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
   (b) Notification number: Not yet available
   (c) Date of acknowledgement of notification
   (d) Title of the project
      An open-label first-in-human single ascending dose study to explore the safety, tolerability and efficacy of subretinal administration of CPK850 gene therapy in patients with retinitis pigmentosa caused by mutations in the RLBP1 gene
   (e) Proposed period of release: From Q2-2018 until Q2-2025

2. Notifier
   Name of institution or company:
   Novartis Pharma AG
   Postfach
   4002 Basel, Switzerland

3. GMO characterisation
   (a) Indicate whether the GMO is a:
      viroid (.)
      RNA virus (.)
      DNA virus (X)
      bacterium (.)
      fungus (.)
      animal
         - mammals (.)
         - insect (.)
(b) Identity of the GMO (genus and species)
Parvoviridae
Genus: Dependovirus
Species: recombinant AAV-derived replication-deficient viral vector
The complete name of the vector is: AAV8-hRLBP1 (CPK850).
AAV8-hRLBP1 is a replication deficient, recombinant adeno-associated viral (rAAV) vector
with serotype 8 capsid and self-complementary AAV2 genome encoding a human
retinaldehyde binding protein 1 (human RLBP1) promoter sequence driving the
expression of the human RLBP1 gene.

(c) Genetic stability – according to Annex IIIa, II, A(10)
The stability in terms of genetic traits is expected to be equivalent to wild-type AAV.
DNA of wild type AAV and of AAV-based vectors persists in transduced cells as circular
(extrachromosomal) episomal concatemers in human tissues.
However, due to the lack of viral Rep and Cap genes, AAV8-hRLBP1 is expected to remain
in the cells as episomes and will not replicate and produce viral particles. The expression
cassette will be transcribed and translated by host cell enzymes leading to expression of
the human cellular retinaldehyde-binding protein.

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?
   If yes:
   Yes ( ) No (x)
   - 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 (x) No (x)
If yes:
   - Member State of notification ...
   - Notification number B/../../...

7. Summary of the potential environmental impact of the release of the GMOs.
AAV8-hRLBP1 is a replication-deficient recombinant AAV vector that will be
administered subretinally by a single injection for the treatment of RLBP1 retinitis
pigmentosa. The intended application of AAV8-hRLBP1 is currently limited to a single hospital centre and the number of patients to be treated is restricted. In addition, in view of the results obtained in pre-clinical studies in rats, mice and non-human primates, a negligible number of particles are expected to be shed from the patients. Due to the extremely low numbers of particles potentially released into the environment during the study, either by accident or through shedding, horizontal gene transfer is unlikely. Even if horizontal gene transfer occurred, AAV8-hRLBP1 sequences would not confer a selective advantage to bacteria: AAV8-hRLBP1 does not contain any prokaryotic promoters, any antibiotic- or other types of resistance genes or any genes, which would enhance or constrain their growth. Therefore, it is unlikely that the vector would interfere with the control of pathogenic microorganisms or that it would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

Due to the lack of viral Rep and Cap genes, the vector will persist as episome and will not replicate or produce viral particles. The expression cassette will be transcribed and translated by host cell enzymes leading to expression of the human cellular retinaldehyde-binding protein.

Although human infections with wild-type AAV are common, this virus is known as non-pathogenic virus in humans and can be classified as a Risk Group 1 biological agent, defined in the EU as ‘one that is unlikely to cause human disease’ according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work.

Wild-type AAV is not known to be involved in environmental processes and none of the genetic modifications made during construction of AAV8-hRLBP1 is expected to have any impact on this property. As such, there is no expected impact to the environment following the release of AAV8-hRLBP1.

The hospital centre will have adequately trained health care professionals involved in the study to ensure the safe handling of GMOs and to have best biosafety practices implemented in order to minimize any accidental exposure to the product, be it personnel, contact persons or the environment. In view of the low risk AAV8-hRLBP1 presents to people and the environment and in view of the biorisk management measures applied to even further reduce the exposure to the vector, its overall risk for people and the environment can be evaluated as negligible.

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) N/A
   (ii) genus Dependovirus
   (iii) species Paroviridae
   (iv) subspecies Adeno-Associated Virus
   (v) strain N/A
   (vi) pathovar (biotype, ecotype, race, etc.) Serotype 8
   (vii) common name Adeno-associated virus or AAV

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)
      Mediterranean (X)
      Boreal 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 (.)
If the organism is an animal: natural habitat or usual agroecosystem: N/A

5. (a) Detection techniques
   Quantitative Polymerase Chain Reaction (qPCR)

(b) Identification techniques
   Quantitative Polymerase Chain Reaction (qPCR)

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
   Yes (X)  No (.)  Not known (.)
   If yes, specify
   Adeno-associated viruses are not known to be associated with any pathogenic effect and thus are not assigned an Advisory Committee on Dangerous Pathogens (ACDP) category. Recombinant AAV-based vectors are usually classified as Biosafety Class 1 or 2 (depending on the Member State).

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
   AAVs are frequently found in humans and animals, but they are not pathogenic, virulent, allergenic, or a carrier (vector) of a pathogen. The known host range includes humans and non-human primates. In natural conditions, wild type AAV can only replicate in humans in the presence of a helper virus. It does not activate latent virus and is not able to colonise other organisms.

8. Information concerning reproduction
   (a) Generation time in natural ecosystems:
       Not applicable since the vector is not capable of replication.

   (b) Generation time in the ecosystem where the release will take place: Not applicable since the vector is not capable of replication.

   (c) Way of reproduction: Sexual  N/A  Asexual  N/A

   (d) Factors affecting reproduction: Reproduction of wild-type AAV is dependent on co-infection with helper virus (Adenovirus or Herpesvirus). AAV8-hRLBP1 is not able to replicate even in presence of a helper-virus.
9. Survivability

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

(i) endospores (.)
(ii) cysts (.)
(iii) sclerotia (.)
(iv) asexual spores (fungi) (.)
(v) sexual spores (fungi) (.)
(vi) eggs (.)
(vii) pupae (.)
(viii) larvae (.)
(ix) other, specify Wild-type AAVs and AAV-based gene therapy vectors have the ability to form extrachromosomal concatemers that remain episomal for extended periods of time.

(b) relevant factors affecting survivability:
Replication of wild-type AAV is dependent on co-infection of helper viruses such as adenovirus or herpes-simplex virus. In presence of helper virus, AAV undergoes productive infection characterized by genome replication, viral gene expression and virion production. In absence of a helper virus co-infection, the virus DNA mainly remains as an extrachromosomal episome or may integrate into the host cell genome and in both cases the virus appears to remain latent.

10. (a) Ways of dissemination
Wildtype AAV is disseminated mainly through airway.

(b) Factors affecting dissemination Co-infection with a helper virus for the wild-type 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

(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
The outcome of the genetic modifications is the deletion of the Rep and Cap viral sequences, leading to the loss of replication ability even in the presence of other viruses, and the insertion of the transgene (human retinaldehyde binding protein 1 (RLBP1) sequence and the human RLBP1 promoter sequence to drive the expression of the cellular RLBP1 in the transduced cells.
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 (.)                    No (X)

   If no, go straight to question 5.

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

   (a) Type of vector
       plasmid (.)
       bacteriophage (.)
       virus (.)
       cosmid (.)
       transposable element (.)
       other, specify ...

   (b) Identity of the vector ...

   (c) Host range of the vector ...

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

       antibiotic resistance (.)
       other, specify ...

       Indication of which antibiotic resistance gene is inserted ...

   (e) Constituent fragments of the vector ...

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

       (i) transformation (.)
       (ii) electroporation (.)
       (iii) macroinjection (.)
       (iv) microinjection (.)
       (v) infection (.)
       (vi) other, specify
5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation
(ii) microinjection
(iii) microencapsulation
(iv) macroinjection
(v) other, specify Transfection of HEK293 cells with three different plasmids carrying the various components needed to produce the vector. Residual plasmid DNA is then removed by Benzonase treatment and downstream processing.

6. Composition of the insert

(a) Composition of the insert
i) Truncated AAV2 inverted terminal repeat (delta TR) from which the terminal resolution site (TRS) has been deleted. Removal of the TRS eliminates the cleavage of the ITR by AAV Rep protein during replication.
ii) Human *RLBP1* promoter (short) followed by a modified SV40 intron and Kozak (mammalian)
iii) Human *RLBP1* cDNA
iv) SV40 polyA signal
v) 3' WT ITR

(b) Source of each constituent part of the insert
i) Inverted Terminal Repeats (ITRs): AAV2
ii) *RLBP1* promoter: human
iii) *RLBP1* gene: human
iv) polyA unit: simian
v) 3' WT ITR: AAV2

(c) Intended function of each constituent part of the insert in the GMO
i) Inverted Terminal Repeats (ITRs): elements necessary for the packaging of the vector genome into the capsid and the formation of the episomal concatemers in the transduced cells. Removal of the TRS eliminates the cleavage of the ITR by AAV Rep protein during replication.
ii) *RLBP1* promoter: drives the expression of the transgene and restricts expression of *RLBP1* to cell types that usually express RLBP1, thus minimizes off-target expression. The SV40 intron enhances intron-mediated gene expression level and the Kozak, is a synthetic sequence regulating translation but not related to functional proteins.
iii) Human *RLBP1* gene: Expression of normal *RLBP1* gene to produce functional protein (CRALBP).
iv) polyA unit: mRNA translation
v) 3'WT ITR: Origins for DNA replication, primary packaging signal.

(a) Location of the insert in the host organism
- on a free plasmid
- integrated in the chromosome
- other, specify Mainly extrachromosomal by formation of episomal concatemers
(b) 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 (.)
  - 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 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

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 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 (X)  No (.)  Not known (.)
   Although following naturally acquired infection, AAV DNA mainly persists as circular double stranded episomes in human tissues it has been shown that some level of integration may occur in the host DNA.

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 (.)
      Due to the removal of the Rep and Cap genes, AAV8-hRLBP1 is replication incompetent even in the presence of wild-type AAV or other viruses.

   (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 (.)
      Due to the removal of the Rep and Cap genes, AAV8-hRLBP1 is replication incompetent even in the presence of wild-type AAV or other viruses.

   (b) is the GMO in any way different from the recipient as far as dissemination is concerned?
      Yes (X)  No (.)  Not known (.)
      The GMO cannot enter an infectious cycle even in the presence of helper function.

   (c) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
      Yes (.)  No (X)  Not known (.)
      Neither wild type AAV nor AAV8-hRLBP1 are pathogenic to humans or the environment.

2. Genetic stability of the genetically modified organism
   AAV8-hRLBP1 is replication incompetent. In absence of an intrinsic mechanism for genetic variation or instability and based on the known genetic stability of wild type AAV, the genetic traits of the organism are expected to be stable.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
   Yes (.)  No (X)  Unknown (.)
   (a) to which of the following organisms?
      humans (.)
Humans are likely infected by wild type AAV through the respiratory tract, sexual and gastrointestinal route. AAV is capable of infecting either non-dividing or dividing cells. In the presence of helper virus (adenovirus or herpes virus), AAV undergoes productive infection characterized by genome replication, viral gene expression and virion production. In the absence of a helper virus co-infection, AAV DNA remains extrachromosomal or may integrate in the host DNA. In both situations the virus remains latent. Wild type AAV is weakly immunogenic. Wild-type AAV-induced immune reaction is seemingly restricted to the generation of neutralizing antibodies. AAV has never been associated with any disease or pathological conditions in humans. AAV is not known to be associated to plants. AAV-hRLBP1 is not expected to be pathogenic and does not interfere with any prophylactic or therapeutic treatments since it does not contain any sequences (no antibiotic-resistance genes) that could affect prophylaxis or treatment of pathogenic microorganism infection.

The human RLBP1 cDNA present in the vector is a naturally occurring sequence in healthy humans. Expression of this protein by infected cells does not induce cytopathic effects.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
The number of vector genomes can be determined by quantitative PCR with primers specific for vector sequences. This technique however is only applicable where sufficient DNA can be recovered for analysis.

(b) Techniques used to identify the GMO
The vector is identified by quantitative PCR with primers specific for vector sequences.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The purpose of the release is a clinical study investigating the safety and efficacy of the subretinal administration of AAV8-hRLBP1 to deliver the human RLBP1 gene to the retinal pigment epithelium (RPE) and Müller cells, to restore the presence of a functional cellular retinaldehyde-binding protein for the treatment of RLBP1 retinitis pigmentosa. No environmental benefit is expected.

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 (.)
If yes, specify: The GMO will be administered subretinally to retinitis pigmentosa patients in a selected hospital centre. Shedding of vector DNA in urine, tears, saliva or faeces can be expected afterwards at very low levels and for a few days only in some of the treated patients, based on results from biodistribution studies of AAV8-hRLBP1 in NHP. Shed AAV-based vectors
are not expected to be infectious.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Vitreoretinal Clinic
St. Erik Eye Hospital
Polhemsgatan 50
SE-112 82 Stockholm
Sweden

(b) Size of the site (m²):
   (i) actual release site (m²): N/A m²
   (ii) wider release site (m²): ...

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
   Not applicable considering that shed material, if any at all, is non-infectious.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
   None.

4. Method and amount of release

(a) Quantities of GMOs to be released:
   A total of up to 21 patients are anticipated to be enrolled in the proposed clinical study. The proposed dose range is 5 x 10⁹ vg/eye to 3 x 10¹¹ vg/eye.

(b) Duration of the operation:
   The complete administration procedure including preparation of the infusion system is expected to take less than twenty-four hours. The maximum DNA shedding duration after treatment in animal studies did not exceed a few days.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
   The investigational medicinal product will be supplied to the single selected hospital centre only. All involved personnel on the site are trained in best biosafety practices to be applied during preparation transport to the operating room for administration, precautions during administration and disposal of any biological waste. Such training involves, among others, wearing adapted protective clothing, gloves, and the constant presence of a spill kit and the decontamination of waste prior to disposal.

5. Short description of average environmental conditions (weather, temperature, etc.)
   Hospital operating room, ambient indoor conditions for administration to clinical trial subjects. Receiving environment for the shed vector particles is most likely waste water and ambient temperature. The investigational medicinal product should be stored at <-70°C until thawing prior to administration.
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.
None available for this vector, however, various AAV-based gene therapy clinical studies have demonstrated the validity of the concept and validated the gene therapy approach for autosomal recessive retinal degenerative diseases. They furthermore demonstrated safety of sub retinal injections of several different recombinant AAV compounds for ocular use in Phase I/II and in Phase III clinical trials. Luxturna (voretigene neparvovec), a gene therapy to treat patients with vision loss due to confirmed biallelic RPE65 mutation–associated retinal dystrophy is currently under review by the EMA and the US FDA.

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 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)
   In treated subjects, AAV8-hRLBP1 is expected to preferentially remain localised in the subretinal area. Transduction of the target eye cells will enable a functional human cellular retinaldehyde binding protein to be expressed at levels resulting in a clinically meaningful improvement in visual function in the patients. The vector DNA is expected to persist in transduced cell by the formation of episomal concatemers.

3. Any other potentially significant interactions with other organisms in the environment
   None expected for this product.

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
   Even in the event of shedding of DNA in waste water no establishment in such a system can be expected.

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
   None.
(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: Highly unlikely. Due to the low numbers of vector DNA copies potentially released into the environment through shedding, horizontal gene transfer is highly unlikely. Even if horizontal gene transfer occurred, the sequences would not confer a selective advantage to other organisms such as bacteria since AAV8-hRLBP1 does not contain any prokaryotic promoters, any antibiotic- or other types of resistance genes or any genes, which would enhance or constrain their growth. Therefore, it is unlikely that AAV8-hRLBP1 would interfere with the control of pathogenic microorganisms or that it would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

(b) from other organisms to the GMO: Highly unlikely. Since AAV8-hRLBP1 contains (parts of) the ITR-sequences of AAV2, there is a (remote) possibility of homologous recombination of the vector with wild type AAV2 in case of a co-infection in exposed persons. The result of such a recombination would be that AAV8-hRLBP1 would gain functional genes of the AAV2 required for replication and encapsidation, but, in turn, would lose the transgene. Hence, recombination would lead to the formation of viruses that are identical to the starting material and replication incompetent.

(c) likely consequences of gene transfer:
The genetic material from the Rep and Cap genes together with the transgene would be too large in size to be packaged in an AAV capsid. Thus it is highly unlikely that the recombination would result in a replication-competent vector containing transgenes.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
No references available, not applicable.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None known or predictable since wild type AAV is not known to be involved in any biogeochemical process.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Collection of body fluids according to clinical protocol and sampling plan and
quantification using a specific DNA qPCR method.

2. Methods for monitoring ecosystem effects
No monitoring is considered necessary.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
The method for detecting transfer of the donated genetic material to other organisms will be qPCR in selected samples. However, it has been shown for other AAV-based vectors, that that the material found in excreta is not infectious and thus transfer of donated genetic material from the patient to other organisms is not envisaged.

4. Size of the monitoring area (m²)
Not applicable.

5. Duration of the monitoring
Not applicable.

6. Frequency of the monitoring
At intervals according to clinical protocol as follows: samples (blood, saliva, tears and nasopharyngeal swab) will be taken at days 2,4,7-9,15, at months 1, 2, 3, 6 and at years 1, 1.5, 2, 3, 4, and 5 (end of study). Samples will be examined for vector distribution and viral shedding until the number of copies of CPK850 is below the limit of quantitation in three consecutive samples at which point the testing of samples collected at subsequent time points may be discontinued.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Decontamination of the IMP administration room by standard procedures will be used after administration. Any material or surface in contact with the product will be decontaminated with effective disinfectants or autoclaved depending on local biosafety procedures. Adeno-Associated Virus is susceptible to 2% sodium hypochlorite (Bleach), 2% glutaraldehyde (Lysate), 0.25% sodium dodecyl sulphate (Virkon), alkaline solutions at pH >9 and 5% phenol. Alcohol is not an effective disinfectant against AAV. AAV is inactivated by autoclaving for 30 minutes at 121°C. Any other disposable instruments or other materials used during the dose preparation procedure will be disposed of in a manner consistent with the standard practice of the institution for potentially biohazardous materials.

2. Post-release treatment of the GMOs
Any open vials or unused material will be destroyed by decontamination according to local biosafety guidelines after treatment will have been confirmed.

3. (a) Type and amount of waste generated
Empty vials and used vials and the used delivery system components (sub retinal injection device, needles and syringes), gauzes, personal protective equipment (e.g. gloves etc) for administration.

(b) Treatment of waste
Disposables such as syringes, tubing and catheters will be decontaminated by immersion in a chemical disinfectant with virucidal activity before incineration.

**Solid waste:** All material having been in contact with CPK850 should be handled and disposed of as potentially contaminated waste in containers for potentially infectious medical waste according to local hospital procedures.

**Sharps:** Use sharps containers for sharps. Waste should be collected and disposed of according to local hospital procedures for contaminated sharps.

**Liquid waste:** Liquids containing CPK850 can be inactivated with chlorine bleach (2% final concentration) for 2 minutes and then be disposed of in the sink.

J. Information on emergency response plans

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

   At the administration site, CPK850 is thawed, diluted and subsequently injected to the patients inside the operating room of a hospital. Due to the restrictive administration conditions, any potential contact of the product with the administration-site environment is extremely limited. The solution of CPK850 for sub retinal injection will be prepared by a trained pharmacist in a contained area inside a flow cabinet.

   In case of spillage the affected area, lineated with absorbing material, will be decontaminated using appropriate disinfectants. A spill kit will be available at all times during the dilution and the administration procedure. Details are given in the Pharmacy Manual for CPK850X2202, describing the handling of the IMP and the administration procedures, that will be handed over to the site prior to starting the study.

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

   The only possibilities for a contact of the administration-site environment with the product would be accidental spillage of product solution to surfaces; accidental self-administration (needle-stick injury), mucous or skin contact with the product or inhalation of aerosolized product by the administering health care professional, which are all very unlikely considering the volumes handled.

   In cases of spills the decontamination of the exposed surfaces should be conducted according to the local biosafety procedures for spills of potentially infectious materials.

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 plants or animals is not expected.

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

   No undesirable effects are expected.