Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/25/BVW4 of the company SparingVision for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

29/07/2025
Ref. SC/1510/BAC/2025_0900

Context

The notification B/BE/25/BVW4 has been submitted by SparingVision to the Belgian Competent Authority in April 2025 for a request of deliberate release in the environment of genetically modified organisms (GMOs) other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

The planned activity concerns a clinical trial with the title : *"An open-label dose-escalation study to assess the safety and tolerability of a single intravitreal injection of SPVN20 gene therapy in subjects with no light perception due to end-stage rod-cone dystrophy, and who retain dormant foveal cone photoreceptors".*

Rod-cone dystrophy (RCD) is primarily characterized by progressive degeneration of rod photoreceptors, followed by cone photoreceptors degeneration, causing visual dysfunction, and eventually leading to total blindness in a subset of patients. Most RCD cases arise from mutations in a single gene locus, mainly affecting the rod photoreceptors and retinal pigment epithelium (RPE) cells. The end stage of the disease is characterized by extreme visual impairment, with limited light perception (LP) or even no light perception (NLP). At this end stage of the disease, rods are absent and only a few cones remain in the macula. They are called dormant cones, as they survived degeneration but have lost their sensitivity to light.
Currently, the only therapy approved is voretigene neparvovec-rzyl (Luxturna®), a gene therapy exclusively indicated for the treatment of RCD caused by biallelic mutations in the RPE65 gene, which only represents 2% of the RCD population. SPVN20 is an investigational gene therapy that aims to restore light sensitivity in dormant foveal cone photoreceptors by allowing an alternative phototransduction cascade in response to a light stimulus.

The primary objective of this phase I study is to assess the safety and tolerability of a single intravitreal injection (IVT) of SPVN20 in subjects with NLP due to end-stage RCD and who retain dormant foveal cone photoreceptors, over six months after IVT.
The active substance of SPVN20 (AAVi-GIRK1(F137S)) consists of an engineered adeno-associated virus (AAV2) vector capsid, encapsidating a transgene that encodes a mutated form of the human GIRK1 (GIRK1(F137S)), a G-protein-gated inward rectifier potassium (K+) channel (GIRK).

Compared to the wild-type AAV virus, the AAV vector lacks the *rep* and *cap* viral sequences rendering it unable to replicate, even in the presence of a helper virus. The vector will therefore persist as episome.

Overall, approximately nine subjects with NLP due to end-stage RCD, and who retain dormant foveal cone photoreceptors will be included in this Phase I study, wherefore, four are expected in Belgium. SPVN20 will be administered at three different dose levels (low, medium and high doses) as a single unilateral IVT in the study eye. This study will be conducted at one clinical site located in Flanders. The national territory is considered as the potential release area of SPVN20.

The dossier has been officially acknowledged by the Competent Authority on 14 May 2025 and forwarded to the Biosafety Advisory Council (BAC) for advice.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Three experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The experts assessed whether the information provided in the notification was sufficient and accurate to state that the deliberate release of the genetically modified organism would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments from the experts.

The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.
The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patients, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

On 13 June 2025, based on a list of questions prepared by the BAC, the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions were received by the Competent Authority on 24 June 2025 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts, and resulted in a second list of questions, which was transmitted to the notifier on 04 July 2025. The answers of the notifier were received on 10 July 2025 and reviewed by the coordinator, after which a third list of questions was transmitted to the notifier on 14 July. The answers of the notifier were received on 22 July 2025, after which the BAC was able to come to a conclusion with respect to the environmental aspects associated to the proposed clinical trial.

In parallel with the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the above mentioned Royal Decree. The Competent Authority received one positive reaction from the public that did not require any comment.

Summary of the scientific evaluation

1. The characteristics of the donor, the recipient or parental organism

The donor, recipient and parental organisms were found to be adequately described in the dossier.

2. Information related to the characteristics of the GMO and the medication

Information related to the molecular characteristics of SPVN20 were adequately described in the dossier.

3. The conditions of the release

The study will consist of three consecutive cohorts of three subjects each with three different doses (low, medium and high). The GMO will be administered as a single unilateral IVT in the study eye, in hospital centres. After administration, subjects will stay at the study site for at least one hour after IVT, for safety monitoring. Subjects will be monitored for six months to assess treatment outcomes (follow-up period). Afterwards, all the subjects will continue the study for long-term assessment of treatment outcomes, up to five years after SPVN20 administration (long-term follow-up period).

According to the information provided by the notifier all involved personnel on the respective sites are required to wear standard hospital personal protective equipment including coats, laboratory goggles and gloves during preparation and administration. The preparation of the IMP for administration is recommended to be conducted in a biological safety cabinet.

Given that currently no shedding data are available for SPVN20 intravitreal injection, and given that in the 3-month pilot safety study SPVN20 shedding was minimal (but not negative) and transient in tears, shedding of rAAV particles in lacrimal fluid (tears) cannot be ruled out. The notifier was therefore requested to make sure precautionary measures for preventing contamination via tears and nasal secretions will be applied. For at least two weeks after the IVT, patients will be instructed to wash their hands thoroughly after touching tears and nasal secretions, after the bathroom visit, and before eating. Tissues and handkerchiefs used to dab eye tearing or nasal secretions will be disposed into a closed garbage bin. The notifier also met the BAC's request to provide a take-home summary with these instructions to the patients.

Vector shedding will be monitored by PCR on the treatment day and thereafter on Days 1-3, Weeks 1-2-4, Months 2-3-6, Years 1-2-3-4-5. For the study, shedding data will be collected from tears and urine until results of three consecutive time points are below the limit of detection of the shedding assay.
Shedding data collected from the study will further contribute to a proper environmental risk evaluation. These shedding data will need to be evaluated in light of the observed quantity of shed viral vector material, and the period during which shedding is observed. Should the PCR analysis reveal detectable presence of vector genome, it will be important to determine whether the observed shed viral vector genome consists out of functional replication-deficient viral vector particles and to adapt the precautionary measures for the patients accordingly, thereby preventing contamination via tears, saliva, sputum, or cough.

Taken together, the information related to the conditions of the release were found to be adequately described in the dossier.

4. The risks for the environment or human health

The GMO is a recombinant, replication-deficient adeno-associated virus-based vector not harbouring any antibiotic or other resistence genes. Like the wild-type AAVvirus, an AAV vector it is not known to be pathogenic. AAV2 was developed through a process called directed evolution. The genetic modification introduced in the AAV2-based vector does not confer the GMO any properties that could pose risks to the human population or the environment.

There is only a remote possibility of homologous recombination between the ITR-sequences of SPVN20 and wild-type AAV in case a triple infection by AAVi-GIRK1(F137S), wild type AAV (providing the *rep* and *cap* functions) and a helper virus occurs in exposed persons. Such recombination event would result in gain of functional genes of AAV required for replication and encapsidation but would in turn lead to the loss of the transgene. It was also remarked that the genetic material from *rep* and *cap* genes together with the transgene would be too large in size to be packaged in AAV capsid, making it impossible to form a replication competent viral particle that would contain the transgene and the *rep* and *cap* genes necessary for multiplication.

In the case of transfer of vector to an unintended immune-competent human recipient, the risks are expected to be considerably reduced as compared to any potential risk for the participant, since the vector is not able to replicate and the transferred 'dose' (from e.g. aerosol, splashing or fomites) will be orders of magnitude lower than that received by patients. Worst case, the receiver develops an immune response to the AAV capsid proteins.

The BAC concludes that, based on the non-pathogenic and non-replicative nature of AAVi-GIRK1(F137S) and the assumed lower amounts of shed and intact viral particles of AAVi-GIRK1(F137S) as compared to the therapic dose, the overall risk associated to exposure and transmission to other individuals can be considered negligible.

5. The monitoring, control, waste treatment and emergency plans proposed by the applicant

While AAV particles are stable outside host organisms, replication of AAV cannot occur outside of a host cell. It is anticipated that AAVi-GIRK1(F137S), like any other rAAV, is stable in a wide pH range (3-9) and like other non-enveloped viruses, is quite resistant to alcohol disinfectants. AAV is readily inactivated by disinfectants such as 0.5% sodium hypochlorite, 0.45% potassium peroxymonosulfate, 0.5% peracetic acid, or 10% bleach.
Since propagation of AAVi-GIRK1(F137S) is very unlikely, the BAC supports the view that, in terms of risk for the environment or human health, the proposed measures as described in the revised documents are proportionate and adequate in the context of the intended trial provided that the additional requests as outlined in the conditions here below are met.

Conclusion

Based on the scientific assessment of the notification made by the Belgian expert, the Biosafety Advisory Council concludes that it is unlikely that SPVN20 developed to treat patients with no light perception due to end-stage rod-cone dystrophy, and who retain dormant foveal cone photoreceptors,

by means of endogenous production of GIRK1(F137S) variant protein will have any adverse effects on human health or on the environment in the context of the intended clinical trial provided that all the foreseen safety measures are followed.

Therefore, the Biosafety Advisory Council issues a **positive advice with the following conditions**:

- The notifier and the investigators must strictly apply the clinical trial protocol, and all the safety instructions as described in the following documents :
    - Latest version of the ICF
    - Latest version of the Protocol_NYRVANA
    - NYRVANA-SPVN20_SNIF_17APR25
    - SPVN20-CLIN-01_AAV_CAF_17APR25_Non Confidential updated with the request to also use goggles in addition to the standard hospital personal protective equipment during
    - preparation and administration of the IMP
    - SPVN20-CLIN-01_AAV_CAF_24JUN25_Confidential
    - SPVN20-CLIN-01_Patient Precaution Information_v2.0

- Any protocol amendment has to be previously approved by the Competent Authority.

- The notifier is responsible to verify that each study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorizations to perform the clinical trial activities inside the hospital (laboratory, pharmacy, hospital room, consultation room...) according to the Regional Decrees transposing Directive 2009/41/EC on Contained use of genetically modified micro-organisms.

- The Biosafety Advisory Council should be informed within two weeks when the first patient starts the treatment and the last patient receives the last treatment.

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report will at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;
    - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - A report on the accidental releases, if any, of SPVN20.

Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex I: Compilations of comments of experts in charge of evaluating the dossier B/BE/25/BVW4 (ref. SC/1510/BAC/2025_0763 and SC/1510/BAC/2025_0854)

Compilation of comments of experts in charge of evaluating the dossier B/BE/25/BVW4
And comments submitted to the notifier

16 June 2025
Ref. SC/1510/BAC/2025_0763

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 05 May 2025.
Coordinator: Rik Gijsbers (KULeuven)
Experts: Anton Roebroek (KULeuven), Nicolas van Larebeke-Arschodt (UGent, VUB), Willy Zorzi (ULiège)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW4** concerns a notification from SparingVision for the deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 14 May 2025 and concerns a clinical trial entitled "An Open-Label Dose-Escalation Study to Assess the Safety and Tolerability of a Single Intravitreal Injection of SPVN20 Gene Therapy in Subjects with No Light Perception Due to End-Stage Rod-Cone Dystrophy, and Who Retain Dormant Foveal Cone Photoreceptors". The investigational medicinal product is an AAV-derived recombinant replication-deficient vector carrying the codon-optimized human cDNA for G protein-gated inwardly rectifying potassium (GIRK) channel 1, encoding a F137S amino-acid substitution (GIRK1(F137S)).

- **INSTRUCTIONS FOR EVALUATION**

Depending on their expertise, the experts were invited to evaluate the genetically modified organism described in the notification, focusingon its molecular characteristics and its potential impact on human health and the environment. The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient fall outside the scope of this evaluation.
The comments of the experts are roughly structured as in
- Annex II (principles for the risk assessment) of the Royal Decree of 21 February 2005
- Annex III (information required in notifications) of the Royal Decree of 21 February 2005
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.

List of comments received from the experts

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 13-06-2025 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

List of comments/questions received from the experts

2. INFORMATION RELATED TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1. Description of the production system

(e.g. maps of the vectors used, characteristics of the cell lines used, possibility of complementation or recombination….)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
Has evaluated this item and has no questions/comments.

2.2. Demonstration of absence of formation of replication-competent virus

(e.g. assessment of risk of generation of replication competent AAV, test methods and test data, ….)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
What is Rep2 DNA?
It is stated that the plasmids are designed to prevent recombination events. How was that done? More information should be provided. Recombination is a general mechanism that can occur (although rarely) even between short sequences.

SBB's comment:
According to CAF confidential document page 9, the presence of rcAAV in SPVN20 batches is followed by qPCR for the detection of *Rep2* DNA. Rep2 protein plays crucial roles in AAV DNA replication and is therefore often used for the detection with qPCR of replication-competent AAV (rcAAV) formation.
The manufacturing process includes transient tri-transfection of HEK293 cells, separating in three different plasmids the AAV Rep/Cap sequences, the adenoviral helper genes required to support AAV replication, and the AAV ITR sequences which constitute the viral origins of replication.
Although it cannot be excluded that small sequences still overlap, these strategies tend to minimize sequence overlaps while maintaining essential components for viral replication and packaging.

Coordinator:
Rep2 refers to one of the Rep (replication) proteins encoded by the AAV2 *rep* gene. The AAV *rep* gene produces four proteins: Rep78, Rep68, Rep52, and Rep40, which are generated from two promoters (p5 and p19) and alternative splicing. In recombinant AAV (rAAV) production, Rep2 proteins are supplied in trans (via a helper plasmid) to support replication and packaging of the therapeutic gene carried by the vector. Thus, only the resulting proteins are part of the rAAV drug product, and screening for the coding DNA sequences is therefore a good approach to assess rcAAV.

2.3. Diagram (map) of the clinical vector

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.
Comment (Expert 3)
Has evaluated this item and has no questions/comments.

2.4. Molecular characterisation of the clinical vector

(e.g. annotated sequence of the genome, genetic stability, ….)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
It is stated that "Evolution of AAV viruses (similarly to other types of viruses) is directed by spontaneous mutations or recombination with other viruses of the same species". However, homologous recombination can also occur between viruses belonging to other species. Recombination between different species can be an important fact in the evolution of a species and in the fylogenetic evolution.

SBB's comment:
This statement is reported in the CAF confidential document page 11. As homologous recombination can indeed also occur between viruses belonging to other species, the notifier could be requested to adapt this sentence in order to be less restrictive.

Coordinator:
I would not adapt the sentence, since it specifically refers to "evolution of AAV viruses". The fact that it can recombine with other sequences is not the topic of the statement here.
I would not go in more detail. The matter of AAV evolution is more complex, and is under study. As indicated in this paper (https://journals.asm.org/doi/10.1128/jvi.00486-21) AAV (here scAAV) helper viruses of AAV infection contribute proteins, such as the HSV-1 protein ICP8. The latter plays an essential role in HSV-1-mediated interference with AAV genome end recombination, indicating that the previously described ICP8-driven mechanism of HSV-1 genome recombination may be underlying the observed changes. Still, it concerns here recombination among AAV sequences triggered by helper virus proteins.

2.5. Description of the insert

(e.g. description of the expression cassette, potential harmful properties of the transgene, ….)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
Has evaluated this item and has no questions/comments.

2.6. Biodistribution and shedding

(e.g. shedding data, administered dose, route of administration, biodistribution data, methods used for detection of viral shedding….)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Additional SBB's comment:
The schedule of the collection of urine and tears samples for the shedding analysis is differently reported in the protocol and the ICF. According to the protocol, both urine and tears samples will be collected on the treatment day and thereafter on Days 1-3, Weeks 1-2-4, Months 2-3-6, Years 1-2-3-4-5. However, according to the ICF, tears will only be collected at Day 1, Week 4, Months 2-3-6 and Years 1-2-3-4-5. To be consistent between the different documents, the notifier could be requested to correct information where applicable.

Coordinator:
Fully agree. I noted a similar comment and would include "Samples should only be collected until shown negative in two consecutive measurements."

SBB's comment:
The comment proposed by the coordinator has been added in the question to the applicant.

Comment (Expert 3)
This section, although very important, provides insufficient clear information. It is stated that DNA extracts of cerebellum, blood, urine and tears returned undetermined cycle threshold values. But in the text it is stated that DNA shedding in tears was minimal and transient. More clear information is needed

SBB's comment:
Table 6, on page 14 of the CAF confidential" provides a "Summary of validation results for the qPCR method used for shedding assessment". According to the results of the qPCR assay reported in the table, DNA extracts from Cynomolgus monkey cerebellum, whole blood, urine and tears returned undetermined Ct values. However, in the text that summarize the results above the table, it is stated that DNA shedding in tears was minimal and transient in the NHP 3-month pilot study. The applicant could be requested to clarify this discrepancy and specify whether target DNA sequence was detected in some samples or not?

Coordinator:

The applicant indicates "*SPVN20 DNA shedding in tears was minimal and transient in the NHP 3-month pilot study (SPVN20 DNA was quantified in only one animal over 3 tested and only on Day 3) while not detected in the tears, urine and saliva from the 6-month GLP study at both doses and at any of the tested timepoints up to Day 84.*" I interpret this as: in the 3month study, one animal out of three showed positive signal in the tears, this signal was minimal and solely detected at D3. In the second study (6month GLP study), no positive signal was detected in any animal for either of the two doses.

We could ask for rephrasing, but to me this is sufficiently clear.
Additionally, these results seem in line with shedding results following intravitreal administration AAV in horses (https://pubmed.ncbi.nlm.nih.gov/39703903/). No vgs were detected in urine or feces before or after injection at any time point ; in the tears signal was detected till D1 in 1/3 high dose samples, and at D1 and some at D3 in low dose samples. At D14 all were negative.

3. INFORMATION RELATED TO THE CLINICAL TRIAL

3.3. Storage of the clinical vector at the clinical site

(e.g. storage location, conditions of storage, …)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
"SPVN20 Drug Product shelf-lives are communicated to the clinical site and Principal Investigator on a rolling-basis" Can these shelf-lives change? Why?

SBB's comment:
This statement is reported on page 19 of the CAF confidential document. According to the IB, page 12, "the shelf-life periods of SPVN20 DP and its diluent are determined on a rolling basis. Shelf-lives will be further extended according to additional stability results gathered from ongoing stability studies."

Coordinator:
Shelf-life is currently being assessed and thus can be extended based on the obtained results, as stated by SBB.

3.4. Logistics for on-site transportation of the clinical vector

(information on logistics of in-house transportation, characteristics of the container, disinfection procedures, labelling of the containers, ...)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)

I do not understand that ”Alternatively, a sterile drape can be used to wrap the syringes and then placed in a non-sterile bag, then sealed” is allowed.

SBB’s comment:
According to the CAF document page 19 : “Once dilution steps are completed at the hospital’s pharmacy, the filled injection syringe containing “Final diluted SPVN20 Drug Product” will be placed in a sterile, leak proof, sealed bag. Alternatively, a sterile drape can be used to wrap the syringes and then placed in a non-sterile bag, then sealed. The sealed bag will be placed into an appropriate closed container (e.g., hard-plastic cooler or box) for transportation to the treatment room (OK), according to the standard hospital procedures. On the outside a biohazard symbol is placed on the container. Only trained staff members are allowed to transport the GMO.”
In both situations, the filled injection syringe will be placed into an appropriately closed and labelled container (e.g., hard-plastic cooler or box) for transportation to the treatment room. Therefore, in-house transportation of the IMP within the hospital is performed in compliance with requirements for biosafety Class 1.

Coordinator:
I agree with SBB.
On the other hand, I do understand the confusion on why one would rely on non-sterile bags. The wrapping of the syringes may be better described (although this is beyond ERA).

3.5. Reconstitution, finished medicinal product and administration to the patients

(e.g. mode of administration, information on dosing and administration schedule, information on concomitant medication,…)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
In the confidential and public CAF the use of specific personal protective equipment (sections 3.6 b)) should be more strictly stated as in the case in the Investigator Brochure (section 3.3). The required use of safety glasses should be included in the CAFs.

SBB’s comment:
This comment has been incorporated into the commentary proposed in section 3.6

Comment (Expert 3)
Why is there an immunomodulatory corticosteroids-based regimen in the protocol?

SBB’s comment:
To prevent or reduce the extent of potential intraocular inflammation, subjects enrolled in the NYRVANA trial will receive oral and topical corticosteroids starting 3 days before SPVN20 IVT, and for several weeks afterward.

Coordinator:
Additionally, immunomodulation with corticosteroids is included to manage immune response to the AAV capsid proteins or the transgene product. This approach is also applied in other AAV gene

therapeutic applications, such as for hemophilia A (see also https://pubmed.ncbi.nlm.nih.gov/35994385/ and https://ashpublications.org/blood/article/140/Supplement%201/10654/491095/The-Effects-of-Immunomodulation-with). The treatment aims to prevent and manage cellular immune responses to transduced cells, by preventing and/or treating immune responses to AAV capsid proteins and thus achieve long-term stable transgene expression.

3.6. Measures to prevent dissemination into the environment

(e.g. control measures, PPE, decontamination/cleaning measures after administration or in the case of accidental spilling, waste treatment, recommendation given to clinical trial subjects, …)

Comment (Expert 1)

In the section 3.6 of the B_BE_25_BVW4_Part3_CAF_Non-confidential_05MAY25 document, it is written that:

b) Personal protective equipment.

> Medical personnel will follow standard hospital hygienic measures, standard hospital personal protective equipment will be worn, such as coats and gloves.

Based requirements reported in the CAF and on sections 3 and 4 of the information for public_BE-EN document, the applicant could be recommended to include laboratory goggles in the PPE in order to protect the eyes from the risk of puncture injuries (needles are used) and of liquid micro-splashes (liquids are injected under pressure into the patient's eye).

SBB's comment:

SBB agrees with experts' comments. According to IB pages 22 and 49, glasses should also be worn while preparing or administering SPVN20. Therefore, the following request could be sent to the applicant:

According to the IB (pages 22 and 49), together with lab coat and gloves, safety glasses should also be worn while preparing or administering SPVN20. However, according to page 21 of the CAF confidential document, standard hospital personal protective equipment will be worn, such as coats and gloves. Glasses are not mentioned in this list of PPE. The applicant is recommended to include laboratory goggles in the PPE in order to protect the eyes from the risk of puncture injuries (needles are used) and of liquid micro-splashes (liquids are injected under pressure into the patient's eye).

Coordinator:

I agree with the suggestion of SBB.

Comment (Expert 2)

Has evaluated this item and has no questions/comments.

Comment (Expert 3)

Has evaluated this item and has no questions/comments.

Additional SBB's comment:

Given that as of now no shedding data are available for intravitreal injection with SPVN20, and given that in the pilot study SPVN20 DNA shedding was minimal and transient in tears (SPVN20 DNA was quantified in one SPVN20-treated animal out of 3 tested on Day 3), shedding of rAAV particles in

lacrimal fluid (tears) cannot be totally ruled out. The notifier could therefore be asked whether he has considered implementing precautionary measures to make sure that the treated eye of the patients is covered by an eye bandage for at least 3 days post-injection until it is proven that there is no shedding detectable at this and later time-points post administration.

If the treated eye of the patients is covered by an eye bandage, patients and family should be advised to handle waste material generated from dressings, tears, and nasal secretion appropriately, which may include storage of waste material in sealed bags prior to disposal. It is also recommended that patients and family wear gloves for eye dressing changes and waste disposal, especially in case of underlying pregnancy, breastfeeding, and immunodeficiency of the family member.

If the treated eye of the patients will not be covered by an eye bandage, the following measures could be followed:

- General hygienic measures should be followed including thorough hand washing after touching eyes or touching secretions such as tears and nasal secretions, after using the bathroom, and before eating.
- If tissues or items such as a handkerchief are used to wipe eye tearing or nasal secretions, these tissues/handkerchiefs should be collected in sealed bags (zip lock or similar) and put into a covered waste container.

Coordinator:
I agree with SBB.
As indicated in https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf for Luxturna, shedding was reported: *"The vector shedding and biodistribution were evaluated in tears from both eyes, serum and whole blood of subjects in the phase 3 clinical study. In 13/29 (45%) subjects receiving bilateral administrations, voretigene neparvovec vector DNA sequences were detected in tear samples; most of these subjects were negative after the day 1 post-injection visit, however, four of these subjects had positive tear samples beyond the first day, one subject up to day 14 post-second eye injection. Vector DNA sequences were detected in serum in 3/29 (10%) subjects, including two with positive tear samples, and only up to day 3 following each injection. Overall, transient and low levels of vector DNA were detected in tear and occasional serum samples from 14/29 (48%) of subjects in the phase 3 study."* In this study the patients receive a single dose of 1.5×10^{11} vector genomes voretigene neparvovec in each eye (into the subretinal space in a total volume of 0.3 mL).
In the current study, injection will be intravitreal, and I found doses in line with Luxturna of lower, ranging from low dose to high dose of SPVN20 (see B_BE_25_BVW4_Protocol_NYRVANA_v1.pdf). Therefore I would propose to align these recommendations.

5. ENVIRONMENTAL RISK ASSESSMENT

(applicability of the specific environmental risk assessment provided for in Section 2 of the '*Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical*' taking into account the specific characteristics of the investigational medicinal product)

Comment (Expert 1)
Has evaluated this item and has no questions/comments.

Comment (Expert 2)
Has evaluated this item and has no questions/comments.

Comment (Expert 3)
The measures planned in the UZGent Hospital seem perfectly adequate to me. However very little information is given concerning the surveillance of possible environmental risks during the follow-up of the treated patients.

SBB's comment:
This comment is in line with the proposed questions formulated in the section 3.6 here above.

Coordinator:
I concur.

6. OTHER INFORMATION

Do you have any other questions/comments concerning this notification that are not covered under the previous items?

Comment (Expert 1)
Has no further questions/comments.

Comment (Expert 2)
The documents 'Information for the public' should explain the abbreviations 'GG0', 'GMO' and 'OGM'. For layman it is not evident to link these abbreviations to particular wordings in the title of the documents.

SBB's comment:
The request to clarify the abbreviations could be reported as a "Typos and other errors/omissions".

Coordinator:
I concur.

Comment (Expert 3)
This remarkable clinical trial might contribute importantly to the treatment of a disease that severely affects the life of the patient. The development of this type of treatments is a step forward in the human quest to limit the impact of errors occurring in nature! A necessary condition for minimizing the probability that this type of progress leads to environmental problems potentially having catastrophic consequences is keeping in mind that an "apprentice sorcerer" aspect is always associated to this type of genetic manipulations. The possibility of the occurrence of rare genetic recombination should never be denied and should also be communicated to the population, while emphasizing the fantastic benefits.

References
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Compilation of the expert's evaluations of the answers of SparingVision on the list of questions for dossier B/BE/25/BVW4

03 July 2025
Ref. SC/1510/BAC/2025_0854

Coordinator: Rik Gijsbers (KULeuven)
Experts: Willy Zorzi (ULiège), Anton Roebroek (KULeuven), Nicolas van Larebeke-Arschodt (UGent, VUB)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW4** concerns a notification from SparingVision for a clinical trial entitled "An Open-Label Dose-Escalation Study to Assess the Safety and Tolerability of a Single Intravitreal Injection of SPVN20 Gene Therapy in Subjects with No Light Perception Due to End-Stage Rod-Cone Dystrophy, and Who Retain Dormant Foveal Cone Photoreceptors".

On 13 June 2025, based on a list of questions prepared by the BAC (SC/1510/BAC/2025_0751), the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions were received by the Competent Authority on 24 June 2025. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

By this way, I would like to let you know:
-that I reviewed the answers of the notifier to the questions raised in June 2025 by the Biosafety Council dossier B/BE/25/BVW4 (clinical trial submitted by SparingVision) related to the use of recombinant AAV for subjects with no light perception due to end-stage rod-cone dystrophy and
-that the notifier addressed correctly and satisfactorily all the comments/questions.

Evaluation Expert 2

Question 1
I do not understand how testing body fluids for the presence of viral sequences can be replaced by immune response monitoring in serum, except if an immune response is normally absent in patients receiving the treatment.

SBB's comment
We acknowledge the answer of the applicant is quite confuse, but the shedding analysis is now correctly reported in the ICF under the procedure named "Afstoten / biodisseminatie". The procedure "Verzamelen van lichaamsvloeistoffen voor IMP-verspreiding (verzameling van bloed en tranen)" was reported by mistake in the table, whereas "Humoral immune response monitoring in serum" was missing and has now been reported in the table.

Question 2

Probably the statement of Prof. Leroy is meant to address this problem. However, in addition to this statement, it would be preferrable that data are presented that indicate that after intravitreal admission no spilling of viral sequences through body fluids have been observed. Apparently insufficient data are available.

SBB's comment

The applicant mentioned the results of Vignal-Clermont et al. (2023) that are based on 5 pooled clinical studies comprising 189 LHON patients who received a single unilateral or bilateral intravitreal administration of lenadogene nolparvovec, an AAV2-based investigational ocular gene therapy, at the dose of 9E+10 vg/eye. In all clinical studies, gene therapy shedding was negligible and transient in the blood, not detected in the urine, and limited and of short duration in patient tears (with a maximum of one week).

Question 3

Apparently the shedding of virus or viral sequences in tears cannot be ruled out, but is probably not a very frequent event. The problem posed here has to do with apprentice-wizard aspect of genetic treatments. In the experience of Prof Leroy no problems occur, but clinical experience cannot rule out the occurrence of rare events.

Evaluation Expert 3

In my view, the notifier addressed correctly and satisfactorily the comments/questions that have been raised in June.

Evaluation Coordinator

Ik ben zelf tevreden met de antwoorden op de vragen die we naar voor schoven.

Enige opmerkingen:

- algemeen: in 'information to the public' wordt er telkens gesproken over het afstoten van virussen in lichaamsvloeistoffen'. Dit moet 'uitstoten' zijn denk ik, en virussen is niet correct, en zou vervangen moeten worden door 'virale vector partikels'.

SBB's comment

Although using correct nomenclature is important, as that the public consultation is over at this time, we'll not ask the applicant to make these changes to these documents

Coordinator's comment

Agreed. This is not ERA related, but we should maybe take into account that proper nomenclature is used.

- reply to Q3: the notifier was asked to clarify whether precautionary measures have been considered to ensure that the treated eye of the patient is adequately protected by an eye bandage for at least 3 days post-injection until it is proven that no shedding is detectable at this and later time points post-administration. To me the arguments presented to underscore that additional measures are not necessary do not hold.
    - No clinical study has been performed yet to assess the shedding of SPVN20 in humans.
    - Nonclinical pharmacokinetic studies showed shedding of SPVN20 in tears in 1 of 3 from non-human primates

- it concerns a new serotype and a different application procedure to the eye => AAV2 data are informative, but not conclusive here
- therefore, until proven otherwise, I would still advise this measure to be installed, until sufficient RWD is available that no shedding is detectable.
    - therefore, until proven otherwise, I would still advise this measure to be installed, until sufficient RWD is available that no shedding is detectable.
    - I fully understand that we want the burden for the patient and the patient's environment to be minimal, but we also want to get the most robust measures in place to make this innovative technology work, and convince the general public that (until proven otherwise), we have all precautionary measures in place to provide this advanced therapy under the most safe circumstances.

SBB's comment

As confirmed by the sponsor, the shedding of rAAV particles in tears cannot be entirely excluded (Vignal-Clermont et al. 2023). Taking into account the intravitreal route of administration, the transient and limited (only few positive events) biodistribution in tears, the non-integrating properties of the viral vector, the BAC could support the demand of the applicant. However, it is very important that patient and family members are well informed about preventive measures and adhere to good hygiene. Since the preventive measures may be difficult to find through the many pages of the Informed Consent Form (ICF), and in order to make sure patients and patient's family can easily consult all the required instructions whenever needed, the applicant is requested to provide a small take home summary (preferably one-page, plasticized document).
The following information should be reported in this instruction sheet :
• Bodily fluids that may contain the viral vector genome.
• Guidelines to minimize contact with potentially contaminated materials or surfaces (e.g., bed linens, towels, tissues, handkerchiefs).
• Instructions and effective solutions for decontaminating possibly contaminated areas, tissues, and skin.
• Safe handling and disposal procedures for waste materials potentially contaminated with tears or nasal secretions, including recommendations for sealed bag storage before disposal.
• The duration during which these precautions must be followed.

Reference:
Safety of Lenadogene Nolparvovec Gene Therapy Over 5 Years in 189 Patients With Leber Hereditary Optic Neuropathy. C. Vignal-Clermont et al. 2023. American Journal of Ophthalmology Volume 249p108-125 May 2023