and the gene for kanamycin resistance to allow for propagation of the plasmid in E.coli.

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

(i) transformation

No

(ii) electroporation

No

(iii) macroinjection

No

(iv) microinjection

No

(v) infection

No

Other

Yes

Specify

triple transfection of the HEK293 cell line with vectors (plasmids): 1) transgene vector a plasmid containing the AAV clinical vector genome with the transgene flanked by ITRs, 2) packaging and pseudotyping vector a plasmid with rep and cap genes and 3) helper vector a plasmid with adenoviral helper genes.

6. Composition of the insert

(a) Composition of the insert

The expression cassette comprises: (1) 3 and 5 AAV2 inverted terminal repeats (ITRs) (2) CAG (CB7) promoter: (2.1) Cytomegalovirus immediate-early enhancer, (2.2) Chicken -actin promoter, (2.3) Chicken -actin intron (3) Humanized anti-VEGF Fab (4) Polyadenylation signal

(b) Source of each constituent part of the insert

(1) 3 and 5 AAV2 inverted terminal repeats (ITRs): Adeno-associated virus serotype 2 (2) CAG (CB7) promoter: (2.1) Cytomegalovirus immediate-early enhancer: Cytomegalovirus, (2.2) Chicken -actin promoter: Chicken, (2.3) Chicken -actin intron: Chicken, (3) Humanized anti-VEGF Fab: Human (4) Rabbit -globin polyadenylation signal: Rabbit

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

(1) 3 and 5 ITR sequences: cis acting sequences required for vector genome replication and packaging (2) Humanized anti-VEGF Fab: therapeutic part of the GMO (3) Chicken -actin intron: Common feature for increased gene expression, shown to enhance accumulation of steady level of mRNA for translation (4) Enhancer/promoter: enhance the expression of the transgene (5) Polyadenylation signal: provides cis sequences for efficient polyadenylation of the mRNA

(d) Location of the insert in the host organism

On a free plasmid
No
Integrated in the chromosome
No
Other
Yes
Specify
The described insert is recombinant and completely replaces the genome of the parental organism wild-type AAV.

(e) Does the insert contain parts whose product or function are not known?

No

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

1. Indicate whether it is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Complete name

(i) Order and/or higher taxon (for animals)
Primates
(ii) Family name (for plants)

(iii) Genus
Homo
(iv) Species
sapiens
(v) Subspecies
sapiens
(vi) Strain

(vii) Cultivar/Breeding line

(viii) Pathovar

(ix) Common name
Human

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

no

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism?

no

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

N/A

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?

No

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

yes

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?
no
Specify
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
yes
Specify
The GMO is unable to replicate, even in the presence of required helper virus, due to the lack of the rep and cap genes required for replication and packaging.
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
yes
Specify
The GMO is unable to replicate since it lacks the rep and cap genes required for replication and packaging. Therefore, though it has the capacity to infect cells, the lack of replicative capacity will severely restrict dissemination.
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
Specify

2. Genetic stability of the genetically modified organism

Generally, DNA viruses like AAVs are stable due to the thermodynamic properties of the DNA molecule. Since the GMO lacks rep and cap genes, it is replication incompetent even in the presence of a helper virus, which even further minimizes the likelihood of genetic variation as result of replication. Additionally, the long-term therapeutic activity of the GMO is not dependent on replication.

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

no
(b) Give the relevant information under Annex III A, point II (A)(11)(d) and II(C)(2)(i):
Point II(A)(11)(d) of Annex III (pathological, ecological and physiological traits): Recombinant AAV viruses are not pathogenic to human and non-human primates, although they can infect cells from humans and non-human primates and may persist within infected cells as episomal form. Recombinant AAV viruses are not toxic, virulent, allergenic, or carriers (vectors) of a pathogen. They do not replicate or activate other latent viruses and cannot colonise other organisms. Point II(2)(i) of Annex III (considerations for human health and animal health, as well as plant health): Recombinant AAV viruses and/or their metabolic products do not have toxic or allergenic effects on humans, animals or plants. Recombinant AAV viruses are not pathogenic and do not have colonisation capacity. Moreover, since the GMO lacks the viral rep and cap genes it cannot replicate, even in the presence of a helper virus.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
The GMO can be detected by different PCR techniques using specific primer/probes against anti-VEGF Fab

coding region.

(b) Techniques used to identify the GMO

PCR based techniques with primers/probes specific to anti-VEGF Fab coding region.

F. Information relating to the release

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

A Randomized, Partially Masked, Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD (ASCENT)

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?

No

3. Information concerning the release and the surrounding area

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

The GMO will be administered to patients in Spain (ES), France (FR), Germany (DE), Italy (IT), Hungary (HU)

(b) Size of the site (m2)

(i) actual release site (m2)
Not applicable
(ii) wider release area (m2)
Not applicable

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

Not applicable

(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:

Dose in patient cohort 1: 6.41010 genome copy (GC)/eye (3.21011 GC/mL) Dose in patient cohort 2: 1.31011 GC/eye (6.51011 GC/mL) The GMO is administered via subretinal delivery (200 L in a single dose) After administration, shedding of infectious AAV particles is considered highly unlikely.

(b) Duration of the operation:

The GMO administered as a single dose in one day.

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

The GMO will be administered to patients in the hospital./operating room. Participant samples (aqueous humor urine, and serum) will be drawn in the clinic and analysed by a qualified laboratory (for transgene protein concentrations and routine lab assessments). During GMO administration and sample draws, established routine practices for dealing with potentially biohazardous materials are in place as well as protective equipment including laboratory coats and gloves. Instructions for collection, processing and transportation of the clinical samples are provided in the Laboratory Manual. Standard practices for the disposal of biohazardous materials in the healthcare setting cover accidental breakages during blood draws.

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

The GMO is shipped to the clinical site at -60 and stored at the hospital pharmacy at 2 to 8 for no more than 8 weeks. The GMO will be administered to patients in a separate operating room under hospital environmental conditions. Shed GMO particles may enter hospital waste waters of an 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

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 organisms (if applicable)

Applicable?
Yes
(i) Order and/or higher taxon (for animals)
Primates
(ii) Family name (for plants)
N/A
(iii) Genus
Homo
(iv) Species
sapiens
(v) Subspecies
sapiens
(vi) Strain
N/A
(vii) Cultivar/Breeding line
N/A
(viii) Pathovar
N/A
(ix) Common name
Human

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

Applicable?
Yes
Specify
It is anticipated that delivery of the gene encoding for anti-VEGF Fab via a one-time administration of the GMO could provide a durable source of anti-VEGF Fab activity in the retina for the treatment of nAMD.

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

No potentially significant interactions with other organisms in the environment are predicted.

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

no

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

The GMO is a replication-incompetent virus derived from AAV2 (ITRs) and AAV8 (capsid). The genetic modifications do not affect its survival outside the host or probable mode of dissemination. However, the lack of replicative ability prevents multiplication and therefore severely limits its ability to disseminate. Shedding of AAV vectors has been monitored in both humans and animals; the shedding is transient and is at the low level. It is not anticipated that the GMO can establish in any known ecosystem.

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 GO to other organisms in the release ecosystem:
Negligible
(b) from other organisms to the GMO:
Negligible
(c) likely consequences of gene transfer**
The only mechanism by which the transgene could be mobilised is through a triple co-infection of the same host cell by the GMO (clinical vector containing the transgene), wild type AAV (providing the rep and cap functions) and a helper virus (adenovirus or herpesvirus). Statistically, such a triple co-infection scenario is a very rare event. If it did occur, it would result in the production of (pseudo)wild type AAV and GMO particles (which would still lack rep and cap genes and consequently could not be self-sustaining).

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 simulated natural environments (e.g. microcosms etc.):

The GMO is a replication-incompetent virus derived from AAV2 (ITRs) and AAV8 (capsid). The genetic modifications do not affect its natural host and tissue tropism. No specific studies have been conducted regarding transmission of the GMO between humans or animals and on the ecological impact of the vector in simulated natural environments.

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

None known or predicted

H. Information relating to monitoring

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Potential GMO release to the environment will be analysed in serum, urine and tears obtained from participants in the US only study RGX-314-2103 (who received the same doses as those being evaluated in RGX-314-3101). The samples will be analysed for GMO detection and quantification based on a specific qPCR. Given the transient and minimal vector shedding of ABBV-RGX-314 following subretinal administration observed in the Phase 1/2a Study RGX-314-001, vector shedding in humans is not further evaluated in the ongoing pivotal trials (RGX-314-2104 and RGX-314-3101). In the pivotal studies, participants will be monitored clinically.
2. Methods for monitoring ecosystem effects
The chance of ecosystem effects is considered negligible, and monitoring is not planned.
3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
No plans for detecting transfer of genetic material to other organisms than to the treated subjects are considered necessary.
4. Size of the monitoring area (m2)
Not applicable.
5. Duration of the monitoring
Not applicable.
6. Frequency of the monitoring
Not applicable.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site

In general terms, decontamination or site management will be performed according to local biosafety guidelines or procedures and BSL-I. In case of spillover, the perimeter of the spill will be limited with paper towels and appropriate virucidal agent will be used to clean the area. All GMOs based on adeno-associated viruses are susceptible to appropriate virucidal disinfectants with activity for non-enveloped viruses, such as Softa-Man acute for disinfecting the hands and Incidin PLUS, alkaline solutions at pH >9, 5% phenol, heat (>80C for 60 minutes), UV radiation and extreme pH (<2 and >12). Effective disinfectants require a minimum of 20 minutes contact time with GMO. The destruction of all material used for GMO manipulation will be performed following internal procedures for management of biological agents and BSL-I.

2. Post-release treatment of the GMOs

In general terms, all equipment used during the procedure will either be disposed of in line with current biological hazard procedures or decontaminated with virucidal agents as dictated by the local biological hazard waste management plan.

3(a) Type and amount of waste generated

Vials, injection device (subretinal cannula, MicroDose syringe & viscous fluid injection tubing), general hospital waste (gloves, gowns, and related accessories, etc.).

3(b) Treatment of waste

Following GMO administration, used vials as well as the used delivery system components will be disposed of in a manner consistent with the standard practice of the institution for biohazardous materials and BLS-I rules. In addition, any disposable surgical instruments or other materials used during the administration procedure or collection of body fluids will be disposed according to standard biosafety practice of the institution. All non-disposable surgical equipment will be cleaned using a chemical disinfectant with proven virucidal activity (e.g. a 1% hypochlorite solution) and then sterilised by autoclaving according to standard practice of the institution.

J. Information on emergency response plans

J. Information on emergency response plans

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

In case of unexpected spread (e.g. spills) the affected area and perimeter will be lineated with absorbing material, and then decontaminated using appropriate disinfectants as described before. In case of injury, the injured site will be disinfected appropriately according to the best biosafety practice standards and internal procedures.

2. Methods for removal of the GMOs of the areas potentially affected

According to BSL-I health personnel involved in the trial will wear protective clothing. In case of spillover, the area will be gently covered with paper towels and appropriate chemical disinfectant such as Incidin PLUS will be used to clean the area. The disinfectant will be applied for a minimum of 20 minutes as contact time before clean-up. Appropriate validated disinfection detergents and methods will be used for decontamination and disinfection. The disinfectant and decontamination procedure are included in the list of the Robert Koch Institute of currently approved disinfectants and disinfectant procedures or the VAH (Verbund fr Angewandte Hygiene e.V) list of disinfectants.

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

Not applicable since exposure of animals and plants etc. are not anticipated.

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

Considering the negligible risk for human health and the environment, no specific plans are deemed necessary.