GENSIGHT

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

GS010
Recombinant AAV vector serotype 2 containing the human wild-type mitochondrial ND4 gene (rAAV2-ND4 vector)

29 May 2015

Sponsor
GENSIGHT Biologics
74 rue du Faubourg Saint-Antoine 75012
France

PART 1 (COUNCIL DECISION 2002/813/EC)

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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 *GERMANY*
(b) Notification number B/DE/16/PEI2505
(c) Date of acknowledgement of notification 10/08/2015
(d) Title of the project : *A Randomized, Double-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 (rAAV2/2-ND4) in Subjects Affected for more than 6 months and to12 months by Leber Hereditary Optic Neuropathy Due to the G11778A Mutation in the Mitochondrial NADH Dehydrogenase 4 Gene*

EudraCT NUMBER: 2015-001266-26

(e) Proposed period of release From 01/01/2016 until 31.12/2017

2. Notifier

Name of institution or company:
Sponsor
GENSIGHT Biologics
74 rue du Faubourg Saint Antoine
75012 Paris
France

3. GMO characterisation
GS010 consists of a recombinant AAV vector serotype 2 containing the human mitochondrial ND4 gene (rAAV2/2-ND4 vector) intended for the treatment of Leber Hereditary Optic Neuropathy (LHON).

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(X)*AAV-derived replication-deficient vector*
bacterium	(.)
fungus	(.)

animal

- mammals (.)
- insect (.)
- fish (.)
- other animal (.)

specify phylum, class …

(b) Identity of the GMO (genus and species)
Parvoviridae
Genus: Dependovirus
Species: AAV-derived replication-deficient vector

(c) Genetic stability – according to Annex IIIa, II, A(10)
Two vector batches have been put on stability. A stability protocol compliant to ICH guidelines has been defined with the following timelines: 0, 6, 12, 18, 24, 36, 48 and 60 months.
To date available results are conform (up to 6 months) for the following stability testing:

- *pH*
- *Purity profile by SDS-PAGE*
- *Viral Genome Titer*
- *Infectious Genome Titer*
- *Sterility (last time point)*

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes (X) No (.)
If yes, insert the country code(s) *FR, UK, IT, DE*

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (X) No (.)
If yes:
- Member State of notification *FR, UK, IT, DE*
- 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 (X) No (.)
If yes:
- Member State of notification *USA*
- Notification number B/../../…

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

GS010 will be administered as a single intravitreal (IVT) injection to LHON patients.
This route of administration should not lead to the release of the GMO in the environment. Indeed:
- *Biodistribution data available so far (please refer to section 1.3.4 of the non-clinical IMPD) have shown that IVT route of administration does not lead to the spread of the GMO to other organs or blood in animals,*

In the case this GMO would nevertheless be released in the environment via body fluids, this should not lead to any incidence for the as the GMO i) is non pathogenic and replication incompetent, and ii) will be destroyed by conventional water treatment.
The intended application of GS010 is limited to one hospital centre and the number of patients to be treated is very restricted (target of 40 patients enrolled for 36 treated patients).
Nonetheless, the hospital centre is required to train the health care professionals involved in the study in the safe handling of GS010 and to have appropriate biosafety practices implemented in order to minimize any accidental exposure to the product, be it personnel, contact persons or the environment.

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)	*Parvoviridae*
(ii)	genus	*Dependovirus*
(iii)	species	*Adeno-associated virus*
(iv)		
(v)	subspecies	…
(vi)	strain	*Serotype 2*
(vii)	pathovar (biotype, ecotype, race, etc.)	…

(viii) common name *AAV2*

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:

Approximately 50 to 80% of the European human population is seropositive to at least one AAV serotype

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (*X*) *for research contained use* No (.)

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

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 : *Mostly frequent human and non-human primate hosts but also other animals.*

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not Applicable

5. (a) Detection techniques
Specific q-PCR to detect the vector DNA

(b) Identification techniques
Specific Q-PCR to detect the vector DNA

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

Adeno-associated viruses (AAV) belong to the family Parvoviridae and there is no known link to any known human illness. AAV viruses are classified biosafety Group/ Class 1.

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

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

If yes:

(a) to which of the following organisms:

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

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

No pathological, ecological and physiological traits are present. In natural conditions, wild type AAV2 in the presence of a helper virus (adenovirus) is found to transmit to humans only and is not known to colonize other species.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
Not relevant since GS010 is a recombinant vector and is not capable of replication.

(b) Generation time in the ecosystem where the release will take place:
Not relevant

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

(c) Factors affecting reproduction:
Reproduction of wild-type AAV is dependent on co-infection with helper virus (Adenovirus or Herpesvirus)

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:
As all vectors based on adeno-associated viruses, GS010 is sensitive to appropriate virucidal disinfectants with activity for non-enveloped viruses such as 1% sodium hypochlorite (for at least 10 minutes), 5% phenol, heat (>80°C for 60 minutes), UV radiation and extreme pHs (<2 and >12).

10. (a) Ways of dissemination
Wild-type (wt) AAV infections are common in human and probably occur from childhood. The ways of dissemination for wt AAV are poorly understood, but is likely to occur through inhalation of aerosolized droplets, mucous membrane contact, parenteral injection, or ingestion.
Further information is available in Section 1.3.4 of the non-clinical IMPD.

(b) Factors affecting dissemination
wt AAV are not able to replicate unless a co-infection with an adenovirus occurs.

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 Applicable

C. Information relating to the genetic modification

1. Type of the genetic modification

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

2. Intended outcome of the genetic modification
GS010 is a rAAV2/2 in which the human ND4 gene has been inserted and the sequences allowing replication have been deleted.
The objective of these genetic modifications is to obtain a replication-defective viral vector able to deliver the correct human ND4 sequence in target cells in LHON patients.

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

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
(i) 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
Recombinant AAV2/2_ND4

(c) Host range of the vector
HEK 293 cells

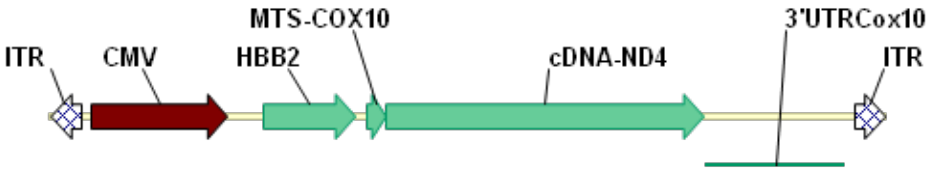
(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (*X*) No (.)

antibiotic resistance	(*X*)
other, specify	…

Indication of which antibiotic resistance gene is inserted
Kanamycin

Note that the final GS010 product is controlled in order to ensure no kanamycin is detected in drug product.

(e) Constituent fragments of the vector
The vector is a rAAV2) encoding the gene of the human NADH Dehydrogenase 4 (ND4) gene under the control of the cytomegalovirus (CMV) immediate early promoter in an intron-containing expression cassette (beta globin intron, HBB2), flanked by the viral inverted terminal repeats (ITR) from AAV2.



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

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

other, specify : *GS010 is manufactured in HEK 293 cells by a triple plasmid transfection technique exempt from an auxiliary virus.*

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

The insert is composed of:

- *a CMV promoter,*
- *the HBB2 intron,*
- *cis-acting elements of the Cox10 mRNA, and*

The human wild-type mitochondrial NADPH Deshydrogenase (MT-ND4) gene.

(b) Source of each constituent part of the insert

Part of the insert	***Source***	***Intended function***
CMV promoter	*CMV*	*Induction of transgene expression in mammalian cells*
HBB2 intron	*human*	*Improvement of the transgene mRNA stability*
Cis-acting elements of the Cox10 mRNA	*human*	*Efficient mitochondrial delivery of the ND4 protein*
ND4 transgene	*human*	*Expression of a wt ND4 protein in the targeted cells*

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

…

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify : *The insert is cloned 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

The following information relates to the organism from which the inserted gene (MT-ND4) 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	*Human*	

2. Complete name

(i)	order and/or higher taxon (for animals)	*Primates*
(ii)	family name for plants	…
(iii)	genus	*Homo*
(iv)	species	*Homo sapiens*
(v)	subspecies	…
(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?
Yes (.) No (*X*) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

humans	(.)
animals	(.)
plants	(.)
other	*Not applicable*

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

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

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (.) No (*X*)

If yes, specify …

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

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

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

Yes (.) No (*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 has been designed to be defective for replication*

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

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

Specify: *GS010 is unable to replicate independently, even in the presence of a helper virus, since it lacks the rep and cap genes required for rescue/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?

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

Specify …

2. Genetic stability of the genetically modified organism

Two vector batches have been put on stability. A stability protocol compliant to ICH guidelines has been defined with the following timelines: 0, 6, 12, 18, 24, 36, 48 and 60 months.

To date available results are conform (up to 6 months) for the following stability testing:

- *pH*
- *Purity profile by SDS-PAGE*
- *Viral Genome Titer*
- *Infectious Genome Titer*
- *Sterility (last time point)*

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

Yes (.) No (.) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other *Not applicable*

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

Neither wild type AAV, nor the GS010 vector is known to be pathogenic to humans.

4. Description of identification and detection methods

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

The presence of GS010 could be detected by qPCR.

(b) Techniques used to identify the GMO

Before batch release, the following quality controls are performed in order to characterize the GS010 viral vector:

Appearance
pH
Osmolality
Sterility test
Endotoxin test by LAL method
Identity test by sequencing analysis of viral DNA
Viral protein identity by Western Blot
Protein purity profile by SDS-PAGE and silver staining
Viral Genome Titer by qPCR
Infectious Genome titer by qPCR

F. Information relating to the release

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

Administration of the GS010 investigational medicinal product (IMP) to LHON patients in the frame of an authorized clinical trial in Munich, Germany.

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

Yes (.) No (.) *Not applicable*

If yes, specify …

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Munich, Germany
University of LMU,
Department of Ophthalmology
Surgery room, approx. 20 m²

(b) Size of the site (m^2): *Not Applicable*
(i) actual release site (m^2): app 20 m^2
(ii) wider release site (m^2): app 250 m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Given the nature of the product administration, scale of release and procedures for waste treatment, the exposure to significant biotopes, protected areas and drinking water supplies is expected to be negligible.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
GS010 is a replication-incompetent virus derived from AAV2/2. The genetic modifications do not affect its natural host and tissue tropism. No transfer of genetic material between the GMO and other organisms is predicted.
Given the nature of the product administration (intravetreal) and the transient/low levels of shedding expected the risk of unintended exposure of flora and fauna to GS010 is minimal.

4. Method and amount of release

(a) Quantities of GMOs to be released:
Dose to be administered for the proposed study is 9^E10 vg as a single intravitreal injection in one eye. Pharmacy instructions will be updated to ensure the correct dose is given, depending on the concentration of vector in the batch supplied.

The proposed clinical trial aims to administer GS010 to 18 patients in Europe.

(b) Duration of the operation:
From Q4 2015 to Q2 2019.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
All hospital staff handling the IMP must wear a gown, gloves, mask and goggles. Preparation of the IMP and dilution will be performed in a clean room at a campaign dedicated production and outside production schedules other preparations. Controlled atmosphere areas will be accessible only to authorized persons. Access is regulated by badge. The preparation is carried out in a microbiological safety cabinet type II by qualified personnel in the preparation and informed the nature of the IMP. The dressing procedures will meet the needs of individual protection from the IMP.

5. Short description of average environmental conditions (weather, temperature, etc.)
The clinical trial of GS010 will occur in Germany which has a temperate climate. The risk of release of GS010 in to the environment is unrelated to climatic characteristics.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
No data available

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)	*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*

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

The target cells for transduction are Retinal Ganglion Cells (RGC). This should result into transgene expression and synthesis of the wild-type ND4 protein inside the mitochondria. This is expected to improve respiratory chain function, which should prevent further RGC loss. Ultimately, further vision impairment and optic nerve damage are expected to be prevented.

3. Any other potentially significant interactions with other organisms in the environment
No such interaction is anticipated.

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
GS010 is incapable of replicating.

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
Not 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	…

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
Not anticipated

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

(c) likely consequences of gene transfer:
Not anticipated

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.):
For information related to the Proof of concept of GS010 efficacy, please refer to the section 1.2.2 of the non-clinical part of the IMPD

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

…

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Based on biodistribution data available, the IMP will remain in the eye i.e. is very unlikely to disseminate outside the human body. Consequently, no GMO-specific monitoring is envisaged at hospital.

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.

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

Not applicable

5. Duration of the monitoring

Not applicable.

6. Frequency of the monitoring

Not applicable.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

It is very unlikely that GS010 is released outside patient's eye.
In case of contamination, the site should be thoroughly cleaned with ethanol and the individuals should be placed under observation for any effect attributed to the IMP.

2. Post-release treatment of the GMOs

All materials, including used vials and other items potentially contaminated by the IMP will be collected in specific containers for the disposal of GMO and destroyed by autoclaving and incineration.

(a) Type and amount of waste generated

The amount of waste generated is a cryovial containing a maximum of 350µL of GS010.

(b) Treatment of waste

At each visit, the responsible hospital staff will examine the drug dispensing form and compare the unused vials. At the end of the study or during the study when necessary all unused vials will be destroyed on site, in accordance with the waste disposal procedures for GMOs (autoclaving and incineration), and the destruction will be documented appropriately.

All materials, including used vials and other items potentially contaminated by the IMP will be collected in specific containers for the disposal of GMO and destroyed by autoclaving and incineration.

Certificates of destruction, or equivalent, must be completed for used and unused bottles and copies should be kept in the record of the trial.

J. Information on emergency response plans

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

Methods and procedures for controlling the dissemination of GMO(s) is defined in standard operating procedures of the TUMCells manufacturing facility and German genetic technology safety regulations (QA-C-017 Verhalten im Gentechnischen Arbeitsbereich, QA-H-003 Reinigung der Reinraumanlage) as follows:
In case of unexpected IMP spill the access to the contaminated area should be blocked and decontamination measures directly taken. The spill should be contained by adsorbing paper towel soaked with Incidin perfect solution.

Decontamination procedure:

Handle with individual protective equipment (appropriate lab clothing, disposable gloves, googles)
Cover the spill area with a paper towel soaked with 3% Incidin perfect solution
After exposure time of 4 hours, clean the zone starting by the outside of the zone to the inside
Additionally, clean the spill area with a paper towel soaked with Biocid A solution
Remove traces of disinfectants from the spill by wiping the surface with 70% isopropanol
Destroy all contaminated items by autoclaving

2. Methods for removal of the GMO(s) of the areas potentially affected
See answer to J.1 above

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
see answer to J.1 above

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

Among the incidents where people could be accidentally exposed to a viral vector include: injury to the skin which is crossed or involving a splash in the eyes, nose, mouth or broken skin and also implies human exposure to fluids and / or to study drug.

In case such an incident occurs, the following procedure shall be implemented:
1. Place injury under a flow of hot water with soap.
2. Wounds should not be 'sucked', cleaned and pressed, as this may damage the tissues and encourage the spread of potential infection.
3. Wounds should be covered with a dry medical bandage.
4. If splashed in the eyes (after removal of contact lenses, if applicable), on broken skin or mouth should be rinsed immediately with intensive amount of water.
5. Follow local safety procedures and immediately report the incident to authorities and departments or other key contacts as defined by the procedures of the hospital.
6. The Sponsor will be contacted for further information or advice.

In case of contamination, the site should be thoroughly cleaned with ethanol and the individuals should be placed under observation for any effect attributed to the IMP.