Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/26/BVW2 of the company AAVantgarde Bio UK Ltd. for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

FINAL version: 04/06/2026
Ref. SC/1510/BAC/2026_0490

Context

The notification B/BE/26/BVW2 has been submitted by AAVantgarde Bio UK Ltd. to the Belgian Competent Authority in February 2026 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, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1) (CELESTE)".*

STGD1 is a hereditary autosomal recessive retinopathy caused by mutations in the retina-specific ATP-binding cassette (ABC) transporter gene (ABCA4) located on chromosome 1. STGD1 is an inherited retinal disease (IRD), frequently quoted in literature as estimated to affect approximately 1 in 8,000 to 10,000 individuals. The age of onset and the rate of progression vary greatly: loss of central vision most commonly occurs in early childhood and young adulthood, but in some individuals, it may occur later in adulthood.

The main goals of this phase I/II study are to assess the safety, tolerability of selected dose level of AAVB-039 and to determine efficacy of AAVB-039 at the selected dose level.
To overcome the packaging capacity limit of individual AAV vectors, AAVB-039 utilizes a dual AAV gene replacement therapy for the production of functional human ABCA4 protein. The delivery of ABCA4 transporter to the retina of patients with Stargardt disease (STGD1) may slow down or stop progression of sight loss due to retinal degeneration and atrophy of the retinal pigment epithelium.

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, up to 75 subjects will be included in this Phase I/II study, wherefore, three are expected in Belgium. AAVB-039 will be administered at three different dose levels (low, mid and high doses) as a single dose via subretinal injection in pediatric and adult participants with Stargardt disease. This study

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will be conducted at one clinical site located in Flanders. The national territory is considered as the potential release area of AAVB-039.

The dossier has been officially acknowledged by the Competent Authority on 23 February 2026 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. Two experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano and one expert from the SBB 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 26 March 2026, 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 21 April 2026 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 May 2026. The answers of the notifier were received on 18 May 2026 and reviewed by the coordinator, 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 reaction from the public that didn't require any feedback from our part.

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 AAVB-039 were found to be adequately described in the dossier.

As the absence of formation of replication-competent virus during the production of a rAAV viral vector drug product is a key safety issue of AAV viral vector production for application in gene therapy, the applicant provided a short description of the rcAAV qPCR method used to detect presence of rcAAV, including the used positive and negative controls, the results and acceptance criteria.

3. The conditions of the release

This phase I/II study will consist of two parts. During Part A, the dose escalation phase, three different doses (low, mid and high) will be evaluated in adults. During Part B, the preferred dose level will be evaluated in adults and paediatric participants. The GMO will be administered via a subretinal injection, in hospital centres. Patients will be discharged either on the day of administration or the following day, post subretinal injection. Subjects will be monitored for 52 weeks to assess treatment outcomes. Afterwards, all the subjects will continue the study for long-term follow-up for a total of five years after AAVB-039 administration.

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. Shedding of AAVB-039 was evaluated in nonclinical studies in serum, tears, and nasal secretions. The proposed clinical trial with AAVB-039 is a first in-human (FIH) study, wherefore no clinical data related vector shedding in humans are available. Viral shedding analysis in blood, tear (from both eyes) and saliva samples will be assessed via quantitative polymerase chain reaction to monitor the duration of viral vector shedding in the environment via biofluid. Shedding will be evaluated at different time points up to 9 months following administration of the treatment, until negative or below limit of quantification on at least three consecutive occasions. Should qPCR analysis reveal a detectable presence of vector genome, it will be important to determine whether the observed shed viral vector genome contains functional replication-deficient viral vector particles and thereby adapt the precautionary measures for patients accordingly to prevente contamination via tears, saliva, sputum, or cough.

Based on the shedding results from Seitz et al. (2017)[1] showing quantifiable shedding one week after subretinal injection of rAAV-8 in non-human primates and on the recommendation provided in the EPAR document form EMA for Luxterna, an AAV vector-based gene sub-retinal therapy for the treatment of adult and paediatric patients with vision loss, the applicant was asked to ensure that the treated eye of the patient is adequately protected by an eye bandage for at least 7 days post-injection. To ensure patient and family are adequately informed, clear instructions will be provided in the ICF.

Consistent with other trial involving a rAAV, patients treated with the IMP must agree to use a highly effective method of contraception for at least 12 months post AAVB-039 administration.

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

[1] I.P. Seitz et al. 2017. Superior Retinal Gene Transfer and Biodistribution Profile of Subretinal Versus Intravitreal Delivery of AAV8 in Nonhuman Primates. Invest Ophthalmol Vis Sci. 2017 Nov 1;58(13):5792-5801

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 resistence genes. Like the wild-type AAV virus, a rAAV vector is not known to be pathogenic. The genetic modification introduced in the AAV-based vector does not confer on the GMO any known 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 AAVB-039 and wild-type AAV in case a triple infection by AAVB-039, wild type AAV (providing the *rep* and *cap* functions) and a helper virus occurs in exposed persons. Such a recombination event would result in a gain of functional AAV genes required for replication and encapsidation but should 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 size would be too large to be packaged in AAV capsid, making it impossible to form a replication competent viral particle that contains the transgene and the *rep* and *cap* genes necessary for multiplication.

In order to align with the instruction given in the product information document (EPAR) of EU registered medicinal products containing recombinant AAV, a lifelong restriction on donating blood, organs tissues and cells for transplantation is recommended.

In the case of transfer of vector to an unintended immune-competent human recipient, the risks are expected to be considerably reduced compared to any potential risk for the participant, since the vector is unable to replicate and the transferred 'dose' (from e.g., aerosol, splashing or fomites) will be orders of magnitude lower than that received by patients. It is believed that in the worst case, the exposed individual will develop immune responses to the AAV capsid proteins.

The BAC concludes that, based on the non-pathogenic and non-replicative nature of AAVB-039 and the assumed lower amounts of shed and intact viral particles of AAVB-039 compared to the therapic dose, the overall risk associated to exposure and transmission to other individuals can be considered low to negligible.

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

Following SBB's request, the composition of the mandatory personal protective equipment, consisting of a laboratory coat, safety glasses, and gloves, has been aligned between the documents.

For the on-site transportation of the prepared clinical vector, the applicant confirmed that clinical vector preparations are transported sealed in a seal bag. The sealed bag containing GMO is further transported on site in a transparent break-free sealed container with biosafety hazard symbol by a dedicated study nurse/coordinator.

Effective disinfectants such as freshly prepared 10% bleach (0.5% sodium hypochlorite) solution, will be used for decontamination of the AAVB-039 preparation area, the administration room after completing administration and in the event of spill. To maintain chlorine strength and ensure bleach effectiveness, it is essential to prepare the solution just before use and to store it in a dark bottle to prevent loss of effectiveness over time. The applicant is aware that the use of 6000 ppm (mg/L) bleach

solution can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns and should be reserved for minor surface spill treatment.

Since growing evidence shows that exposure to cleaning products and disinfectants raises the risk of respiratory diseases, spraying in the air of a clinical room cleaning and disinfection solutions, is no longer appropriate and should be avoided as much as possible, the applicant updated instructions relating to decontamination/cleaning measures by clearly stating that spraying a validated viricidal disinfectant should be avoided.

Since propagation of AAVB-039 is 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 experts, the Biosafety Advisory Council concludes that it is unlikely that AAVB-039 developed to treat patients with Stargardt Disease, by means of endogenous production of a functional human ABCA4 protein transporter to the retina of patients, 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
    - SNIF public and confidential v3.0
    - CAF_v3.0_non confidential
    - CAF_confidential
    - M24-528 – Investigative Site Pharmacy Manual_v3.0

- As committed by the applicant in his responses to SBB requests on 20-Apr-2026, the ICF will be updated by adding the recommendation to refrain from donation of blood, organs, tissues, and cells

- As committed by the applicant, the ICF will be updated to include clear instructions regarding eye dressing management. Specifically, the treated eye will be covered with an ocular patch and protective eye shield for a minimum of 7 days, in accordance with local clinical practice. Participants and their family members/caregivers will be instructed not to touch or rub the treated eye, to maintain appropriate hand hygiene, and to wear gloves when contact with bodily fluids is anticipated. In addition, all used dressings, tissues, swabs, and other potentially contaminated materials should be placed in sealed bags prior to disposal. Updated ICF will be submitted for Belgium Ethics Committee in the next substantial modification.

- In both SNIF documents (public and confidential) will be updated as follows and provided as soon as possible: the use of alcohol wipes following disinfection with 10% bleach (0,5% sodium hypochlorite) is still described. However, as previously indicated, bleach solutions should not be used in combination with alcohol wipes, as this may produce toxic chloroform vapours. Therefore, both documents should be revised either by removing the recommendation to use alcohol wipes or by specifying that the sodium hypochlorite solution must first be neutralized using a 3% sodium thiosulfate solution prior any application of alcohol. Since alcohol is not considered as an effective disinfectant against AAV, we recommend avoiding the use of alcohol-based wipes altogether.

- 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 enrolled 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 contain as a minimum:
    - The total number of patients enrolled in the trial and the number of patients from Belgium;
    - A summary of all adverse events documented by the investigators as likely or definitely related to the study medication;
    - A report on the accidental releases, if any, of AAVB-039.

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/26/BVW2 (ref. SC/1510/BAC/2025_0334 and SC/1510/BAC/2025_0427)

Adviesraad voor Bioveiligheid
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Compilation of comments of experts in charge of evaluating the dossier B/BE/26/BVW2
And comments submitted to the notifier

26 March 2026
Ref. SC/1510/BAC/2026_0334

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 17 February 2026.
Coordinator: Anton Roebroek (KULeuven)
Experts: Amaya Leunda (SBB), Rik Gijsbers (KULeuven), Willy Zorzi (ULiège)
SBB: Katia Pauwels and Sheela Onnockx

INTRODUCTION

Dossier **B/BE/26/BVW2** concerns a notification from AAVantgarde Bio UK Ltd. 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 23 February 2026 and concerns a clinical trial entitled "An Open-label, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1) (CELESTE)". The investigational medicinal product, AAVB-039 is a dual AAV8.ABCA4 gene replacement therapy for the production of functional human ABCA4 protein, targeting ABCA4-associated Stargardt disease.

♦ INSTRUCTIONS FOR EVALUATION

Depending on their expertise, the experts were invited to evaluate the genetically modified organism considered in the notification as regards 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 are 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 26-03-2026 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 1
Has evaluated this item and has no questions/comments.

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

Comment 3
Has not evaluated this item.

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 1
Has evaluated this item and has no questions/comments.

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

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

Comment coordinator

In the confidential CAF (p12/23) in the section entitled “2.2. Demonstration of absence of formation of replication-competent virus” valid information is provided concerning measures to ensure microbial and viral safety of the AAVB-039 (Dual AAV8.ABCA4) drug product. However, demonstration of absence of formation of replication-competent virus is not addressed specifically. Info about absence of formation of replication-competent virus can only be deduced from Table 99: Drug Substance Batch Release Specification on page 11/23. No special reference is made in this section to the relevant info in the table.

As absence of formation of replication-competent virus during the production of a AAV viral vector DP is a key safety issue for of AAV viral vector production for application in gene therapy, the applicant is requested to present a short description of the rcAAV qPCR method used to detect presence of rcAAV, including the used positive and negative controls, the results and acceptance criteria.

2.3. Diagram (map) of the clinical vector

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

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

Comment 3
Has not evaluated this item.

2.4. Molecular characterisation of the clinical vector

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

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

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

Comment 3
Has not evaluated this item.

2.5. Description of the insert

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

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

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

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

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

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

Additional SBB comment
According to the EPAR document, patients treated with sub-retinal Luxterna, an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of adult and paediatric patients with vision loss are strongly advised to wear an eye dressing for at least 14 days after administration. Furthermore, patients/caregivers should wear gloves for dressing changes and waste disposal and should place any waste material generated from dressings, tears and nasal secretion in sealed bags prior to disposal (https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf).
Based on this information and on the shedding results provided in the CAF confidential document, the following request could be sent to the applicant:
According to the CAF confidential document page 22, vector shedding in serum, tears and nasal secretions from Cynomolgus macaques receiving a single subretinal injection of AAVB-039 in the right eye, was dose-dependent and transient. Duration of vector shedding in serum, tears and nasal swabs was consistent with what previously reported in NHPs receiving similar doses of AAV8 (Seitz, 2017).
The applicant is requested to provide details of the procedure and results obtained from this analysis in cynomolgus macaques.

According to the article from Seitz (2017), shedding via the tear film showed a pronounced dose-dependent effect, both groups (intravitreal and subretinal injection) showed quantifiable shedding one week after treatment. Shedding via nasal secretions was less dependent on dosage than shedding through tears and urine. In the low-dose subretinal cohort, shedding declined more rapidly, with a half-life of 4 days compared with 7 days in the high-dose cohort.
In light of these results and based on the recommendation provided in the EPAR document form EMA for Luxterna, an AAV vector-based gene sub-retinal therapy for the treatment of adult and paediatric patients with vision loss, the applicant is asked to ensure that the treated eye of the patient is adequately protected by an eye bandage for at least 7 days post-injection until it is proven that no shedding is detectable at this and later time points post-administration.
Patients and family should be advised on how 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 their family members wear gloves when changing eye dressing and handling waste, particularly in cases where a family member is pregnant, breastfeeding, or immunocompromised. All these recommendations should clearly be reported in the applicable documents.

Coordinator comment:
In a number of trials involving AAV vectors, we have noted regarding the donation of tissue and cells, etc., for transplantation purposes that patients are not permitted to donate, unless there are arguments to deviate from this: “Since there is a lack of experience with donation of blood or organs, tissues and cells for transplantation following AAV vector-based gene therapy, the notifier is requested to revise the instructions regarding blood, organs, tissues and cells and to align these with the instruction given in the product information document (EPAR) of EU registered medicinal products containing recombinant AAV (Glybera, Zolgensma, Roctavian, Luxturna, Upstaza, Hemgenix) : ‘Patients treated must not donate blood, organs, tissues, and cells for transplantation’.

Alternatively, the notifier is requested to give a rationale why instructions could deviate from measures commonly taken for current EU marketing authorized medicinal products containing recombinant AAV." For the current file, I would nevertheless like to propose adding the English text as above to the additional question.

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 1
Has evaluated this item and has no questions/comments.

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

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

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 1
Has evaluated this item and has no questions/comments.

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

Comment 3
There are no specific instructions for on-site transportation of the prepared clinical vector. The only guidance is to follow the clinical site's established procedure.
I would point out that transport must take place in a double packaging with the outer packaging consisting of a leak-proof container.

SBB comment
The expert's comment is acknowledged and could be communicated to the applicant as follows:

There are no specific instructions for on-site transportation of the prepared clinical vector. The only guidance is to follow the clinical site's established procedure. The applicant is requested to specify in relevant document such as the Pharmacy manual and the concise overview (a 1–2 page instruction sheet) summarizing all relevant handling procedures that transport must take place in a double packaging with the outer packaging consisting of a leak-proof container.

Coordinator comment:
I agree with the proposition to send this comment as proposed.

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 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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 1

I) In the B_BE_26_BVW2_Part 3_SNIF_V1.1_confidential file, it is written in point 9.1. Survivability part b. that ' *10% bleach (0.5% sodium hypochlorite) is a routine disinfectant used for disinfecting AAV-contaminated surfaces'*

II) In p10 of the B_BE_26_BVW2_Part 2_CAF public_BEL_V1.1 it is written point c) that '*Any non-disposable instruments such as the trays that have been used during the dose preparation and administration procedures and have potentially come into contact with AAVB- 039, will be sprayed with a viricidal disinfectant in accordance with local guidelines and institutional procedures related to the management of Risk Group 1 GMO*.'
And further on the ' *In case of occupational IMP spillage, the spill will be contained, and the area will be decontaminated using a viricidal disinfectant.*'

III) This previous section is reproduced in page 6, point 8. of B_BE_26_BVW2_Technical Dossier GMO_confidential file.

IV) In p2 of B_BE_26_BVW2_Biosafety_data_sheet_for ABCA4, it is indicated that '*A 10% bleach solution should be used for decontamination. An inert absorbent material should be used to soak up any spills, after the application of the bleach solution, and stored in a closed container until disposal. Other appropriate alternative methods can be used for decontamination*'.

Regarding the points I), II), II), IV):

1) Please complete the information for the bleach solution preparation by indicating that this solution must be freshly prepared. To maintain chlorine strength and ensure bleach effectiveness, it is crucial to prepare the solution just before use and to store the solution in a dark bottle, to avoid loss of effectiveness over time.

2) Please consider that 10% bleach solution is not the usual concentration for treating all the spill-contaminated aera because, at this concentration, its can generate ocular irritation or

oropharyngeal, oesophageal, and gastric burns. This treatment at this concentration must be only reserved for minor aera spill treatment.

3) The usual concentration for the decontamination of Adenovirus is 6000 ppm (Rutala et al., 2006). The ready to use solutions can contain in Belgium between 5 and 36 °Chl. So the dilution (1:10 or 10%) of the Household Bleach (for the "USA") is depending of this initial concentration (cf. Rulata & Weber, 2024). We invite the applicant to change the ambiguous terms "10% Bleach solution" in "6000 ppm (mg/L) Bleach solution".

For the "USA" :

Expected Chlorine Concentrations by Various Dulitions of Househod Bleach (5.25-6.15% sodium hypochlorite)

Dilution	Chlorine (ppm)
None	52,500–61,500
1:10	5,250-6,150
1:100	525-615
1:1000	53-62

4) Although the Bleach solution at concentration 6000 ppm is available for eliminating non-enveloped RNA viruses, its use should not be considered "universal" because it corrodes or damages stainless steel, aluminium and the most rubbers components of surfaces.

5) In the event of a biological spill treatment using Bleach solution, to protect the eyes and the face from the risk of bleach (splashes) and to ensure clear and consistent guidance for healthcare personnel, the PPE has been aligned across all relevant documentation of this dossier as follows: In the event of a biological spill treatment, protective eyewear, lab coat, overshoes, gloves, mask and protective eyewear should be worn.

6) In p10 of the B_BE_26_BVW2_Part 2_CAF public_BEL_V1.1 it is written that: '*Any non-disposable instruments such as the trays that have been used during the dose preparation and administration procedures and have potentially come into contact with AAVB- 039, will be sprayed with a viricidal disinfectant in accordance with local guidelines and institutional procedures related to the management of Risk Group 1 GMO*.

The procedure described here must be changed because spraying a viricidal disinfectant is not appropriate. Such as reported in the following article Kumbhar *et al.,* 2025, where it is mentioned that '*Spray cleaning and disinfection solutions typically contain complex chemical mixtures, including volatile organic compounds, primarily used as solvents and fragrances, preservatives, and disinfectants. Consequently, inhalation exposure is likely higher after spray application than other liquid application methods. Healthcare workers are exposed to high concentrations of various cleaning and disinfection chemicals. Hospitals are increasing disinfection efforts to protect patients from healthcare-associated infections (HAIs). Growing evidence shows that exposure to cleaning products and disinfectants raises the risk of respiratory diseases, including asthma. Although the exact causes remain unclear, bleach, quaternary ammonium compounds (quats), ammonia, medical equipment cleaning supplies, and spray-form products have all been linked to a higher risk of respiratory issues*

7) In conclusion:

The applicant could be requested to provide a 'handling manual in order to ensure that clear and detailed instructions are provided on :
- the use of personal protective equipment (PPE) for healthcare personnel (It should be specified which PPE is mandatory)
- the procedures in the event of accidental occupational exposure such as a splash in the eyes or on the mucous membranes
- the instructions for treatment of accidental spills. Please consider that 10% bleach solution is not the usual concentration for treating all the spill-contaminated surfaces because, at this concentration, its can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns. This treatment at this concentration must be only reserved for minor surface spill treatment.
-a list of disinfecting agents with viricidal activity against adenovirus other than 10% Bleach is required, because the use of bleach at this concentration for the decontamination must be strictly limited to treat small surfaces whose composition is chemically compatible and without stainless steel, aluminium and the most rubbers.

SBB comment

The expert touches upon a valid point regarding the percentage of sodium hypochlorite that may possibly vary between different brands of household bleach products. As suggested by the expert, recommendations on the use of bleach solutions are preferably expressed in terms of % sodium hypochlorite or ppm (mg/L).

The expert's remark is supported and could be communicated to the applicant as follows:

The procedures for managing accidental spills or breakage of vials containing the GMO should be described in detail. Specifically, the documentation should clearly indicate the type of disinfectant to be used, its concentration, the required contact time, and the method of application.
The use of 10% bleach solution is mentioned in B_BE_26_BVW2_Biosafety_data_sheet_for ABCA4 and B_BE_26_BVW2_Part 3_SNIF_V1.1_confidential file. It should be noted that recommendations on the use of bleach solutions are preferably expressed in terms of % sodium hypochlorite or ppm (mg/L). Also, it should be remarked that the use of 6000 ppm (mg/L) bleach solution can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns and should be reserved for minor surface spill treatment. The applicant is recommended to provide a list of disinfecting agents with viricidal activity against adenovirus- associated virus other than 6000 ppm (mg/L) bleach solution, because the use of bleach at this concentration for the decontamination must be strictly limited to treat small surfaces whose composition is chemically compatible and without stainless steel, aluminium and the most rubbers.

With respect to the use of such viricidal disinfecting agents with activity against adenovirus- associated virus other than 6000 ppm (mg/L) bleach solution, it should be noted, that clear instructions should be provided how to use these agents safely. Spraying of these agents should be avoided as much possible, since they typically contain complex chemical mixtures, including volatile organic compounds, primarily used as solvents and fragrances, preservatives, and disinfectants. Consequently, inhalation exposure is likely higher after spray application than other liquid application methods (Kumbhar & Geddugol, 2025).

In addition, the SNIF documentation should consistently and explicitly specify the mandatory personal protective equipment (PPE) required for healthcare workers handling the product (as reported in section 7.1 of the pharmacy manual V2.0 p16/40), or CAF Public, 3.6. b.) as well as clear instructions on the collection and handling of samples (blood, saliva etc.) to prevent dissemination to the environment.

Furthermore, we recommend that all medical personnel involved in the study receive a concise overview (a 1–2 page instruction sheet) summarizing all relevant handling procedures, including detailed instructions in case of accidental spills, waste management requirements, and other risk management measures. Providing such a consolidated document would greatly assist medical personnel in their daily practice, as it would ensure that all essential information is readily accessible in a clear and practical format, thereby facilitating safe and compliant handling of the product. This sheet should include all relevant handling instructions, detailed procedures to handling a spill including appropriate disinfectants, waste management and other risk management measures:
- the use of personal protective equipment for health care workers (e.g. specify which PPE are mandatory)
- procedure in the event of accidental occupational exposure through a splash in the eyes, mucous membrane, needle-stick injury or contact with skin and clothing
- procedures for treatment of accidental spill (disinfectant, concentration of disinfectant, contact time)
- procedures to prevent and to deal with direct exposure to blood, urine, vomit or other bodily fluids from patients in the initial period after administration of the IMP
- waste management

Coordinator comment:
I agree with the proposition to send this comment as proposed together with the proposed additional text. Second point has been added based on the text provided by the expert.

Comment 2

p16/40 in B_BE_26_BVW2_CELESTE Pharmacy Manual v2.0.pdf: "*In case of occupational IMP spillage, appropriate measures should be taken, as per local hospital guidelines, procedures and risk assessments. In case of spillage, this should be recorded in the Pharmacy Binder with an estimate of IMP volume spilt*." Preferably a protocol is provided, making sure pillage is handled alike at all locations.

SBB comment

The expert's comment is acknowledged and could be communicated to the applicant as formulated here above (under *Comment 1*).

SBB additional comment:
According to the inclusion criteria 5 mentioned of the protocol (p35/105) and the proposed ICF (p25/42 in document 'B_BE_26_BVW2_Main Adult PIS-ICF', WOCBP and partners of trial participants must agree to use a highly effective method of contraception for at least 12 months post AAVB-039 administration. Males must agree with their partner to use 2 forms of contraception, including 1 barrier method for at least 12 months following AAVB-039 administration.
However, according to 'B_BE_26_BVW2_Part 2_CAF_confidential_annex_1, participants are recommended to use barrier contraception methods for 3 months after treatment. There appears to be an inconsistency between these documents regarding the required duration of contraception.

Therefore, the applicant could be requested to clarify the intended duration of contraception and to revise the documents as appropriate to ensure that the recommendation on the duration of barrier contraception is consistently reflected throughout the dossier.

Coordinator comment:
I agree with the proposition to send this comment (with some suggested corrections/changes).
Page 35 should be page 39

Comment 3

1. There are inconsistencies across different documents and within the same document regarding the use of a biosafety cabinet for the clinical vector preparation:
Pharmacy manual:
P16:
… *the contents of the thawed IMP and diluent vial(s) are mixed using aseptic techniques in a biosafety cabinet by gently inverting 5 times* …
Later in the text (p16/40):
'*The preparation procedure needs in the performed in a biologic safety cabinet (BSC) or operating theatre and needs to be appropriate to ensure the following risks are minimised*': …

SNIF (confidential): p1/12
J. Information on emergency response plans
1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread : '*The solution of AAVB-039 for sub-retinal injection will be prepared by the hospital pharmacist or designee in a contained area inside a flow cabinet in the hospital centres'*.

SBB comment
The expert's remark is supported and could be posed to the applicant as follows:
According to p16/40 in B_BE_26_BVW2_CELESTE Pharmacy Manual v2.0.pdf '*the contents of the thawed IMP and diluent vial(s) are mixed using aseptic techniques in a biosafety cabinet by gently inverting 5 times* '. And further in the document (same page) '*The preparation procedure needs in the performed in a biologic safety cabinet (BSC) or operating theatre and needs to be appropriate to ensure the following risks are minimised'*:
On p1/12 in the B_BE_26_BVW2_CELESTE Part3_SNIF_V1.1 it is stated that '*The solution of AAVB-039 for sub-retinal injection will be prepared by the hospital pharmacist or designee in a contained area inside a flow cabinet in the hospital centres'*.
The applicant is requested to update the relevant document(s) as necessary to ensure consistency across all submitted materials.

Coordinator comment:
I agree with the proposition to send this comment as proposed.

2. Use of adequate decontamination procedure: In the various documents, 10% bleach is a recommended product for decontaminating surfaces. Other disinfectants can be chosen by the clinical site provided they are virucidal.
If 10% bleach is recommended it is advisable to specify that the solution to be effective must be prepared as follow: a 1:10 dilution of household bleach 5000 ppm of sodium hypochlorite to be freshly prepared. A minimal time contact of 20 minutes is also required.

SBB comment

The expert's comment is acknowledged and could be communicated to the applicant as formulated here above (SBB comment under Comment 1 of section 3.6).

Coordinator comment:

I agree with the expert's and SBB comments.

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 1

Has evaluated this item and has no questions/comments.

Comment 2

On p1/6 in B_BE_26_BVW2_Health_Environmental Risk Assessment.pdf: "*Systemic shedding (urine, saliva, blood) is very rare in ocular AAV delivery, and for that reason the precautions advised for clinical trial participants and caregivers are mainly relevant to ocular secretions after AAVB-039 administration, and reflect the low environmental risk associated with AAV-based gene therapy as described herein*." This description is not correct, considering the later statement in the same document on p5/6 where the LD and HD groups were indicated to show DNA in these fluids until D8 and D29. In my opinion we may be more strict, and consider the ERA deliberate release as low rather than negligible (p6/6 in B_BE_26_BVW2_Health_Environmental Risk Assessment.pdf). I agree that peak values lower quickly.

SBB comment

1.The expert's comment regarding the applicant's claim on the likelihood (very rare) of systemic shedding after ocular AAV delivery is acknowledged. The applicant could be advised to refrain from drawing overly conclusions, particularly as no clinical data with AAVB-039 have been obtained yet and the document 'B_BE_26_BVW2_Health_Environmental Risk Assessment.pdf' solely reports non-clinical shedding data in serum, nasal secretions and tears in animals (p2/6).

A question for the applicant could be formulated as follows, by including a remark on the CAF confidential document as well :

'Since shedding has only been assessed in limited number of bodily fluids (serum, nasal secretions and tears) in animals and no clinical data with AAVB-039 are available, the following overly statement on p1/6 in B_BE_26_BVW2_Health_Environmental Risk Assessment.pdf: '*Systemic shedding (urine, saliva, blood) is very rare in ocular AAV delivery*,' should be reconsidered/ rephrased and should rely on evidence-based data available for AAVB-039. The same comment applies to the statement ' AAV vectors are not expected to spread to non-ocular tissues following sub-retinal injection' as stated in the B_BE_26_BVW2_CAF Confidential annex. '

2. Regarding the qualification of the ERA, suggested by the expert to be low rather than negligible, it should be noted that risk qualification results from the identification and characterization of hazards and an estimation of the likelihood of occurrence (exposure characterisation). Although the presence of viral vector DNA in urine and saliva may indicate there is a likelihood of deliberate release of the vector particles in the environment, the overall properties of the vector particles are such that the overall environmental risk estimation as 'negligible' seems acceptable. This is in accordance with the '*Good*

Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors ' available at https://health.ec.europa.eu/system/files/2022-01/aavs_gp_en.pdf.

Coordinator comment:
I agree with the proposition to send the question as proposed in SBB comment 1. I also agree with comment 2.

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

6. OTHER INFORMATION

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

Comment 1
Has no further questions/comments.

Comment 2
Has no further questions/comments.

Comment 3
Has no further questions/comments.

References

William A Rutala, Jeffrey E Peacock, Maria F Gergen, Mark D Sobsey, David J Weber (2006). Efficacy of Hospital Germicides against Adenovirus 8, a Common Cause of Epidemic Keratoconjunctivitis in Health Care Facilities. Antimicrob Agents Chemother. 2006 Apr;50(4):1419–1424. doi: 10.1128/AAC.50.4.1419-1424.2006

William A Rutala, David J Weber and the Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for disinfection and sterilization in Healthcare Facilities, 2008. Update : June 2024. https://www.cdc.gov/infection-control/media/pdfs/guideline-disinfection-h.pdf.

Kumbhar & Geddugol (2025). Prevalence of Health Effects Due to Disinfectant Exposure and its Impact on Selected Physiological Parameters Among Class D Workers : A Descriptive Cross-Sectional Study. Cureus 17(3): e79994. DOI 10.7759/cureus.79994.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Solid Biosciences Inc. on the list of questions for dossier B/BE/26/BVW2

04 May 2026
Ref. SC/1510/BAC/2026_0427

Coordinator: Anton Roebroek (KULeuven),
Experts: Willy Zorzi (ULiège), Rik Gijsbers (KULeuven), Amaya Leunda Casi (SBB)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/26/BVW2** concerns a notification from Solid Biosciences Inc. 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 23 February 2026 and concerns a clinical trial entitled "An Open-label, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1) (CELESTE)". The investigational medicinal product AAVB-039 is a dual AAV8.ABCA4 gene replacement therapy for the production of functional human ABCA4 protein, targeting ABCA4-associated Stargardt disease.

On 26 March 2026, based on a list of questions prepared by the BAC (SC/1510/BAC/2026_0333), 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 21 April 2026. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

I reviewed the answers of the notifier and overall, I reckon these were addressed correctly and satisfactorily for Q1-4, Q6-7.

I have some additional comments for:
Q5- shedding data from NHP are interesting, but we should be cautious to readily translate these to human settings. Virus are species specific and their distribution and shedding as well. Based on the literature I could find, overall NHPs distribution (or lack thereof) is translated to human settings (see https://doi.org/10.1016/j.omtm.2023.02.002). Considering the low dose, and local administration, I agree that the data presented are sufficient to support safety and very minimal shedding.

Comment coordinator:
I agree.

Evaluation Expert 2

I would like to inform you that the notifier has responded correctly and satisfactorily to the comments/questions, with the exception of the following details:

A) Question 3 of the BAC stated that:

“Spraying of these agents should be avoided as much possible, since they typically contain complex chemical mixtures, including volatile organic compounds, primarily used as solvents and fragrances, preservatives, and disinfectants. Consequently, inhalation exposure is likely higher after spray application than other liquid application methods (Kumbhar & Geddugol, 2025).”

However in p11 of the BE_CAF_V2.0, it is written that :
“Any non-disposable instruments such as the trays that have been used during the dose preparation and administration procedures and have potentially come into contact with AAVB- 039, will be sprayed with a viricidal disinfectant in accordance with local guidelines”.

The procedure described above needs to be modified because spraying a virucidal disinfectant is no longer appropriate.
Such as reported in the following article from Kumbhar & Geddugol (2025) :

> Consequently, inhalation exposure is likely higher after spray application than other liquid application methods [3].

> Healthcare workers are exposed to high concentrations of various cleaning and disinfection chemicals. Hospitals are increasing disinfection efforts to protect patients from healthcare-associated infections (HAIs). Growing evidence shows that exposure to cleaning products and disinfectants raises the risk of respiratory diseases, including asthma. Although the exact causes remain unclear, bleach, quaternary ammonium compounds (quats), ammonia, medical equipment cleaning supplies, and spray-form products have all been linked to a higher risk of respiratory issues [4].

> Spray cleaning and disinfection solutions typically contain complex chemical mixtures, including volatile organic compounds, primarily used as solvents and fragrances, preservatives, and disinfectants.

SBB comment:
The expert’s remark is supported and could be formulated as follows:
Although it was previously recommended to avoid spraying viricidal disinfecting agents with activity against adeno-associated virus, it is still written in section 3.6.c of the CAF document that “Any non-disposable instruments such as the trays that have been used during the dose preparation and administration procedures and have potentially come into contact with AAVB-039, will be sprayed with a viricidal disinfectant”
Since growing evidence shows that exposure to cleaning products and disinfectants raises the risk of respiratory diseases, spraying in the air of a clinical room cleaning and disinfection solutions that contains complex chemical mixtures, including volatile organic compounds primarily used as solvents and fragrances, preservatives, and disinfectants, is no longer appropriate and should be avoided as much as possible (Kumbhar & Geddugol, 2025).
Therefore, the applicant is requested to update the instructions relating to decontamination/cleaning measures by clearly stating that spraying a validated viricidal disinfectant should be avoided.

Coordinator comment:
I agree with the proposition to send this comment as proposed.

B) In the BE_CAF_V2.0 document, it is written : “The appropriate personal protection equipment (PPE) (laboratory coat, safety glasses and gloves etc.)”.
It is also written in the SNIF, page 16.
And idem in p22 of the SNIF_V2.0_Confidential_track change.

It is required to remove the term "etc." from all documents describing "the appropriate personal protective equipment," as this results in an incomplete list of PPE components and can lead to errors and a lack of standardization. The proposed list must be as complete and precise as possible, as the described procedure allows for no approximations.

SBB comment:
The expert’s remark is supported and could be formulated as follows:
According to page 15/17 of the SNIF_Public, page 22/23 of the SNIF confidential and page 10/14 of the CAF, the appropriate personal protection equipment (PPE) includes “laboratory coat, safety glasses and gloves etc.”. The use of “etc.” introduces ambiguity and results in an incomplete list of required PPE. This lack of precision may lead to inconsistent interpretation, errors in implementation, and reduced standardization across users.

It is therefore requested that the term “etc.” be removed from all documents referring to “appropriate personal protective equipment.” Instead, PPE requirements should be as complete and precise as possible for each procedure.

Coordinator comment:
I agree with the proposition to send this comment as proposed.

Evaluation Expert 3

Answers are ok.

Additional SBB comment

To question 3:

The procedures for managing accidental spills or breakage of vials containing the GMO still need to be described in detail both in the SNIF and the CAF documents. Specifically, the documentation should clearly indicate the type of disinfectant to be used, its concentration, the required contact time, and the method of application.
Furthermore, the documents should also be updated by taking into account the following points:
- Whenever hypochlorite solution is used (e.g. for the decontamination of work areas), attention should be given to the use of freshly prepared hypochlorite solution and stored in a dark bottle
- Bleach solution and alcohol can react and can produce toxic vapors as chloroform. The notifier should include this note in the documents cited here above or should avoid suggesting the use of alcohol wipes in combination with bleach

- Hypochlorite solution cannot be proposed as a universal decontaminant or disinfectant because it can corrode or damage stainless steel, aluminum and the most rubbers components of surfaces. A list of adequate of decontamination / disinfection solutions for areas that cannot be decontaminated with bleach is therefore required.

Coordinator comment:
I agree with the SBB comment and propose to send this comment to the applicant.

To question 6:

In light of the shedding results from Seitz (2017) and in alignment with the recommendations outlined in the EPAR document issued by the European Medicines Agency for Luxterna, the CAF document still need to be updated to clearly specify that patients should wear an eye dressing following injection, including explicit instructions on the duration of use and the appropriate disposal of related waste materials.
To ensure patient and family are adequately informed, the ICF should also be updated to explicitly include the following instructions:

- An eye dressing should be worn after injection
- The dressing should be worn for a minimum of 7 days post-injection
- Clear guidance should be provided on the safe handling and disposal of waste materials (e.g. dressings, tears, and nasal secretions), including, where appropriate, storage of such materials in sealed bags prior to disposal.

The applicant is requested to make sure both the CAF and the ICF are updated accordingly.

Coordinator comment:
I agree with the SBB comment and propose to send this comment to the applicant.

Additional comment by the coordinator:

To question 7:

According to the answer in the document AAV 039-101_BE_Responses Assessment Queries SBB_20Apr2026 to question 7 the applicant agrees to update the protocol inclusion criteria and ICF instructions regarding donation of blood, organs, tissues and cells with the EPAR of approved AAV products with: ‘Patients treated must not donate blood, organs, tissues, and cells for transplantation’. To be consistent this update should also be incorporated into the CAF.

References

Kumbhar & Geddugol (2025). Prevalence of Health Effects Due to Disinfectant Exposure and its Impact on Selected Physiological Parameters Among Class D Workers: A Descriptive Cross-Sectional Study. Cureus 17(3): e79994. DOI 10.7759/cureus.79994.