Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/24/BVW4 of the company Sarepta Therapeutics, for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

27/05/2024
Ref. SC/1510/BAC/2024_0731

Context

The notification B/BE/24/BVW4 has been submitted by Sarepta Therapeutics to the Belgian Competent Authority in January 2024 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 and the title of the notification is: ***"A phase 3 multinational, open-label, systemic gene delivery study to evaluate the safety and efficacy of SRP-9003 in subjects with limb girdle muscular dystrophy 2E/R4".***

The purpose of this study is to assess the safety and the efficacy of the study treatment SRP-9003 in in subjects who are at least 4 years old with a genetic diagnosis of Limb girdle muscular dystrophies type 2E/R4 (LGMD2E/R4).

The limb-girdle muscular dystrophies (LGMDs) are a group of rare, genetically heterogeneous disorders caused by defects in multiple genes encoding for proteins residing within the sarcolemma, cytosol, or nucleus of the muscle cell. LGMD type 2E/R4 is caused by a genetic mutation in the β-sarcoglycan (SGCB) gene, leading to SGCB deficiency. The lack of functional β-sarcoglycan protein progresses to loss of ambulation, potential respiratory insufficiency and often premature mortality.

As a gene therapy product, SRP-9003 has the potential to deliver functional human β-sarcoglycan (hSGCB) protein, in cardiac and skeletal muscle, thereby addressing the root cause of the disease. The non-replicating, recombinant adeno-associated virus (rAAV) serotype rh74 contains the sequence coding for the full length β-sarcoglycan (β-SG) under the control of the MHCK7 promotor/enhancer that has been optimized for driving expression in cardiac and skeletal muscle (Rodino-Klapac *et al*. 2013)[1].

1. Rodino-Klapac, L. R., P. M. Janssen, K. M. Shontz, B. Canan, C. L. Montgomery, D. Griffin, K. Heller, L. Schmelzer, C. Handy, K. R. Clark, Z. Sahenk, J. R. Mendell, and B. K. Kaspar. 2013. 'Micro-dystrophin and follistatin co-delivery restores muscle function in aged DMD model', Hum Mol Genet, 22: 4929-37

Overall, approximately fifteen patients will be included in this Phase III study and two to four patients will be included in Belgium, each receiving one single intravenous infusion into a peripheral limb vein (arm or leg). This study will be conducted at two clinical sites located in Flanders.

The dossier has been officially acknowledged by the Competent Authority on 09 February 2024 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 assisted by its Secretariat, contacted experts to evaluate the dossier. Three experts, from the common list of experts drawn up by the BAC answered positively to this request.
The experts assessed whether the information provided in the notification was sufficient and accurate in order 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 raised by 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 exclusive medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

On 18 March 2024, 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 23 April 2024 and transferred to the secretariat of the BAC the subsequent 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 06 May 2024. The answers of the notifier were received on 16 May 2024 and transmitted to the BAC, 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 to 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 didn't receive any reaction from the public.

Summary of the scientific evaluation

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

Following BAC's request, some inconsistencies within the composition of the self-complementary scAAVrh74.MHCK7.hSGCB vector genome have been clarified. The BAC is of the opinion that, the donor, recipient and parental organisms are adequately described in the dossier.

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

The production of SRP-9003 is accomplished via a triple transfection using three different plasmid DNA constructs: the “transfer vector” which contains the therapeutic gene of interest (GOI) - pAAV.MHCK7.hSGCB, the “AAV Rep/Cap” plasmid, and an “Ad helper” plasmid which contains some adenovirus genes. These three plasmids as well as the production procedure are satisfactorily described in the confidential documents.

3. The conditions of the release

The study has two cohorts. Cohort 1 will include approximately 8-10 ambulatory subjects. Cohort 2 will include approximately 5-7 non-ambulatory subjects. All subjects will receive one-single intravenous dose of SRP-9003 at a dose of 7.41×10^{13} vg/kg. All patients will remain for approximatively 6h at the hospital so that the trial nurses and trial staff can monitor vital signs and ensure that the patient has no negative reactions. After this monitoring period the patient can be discharged from the hospital.

Shedding analysis is planned during this clinical trial to examine saliva, urine and stool samples collected at baseline and Days 1,2,7,14,28,42,60 and Months 3,6,9,2,18,24,36,48,60. Monitoring of vector shedding will continue until three consecutive measurements are obtained at or below the lower limit of detection of the shedding assay or through the end of the clinical study. Preliminary results from shedding analysis obtained from the ongoing clinical trial SRP-9003-101 with the same IMP have been described in the confidential CAF document.

In an effort to assess germline transmission, the applicant provided preliminary results from an ongoing maternal foetal reproductive transmission pre-clinical study in murine models. Taking these results into account together with the nonintegrating properties of the viral vector and the requirement of participants, who are fertile and sexually active, to use barrier and spermicide contraception for at least 24 months following treatment, the BAC supports the conclusion that SRP-9003 is at low risk of germline transmission.

4. The risks for the environment or human health

SRP-9003 is a recombinant, replication deficient adeno-associated virus-based vector not harbouring any antibiotic or other resistance genes. Like its parental virus strain, it is considered not pathogenic. The genetic information introduced in this AAVrh74 derived vector is not expected to confer the GMO with properties that could confer risks to the human population or the environment.

There is a remote possibility of homologous recombination between the ITR-sequences of AAVrh74 in the IMP and wild-type AAV, if triple infection by SRP-9003, wild type AAV (providing the rep and cap functions) and a helper virus occurs simultaneously in exposed persons. Such a recombination event would result in a gain of the AAVrh74 functional genes required for replication and encapsidation but would also lead to loss of the human β-sarcoglycan transgene. Moreover, the genetic material from the rep and cap genes together with the hSGCB transgene would be too large for packaging in the AAV capsid, making it impossible to form replication competent viral particles containing the transgene plus the rep and cap genes necessary for replication.

In the case the vector was accidentally transferred to an unintended immune-competent human recipient, the risks are expected to be considerably lower than the patient participant because the vector is non-replicative and the 'dose' that could be inadvertently transferred (from e.g. aerosol, splashing or fomites) would be orders of magnitude lower than that administered to patients. Even under the worst case scenario, the recipient's immune response should clear the AAVrh74 capsid.

The BAC concludes that, based on the non-pathogenic and non-replicative nature of SRP-9003, the expected lower amounts of intact viral particles of SRP-9003 shed as compared to the therapeutic dose, and the strict implementation of the precautionary measures for preventing accidental contamination, the overall risk associated to exposure and transmission to other individuals can be considered negligible.

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

After administration of SRP-9003, patients and the patient's family will be provided with detailed instructions on the precautionary measures for the 4-week period immediately following treatment to avoid any potential transmission of the virus to other individuals or the environment outside the hospital setting. Resulting from the BAC's request, the notifier has now identified the specific disinfectant to use for decontaminating hard surfaces. It was also noted that alcohol at any percentage is not an effective decontamination solution for this gene therapy product. The notifier has also specified the minimum water temperature to be used for laundry, the procedure for washing dishes, glasses and other utensils and the obligatory use of disposable tissues.

All of the instructions, for patients and the patient's family, concerning good hygiene practices have been detailed in a short, easily readable document.

Recommendations for sexually active subjects enrolled in this clinical trial are provided in the patient Informed Consent Form and will also be included in the Investigator Brochure. Concerning the instructions regarding the donation of blood, organs, tissues and cells for transplantation, the notifier aligned the instructions reported in different documents by clearly stating that patients are prohibited from these donations for a period of 2 years following SRP-9003 administration.

Following the BAC's request, some instructions for health care workers have been updated and described in greater detail in the SNIF, the Public CAF and the CAF confidential (see below). The notifier also prepared a 2-4 page technical sheet, which includes all relevant handling instructions, detailed instructions in case of a spill, waste management and other biosafety measures. This concise document is important because those handling the experimental treatment need to have all the pertinent information on hand in a single document.

Needles and sharps must be placed in a sharp biohazard container as the primary container to avoid needle stick injuries. Needles must either be removed from the syringe using a hands-free sharp biohazard container designed for safety or the entire syringe/needle assembly must be placed intact into a rigid, leak-proof biohazard container for sharps.

A freshly prepared sodium hypochlorite solution must be used as a clean-up solution and/or disinfectant. Alcohol combined with bleach can produce toxic vapors such as chloroform so the sodium hypochlorite solution used first must be neutralized with 3% sodium thiosulfate solution before applying alcohol.

The notifier has also taken into consideration and answered the remarks and requests addressed by the BAC regarding the procedures to follow in case of accidental spill or breakage of a GMO containing vial.

Personal protective equipment includes lab coats, safety goggles, gloves, and sleeve covers. The notifier has clearly indicated that the use of double gloves corresponds to standard working procedures.

In order to reduce study burden while maintaining ongoing in-person surveillance by the study site, some visits will be performed remotely. Following the BAC's request, a study nurse, who will visit the patients at home, will receive clear instructions on protocols to follow to avoid any potential dissemination of the recombinant virus to the environment during such visits.

Given the assessment of improbability of further propagation of SRP-9003, 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 proposed clinical trial.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that SRP-9003, developed as a gene therapy approach for the treatment of limb girdle muscular dystrophy 2E/R4 disease, will have adverse effects on human health or the environment in the context of the intended clinical trial provided that all of the foreseen safety measures are followed in detail as described in the following updated documents:

- Pharmacy Manual (v1.0, 10 August 2023)
- Biohazardous Safety Data Sheet (v4.0, July 2023)
- Hygiene-Guide_BE_07May2024
- Dose Administration Manual (v1.0, 11 August 2023)
- Safety-Instructions-for-INV-and-Staff_BE (May 2024)
- Main ICF BE (v1.0, 20 March 2024)
- BE_GMO_Public CAF (April 2024)
- BE_GMO_Confidential Annex (v1.2, April 2024)
- BE_GMO_SNIF (May 2024)
- PMC_Standard Precautions Instructions Sheet
- CMRN Mobile Visit Training
- CMRN Mobile Visit Training Accidental Spills Sheet

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 version 1, and all of the safety instructions as described in the dossier and the updated/new documents listed above.

- As committed by the applicant, specific recommendations must be provided to pregnant women, lactating women and sexually active subjects enrolled in this clinical trial and on the length of time these recommendations need to be applied. These recommendation must be included in the next version of the IB.

- As confirmed by the applicant, recommendations for donating blood, organs, tissues and cells for transplantation and the length of time they must applied, will be included in the next version of the IB.

- Regarding the study specific instructions for caregivers that visit patients at home, the notifier is requested to also include instructions for collecting and disposing of waste generated during the visit.

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

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

- At the latest 15 days after the start of the trial, the notifier must provide, along with the delivery of a control sample, the detailed methodology protocol for conservation and analysis of the control sample.

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

- At the latest six months after the final visit of the last patient included in the trial, the notifier must send the competent authority (attention to the Biosafety Advisory Council) a report detailing the biosafety aspects of the project. This report minimally includes:
    - The total number of patients included in the trial and the number of these patients that were included in Belgium;
    - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - A report on the accidental releases, if any, of SRP-9003;

Prof. 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/24/BVW4 (ref. SC/1510/BAC/2024_0383 and SC/1510/BAC/2024_0642)*

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/24/BVW4
And comments submitted to the notifier

18 March 2024
Ref. SC/1510/BAC/2024_0383

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 06 February 2024.
Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Willy Zorzi (ULiège)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/24/BVW4** concerns a notification from Sarepta Therapeutics, 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 06 February 2024 and concerns a clinical trial entitled “A phase 3 multinational, open-label, systemic gene delivery study to evaluate the safety and efficacy of SRP-9003 in subjects with limb girdle muscular dystrophy 2E/R4”. The investigational medicinal product is a self-complementary, non-replicating, recombinant AAVrh74 vector containing full-length sarcoglycan-beta (SGCB) cDNA under the control of the MHCK7 promoter.

♦ 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 15-03-2024 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

In the confidential CAF (section 2.1, page 2/28 to 8/28) pAAV.MHCK7.hSGCB.KAN is described (text, figure 1 and table 2). The self-complementary nature of the final clinal AAV-vector would be explained more accurately if the text and table would mention that the 5'ITR has a deletion of the terminal resolution site (TRS). This deletion of the TRS is essential to understand the design of this self-complementary clinical AAV-vector. This would explain at the same time why the 5'ITR is 20 bp smaller than de 3'ITR as stated in the table 2. Also table 6 (section 2.3, page 11/28 and 12/28) should be updated accordingly.

SBB's comment

As stated in tables 2 and 6 of the confidential CAF document, the 5' ITR is 20 bp smaller than the 3' ITR. According to Pozsgai et al (2016), in their construct scAAVrh74.tMCK.hSGCB, the self-complementary AAV vector with the full-length β-sarcoglycan cDNA under control of a muscle-specific promoter (tMCK), the terminal resolution site from one of the the AAV terminal repeat sequences has been deleted. The notifier is requested to explain this difference in size between both ITR.

Comment 3

The production of the rAAV particles is not described. The plasmids were described in detail, and the method to produce the respective plasmids for production. However, no details were included on the type of production (suspension or adherent cells, transfection reagent, …).

SBB's comment

Three bacterial cell banks were used to produce the three plasmids. In section 2.1.2 of the confidential CAF document, the three plasmids and the methodology for producing them were described in detail. However, no details were provided concerning the type of production (suspension or adherent cells, transfection reagent, …), and so the notifier is requested to provide the missing information.

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.

2.3. Diagram (map) of the clinical vector

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

Comment 2
See 2.1

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

2.4. Molecular characterisation of the clinical vector
(e.g. annotated sequence of the genome, genetic stability, ….)

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

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

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

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

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

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

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

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

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

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

Comment 3
- *Biodistribution and toxicity has been assessed in mouse models. While this may be standard practice, this cannot be readily translated to the human clinical settings. In my opinion it is important to keep this in mind.*
- *The applicant also provides safety and efficacy results for preliminary results in different cohorts, but no specific info on shedding. As to biodistribution, the section 6.8 in B_BE_24_BVW4_Investigator's-Brochure _V6.0_06Sep2023.pdf is very incomplete. Even though the applicant indicates 'pregnancy', 'lactation', I would advise to clearly indicate here that the product should not be provided to lactating, or pregnant patients.*
- *There is no shedding info (Point 6.11.2 in B_BE_24_BVW4_Investigator's-Brochure _V6.0_06Sep2023.pdf). It is indicated that there are studies that show shedding for 2-4 weeks. The studies referred to are very old and one of them concerns a intratumoral injection (lower dose and regional administration), and are therefore not relevant for the current study. It is appreciated that the applicant indicates that the shedding is being studied as part of SRP-9003-101 and SRP-9003-102 studies. Patients are prohibited to donate blood, but this should be extended to tissues and blood-derived products. Vector shedding will be assessed by ddPCR, which is currently the most sensitive method: it is however not clear what is detected (what is the specific region or regions targeted in the ddPCR).*

SBB's comment:

- As stated in the title of the section, section 6 of the Investigational brochure should provide both a summary of the data and detailed guidance for the investigators. Therefore, the notifier is requested to clearly indicate in this section recommendations that should be given to pregnant women, to lactating women and to sexually active subjects enrolled in this clinical trial and the length of time these recommendations should be applied.

- Section 4.5.1 of the IB provides data on shedding analysis in urine and feces samples and biodistribution results from male and female mice IV injected with SRP-9003 (study SR-20-055). Section 4.5.3 of the IB provides shedding analysis and biodistribution results obtained from mice or homozygous mutant mice IV injected with SRP-9003 (study SR-21-030). As these studies are somewhat outdated and not directly relevant to the present study. Section 6.11.2 states that vector shedding analysis in humans is currently ongoing in two clinical trials (studies SRP-9003-101 and SRP-9003-102) and will also be analyzed in future studies making these data very important to provide as soon as possible, particularly if preliminary data is currently available.

- According to section 6.11.2 of the IB (page 78/91) and page 21/52 of the Main ICF, subjects are prohibited from donating blood for 2 years following vector injection. However, nothing has been said regarding organs, tissues, and cells for transplantation donation. According to the SNIF page 14/22, patients are prohibited from donating blood, organs, tissues, and cells for 2 years following SRP-9003 administration. The notifier is requested to update both the IB and the Main ICF regarding the donation of organs, tissues, and cells.

- According to the confidential CAF document, section 2.6.4.2, vector shedding analysis in the ongoing clinical study, SRP-9003-101, is performed by droplet digital PCR (ddPCR), which can detect a DNA sequence of SRP-9003. According to the SNIF, page 14/22, the probe will be specific to the MHCK7 promoter but more detailed information on the location and sensitivity should be provided.

3. INFORMATION RELATED TO THE CLINICAL TRIAL

3.3. Storage of the clinical vector at the clinical site

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

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

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

p 9, In the B_BE_24_BVW4_Part1B_GMO_CAF Confidential Annex_BEL_v1.1_Jan2024 document, section 3.6. measures to prevent dissemination into the environment.
Concerning the biohazard waste procedure applied for needles, it is better to use a « needle and sharps biohazard container » as primary container instead of a bag to avoid the needle injuries through the plastic bag.

This modification should be implemented in all documents in the dossier related to this aspect.

Ex : p14 of SRP-9003-301 Pharmacy Manual, Version 1.0 10-AUG-2023 document
The infusion set and dosing syringe used for delivery of SRP- 9003 should be placed in a biohazard bag and destroyed per site pharmacy and institutional policy.

SBB's comment

According to the Dose-Administration-Manual (p9/14), the confidential CAF document (p24/29), the public CAF document (p8/12) and the SNIF (p19/22) : "The infusion set and dosing syringe used for delivery of SRP- 9003 should be placed in a biohazard bag and destroyed in accordance with the site's pharmacy and institutional policy". However, needles and sharps must be placed in a sharp biohazard container as the primary container to avoid needle stick injuries from the plastic bag. To avoid any confusion in this matter, it is critical that the notifier clearly indicate that needles must either be removed from the syringe using a hands free sharp biohazard container designed to safely remove the needle or the entire syringe/needle assembly should be placed together into a rigid, leak-proof biohazard container for sharps.

Comment 2

Several document describe the procedure how to handle in case of a spills of the vector. SRP-9003-301 Dose Administration Manual Version 1.0, dated 11-Aug-2023 (page 7/13) and SRP-9003-301 Pharmacy Manual Version 1.0, dated 10-Aug-2023 (page 14/32) mention to use a bleach solution followed by alcohol wipes. The hypochlorite solution should be neutralized with 3% sodium thiosulfate solution to avoid formation of toxic vapors as chloroform when using alcohol wipes.

SBB's comment:

This point has been included within the SBB's comment for "Comment to expert 3" here below.

The SRP-9003-301_Belgium_Gene Therapy Sheet and Hygiene Guide_ENG 24Jan2024 and the versions in other languages mention to wash clothing, linen, pillows, blankets, and towels with laundry detergent in hot water. Should a minimal water temperature be stated (40 or 60 °C)?

SBB's comment:

The following question could be sent to the notifier, by combining this comment together with the comment from expert 3 in section 3.6 here below :
The Belgium_Gene Therapy Sheet and Hygiene Guide document needs additional information:

- State the minimum water temperature (40° or 60 °C) to be used for cleaning laundry

- Identify the disinfectant to be used for cleaning hard surfaces such as tables, counters and door handles and contact times.

Coordinator's comment:

Ok

Comment 3

- On p3/4 (at the bottom) in B_BE_24_BVW4_Biohazard-Safety-Data-Sheet_V4.0_26Jul2023.pdf "Decontaminate the area twice with an appropriate solvent". Please provide more details on which solvent to be used. Also for disposal (next paragraph, it would be best to indicate more detailed the solutions and protocol advised). In other documents, " 1:10 dilution of 5.25% sodium hypochlorite (bleach) solution" is indicated.

SBB's comment:

The document Biohazard Safety Data Sheet summarizes the instructions to help health care personnel when handling the vaccine. In order to bring together all information in one document, the following sections of the Biohazard Safety Data Sheet need to be improved:

1- In section 8, p3/4, the appropriate solvent and concentration to use in case of an accidental spill and how the contaminated material should be disposed must be stated.

2- In section 8, based on the information provided in the SNIF and the CAF documents, the waste management needs to be detailed in this document.

3- In section 8, based on the information provided in the SNIF and the CAF documents, and taking into account the remarks provided in the comment below, spill management also need to be detailed in this document.

4- In section 7, details of how to manage inadvertent exposure by health care workers to patient blood, urine, vomit or other bodily fluids during the hospital stay needs to be described in detail.

In addition, this data sheet should be plasticized (2 sheets back and front) and described to the investigators as something that personnel should have readily available with them when handling or administering the vaccine or working with patients in the period immediately following administration.

Furthermore, based on the comment from the experts about the disinfectant and based on questions that have already been raised in the past in previous applications submitted by the same notifier, the following questions could be sent to the applicant for this trial:

In addition, some clarification and missing details are necessary concerning the clean-up disinfectant to be used in SNIF p20/22, in CAF_Public p9/12, the CAF confidential p26/29 and in the Pharmacy Manual p14/33, in the Dose Administration Manual 7/14 and in the Biohazard safety data sheet p2/4. The notifier should improve these documents as follows:

1- The concentration of sodium hypochlorite in standard bleach solutions varies between manufacturers, making it necessary that for all decontamination procedures involving this solution, the precise mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution is identified.

2- Whenever solution is used (e.g. for the decontamination of work areas), it must be stated that a freshly prepared solution should be used.

3- Sodium hypochlorite used with alcohol can cause a reaction that produces toxic vapors, such as chloroform. When using alcohol wipes, the sodium hypochlorite solution should first be neutralized with a 3% sodium thiosulfate solution to avoid this effect. The notifier should either include a notice to this effect in the documents cited above or should avoid the suggestion of using alcohol wipes following sodium hypochlorite decontamination.

4- Sodium hypochlorite solutions cannot be proposed as a universal decontaminant or disinfectant because contaminated work surfaces may have different properties: porous and nonporous materials, stainless steel, solid surface, floor or table, etc. A list of appropriate and effective decontamination/disinfection solutions specific for the vector is required.

Coordinator's comment:
Ok

In p8/13 in point 4.2 of B_BE_24_BVW4_Dose-Administration-Manual_V1.0_11Aug2023.pdf they refer to papers soaked in disinfectant, this is not clear (here bleach solution is meant, since EtOH does not inactivate AAV sufficiently). Higher up in the paragraph, bleach solution followed by alcoholic wipes is indicated.

SBB's comment:
Based on questions that have already been raised in the past in previous applications submitted by the same notifier, the following questions, including the expert's question, could be sent to the applicant for this trial:
It is important to provide clear and concise instructions to the health care personnel. The notifier is therefore requested to adapt the procedure to be followed in case of accidental spill or breakage in the SNIF p20/22, in the CAF confidential p26/29, in the CAF Public p9/12, in the Dose Administration Manual 7/14 and in the Pharmacy Manual p14/33 by adding the following points:
1- When a spill occurs, before evacuating the area, contaminated PPE such as the lab coat, shoes and other clothing must be removed so that they do not leave the area.
2- A "DO NOT ENTER" message must be posted on the door.
3- After sufficient time for decontamination, a clean lab coat, disposable gloves, glasses, disposable shoe covers and a mask should be worn when entering the area.
4- Because sodium hypochlorite and alcohol react and produce toxic vapors, such as chloroform, the notifier must state this in the procedure as a warning.
5- The spill area must be cleaned with fresh paper towels soaked in disinfectant. In order to avoid any confusion, the type and concentration of disinfectant that effectively destroys the vector and the length of exposure time must be detailed here.
6- The medical staff must report any incidents to the person responsible at the site
7- A spill kit must be made available in the facility/room where the vector is handled and/or the patient is accommodated and this spill kit must contain the appropriate disinfectant, personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, shoe covers, mask), tongs or forceps for picking up broken vials, absorbent paper towels, and biohazard waste bags.

Coordinator's comment:
Ok

- On p7/13 in B_BE_24_BVW4_Dose-Administration-Manual_V1.0_11Aug2023.pdf it reads "Handling of SRP- 9003 will follow compliance standards for Biosafety Level 1 (BSL-1) vectors following the NIH Guidelines, Centers for Disease Control and Prevention (CDC) Biosafety in Microbiology and Biomedical Laboratories (BMBL) for Risk Group 1 agents in the United States, and the World Health Organization (WHO) Laboratory Safety Manual outside the United States." This is not relevant and should be adapted to the European/Belgian setting.
Further on the same page (in 4.2) the bleach solution is not specified (conc?).

SBB's comment:
Remarks about the bleach solution have been combined into one SBB comment here above in the same section for the same expert.

Coordinator's comment:
Ok

- On p7/13 in point 4.1 of B_BE_24_BVW4_Dose-Administration-Manual_V1.0_11Aug2023.pdf: instead of human, maybe this should be "if an employee or caretaker/parent/sibling comes in bodily contact". Alternatively, maybe indicate "if anybody different than the intended person, the patient, comes in bodily contact…"

SBB's comment:
This point could be reported as a "Typos and other errors/omissions"

Coordinator's comment:
Ok

- P9/13 in B_BE_24_BVW4_Dose-Administration-Manual_V1.0_11Aug2023.pdf: upon exposure washing with soap and water is advised. What kind of soap? Conc? AAV is not inactivated by soap, the viral vector will be washed away, but upon needle stick this is not sufficient.

SBB's comment:
According to the National Institute for Occupational Safety and Health (NIOSH), as part of the Centers for Disease Control and Prevention in the United States, healthcare personnel should wash needlesticks and cuts with soap and water (https://www.cdc.gov/niosh/newsroom/feature/needlestick_disposal.html).

Coordinator's comment:
OK, but if I were doing it, I would decontaminate the area including the wound first with an appropriate disinfectant that inactivates the vector and not cause tissue damage, such as 70% alcohol. This is why it is important that they provide a list of the appropriate disinfectants for their vector so that in the case of an injury to personnel there are options.

SBB's comment:
AAV is quite resistant to alcohol disinfectants (J. Korte *et al.* 2021). The following question could be provided to the applicant:
The document Dose-Administration-Manual_V1.0_11Aug2023 indicates that following exposure to the AAV viral vector, the exposed area will be washed with soap and water. However, AAV is not inactivated by soap. The applicant is requested to clearly indicate the appropriate disinfectant to be used in the case of an injury to personnel that inactivates the vector without causing tissue damage.

Coordinator's comment:
It is fine, including the sentence you suggested for human tissue disinfection

- The first aid measures are not sufficiently detailed in B_BE_24_BVW4_Drug-Product-Safety-Data-Sheet_V3.0_18Oct2020.pdf. Additionally, in section12, ecotoxicity should also discuss potential toxicity of the AAV particles in the DP, not only the chemical components. Also here, the composition is

different than the one indicated in B_BE_24_BVW4_Investigator's-Brochure _V6.0_06Sep2023.pdf, Table2. For example poloxamer188 is not indicated and the rAAV vector.

SBB's comment:
In addition to the chemical identification of the components in the drug product, the Safety Data Sheet should also include information about the potential hazards associated with the presence of recombinant AAV. Therefore, the notifier is requested to expand section 12 (ecotoxicity) of the Drug Product Safety Data Sheet by discussing the potential toxicity of the AAV particles in the drug product. Furthermore, the composition reported in the Safety Data Sheet is not the same as the composition reported in the Investigator Brochure (Table 2, section 3.4, page 20/91). Therefore, the notifier is requested to provide accurate and consistent information and data across all documents.

- In B_BE_24_BVW4_Gene Therapy Sheet_Hygiene Guide_BEL_ENG_24Jan2024.pdf it would be good to indicate for the caretakers and parents how the material should be disposed and inactivated. It now reads "Put potentially contaminated materials in a sealable bag; double bag them before throwing them away." => should only be thrown in the waste that will be incinerated. "Use a disinfectant to clean hard surfaces" => indicate what kind of disinfectant.

SBB's comment:
The "Gene Therapy Sheet_Hygiene Guide" will be provided to patients and patient's family to adhere to and practice good hygiene. The recommendation, involving placing any potentially contaminated materials within a sealed bag before being placed in the household trash is consistent with recommendations provided for previous clinical studies involving the use of a similar recombinant adeno-associated viral vector, SRP-9001.
A question asking to specify the disinfectant to use to clean hard surfaces has been included in the SBB's comment for expert 2 in section 3.6 here above.

Coordinator's comment:
Ok

- Based on the provided ages in Table10 patients for now are <18y (B_BE_24_BVW4_Investigator's-Brochure _V6.0_06Sep2023.pdf): it is known from other studies that the seminal fluid also turns up positive in PCR testing for AAV vector DNA. Should this be indicated as well in the leaflets for candidate patients and their family?

SBB's comment:
Table 10 in the IB refers to the ongoing studies 9003-101 and 9003-102 with SRP-9003, but not to the currently study. According to the protocol, subjects must be ≥ 4 years of age, with no maximum limit of age reported. As per inclusion criteria 8, male or female who are of childbearing potential must agree to use, through Month 24, a highly-effective method of contraception.
In the study SR-20-055 (IB p29/91), SRP-9003 was detected in all samples of tested animals following administration of SRP-9003. In the study SR-21-030 (IB p35/91), animals administered with SRP-9003 demonstrated a dose-dependent response in quantities of SRP-9003 vector DNA across all tissues following administration. Although no shedding analysis in sperm has been reported in the IB, the notifier claimed in the IB p13/91 that biodistribution studies with SRP-9003 in GLP-compliant pivotal studies and a non-GLP investigative study didn't indicate germline transmission in the testes or ovaries. The notifier could be requested to clarify which analysis have been done to conclude that no germline transmission in the testes or ovaries occurred.

Coordinator's comment:
I think that this is an important clarification as it was detected in multiple tissues in previous studies – they must provide the supporting data.

- In 3.6 of B_BE_24_BVW4_Part1B_GMO_CAF Confidential Annex_BEL_v1.1_Jan2024.pdf it is indicated "All surfaces will be decontaminated with appropriate agents, such as a 1:10 dilution of 5.25% sodium hypochlorite (bleach) solution". This is not possible, since bleach will be corroding stainless steel surfaces => alternative solutions should be provided.

SBB's comment :
This point has been combined together with the first SBB comment for this section (see point 5)

Coordinator's comment:
Ok

- P26 point G in B_BE_24_BVW4_Part1B_GMO_CAF Confidential Annex_BEL_v1.1_Jan2024.pdf: besides the donating of blood (2 years), also tissue donation should be disadvised. It should be checked whether in other AAV therapies, the donation of blood or derived products was disadvised. Maybe not relevant for the current patient population, but should the donation of sperm also be considered?

SBB's comment :
See SBB's comment to expert 3 in section 2.6 here above.

Coordinator's comment:
Ok

Additional SBB's comment:
Based on questions that were submitted to the same notifier for previous clinical trials involving a similar vector, the following questions could also be sent to the notifier for this dossier:

1- According to page 15/22 of the SNIF and page 13/33 of the Pharmacy Manual, the personal protective equipment (PPE) should include "gloves (consider double gloving)". This should be changed to "use of double gloves is a standard working procedure", and not only considered as currently stated in both documents.
2- Since a waiting period is required before decontamination, in order to allow aerosols to be carried away and heavier particles to settle, the notifier could be requested to adapt on page 20/22 of the SNIF, the following sentence by omitting the word "immediately" as decontamination should not proceed immediately after the accidental spill: "In case of accidental spillage of SRP-9003 during vaccine preparation and/or administration the area must be closed off with appropriate signage and only after the indicated waiting period, which is necessary to remove aerosols and allow particles to settle, can the spill be disinfected".

Coordinator's comment:
Ok

5. ENVIRONMENTAL RISK ASSESSMENT

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

- applicant provides safety and efficacy results for preliminary results in different cohorts, but no specific info on shedding. As to biodistribution, the section 6.8 in B_BE_24_BVW4_Investigator's-Brochure _V6.0_06Sep2023.pdf is very incomplete. Even though the applicant indicates 'pregnancy', 'lactation', I would propose to clearly stipulate advise for the patient.
- Also the refraining of organ donation should be indicated.

SBB's comment :

See SBB's comment to expert 3 in section 2.6 here above.

Coordinator's comment:

Ok

6. OTHER INFORMATION

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

Comment 1

None

Comment 2

In the SNIF (page 8/22, 10/22 and 13/22), the human dystrophin gene or the human dystrophin protein is mentioned. This should be corrected because the transgene in this clinal vector encodes the SGCB gene and not the dystrophin gene (DMD gene)

SBB's comment:

This point could be reported as a "Typos and other errors/omissions"

Coordinator's comment:

Ok

Comment 3

- Composition of the DP is indicated in Point3 p1/7 of the B_BE_24_BVW4_Drug-Product-Safety-Data-Sheet_V3.0_18Oct2020.pdf. For me this is not correct, next to 'chemicals', synthetic polyadenylation is indicated and ITR (among other genetic elements), this is not correct and should be corrected. Maybe better to indicate that the DP contains viral vector?

Additional SBB's comment:

The following points could also be reported as "Typos and other errors/omissions":

- In section 2.6.2.1 of the confidential CAF document, p17/29, the following sentence seems to be incomplete and should be updated: "In the clinical experience gained to date, it was observed that SRP-9003 did not elicit any concerning immune responses."

  Coordinator's comment:

  Ok. "Based on the clinical experience to date, no troubling immune responses elicited by SRP-9003 were observed."

- On page 7/22 of the SNIF, the following sentence has been reported : "Wild type AAV vectors are possibly transmitted by the ingestion, inhalation of aerosols or droplets, contact with mucous membranes, bodily fluids and faecal matter". However, "wild type AAV vectors" is not correct and should be corrected to "wild type virus" or "recombinant AAV vectors"

  Coordinator's comment:

  Ok.

References

ER. Pozsgai *et al*. Gene Therapy (2016) 23, 57–66. β-Sarcoglycan gene transfer decreases fibrosis and restores force in LGMD2E mice

J. Korte *et al*. Hum Gene Ther. 2021 Jul;32(13-14):771-78. Inactivation of Adeno-Associated Viral Vectors by Oxidant-Based Disinfectants.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Sarepta Therapeutics on the list of questions for dossier B/BE/24/BVW4

07 May 2024
Ref. SC/1510/BAC/2024_0642

Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB))
Experts: Anton Roebroek (KULeuven), Willy Zorzi (ULiège), Rik Gijsbers (KULeuven)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/24/BVW4** concerns a notification from Sarepta Therapeutics for a clinical trial entitled "A phase 3 multinational, open-label, systemic gene delivery study to evaluate the safety and efficacy of SRP-9003 in subjects with limb girdle muscular dystrophy 2E/R4".

On 15 March 2024, based on a list of questions prepared by the BAC (SC/1510/BAC/2024_0379), 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 23 April 2024. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

The applicant addressed the comments/questions correctly and satisfactorily.

Evaluation Expert 2

The notifier addressed correctly and satisfactorily the comments/questions of the Biosafety Council that have been raised in March 2024, for the dossier B/BE/24/BVW4 (clinical trial submitted by Sarepta Therapeutics) related to the use of recombinant AAV for subjects with Limb Girdle Muscular Dystrophy.

Evaluation Expert 3

Q2:
The response is in my opinion poor and not informative (company details should not be included, but somewhat more detail is essential). The manufacturing is described only at high level. Type of bioreactor, transfection reagent is not provided. The notifier indicates that 'at the end of virus production, cells were lysed'. Virus should be replaced with 'viral vector', and "lysis buffer" could be provided (chemicals may be part of the final DP, was plasmid DNA and cellular DNA removed by DNAse treatment?). The two "column operations" could be briefly explained, and it is not clear which impurities are removed and how this is assessed.

SBB's comment:

The level of detail in the description of the manufacturing process varies from one dossier to another. Generally, not much detail of the manufacturing process is provided in the CAF document. The Investigational Medicinal Product Dossier (IMPD) contains data on the quality, production and control of the medicinal product being researched and is evaluated by the FAMHP. Furthermore, following the guidance described in the CAF templates, description of manufacturing related steps are focusing on characterisation of vectors used for recAAV production and demonstration of absence of formation of replication-competent virus. Aspects pertaining to presence of impurities, type of bioreactor are out of the scope of the evaluation by the BAC (as these pertain merely to the quality evaluation of GMP aspects).

Q4:

I agree with the reply of the notifier that the studies in animal models (non-clinical) are interesting and relevant in as far that they help in designing and informing on how sample collection and dose could be tuned for an effective clinical trial.

However, it should be clear that shedding info in animal models cannot be translated to human conditions. This is also indicated by the FDA in https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Design-and-Analysis-of-Shedding-Studies-for-Virus-or-Bacteria-Based-Gene-Therapy-and-Oncolytic-Products--Guidance-for-Industry.pdf :

"To inform the design of human shedding studies, shedding data may be collected in animals following administration of the VBGT or oncolytic product. These data can help estimate the likelihood and potential shedding profile in humans, particularly when there is concern about transmission to untreated individuals. However, such data cannot substitute for human shedding studies for several reasons. For example, a VBGT or oncolytic product may be derived from a human-specific strain; therefore, animals may not adequately predict the shedding profile in humans. Similarly, various animal species/models may not adequately address patient-specific factors, such as differences in the immune status at the time of product administration, which may contribute to the potential for shedding in humans (for more details refer to section VII.B. of this guidance)."

Yet, I do not agree with the conclusion and the statements of the notifier, indicating that the animal study (SRP-9003) allows to identify the shedding profile in human. The conclusion that the risk of transmission is minimal will depend on the time after application of the therapy is not correct. I agree that the PCR test does not allow us to conclude that the detected material is infectious, but we should be careful and caretakers, parents and health care personnel should be informed to be cautious. Additionally, if the particles are shed in seminal fluid, for example, this could result in 'shedding' during intercourse.

SBB's comment:

Shedding information in animal models cannot be translated to human conditions. According to the notifier, shedding analysis and biodistribution results from nonclinical studies are considered relevant to the present clinical study, in informing clinical sample collection, relevance of PCR methodology, and similarity of results between nonclinical and clinical data.

In this clinical trial, patients will be provided with an information sheet that will contain all information and instructions for patients and patient's family to avoid potential transmission of the viral vector to other people or to the environment, if any, when patients are leaving the hospital setting. This document specifies, among other things, which bodily fluids could potentially contain viral vector genome and what precautionary measures the patient should take for a period of 4 weeks to avoid potential transmission of the viral vector. According to the Inclusion criteria reported in the protocol section 8.1, male or female

who are of childbearing potential must agree to use, through Month 24, a highly-effective method of contraception. A technical sheet that will include all relevant handling instructions will be provided to the study staff.

Q6:
The notifier provided data collected in mouse experiments on the possibility of germ line transmission. In my opinion it is key to communicate clearly when discussing animal experiments or experiments in human. Referring to study 2023-024 as an ongoing “maternal fetal reproductive transmission study”, would be better “maternal fetal reproductive transmission study in mice” to exclude possible confusion.
I agree that currently the field employs assays (current shedding assays measure vector DNA), that are unable to distinguish between vector particles versus different forms of DNA (free, episomal, or integrated). Therefore, the detection of vector DNA in body fluids does not necessarily imply an infectious risk.
Also, as indicated higher, even though the experiments are interesting, the fact that there is no transmission in a mouse model does not allow to translate these findings to human settings (as discussed in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5758940/). Animal models are key in tackling several hurdles in AAV gene therapy, but shedding and transmission should be addressed with caution. This is corroborated in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6807344/. For example, they report that shedding (PCR positive signal) in semen is transient but can be detected for more than a year in human (Table2). Even though germ line transmission is not observed in animal experiments, this should be treated with caution in clinical trials and patients should be informed.

SBB’s comment:
As mentioned in the previous comment, according to the Inclusion criteria reported in the protocol section 8.1, male or female who are of childbearing potential must agree to use, through Month 24, a highly-effective method of contraception. This restriction together with examples of highly effective methods of birth control can be found in the ICF that will be provided to the patient.

Q7:
Considering the reply of the notifier, it should be clearly indicated that pregnant and lactating women are not eligible. This could/should be indicated in the IB (sections 6.8.1, 6.8.2 and 6.8.3). The current message one gets when reading through is confusing.

SBB’s comment:
According to the ICF (page 27/52) for the patients, female participant will not be allowed to take part in this trial if they are pregnant, or wish to become pregnant in the near future or are breastfeeding. The notifier commits to update next IB by adding this additional guidance.

Q10:
Here it may be interesting to indicate the concentration of bleach solution. Most household bleach contains 5%–9% sodium hypochlorite.
As advice by the CDC, it would be good to indicate “do not use a bleach product if the percentage does not contain 5%–9% sodium hypochlorite or is not specified. This includes some types of laundry bleach or splashless bleach, which are not appropriate for disinfection.” – see also https://www.cdc.gov/hygiene/cleaning/disinfecting-bleach.html#:~:text=Most%20household%20bleach%20contains%205,range%20or%20is%20not%20specified.

I would also advice that the use of EtOH should be clearly disadvised since this is not a proper decontaminant for AAV viral vectors.

SBB's comment:

The expert's comment is supported and could be forwarded to the notifier as follows:
According to the Hygiene_Guide_BE document, 1:10 dilution of bleach solution should be used as disinfectant. However, concentration of sodium hypochlorite in standard bleach solutions varies between manufacturer. Most household bleach contains 5%–9% sodium hypochlorite. According to the Centers for Disease Control and Prevention (CDC; https://www.cdc.gov/hygiene/cleaning/disinfecting-bleach.html#:~:text=Most%20household%20bleach%20contains%205,range%20or%20is%20not%20specified.), one should not use a bleach product if the percentage is not in this range or is not specified. As some types of laundry bleach or splashless bleach are not appropriate for disinfection, the notifier is requested to clearly indicate that bleach used as disinfectant should contains 5%–9% sodium hypochlorite. Furthermore, as alcohol is not an appropriate decontamination solution for the AAV gene therapy product, the use of ethanol should be clearly disadvised.

SBB's additional question

The document 09_SRP-9003-301_Safety-Instructions-for-INV-and-Staff_BE_ENG_Apr2024 should also contain the 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 as well as 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.

SBB's additional question

According to Main ICF_BE, page10/52, "in addition to the trial site where your trial doctor is located, trial procedures may also be performed at an alternative location, such as your home".
Will these visits at home also be planned in Belgium? If so, to give study nurses, who will visit the patients at home, adequate instructions to avoid any potential dissemination of the recombinant virus in the environment during the remote visits, the notifier is requested to provide an instruction sheet for caregivers. Among others, the following instructions will be mentioned:

- The personnel protective equipment
- The disinfectant to be used
- The procedure to be followed in case of accidental spillage
- Instructions for collecting and disposing of waste generated during the visit
- The transport of collected samples back to the hospital

Evaluation Coordinator

The guidelines for both investigators/nurses and patients/caregivers were really lacking.
Also we must explicitly prohibit them for storing and returning the used vials - they always want to do this as some sort of control but it creates additional biohazard risks for absolutely no reason other than their need to make sure no one else gets the product. It should be specified that it is destroyed immediately after use on site.

SBB's comment:

The comments reported by the coordinator on the technical sheet for site staff and the instruction sheet for patients were transcribed in the form of questions for the notifier.