Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/25/BVW8 of the company Solid Biosciences Inc. for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

FINAL version : 12/05/2026
Ref. SC/1510/BAC/2026_0441

Context

The notification B/BE/25/BVW8 has been submitted by Solid Biosciences Inc. to the Belgian Competent Authority in December 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 : *"A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy of a Single Intravenous Dose of SGT-003 in Ambulant Males With Duchenne Muscular Dystrophy".*

Duchenne muscular dystrophy (DMD) is a X-linked degenerative neuromuscular disease caused by mutations in the dystrophin gene. It predominantly affects boys. The lack of functional dystrophin protein results in progressive muscle weakness and wasting. Ultimately, heart and respiratory muscles are affected, causing premature death of DMD patients. There is no cure for the disease yet, but treatments such as corticosteroids and gene therapy can slow down its progression.

The primary objective of this phase III study is to assess the efficacy of a single intravenous dose of SGT-003 compared to placebo by assessing change in muscle function in patients aged seven to eleven inclusive with Duchenne muscular dystrophy.
SGT-003 is a replication-incompetent recombinant AAV containing a functional five-repeat human microdystrophin (h-μD5) gene. SGT-003 is utilizing a novel muscle-tropic capsid serotype (AAV-SLB101) to deliver the transgene to cardiac and skeletal muscle cells. SGT-003 is a gene therapy developed to increase the expression of microdystrophin in the patients in order to strengthen the muscles and slow down or halt the damage caused by the disease.

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 80 subjects will be included in this Phase III study, wherefore, six are expected in Belgium. In this clinical trial, a single dose of the investigated medicine SGT-003 will be administered intravenously to boys with Duchenne muscular dystrophy. This study will be conducted at two clinical

sites located in Flanders and Brussels. The national territory is considered as the potential release area of SGT-003.

The dossier has been officially acknowledged by the Competent Authority on 23 January 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. Four 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 02 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 19 March 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 27 March 2026. The answers of the notifier were received on 09 April 2026 and reviewed by the coordinator, after which a third list of questions was transmitted to the notifier on 15 April. The answers of the notifier were received on 30 April 2026, 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 five reactions from the public wherefore one required feedback from our part. According to Article 16 §2 of the Royal Decree of 21 February 2005, the comments that are relevant for biosafety received in the framework of the public consultation, have been taken into account in the preparation of the advice below.

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.

The helper plasmid used transiently during manufacturing to provide adenoviral helper functions in trans includes coding sequences for adenovirus encapsidation protein and assembly protein. These sequences are not intended to be packaged into the final AAV GMO. Following BAC's request, the applicant demonstrated the absence of residual adenoviral proteins in SGT-003 final product.

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

Information related to the molecular characteristics of SGT-003 were adequately described in the dossier.

3. The conditions of the release

This phase III study will take place in two parts with two treatment groups (SGT-003 and Placebo). In the first phase, some participants receive the GMO treatment, while others get a placebo. In the second phase of the trial, those who received placebo in the first phase will get the GMO treatment if they remain eligible. The GMO drug product will be administered via a single intravenous injection at a qualified hospital centre. After administration, participants will be monitored for a minimum of 6 hours post-administration. Participants will participate in the trial for up to a maximum of 6.5 years. This includes two administration periods (Phase 1 and Phase 2), each lasting 1.5 years, followed by a minimum of 5 years of long-term follow-up after the SGT-003 dosing date.

Shedding data collected from the study will further contribute to a suitable 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. Viral shedding analysis in feces (when available), urine, saliva, and blood samples will be assessed in this trial via a quantitative PCR assay to monitor the duration of viral vector shedding in the environment via biofluid. Viral shedding is also currently being studied in the ongoing Phase 1/2 clinical trial of SGT-003 (protocol SGT-003-101). 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 prevent contamination via tears, saliva, sputum, or cough…

As a safeguard against potential vector transmission to other individuals or release into the environment once the patients leave the hospital setting, the notifier will provide a hygiene and precaution guide explaining and summarizing all the critical information and instructions for patients and their families.

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 resistence genes. Like the wild-type AAV virus, an 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 SGT-003 and wild-type AAV in case a triple infection by SGT-003, 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 instructions 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.

Although biodistribution studies have shown a modified expression profile of SGT-003 in DMD^{mdx} mice with an increased presence in the quadriceps[1], semen and seminal fluid was not collected and tested for the presence of vector genomes. As a result, some uncertainties remain. However, this study involves children aged 7 to 12 and the protocol, includes appropriate contraceptive measures requiring participants of reproductive potential to use two highly effective forms of contraception for 12 months following administration of the study drug.

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) is expected to 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 SGT-003 and the assumed lower amounts of shed and intact viral particles of STG-003 compared to the therapic dose, the overall risk associated with exposure and transmission to other individuals can be considered low to negligible. Nevertheless, a needlestick injury may represent a higher-risk exposure scenario and should therefore be managed with appropriate precautionary measures.

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

Following SBB's request, the compostion of the mandatory personal protective equipment, consisting of a laboratory coat, safety glasses, and gloves, has been aligned between the documents.
In the event a spill of the IP occurs, the spill will be contained, and the area will be decontaminated with an approved disinfectant such as freshly prepared 5000 ppm (mg/L) sodium hypochlorite solution. To maintain chlorine strength and ensure bleach effectiveness, it is essential to prepare the solution just before use to prevent loss of effectiveness over time.
The procedures for controlling the dissemination of the GMO(s) in the case of unexpected spill has been improved by including proper PPE use, containment measures, and the controlled use of sodium hypochlorite at 5000 ppm. Alternative effective disinfectants for incompatible surfaces have been provided. Ans the use of alcohol has been removed as alcohol-based disinfectants are not suitable for eliminating AVV in cases of laboratory surface disinfection, needle stick injury or contamination of intact skin.

[1] Solid Biosciences Reports Additional Preclinical Data Demonstrating that its Novel Capsid, AAV-SLB101, Provides Superior Transduction Efficiency and Enhanced Distribution to Skeletal Muscle. October 17, 2022

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[2], the applicant updated instructions relating to decontamination/cleaning measures by clearly stating that spraying a validated viricidal disinfectant should be prohibited .
A spill kits will be available at all times during all steps of handling the investigational product, including reception, storage, preparation, transport, administration, and disposal of contaminated materials.
The notifier also provided a 2 page technical sheet 'Instructions for study site personnel' giving an overview of all relevant handling instructions, detailed instructions in case of a spill or inadvertent exposure to a human, waste management and other risk management measures.

Since propagation of SGT-003 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 STG-003 developed to treat patients with Duchenne muscular dystrophy (DMD), by means of endogenous production of a human 5-repeat microdystrophin (h-μD5), 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 BE v3
    - Public CAF_BE v3
    - CAF_BE v3
    - SGT-003-301 Handling Procedures for Medical Personnel Instruction Sheet v2.0
    - SGT-003-301 BEL_Hygiene and Precautions guidance v2
    - SGT-003-301 Handling Procedures_v3.0 adapted as requested here below

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

- The Handling procedure document should be updated as follows and provided as soon as possible:
    - Page 2 : Procedures to be applied in case of accidental exposure e.g., needlestick injury, skin, eye exposure or blood, urine, vomit or other bodily fluids from patients in the initial

[2] Kumbhar VR, Geddugol SB. 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

period after administration of the IMP are currently unclear and inconsistently presented. Guidance for each type of exposure should be clearly defined and addressed separately

- Alcohol is still recommended as disinfectant several times in the document : “Disinfect exposed skin with alcohol gel” ; “Apply disinfectant (0.5% [5000 ppm] sodium hypochlorite, or hydrogen peroxide/alcohol based disinfectant), followed by alcohol wipes”. However as demonstrated by Korten at al. (2021)[3], alcohol-based disinfectants are not suitable for eliminating AVV in cases of laboratory surface disinfection, needle stick injury or contamination of intact skin. Alcohol-based treatments (e.g. alcohol gel and alcohol wipes) must be removed and other alternative disinfection treatments for cases of laboratory surface disinfection after accidental spills and for needle sticks or contamination of intact skin must be reported.

- 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 after 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 minumum:
  - 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 accidental releases, if any, of STG-003.

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/BVW8 (ref. SC/1510/BAC/2026_0230, SC/1510/BAC/2026_0350 and SC/1510/BAC/2025_0394)
Annex II: Answers to the public reaction to dossier B/BE/25/BVW8 in NL (ref. SC/1510/BAC/2026_0442) and FR (ref. SC/1510/BAC/2026_0442)

[3] Korte J. et al. 2021. Inactivation of Adeno-Associated Viral Vectors by Oxidant-Based Disinfectants. Hum Gene Ther. 2021 Jul;32(13-14):771-781. doi: 10.1089/hum.2020.120

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Compilation of comments of experts in charge of evaluating the dossier B/BE/25/BVW8
And comments submitted to the notifier

02 March 2026
Ref. SC/1510/BAC/2026_0230

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 05 January 2026.
Coordinator: Karen Willard Gallo (Institut Jules Bordet)
Experts: Willy Zorzi (ULiège), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Aline Baldi
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW8** 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 January 2026 and concerns a clinical trial entitled "*A phase 3, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy of a single intravenous dose of SGT-003 in ambulant males with Duchenne Muscular Dystrophy"*. The investigational medicinal product is recombinant AAV-based gene therapy that delivers a codon-optimized and CpG island-minimized human 5-repeat microdystrophin (h-μD5) by using a novel muscle-tropic capsid.

♦ 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 02-03-2026 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

The adenovirus helper plasmid is novel to my knowledge. In addition to the genes that were previously reported to be necessary for AAV replication and encapsidation (E2A, E4orf6 and VARNA) it also contains the coding sequence for adenovirus encapsidation protein and assembly proteins. The L4 region was recently shown to increase AAV production 1,2 (Adsero A et al. 2024 DOI: 10.1089/hum.2023.146 ; Nie Y et al 2024 doi.org/10.1016/j.omtm.2024.101370).

My understanding is that hexon assembly protein coding region cannot be easily mutated or deleted since it overlaps E2A promoter.

Did the applicants evaluated the risk of exacerbated immune response to Adenovirus protein expressed by their construct? Are these coding sequences also present in Adeno helper plasmids used for AAV production in previous Phase III clinical trials?

The purification method of the final product is probably sufficient to remove these adenoviral proteins and eliminate any risk in case of accidental exposure. However, I did not find any information about these issues.

SBB comment:

As medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient are outside the scope of this evaluation, the question could be adapted as follow:

The applicant indicates that the construct includes coding sequences for the adenovirus encapsidation protein and assembly proteins. Has the applicant assessed the potential impact of these modifications on risks in case of environmental or non-patient human exposure? In particular, the applicant is request to clarify whether the purification method of the final product is sufficient to remove these adenoviral proteins or could residual adenoviral coding sequences or proteins still be present in the final GMO preparation. Are these coding sequences also present in Adeno helper plasmids used for AAV production in previous Phase III clinical trials?

Coordinator comment:

I agree that it is important to make this comment.

Comment 4
No details have been provided on the specific serotype used (only that it is an AAV9 modified serotype). This may be important to determine distribution patterns (shedding and biodistribution). I'm not sure whether this should be part of the IMPD. Can this be provided?

SBB comment :
Information on the vector genome map as well as the description of the genome elements, including location of the sequences encoding the transgene expression cassette and its regulatory elements are confidential and can be found in the confidential CAF document. Specific information on the capsid can be found in the IMPD Quality and in the IB.

Comment 5
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 4
Has evaluated this item and has no questions/comments.

Comment 5
Has not evaluated this item.

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 evaluated this item and has no questions/comments.

Comment 4
P4/11 confidential CAF: The map of the packaging plasmid reads 'modified AAV2 Rep' whereas the accompanying table does not indicate that. There is no info provided on the modification. Please clarify.

Same for the capsid plasmid. What are the specific modification relative to AAV9? Are these substantial or minute?

SBB comment:
On page 4/11 of the CAF confidential document, the RepCap Plasmid is shown and the table below the plasmid does correspond to a description of the plasmid. Annex 4 of the CAF confidential document provides a confidential description of the transgene map
Furthermore, Table 14 of the IMPD-Quality lists details on the RepCap plasmid components and nucleotide position.

Comment 5
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 evaluated this item and has no questions/comments.

Comment 4
Maybe I missed it, but no information has been provided on the characterisation of the viral vector once produced. What is the full to empty capsid ratio for example? Which purification method and polishing methods have been used?

SBB comment:
Information on the pharmaceutical quality of the investigational product (manufacture, control, and testing) can be found in the Investigational Medicinal Product Dossier – Quality (IMPD-Q) and will be assessed by the quality experts.

Comment 5
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 not evaluated this item.

Comment 4
Has evaluated this item and has no questions/comments.

Comment 5
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.

Comment 4
As to shedding and biodistribution we should be cautious with engineered serotypes. The redirected tropism may result in more (or less) shedding, and targeting of reproductive organs in human, whereas this is not demonstrated in model organisms. Biodistribution cannot be deduced from earlier clinical trials with different serotypes. Presence in seminal fluid is to be assessed, to prevent spreading to partners. I agree that in the case of DMD this is probably not a major issue. Still, since studies with the current serotype will be later extrapolated for other applications, this analysis seems key to me.

SBB comment:
Engineered AAV serotypes may indeed exhibit altered tropism compared with naturally occurring serotypes, which could affect both shedding and biodistribution. Consequently, data from previous trials with different serotypes cannot be assumed to fully predict the behaviour of a modified AAV9 vector in humans. Although assessment of the potential presence in seminal fluid will not be possible for this clinical trial as the population designed for this clinical trial corresponds to ambulant pediatric males with DMD aged 7 to <12 years.

Coordinator comment:
So I think we should make this comment. They cannot make something that is confidential because it is new and then assume that known data from other AAV serotypes applies.

SBB comment:
Based on expert's comment, the following question could be sent to the applicant:
No non-clinical shedding analysis was identified in the submitted documentation.
With regard to shedding and biodistribution, particular caution is warranted when considering engineered or novel serotypes. The modified or redirected tropism of such vectors may result in altered shedding patterns (either increased or decreased) compared to parental or naturally occurring

serotypes. In addition, engineered vectors may exhibit tissue targeting profiles that differ from those observed in conventional animal models, including potential distribution to reproductive organs in humans, which may not be adequately predicted by preclinical species.

Therefore, biodistribution and shedding data generated from earlier clinical trials using different serotypes cannot be considered fully representative or extrapolatable to SGT-003. Each engineered construct should be assessed on its own characteristics.

The applicant is requested to provide any non-clinical and/or clinical shedding studies performed with SGT-003. Shedding assessments should specify the biological matrices (which may include saliva, nasal and/or nasopharyngeal swabs, tears, urine, feces or semen), the analytical methods used (e.g., qPCR for vector genome detection, assays for replication-competent virus if applicable), the duration and frequency of sampling and the limit of detection and quantification

In the IMPD genotox and reproductive/developmental tox has been assessed in mice. This is not relevant to me, since these features for rAAV (and the parental virus) are species specific. This should be considered in the set-up of the clinical trial. Can this be assessed in the human samples (eg seminal fluid, …). Considering the age of the envisioned participants this may not be relevant/possible. Still, this topic should be taken with caution. Beyond stool, saliva and urine (p33/42 in IMPD) also semen would best be assessed if possible.

SBB Comment:

According to IMPD page 15/42, reproductive and developmental toxicity has been assessed in GLP-compliant toxicology studies of SGT-003 both in mdx mice and cynomolgus monkeys, with a single IV administration of SGT-003.

References on biodistribution of rAAV to gonads only include distribution of rAAV2 vectors (Arruda et al. 2001; Schuettrumpf et al. 2006). However, SGT-003 is a modified recombinant non-replicative AAV serotype 9. Therefore, the following question could be sent to the applicant:
Although animal studies suggest that recombinant AAV vectors generally present a low risk of genomic integration and germ line transmission, even following high exposure to the testes, the applicant is requested to provide data specific to AAV9 serotype used in this notification, where available.
In particular, clarification is sought regarding the biodistribution profile of the AAV9 vector, including potential distribution to the gonads and the possible presence in seminal fluid. Given that engineered or distinct serotypes may exhibit altered tropism, biodistribution data generated with other AAV serotypes cannot be assumed to be fully predictive. Furthermore, although semen samples cannot be obtained from paediatric patients, this issue remains relevant.
Therefore, all relevant biodistribution routes should be carefully assessed in the context of first-in-human use, with particular attention to potential implications for environmental or secondary human exposure.

Coordinator comment

It may be pertinent here to add that although semen specimens are unavailable from pediatric patients there is some relevance here in the (unknown) case that biodistribution to the developing gonads might be different than what is observed in mature animals, including monkeys, mice and humans. Were any tests done in young mice or monkeys? This is also a question we could ask.

SBB comment:
The following request could be added to previous question:
In particular, it cannot be excluded that biodistribution to developing gonadal tissue may differ from that observed in sexually mature animals, including adult mice, non-human primates, and humans. Developmental stage-dependent differences in tissue tropism could potentially result in distinct distribution patterns in immature individuals.
The applicant is therefore requested to clarify whether biodistribution studies have been conducted in juvenile animals (e.g., young mice or juvenile non-human primates). If such studies were not performed, a scientific justification should be provided, including an assessment of the potential risk of vector distribution to developing gonads.

Comment 5
Has evaluated this item and has no questions/comments.

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.

Comment 4
Has evaluated this item and has no questions/comments.

Comment 5
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
Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5
Has evaluated this item and has no questions/comments.

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
I did not find information about how the pharmacist will prepare the IV bag from the frozen vials. Dilution factor? How many vials per bag? Will the dilution be performed in a safety cabinet?

SBB Comment:
According to section 3.6.a of the public CAF document, SGT-003 will be prepared for dose administration at the pharmacy of the clinical site in a biosafety cabinet. However, no information regarding the preparation of the IMP was provided in the various documents. Therefore, the following question could be submitted to the applicant :
No details on the preparation of the intravenous product from the frozen vials could be found in the documents. The applicant is requested to provide the dilution process applied to the vector during preparation, the number of vials combined per final preparation and any measures in place to prevent unintended exposure to personnel or the environment during preparation.

Coordinator comment:
I found the information/instructions in the investigators brochure to be very superficial. They need to make detailed instructions on the preparation, handling and administration of the product for the pharmacy, medical doctors and nurses involved in the study. There also need to be clear instructions on how to handle accidental exposure, spills or injection. Further we should ask for a laminated summary of these procedures - one for the pharmacy and one for the nurse to have on hand while handling the product. Finally, as mentioned further down, there need to be clear instructions on precautions for the family who will be responsible for the pediatric patient. Maybe I missed it but I could not find this information anywhere. Needs to be much more extensive than this - as stated above.

SBB comment:
The request could be adapted as follow:
Information/instructions in the investigators brochure, the SNIF and the CAF document were found to be very superficial. Comprehensive and detailed guidance should be included regarding the preparation, handling, storage, and administration of the investigational product for the pharmacy, medical doctors and nurses involved in the study. In particular, no detailed description was identified concerning the preparation of the intravenous product from frozen vials. Clear procedural instructions should be provided covering the dilution process applied to the vector during preparation, the number of vials combined per final preparation and any measures in place to prevent unintended exposure to personnel

or the environment during preparation. Clear and detailed instructions must also be provided for the management of accidental exposure, including spills, needlestick injuries, or inadvertent injection.

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

Comment 4
Has evaluated this item and has no questions/comments.

Comment 5
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

With respect to recommendations on donation of blood/cells/tissues/organs by the clinical trial subject the dossier should be corrected as the BAC stipulates in similar dossiers that patients treated must not donate blood, organs, tissues and cells for transplantation. All relevant documents like SNIF, public CAF, etc. should be updated with this requirement.

SBB comment:
Indeed, the following question has often been sent to the applicant and could also be sent for this notification:
According to the Public CAF document p 11, based on the *Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors* document, no recommendations on donations of blood/cells/tissues/organs by the clinical trial subject are planned. However, according to 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'.

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 either align these with the instruction given in the EPAR, or to provide the rationale why instructions could deviate from measures commonly taken for current EU marketing authorized medicinal products containing recombinant AAV.

Coordinator comment:
Absolutely critical

Clear instruction should be given to the treated patient and patient's family with respect to good hygiene practices in order to minimize spread of shedded vector to other people and the environment. Such instructions should be provided in a short readable format document that will be given to each patient.

SBB comment
The following question could be sent to the applicant:
According to the CAF document, page 11/14, clinical trial subjects will be informed of the potential risk of dissemination and recommended to discuss specific precautions with their study team to maintain good hygiene and minimize contact. However, no precautions are reported on how clinical trial subjects should avoid dissemination of the product.
According to the results of the viral shedding analysis that has been performed on participants enrolled in the ongoing Phase 1/2 study with SGT-003 (Study SGT-003-101), following a single IV infusion of SGT-003, viral shedding was detectable post-infusion up to 30 days in the saliva, 14 days in the urine and observed in the stool up to 180 days. Based on these preliminary results, please clarify in the appropriate documents (SNIF, CAF, ICF…) which instructions will be given to the patients.

Furthermore, for patients and their family to adhere to and practice good hygiene, it is important to explain why these measures must be taken and what are the likely sources of contaminated material bodily fluids/waste. All instructions should be compiled in a simple and clearly written (for a layman) single document to facilitate compliance by patients and their caretakers. It is highly recommended that the applicant prepare a small take home summary (preferably one-page, front and back if necessary, plasticized document) which covers all the information and instructions needed by patients and family to avoid potential transmission of the viral vector to other individuals or the environment when patients leave the hospital setting.
The following information (with their duration) should be reported in the patient instruction sheet:
- Which bodily fluids are anticipated to contain viral vector genome (albeit very low levels)
- Instructions to limit contact with materials or surfaces that may be contaminated with bodily fluids (e.g. avoid sharing foods or drinks, have a separate bathroom, if possible, decontaminate toys…)
- Instructions detailing how good hygiene should be practiced
- Instructions and effective disinfectants for decontaminating any and all potentially contaminated areas, including dishes and glasses, toys, skin, clothes…
- Procedures to deal with exposure to blood, urine, vomit or other bodily fluids from patients, particularly during the initial period following vector administration where high numbers of transduced cells are anticipated.

Coordinator comment:
Instruction document is absolutely necessary and missing.
What the study team needs to communicate to the patients family must be clearly stated in the investigators brochure.

SBB comment:

The following comment could be added to the request:

The information that the study team is required to communicate to the patient's family should be clearly and explicitly described in the Investigator's Brochure. This should include specific guidance on key risk information, safety precautions, potential shedding considerations (if applicable), and any necessary measures to minimise secondary exposure.

The instructions on how to handle accidental spills or breakage of a GMO containing vial should be worked out in detail (which disinfectant and how to apply, etc.) and not only in very general terms. Documents like the SNIF, public CAF and other relevant documents (Pharmacy Manual?) etc. should be updated with this detailed information. All medical personnel involved need to receive an overview of all relevant handling instructions, detailed instructions in case of spill, waste management and other risk management measures.

SBB comment

Instructions on how to handle accidental spills or breakage of a GMO containing vial are indeed described in very general terms in the public CAF. But they have been detailed in the SNIF section J.1 (page 21/22). However, some instructions could be adapted. Therefore, the following recommendations could be sent:

The procedures for controlling the dissemination of the GMO(s) in the case of unexpected spread described in the SNIF page 21/22 could be improved by ensuring that :

- Potential contaminated personal protective equipment (PPE) is removed before leaving the area (PPE should be discarded in the biohazard bag)
- During the period of 30 minutes to allow agents to settle, the area should be closed and a "DO NOT ENTER" sign should be posted.
- Before initiating the spill response procedure, appropriate PPE must be worn by the personnel. In the event of a biological spill treatment with 6000 ppm (mg/L) bleach solution, protective eyewear, lab coat, overshoes, gloves, mask and protective eyewear are recommended.
- A list with concentrations for all disinfectants (including alternative to sodium hypochlorite) with demonstrated effectiveness against AAV viral vectors is requested
- Personnel are aware that bleach solution and alcohol can react and can produce toxic vapors as chloroform. Before using alcohol wipes, the bleach solution should first be neutralized (by for example thiosulfate solution) or rinsed with water and dried before application of alcohol, to avoid toxic vapors.
- The medical staff should report the incident to the principal investigator of the study and the biosafety officer at the site.

The notifier is also requested to make sure all documents have been updated accordingly (SNIF, CAF, Pharmacy manual…). These instructions should also be included in the Investigator's Brochure to ensure that all personnel involved in the study are fully informed and consistently aware of the necessary procedures, precautions, and safety measures.

Coordinator comment:

In my opinion this is insufficient. They need to be in the investigator brochure so that the workers involved are sure to be informed. Also need a plasticized 1-2 page (front and back) summary of procedures for administration and any accidental exposures. For me this is an absolute necessity.

They should provide a list with concentrations for all disinfectants that completely destroy their vector. Some instruments and surfaces cannot be treated with bleach. Also, better to say sodium hypochlorite.

Same, alternatives to bleach if possible need to be listed.

SBB comment
Request has been improved by adding coordinator's comment

Use of anticonception by a sexually active treated patient is only mentioned in the ICFs, whereas such requirement should also be included in the SNIF and CAF and potentially other relevant documents of the dossier.

SBB comment
Use of anticonception by a sexually active patient is indeed mentioned in the ICF. It is also mentioned in the protocol, but not in the SNIF or the CAF. The notifier could indeed be requested to also mention the use of anticonception in both documents.

Coordinator comment:
Yes but as these are children it may not be relevant.

Comment 2
P13 point c) of the B_BE_25_BVW8_Part3_SNIF document, it is written that:

E. INFORMATION RELATING TO THE GENETICALLY MODIFIED ORGANISM

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

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

Yes ☐ No ☒ Not known ☐

Please specify

The GMO is secreted in bodily fluids and has similar survival and stability to wild-type AAV. The GMO is devoid of any viral genes required for replication, and as such, is unable to replicate in the presence of a helper virus. All AAVs are susceptible to appropriate virucidal disinfectants, such as 1% to 10% sodium hypochlorite (for at least 20 minutes), alkaline solutions at pH >9, 5% phenol, heat (>80ºC for 60 minutes), UV radiation and extreme pH (<2, >12). Effective disinfectants require 20 minutes' contact time.

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 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 surfaces because, at this concentration, bleach can generate vapors with potential ocular irritation or oropharyngeal, oesophageal, and gastric burns. This treatment at this concentration must be only reserved for "small surface (< 1 m2)" spill treatment.

3)The usual concentration for the decontamination of Adenovirus is 6000 ppm (cf.ref 1). 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. We invite the notifier to change the ambigous terms "10% bleach solution" in "6000 ppm (mg/L) bleach solution".

Ref 1 :
Antimicrob Agents Chemother

. 2006 Apr;50(4):1419–1424. doi: 10.1128/AAC.50.4.1419-1424.2006
Efficacy of Hospital Germicides against Adenovirus 8, a Common Cause of Epidemic Keratoconjunctivitis in Health Care Facilities
William A Rutala 1,2,*, Jeffrey E Peacock 3, Maria F Gergen 1, Mark D Sobsey 3, David J Weber 1,2

Ref 2 :
For the "USA" :

Expected Chlorine Concentrations by Various Dulitions of Household 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

Source:

Accessible version: https://www.cdc.gov/infection-control/hcp/disinfection-and-sterilization/index.html

Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008

Update: June 2024

William A. Rutala, Ph.D., M.P.H.[1,2], David J. Weber, M.D., M.P.H.[1,2], and the Healthcare Infection Control Practices Advisory Committee (HICPAC)[3]

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 its corrode or damage stainless steel, aluminium and the most rubbers components of surfaces.

SBB's comment

The recommendations proposed by the expert could be summarized as follow :
According to section E.1.a of the SNIF document (page 13/22), in the event a spill of the IP occurs, the spill will be contained, and the area will be decontaminated with a bleach solution.

- It is preferable to use the term sodium hypochlorite rather than the generic term "bleach," to ensure clarity and precision regarding the chemical agent to be used.
- Given that to maintain chlorine strength and ensure bleach effectiveness, it is crucial to prepare the solution just before use to avoid loss of effectiveness over time, the notifier is requested to complete the information by indicating that this sodium hypochlorite solution must be freshly prepared and stored in a dark bottle.
- As 10% bleach solution is not the standard concentration for treating general spill-contaminated surfaces because, at this concentration, bleach can generate vapors capable of causing ocular

irritation as well as oropharyngeal, oesophageal, and gastric burns, the notifier is requested to indicate this in the document

- According to Rutala et al. (2006), the usual concentration for the decontamination of Adenovirus is 6000 ppm (cf. ref 1). As household bleach concentrations vary (between 5 and 36 °Chl in Belgium), the expression "10% bleach solution" is ambiguous and should be replaced by "6000 ppm (mg/L) bleach solution."
- 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 can corrode or damage stainless steel, aluminium and the most rubbers components of surfaces. A list of adequate of decontamination / disinfection solutions for areas that cannot be decontaminated with bleach is required
- Hypochlorite concentration in household bleach solutions varies by manufacturer. All decontamination procedures involving the use of sodium hypochlorite solution should therefore specify the precise mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution.

Coordinator comment

I repeat that alternatives to sodium hypochlorite need to be provided (with demonstrated effectiveness) for areas that cannot be decontaminated with bleach. The use of the term bleach is ok for the family as this is a household word but the first time it is used in the professional documents it needs to be clearly defined as sodium hypochlorite at a final concentration of 6000 ppm. In addition, an effective alternative must be provided to materials that cannot be disinfected with bleach.
Using % is not acceptable as the stock solutions vary considerably - it must be the concentration in ppm.

SBB comment

Request has been improved by adding coordinator's comment

P16 point c) of the B_BE_25_BVW8_Part3_SNIF document, it is written that:

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

The risks related to the release into the environment of the GMO or risks to personnel in the event there is a breach in container integrity and/or storage or accidental spillage at the site or during shipping/storage, is considered to be negligible. In the event that a spillage did occur, the product is non-pathogenic and non-replicative, limiting spread and risks to the environment or personnel. The spill will be contained, and the area will be decontaminated using a viricidal disinfectant as per local guidelines and institutional procedures.

In the event of a biological spill treatment using a viricidal disinfectant as 6000 ppm (mg/L) 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 follow: "In the event of a biological spill treatment with 6000 ppm (mg/L) bleach solution, protective eyewear, lab coat, overshoes, gloves, mask and protective eyewear should be worn."

P21 point J.1) of the B_BE_25_BVW8_Part3_SNIF document, it is written that:

SBB's comment

The expert's remark has been implemented in the proposed request to the notifier under section 3.6 Expert 1.

Additional SBB's comment

According to the CAF document, section 3.6.b (page 10/14), the required personal protective equipment includes a laboratory coat, safety glasses and gloves. The SNIF document, section F.4.a (page 16/22), additionally specify the use of sleeves alongside the lab coat, safety glasses and gloves. The applicant is requested to update the relevant document(s) as necessary to ensure consistency across all submitted materials (CAF, SNIF, Pharmacy manual…).

J. INFORMATION ON EMERGENCY RESPONSE PLANS

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

In case of accidental spillage of SGT-003, the spill will be contained, and the area will be decontaminated using a viricidal disinfectant as per local guidelines and institutional procedures. A spill kit will be available at all times during all the steps, but at a minimum during the dose preparation and administration procedure. Healthcare professionals should ensure suitable personal protection during removal of spillages.

Contaminated liquids will be disposed of as biohazardous waste as per local guidelines and institutional procedures. These procedures may include:

- Evacuate area, remove contaminated personal protective equipment (PPE) and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure.
- Cover the spill with absorbent material. Starting at the edges and work towards the center.
- Carefully pour disinfectant (fresh 10% bleach solution followed by alcohol wipes) over the absorbed spill, again starting at the edges. Saturate the area with disinfectant.

Alcohol wipes using after a treatment of the contaminated surface with 10% bleach could produce toxic vapors such as chloroform. Before using alcohol wipes, the bleach solution should first be neutralized (by for exemple thiosulfate solution) to avoid this effect. The notifier is invited to inform about this effect in the document.

SBB's comment

The expert's remark has been implemented in the proposed request to the notifier under section 3.6 Expert 1.

Coordinator comment

People tend to panic a bit if there is an accident - for this reason a simple and straightforward means to decontaminate needs to be recommended throughout all of the documents and in particular the plasticized document that the health care worker will have on hand (pharmacy or nurse). If there is an alternative to bleach this should be the top recommended approach.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

- P10/14 Public CAF: containment and decontamination should discussed in more detail providing more detailed info and procedure (describe solution, procedures, …). As per local guidelines is not sufficient. Also best to provide a flow chart for the caretakers at home. What about tears, tissues, …?

SBB Comment:
A proposed request to the notifier has been provided in this section 3.6 under Comment Expert 1 here above.

No home visits by the caretakers have been planned for this clinical trial. The Duchenne Video Assessment will be conducted remotely in a home environment by the patient and patient's family without the intervention of caretakers.

- P11/14: waste samples should be treated as medical waste: how will the parents/care takers deal with this at home? Describe in more detail how they should deal with this (should these be collected and returned to the hospital?).

SBB Comment:
A proposed request to the notifier has been provided in this section 3.6 under Comment Expert 1 here above.

- P11/14: donation of blood and organs: even though this will not be considered, taking into account the disease (DMD) here, the statement "The risk of latent infection from AAV particles in blood/cells/tissues/organs that may be donated by clinical trial subjects has been considered negligible in the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors document, developed by the European Commission, due to the low infectivity rate and non-pathogenic nature of AAVs. Accordingly, no recommendations on donation of blood/cells/tissues/organs have been provided." should be rephrased in my opinion. This decision cannot be made by the subjects due to their genetic illness. In line with other trials I would advise not to allow donation.

SBB Comment:
A proposed request to the notifier has been provided in this section 3.6 under Comment Expert 1 here above.

Comment 5
A spill kit should be available in the facility, this spill kit should contain appropriate disinfectant, personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, mask), absorbent paper towels, biohazard waste bags.
In case of accidental spills the PPE should be discard in the biohazard bag. The lab coat should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.

SBB Comment:
According to section 3.6.b of the CAF, "A spill kit will be available at all times during all the steps, but minimally during the preparation and administration procedure."
The expert's remark has been implemented in the proposed request to the notifier under section 3.6 Expert 1.

Coordinator comment
Should be available at all steps from receiving, storage, preparation, transport to patient room, administration and disposal of contaminated materials. This is an absolute necessity.

It is indicate in the CAF that fresh 10% bleach solution followed by alcohol wipes are used for disinfection in case of a spill. The main risk is the formation of toxic gases (chloroform vapor). If protocol requires both, bleach should be rinse with water and dry before application of alcohol. Avoid directly applying alcohol onto wet bleach. Bleach degrades rapidly. It should be clearly label on the fresh preparation: the concentration, the date prepared and the expiry (same day recommended) and store it in a dark bottle. The contact time should also be indicate in a procedure taking into account the high-titer AAV.

These procedures should be posted in the hospital room where the treatment should take place and where it is prepared.

SBB Comment:
The expert's remark regarding the combination of bleach and alcohol has been implemented in the proposed request to the notifier under section 3.6 Expert 1.
The expert's remark regarding bleach freshly prepared has been implemented in the proposed request to the notifier under section 3.6 Expert 2.

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
See comment 3.6. With correct recommendations and compliance to these recommendations the overall environmental risk will be negligible.

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

Comment 3
Has not evaluated this item.

Comment 4
Shedding with the current serotype seems limited. Yet, only very few bodily fluids were tested (p33/42 IMPD – saliva, urine, stool). What about tears and blood? Distribution of the AAV particles to gonads (semen) and other biodistribution routes should be carefully considered in the first human trials, since the results of earlier serotypes do not readily translate.

SBB Comment:
Viral shedding analysis has been performed for all participants enrolled to date in the ongoing Phase 1/2 study with SGT-003 (Study SGT-003-101). Samples (saliva, urine and stool) were collected frequently in the first weeks post-dosing and continued at a lower frequency up to 1 year SGT-003 dosing.
The expert's remark has been implemented in the proposed request to the notifier under section 2.6 Expert 4.

Coordinator comment

It seems appropriate that further analysis of shedding in bodily fluids should be included in this study not only for this particular application but also to provide important data for future studies.

SBB Comment:
During this clinical trial, blood, urine, saliva, and feces samples will be collected from participants at post-dosing timepoints for shedding analysis.

Comment 5
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 comment

Comment 2
Has no further comment

Comment 3
Has no further comment

Comment 4
- In the files the word 'virus' is used where 'viral vector' is meant. Please update to the wording that is used elsewhere in the file 'recombinant AAV-based gene therapy'. Correct wording is key. (e.g. B_BE_25_BVW8_IB_SGT-003.pdf p9, 11, 17,… /42

SBB Comment:
The term virus has correctly been used in the IB document. However, incorrect wording has been found in both ICF documents. Therefore, the following points could be reported as a "Typos and other errors/omissions":

- In the ICF_FR (p9/56), the following sentence is not correct: "Le virus adéno-associé est un vecteur (porteur) de virus, soit la partie du SGT-003". And should be corrected as follow : « Le virus adéno-associé est utilisé comme vecteur de transfert de genes ». Same correction should be done in the NL version (p9/53)
- In the ICF_FR (p20-26/56), the following sentence should be adapted : « Le VAA est la partie du SGT-003 ». Written like this, it suggests that the virus AAV is within the vector. The sentence should be corrected as follow : "AAV est un virus utilisé comme vecteur viral". Same correction should be done in the NL version (p19-24/53)
- In the ICF_FR (p22/56), the following sentence should be adapted : « Excrétion virale (pour vérifier la quantité de virus libérée dans l'environnement) ». During a shedding analysis, viral vector particles are measured, therefore, the sentence should be corrected into : « Excrétion virale (pour vérifier la quantité de matériel génétique viral libérée dans l'environnement) ». Same correction should be done in the NL version (p21/53)
- In the ICF_FR and NL (p30/56), the term "virus" is used where "viral vector" is meant. The applicant is requested to update the wording where applicable

Coordinator comment:

The applicant needs to be told to carefully check all of their documents and correct where necessary.

- In 6.5.1 in IB (p33/42) the IB mentions FDA guidance for industry will be followed. Is this guidance the same as EMAs? This should be adapted.

SBB Comment:

Section 6.5.1 in IB (page 33/42) mentioned two FDA guidance:

- 'Long Term Follow-up After Administration of Human Gene Therapy Products' (January 2020) that can be found on the following internet site : https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products
- 'Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT)' (2021)

Comment 5

Has no further comment

References

1. Nie, Y. *et al.* Characterization of the function of Adenovirus L4 gene products and their impact on AAV vector production. *Molecular Therapy - Methods & Clinical Development* **32**, 101370 (2024).

2. Adsero, A. *et al.* A Novel Role for the Adenovirus L4 Region 22K and 33K Proteins in Adeno-Associated Virus Production. *Human Gene Therapy* **35**, 59–69 (2024).

Compilation of the expert's evaluations of the answers of Solid Biosciences Inc. on the list of questions for dossier B/BE/25/BVW8

30 March 2026
Ref. SC/1510/BAC/2026_0350

Coordinator: Karen Willard Gallo (Institut Jules Bordet)
Experts: Willy Zorzi (ULiège), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Aline Baldi
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW8** 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 January 2026 and concerns a clinical trial entitled "A phase 3, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy of a single intravenous dose of SGT-003 in ambulant males with Duchenne Muscular Dystrophy". The investigational medicinal product is recombinant AAV-based gene therapy that delivers a codon-optimized and CpG island-minimized human 5-repeat microdystrophin (h-μD5) by using a novel muscle-tropic capsid.

On 2 March 2026, based on a list of questions prepared by the BAC (SC/1510/BAC/2026_0228), 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 19 March 2026. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

Response Q1: It is not clear to me why the applicant indicated that these AdV sequences are part of the production construct. The explanation provided now does not address the specific question put forward. Point is that these proteins are not tested for. L4-33K gene products were found to impact AAV production in both the producer cell line and transient transfection platforms. Optimization of Adenovirus L4-22K/33K expression to facilitate efficient expression and splicing of AAV rep/cap transcripts therefore represents a unique opportunity to optimize AAV vector production (see Adsero et al. 2024 ; Nie et al. 2024). Still, as far as I understand this was not reported in clinical production of AAV and thus we should be cautious on potential effects.

SBB comment:
Adenoviral L4 and hexon sequences are not part of the AAV vector genome. Information related to recent literature indicating that adenoviral L4 gene products (in particular L4-22K/33K) may facilitate efficient expression and splicing of AAV rep/cap transcripts and overall vector production efficiency have been combined to the proposal question reported under Expert comment 4.

Response Q2: Viral vector shedding instead of viral shedding is meant I reckon. Since experiments are ongoing, we could request the applicants to provide all info available, or when it becomes available. This will be key to determine the environmental risk associated to the current proposed setups, and for future applications employing the same serotype.

SBB comment:
Indeed, shedding data collected from previous studies will contribute to a proper environment risk evaluation. In section 1.3.2. "Viral shedding" section of the IMPD, preliminary shedding results performed for all participants enrolled to date in the ongoing Phase 1/2 study with SGT-003 (Study SGT-003-101) have been reported.

Response Q3: The applicant argues that for rAAV2 vectors, distribution to the gonads was observed in several species in nonclinical studies: however, vector DNA was either not detected in semen or detected only transiently at early post dose timepoints, with no evidence of germline transmission (Arruda et al., 2001; Schuettrumpf et al., 2006). These studies are old, and current detection methods are more powerful/sensitive (ddPCR for example). Also presence in the seminal fluid is important to assess, since this can allow spreading of the vector during intercourse. Patients should be informed about that, and appropriate post-treatment advice should be provided to limit spreading. I agree that this is maybe not relevant for the currently envisioned patient population, but it is important that we take this into account. I'm not sure how to best address this.

SBB comment:
The following question could be sent to the applicant:
The applicant argues that for rAAV2 vectors, gonadal distribution was observed in several species in nonclinical studies: however, vector DNA was either not detected in semen or detected only transiently at early post dose timepoints, with no evidence of germline transmission (Arruda et al., 2001; Schuettrumpf et al., 2006). Given that these studies were conducted using less sensitive detection methods, and that seminal fluid has not been assessed for SGT-003 in nonclinical or clinical shedding studies to date, the applicant is requested to discuss whether additional investigations using current high-sensitivity methods (e.g., ddPCR) are warranted to evaluate the persistence of rAAV9 vector DNA in gonadal tissue and seminal fluid, particularly with respect to potential germline transmission risk.

Coordinator comment:
See the edits in the LOQ

Responses to Q4-5-6-7-8-9-10: fine for me

Evaluation Expert 2

After evaluation of the answers of the notifier, I have the opinion that the notifier addressed correctly and satisfactorily the comments/questions that have been raised.

Evaluation Expert 3

I hereby inform you that the notifier for the dossier B_BE_25_BVW8 dossier has responded correctly and satisfactorily to all comments and questions. However, a few additional remarks should be made, particularly regarding the CAF document relating to IMP_AAV-SGT-003_BE-DR_TC.pdf file :

1.In p13, it is written that non-disposable instruments will be sprayed with an appropriately validated viricidal disinfectant :

2 remarks must be done :
1.a. The procedure described here above must be changed because spraying a viricidal disinfectant is now not appropriate.
Such as reported in the following article:

Cureus
Part of SPRINGER NATURE

Prevalence of Health Effects Due to Disinfectant Exposure and Its Impact on Selected Physiological Parameters Among Class D Workers: A Descriptive Cross-Sectional Study

Vijaya R. Kumbhar [1], Seema B. Geddugol [1]

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.

1.b. The notifier is invited to add that the appropriate validation of virucidal disinfectants should concern both their effectiveness against SGT-003 but also their compatibility with other additional procedures suggested by the notifier (such as autoclaving) because most of them are not suitable for further treatment by autoclaving (in this case, the problems of generating toxic fumes or risk of explosion must be taken into account in the validation…).

Regarding the remarks 1.a. et 1.b, we could propose to change the sentence as following:
Non-disposable instruments, such as trays that have been used during the dose preparation and administration procedures and have potentially come into contact with SGT-003, will be decontaminated with a wipe soaked with an appropriately viricidal disinfectant prior any additional procedures in accordance with local guidelines and institutional procedures related to the management of BSL-1 GMOs. In case of further autoclaving treatment, it is important to pay attention that the chosen viricidal disinfectant must be validated to support high temperature without risk of explosion or release of toxic vapors within the in the lab.

SBB comment:
The question proposed by the expert could be sent to the applicant.

Coordinator comment:
See edits in the LOQ

2. In p13, further, it is written that “appropriate PPE (e.g. eye protection, gloves, and lab coat) should be wear in case of accidental spills

Regarding this part, 3 remarks should be made:

2.a. In the procedures relating to accidental spills, we propose to keep overshoes in the composition of PPE in order to protect workers' footwear during decontamination, thus avoiding any biological contamination from the distinguishable spill or indistinguishable microspill on the floor or any chemical contact with the disinfectant used to treat the spill.

2.b. Regarding the wearing of masks, it should be emphasized that in the event of spill remediation, it is common practice to protect the worker's face preventively from the risks of splashes from both the contamination being treated and products such as concentrated bleach used in these conditions.

2.c. We also propose removing the wording “e.g.” that invites a non-exhaustive list of PPE components.

The proposed list must be as complete and precise as possible, as the described procedure allows for no approximations.

SBB comment:
The following question could be sent to the applicant:
Overshoes and masks have been removed from the list of personal protective equipment (PPE) to be worn by site staff involved in the disposal of contaminated materials following spill clean-up. However, it is recommended that both overshoes and masks be reinstated. Overshoes are important to protect footwear from potential biological contamination arising from visible spills or undetected microspills on the floor, as well as from contact with chemical disinfectants used during decontamination.
In addition, during spill decontamination, it is standard practice to provide preventive facial protection against potential splashes, both from the biological material being treated and from chemical agents such as concentrated bleach.
Finally, it is recommended to remove the wording “e.g.”, as it suggests a non-exhaustive list of PPE components and may introduce ambiguity regarding the required protective equipment.

Coordinator comment:
“Mask and/or a face shield” to be added as facial protection

Additional SBB comment:
Potentially contaminated personal protective equipment (PPE) is removed before leaving the area (PPE should be discarded in the biohazard bag). However, as reported currently in the SNIF, page 22/24, personnel should first “evacuate area, then remove contaminated PPE”. Please update the text in order to clearly indicate that removal and appropriate disposal of contaminated PPE should be performed prior to leaving the area. Please also update the “Handling guidance for SGT-003” accordingly and other applicable documents.

Evaluation Expert 4

Question 1 :

The applicant states that HEK293 human proteins are absent from SGT-003, as demonstrated by the use of an assay using polyclonal antibodies against human proteins. As mentioned by the applicant The protein “assay employs a polyclonal antibody that is not expected to detect adenoviral proteins”. Actually, this assay showed that the amount of human proteins is below the threshold. They further assume that, given these data, it is unprobable that the purification process did not remove the viral proteins.
This demonstration is indirect and not convincing. Indeed :
i) The amount of L4 proteins expressed by multiple copies of helper plasmid DNA during the viral production by transfction cannot be compared with the amount of cellular proteins. Thus

the amount of residual L4 and hexon assembly proteins could be significantly higher than the amount of cellular proteins.
ii) The removal of proteins during the purification process probably depends on the particular protein properties.

In addition, the applicant showed that “residual helper DNA sequences (which would include the L4 and Hexon assembly coding sequences) are present at very low levels, typically <0.2%”. Uncertainties that should be clarified are raised by these data as presented:

i) We don’t know the proportion of this “residual helper DNA sequence which contains the necessary elements for expressing L4 or Hexon assembly proteins.

ii) Can this residual contaminant DNA enter into caregivers’ cells together with the AAV particles in case of an accident during the preparation of the injectable solution? If yes, how much proteins would be expressed?

In the absence of direct measurement of the amount of adenoviral proteins present in SGT-003, it is difficult evaluate the risk of residual L4 and hexon assembly proteins.

SBB comment:
The applicant states that HEK293-derived proteins are absent from SGT-003 based on an assay using polyclonal antibodies against human proteins, which are not expected to detect adenoviral proteins. Based on these results, the applicant assumes that residual viral proteins are also unlikely to be present. However, this conclusion is indirect. In particular, the assay used does not detect adenoviral proteins, and therefore does not provide direct evidence regarding their presence or absence. Furthermore, the expression levels of adenoviral helper proteins (e.g., L4 and hexon assembly proteins) during production may differ significantly from those of host cell proteins, and their clearance during purification may depend on specific physicochemical properties. Recent literature has indicated that adenoviral L4 gene products (in particular L4-22K/33K) may facilitate efficient expression and splicing of AAV rep/cap transcripts and overall vector production efficiency (Adsero et al. 2024 ; Nie et al. 2024). In addition, residual helper DNA sequences, including L4 and hexon coding regions, are present at very low levels, but it is unclear whether they could lead to protein expression in case of accidental exposure.

The applicant is therefore requested to provide data or justification demonstrating the absence of residual adenoviral proteins in SGT-003. In particular, please clarify whether specific, suitably sensitive analytical methods targeting adenoviral proteins have been employed, or justify why such analyses are not considered necessary.

Coordinator comment:
I think it is important to insist that this is based on solid data not just an idea

Question 9

A satisfactory response has been provided and included in relevant documents.

Expert 5

I have read the answers to my questions and they are satisfactory; they have added a lot of detail and clarification in the CAF, it is much more complete and clearer, especially regarding disinfection.

Coordinator comment

In addition, on page 4 of the "SGT-003_301_BEL_Hygiene and Precautions Guidance _v.1.1 Final" the statement:
"These recommendations apply to trial participants, caregivers, and peoples who help with his care. These people should follow the steps below for at least 4 weeks."

Is confusing and grammatically incorrect.

It should be:
“These recommendations apply to trial participants, caregivers, and individuals who help with their care. The individuals involved should follow the precautions listed below for at least 4 weeks."

For the list,

"If possible, have participants use a separate bathroom from other unexposed household members during this period." This is wrong, they are all exposed if they are in the same house. The word unexposed should be removed.

" For at least the first 7 days, place items that may have come into contact with bodily fluids (such as tissues) into a sealable plastic bag (e.g., zip-lock). Seal the bag tightly and dispose of it in your regular household trash." This needs to be clarified that this does not include toilet paper which should be flushed with the waste.

"Avoid sharing toys with people who have not been exposed. If possible, clean and disinfect toys before re-use." Should be: Avoid sharing toys or other items with other household members. Clean and disinfect all items before re-use.

"Avoid sharing food or drinks with people who have not been exposed" should be : Avoid sharing food or drinks handled by the patient with anyone else.

References

Adsero A. *et al.* 2024. A Novel Role for the Adenovirus L4 Region 22K and 33K Proteins in Adeno-Associated Virus Production. Hum Gene Ther. 2024 Jan;35(1-2):59-69.

Arruda et al., 2001. Lack of germline transmission of vector sequences following systemic administration of recombinant AAV-2 vector in males. Mol Ther. 2001 Dec;4(6):586-92.

Nie Y. *et al.* 2024. Characterization of the function of Adenovirus L4 gene products and their impact on AAV vector production. Mol Ther Methods Clin Dev. 2024 Nov 4;32(4):101370.

Schuettrumpf et al., 2006. Inadvertent germline transmission of AAV2 vector: findings in a rabbit model correlate with those in a human clinical trial. Mol Ther. 2006 Jun;13(6):1064-73.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Solid Biosciences Inc. on the second list of questions for dossier B/BE/25/BVW8

14 April 2026
Ref. SC/1510/BAC/2026_0394

Coordinator: Karen Willard Gallo (Institut Jules Bordet)
Experts: Willy Zorzi (ULiège), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Rik Gijsbers (KULeuven), Aline Baldo
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW8** 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 January 2026 and concerns a clinical trial entitled "A phase 3, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy of a single intravenous dose of SGT-003 in ambulant males with Duchenne Muscular Dystrophy". The investigational medicinal product is recombinant AAV-based gene therapy that delivers a codon-optimized and CpG island-minimized human 5-repeat microdystrophin (h-μD5) by using a novel muscle-tropic capsid.

On 27 March 2026, based on a list of questions prepared by the BAC (SC/1510/BAC/2026_0345), 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 09 April 2026. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation expert 1

As to Q3: I agree that the evidence is low for AAV persistence in germ cells (stable germ line transmission/integration). However, the point of the question was that the applicant argued that for rAAV2 vectors, gonadal distribution was observed in several species in nonclinical studies.
I'm not referring to germline transmission, rather to the fact that possibly AAV particles are present in the semen, and thus may be transferred upon intercourse.
The papers are not referenced ("available nonclinical evidence indicates a very low likelihood of germline transmission, even under conditions of direct and high local exposure to the testes"). This concerns work in animal models, and we know that transduction potential is not readily translatable to human settings.

The risk of germline transmission for SGT-003 is considered low, yet presence in the seminal fluid for example may be relevant. Employing the most sensitive detection methods is therefore key in my opinion. Arguing that additional investigations using higher-sensitivity analytical methods (e.g., ddPCR) would be unlikely to provide information that materially alters the biological risk assessment, is therefore for me not reasonable. This would allow us to judge whether this is an ERA concern or not.
As a precautionary measure the applicant indicates that participants in Study SGT-003-301 and their partners of childbearing potential are required to use one barrier method and one highly effective method of contraception for 12 months following dosing. I agree with this measure, but if beyond 12 months there is detectable levels of AAV, this should be reconsidered.
See also "Based on the FDA guidance, the minimum panel of tissue collection in a preclinical GLP-compliant biodistribution study should include the liver, spleen, kidney, lung, heart, brain, gonads, blood, and possibly the injection site. Additional organs might be required for specific routes of administration, e.g., the spinal cord for CSF delivery.", in https://www.mdpi.com/1999-4915/17/2/239 => FDA requirement is maybe more strict than EMA?

I do agree however, that the use of ddPCR and qPCR (when applying the correct protocol settings => addition of plutonic F68) can result in very similar data => still it is key that the most sensitive approaches are applied. See https://pmc.ncbi.nlm.nih.gov/articles/PMC7377043/.

SBB comment

According to section 4.2 of the IB, widespread biodistribution of SGT-003 following IV administration in both mdx mice and cynomolgus monkeys has been observed. The GLP-compliant toxicology studies of SGT-003 in mdx mice and cynomolgus monkeys show that vector genomes and microdystrophin mRNA were detected in the testes of mdx mice and cynomolgus monkeys. However, it has not been specified whether the vector was also observed in the semen, and may therefore be transferred upon intercourse. The applicant could therefore be requested to clarify, by providing all relevant information (results, method used, timepoints…), whether the presence of the vector has been tested in semen or seminal fluid.

Furthermore, even though Duchenne Muscular Dystrophy (DMD) is a X-linked disease primarily affecting males, the applicant could be requested to also provide all relevant information on ovarian (and broader female reproductive tissue) biodistribution studies. Indeed, female subjects may be exposed in accidental exposure situations during handling of the medical product. Therefore, any potential human exposure scenario should be characterized and not just for the target indication population.

Evaluation expert 2

According to me, the notifier addressed correctly and satisfactorily the comments/questions that were raised in March 2026.

Evaluation expert 3

After examining the notifier's responses on the second list of questions of the Biosafety Advisory Council for dossier dossier B/BE/25/BVW8 (clinical trial submitted by Solid Biosciences Inc. related to the use of recombinant AAV for subjects with Duchenne Muscular Dystrophy) , we would like to propose an additional comment concerning:
In p13 of the CAF document, it is written that :

Any disposable consumables/instruments used during the handling, dose preparation and administration procedures, including syringes and needles used for dose preparation, will be disposed of according to local procedures in a manner consistent with the standard practice of the institution for BSL-1 GMOs. In the medical facility, this will involve containment in sharps bins or clearly marked bags (e.g. biohazard, medical waste) prior to autoclaving and/or incineration either on or off site as per local institutional guidelines. Non-disposable instruments, such as trays that have been used during the dose preparation and administration procedures and have potentially come into contact with SGT-003, will be sprayed with an appropriately validated viricidal disinfectant in accordance with local guidelines and institutional procedures related to the management of BSL-1 GMOs.

One remark must be done :
The virucidal disinfectant spraying procedure described above must be modified because spraying a viricidal disinfectant in the air of a clinical room is now, no longer appropriate and should be prohibited in Good Clinical Practice.
Such as reported in the article from Vijaya R. Kumbhar et Seema B. 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.

Regarding the previous remark we could propose to change the sentence as following:

Non-disposable instruments, such as trays that have been used during the dose preparation and administration procedures and have potentially come into contact with SGT-003, will be decontamined with a wipe soaked with an appropriately viricidal disinfectant (without spraying) prior any additional procedures in accordance with local guidelines and institutional procedures related to the management of BSL-1 GMOs.

SBB comment
The following question could be submitted to the applicant:
Since growing evidence shows that exposure to cleaning products and disinfectants raises the risk of respiratory diseases, spraying cleaning and disinfection solutions that contains complex chemical mixtures, including volatile organic compounds primarily used as solvents and fragrances, preservatives, and disinfectants, spraying a viricidal disinfectant in the air of a clinical room 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 an validated viricidal disinfectant should be avoid.

Evaluation expert 4

Question 1

The additional experiment performed convincingly demonstrates the absence of adenoviral hexon protein expressed by the helper plasmid in the final product. It is most likely that the same holds true for L4 protein.

Question 3
The evidence provided is indirect. Indeed, the pre-clinical studies cited were performed in mouse test

i) AAV serotypes infectivity can differ between species. (e.g.Hordaux, J., et al. (2018). The neurotropic properties of AAV-PHP.B are limited to C57BL/6J mice. Mol. Ther. 26, 664–668. doi:10.1016/j.ymthe.2018.01.018). Are there data in non-human primate?

ii) Not only testicles but also ovaries should be tested. The rationale to refer to studies in testes only holds indeed for patients, who are exclusively males but not for the caregivers.

iii)This is an application for a Phase III clinical trial. It is surprising that in previous trials, patients' sperm was not tested for the presence of vector genome copies.

SBB comment

Point i: According to sections 4 and 4.2 of the IB, biodistribution studies with SGT-003 have been performed in male *mdx* mice and also in juvenile cynomolgus monkeys.

Point II: A proposed question has been included in the SBB comment to expert 1

Point iii: See SBB comment for expert 1 where non-clinical results in sperm and seminal fluids have been requested. As mentioned in the inclusion criterion 1, participants will be aged 7 to under 12 years old.

Evaluation expert 5

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References

Kumbhar VR, Geddugol SB. 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

Antwoorden van de Adviesraad voor Bioveiligheid op opmerkingen gekregen tijdens de publieksraadpleging over de kennisgeving B/BE/25/BVW8 van Solid Biosciences Inc. voor doelbewuste introductie in het leefmilieu van genetisch gemodificeerde organismen met uitzondering van hogere planten voor onderzoek en ontwikkeling

Final versie – 12/05/2026
Ref. SC/1510/BAC/2026_0442

Contexte

De kennisgeving B/BE/25/BVW8 werd in december 2025 door Solid Biosciences Inc. bij de Belgische bevoegde overheid ingediend voor een verzoek om doelbewuste introductie in het leefmilieu van genetisch gemodificeerde organismen, met uitzondering van hogere planten voor onderzoek en ontwikkeling, overeenkomstig hoofdstuk II van het koninklijk besluit van 21 februari 2005. De kennisgeving kon opgestart worden door de bevoegde overheid (BO) op 23 januari 2026.
Volgens artikel 17 van het koninklijk besluit organiseerde de BO een openbare raadpleging van het publiek voor een periode van 30 dagen. Als resultaat van deze raadpleging heeft de BO de opmerkingen van het publiek doorgestuurd naar de Adviesraad voor Bioveiligheid, waarvan een aantal opmerkingen betreffende bioveiligheid.
Overeenkomstig artikel 16§2 van het koninklijk besluit zijn deze opmerkingen in beschouwing genomen bij het uitbrengen van het advies van de Adviesraad voor Bioveiligheid (referentie BAC_2026_0441). Het antwoord op deze opmerkingen wordt hieronder gegeven.
Vragen/opmerkingen van het publiek die niet relevant zijn inzake bioveiligheid (zoals patiënt gerelateerde vragen, economische of ethische kwesties) worden door de Bioveiligheidsraad niet in aanmerking genomen.

Vraag 1: Vooronderzoek in muis toonde exclusieve expressie in spier (2.5), maar er wordt niet vermeld of dit enkel skeletspieren betreft, of ook hartspier en/of ademhalingsspieren.

SBB Comment:
In het GLP-toxicologieonderzoek dat werd uitgevoerd met *mdx*-muizen en cynomolgusapen, bleek het transgene eiwit tot expressie te komen in spieren. Met spieren wordt bedoeld in tegenstelling tot niet-spierweefsel en omvat alle spierweefsels.

Vraag 2: Document 'Informatie voor het publiek' en 'Application form' vermelden andere locatie: Hop Reine Fabiola Av JJ Crocq 15 vs. CHU Brugmann Av JJ Crocq 4. Veel confidentiële elementen in het dossier, waardoor beoordeling wordt bemoeilijkt. Verwacht aantal deelnemers van 80 lijkt een eerder onrealistisch hoog aantal, derhalve impact van de studie vermoedelijk minder groot dan voorspeld.

SBB Comment
De klinische studie zal plaatsvinden in het Queen Fabiola Kinderziekenhuis in Brussel. Het officiële adres van de locatie is Avenue Jean-Joseph Crocq 15, 1020 Brussel.

Er zullen naar verwachting ongeveer 80 deelnemers worden behandeld in deze studie op verschillende locaties in Europa, het Verenigd Koninkrijk, Canada en Australië, waaronder ongeveer 6 deelnemers in België. De steekproefgrootte in een klinische studie wordt niet willekeurig gekozen, maar berekend om ervoor te zorgen dat de studie een betekenisvol effect betrouwbaar kan detecteren en tegelijkertijd onnodige blootstelling van deelnemers kan voorkomen. Het proces is gebaseerd op statistiek en hangt af van verschillende belangrijke factoren. De steekproefgrootte werd bepaald op basis van het primaire doel om de werkzaamheid van een eenmalige intraveneuze dosis SGT-003 te onderzoeken.

Vraag 3: Rationale voor het gebruik van een hybride AAV2 / AAV9 vector wordt onvoldoende gekaderd. Waarom ITR van AAV2 en red/cap van AAV9? Commerciële of moleculair-technische keuze?

SBB Comment:
AAV2 (adeno-geassocieerd virus serotype 2) ITR's, de enige virale sequenties die behouden blijven in recombinante AAV-vectoren, zijn goed gekarakteriseerd, zeer efficiënt en compatibel met een breed scala aan capsiden, waaronder van AAV9 afgeleide en gemodificeerde varianten. AAV2 ITR's zorgen voor betrouwbare replicatie en verpakking tijdens de vectorproductie en hebben een bewezen veiligheidsprofiel, dat erkend wordt door regelgevende instanties. AAV9 wordt gekenmerkt door een breed, systemisch tropisme en kan efficiënt een grote verscheidenheid aan weefseltypen transduceren, met een bijzondere affiniteit voor het centrale zenuwstelsel, het hart, de skeletspieren en de lever. De van nature voorkomende capside-eiwitsequentie van het AAV9-serotype werd gemodificeerd om een nieuw capside-serotype (AAV-SLB101) te creëren met een verbeterd spiertropisme, om een transgeen dat codeert voor een functioneel humaan microdystrofine met vijf herhalingen (h-μD5) af te leveren aan hart- en skeletspiercellen.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Réponse du Conseil consultatif de Biosécurité aux observations formulées pendant la consultation du public concernant la notification B/BE/25/BVW8 de Solid Biosciences Inc. pour l'introduction volontaire dans l'environnement, à des fins de recherche et développement, d'organismes génétiquement modifiés autres que les plantes supérieures

Version finale - 12/05/2026
Ref. SC/1510/BAC/2026_0443

Contexte

La notification B/BE/25/BVW8 a été soumise en décembre 2025 par Solid Biosciences Inc. à l'autorité compétente belge pour une demande de dissémination volontaire dans l'environnement, à des fins de recherche et développement, d'organismes génétiquement modifiés autres que les plantes supérieures, conformément au chapitre II de l'arrêté royal du 21 février 2005. La notification a été lancée par l'autorité compétente (AP) le 23 janvier 2026.
Conformément à l'article 17 de l'arrêté royal, l'AC a organisé une consultation du public pendant une période de 30 jours. À la suite de cette consultation, l'AC a transmis les observations du public au Conseil consultatif de biosécurité, parmi lesquelles un certain nombre d'observations pertinentes en matière de biosécurité.
Conformément à l'article 16§2 de l'arrêté royal, ces observations ont été prises en compte lors de la préparation de l'avis du Conseil consultatif de Biosécurité (référence BAC_2026_0441). La réponse à ces observations est donnée ci-dessous.
Les questions/observations du public qui ne sont pas pertinentes en matière de biosécurité (telles que les questions liées au patient, les questions économiques ou éthiques) ne sont pas prises en compte par le Conseil de Biosécurité.

Question 1: Des recherches préliminaires sur des souris ont montré une expression exclusive dans les muscles (2,5), mais il n'est pas mentionné si cela concerne uniquement les muscles squelettiques, ou également les muscles cardiaques et/ou respiratoires.

SBB Comment :
Dans l'étude toxicologique GLP réalisée sur des souris *mdx* et des macaques cynomolgus, il a été observé que la protéine transgénique s'exprime dans les muscles. Le terme « muscles » s'oppose aux tissus non musculaires et englobe tous les tissus musculaires.

Question 2: Les documents « Informations destinées au public » et « Formulaire de candidature » mentionnent des adresses différentes : Hop Reine Fabiola Av. JJ Crocq 15 et CHU Brugmann Av. JJ Crocq 4. Le dossier contient de nombreux éléments confidentiels, ce qui complique l'évaluation. Le nombre attendu de 80 participants semble irréaliste ; par conséquent, l'impact de l'étude est vraisemblablement moins important que prévu.

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SBB Comment :
L'essai clinique se déroulera à l'Hôpital universitaire Reine Fabiola pour enfants de Bruxelles à l'adresse est la suivante : Avenue Jean-Joseph Crocq 15, 1020 Bruxelles.

Environ 80 participants devraient être inclus dans cette étude, répartis sur plusieurs sites en Europe, au Royaume-Uni, au Canada et en Australie, dont environ 6 en Belgique. La taille de l'échantillon dans un essai clinique n'est pas choisie arbitrairement ; elle est calculée afin de garantir que l'étude puisse détecter un effet significatif de manière fiable, tout en évitant une exposition inutile des participants. Ce processus repose sur des données statistiques et dépend de plusieurs paramètres clés. La taille de l'échantillon a été déterminée en fonction de l'objectif principal, qui est d'étudier l'efficacité d'une dose unique de SGT-003 administrée par voie intraveineuse.

Question 3: Le choix d'un vecteur hybride AAV2/AAV9 est insuffisamment justifié. Pourquoi l'ITR de l'AAV2 et la protéine rouge/capuchonnée de l'AAV9 ? S'agit-il d'un choix commercial ou d'un choix technico-moléculaire ?

SBB Comment :
Les ITR de l'AAV2 (virus adéno-associé de sérotype 2), seules séquences virales conservées dans les vecteurs AAV recombinants, sont bien caractérisées, très efficaces et compatibles avec une large gamme de capsides, y compris les variants dérivés de l'AAV9 et les variants modifiés. Les ITR de l'AAV2 garantissent une réplication et un encapsidage fiables lors de la production du vecteur et présentent un profil de sécurité bien établi, reconnu par les autorités réglementaires. L'AAV9 se caractérise par un tropisme systémique étendu et peut transduire efficacement une grande variété de tissus, avec une affinité particulière pour le système nerveux central, le cœur, les muscles squelettiques et le foie. La séquence protéique de la capside naturelle du sérotype AAV9 a été modifiée pour créer un nouveau sérotype de capside (AAV-SLB101) présentant un tropisme musculaire amélioré, afin de délivrer un transgène codant pour une microdystrophine humaine fonctionnelle à cinq répétitions (h-µD5) aux cellules cardiaques et musculaires squelettiques.