Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/22/BVW6 of the company Sarepta Therapeutics, for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

25/08/2023
Ref. SC/1510/BAC/2023_0823

Context

The notification B/BE/22/BVW6 has been submitted by Sarepta Therapeutics to the Belgian Competent Authority in October 2022 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, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 in Non-Ambulatory and Ambulatory Subjects With Duchenne Muscular Dystrophy (ENVISION)".***

The purpose of this study is to assess the safety and the efficacy of the study treatment SRP-9001 in in male subjects with no age limit (Cohort 1) and aged from ≥8 to <18 years (Cohort 2), with a genetic diagnosis of Duchenne Muscular Dystrophy (DMD).

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.

As a gene therapy product, SRP-9001 has the potential to deliver functional truncated dystrophin, called micro-dystrophin, in cardiac and skeletal muscle, thereby addressing the root cause of the disease. The non-replicating, recombinant adeno-associated virus (rAAV) serotype rh74 contains an abbreviated version of the human dystrophin gene referred to as "micro-dystrophin" 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 one hundred sixteen patients will be included in this Phase III study and ten 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 one clinical site located in Flanders.

The use of the same GMO in a clinical trial, SRP-9001, also referred to as delandistrogene moxeparvovec, has already been assessed by the BAC in the framework of notification B/BE/21/BVW5[1] and B/BE/22/BVW5[2], submitted by Sarepta Therapeutics and F. Hoffmann – La Roche Ltd.

The dossier has been officially acknowledged by the Competent Authority on 24 March 2023 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. Two 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 04 May 2023, 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 18 July 2023 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 26 July 2023. The answers of the notifier were received on 17 August 2023 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 did receive one reaction from the public with two questions related to biosafety issues.

[1] Advice of the Belgian Biosafety Advisory Council on the notification B/BE/21/BVW5 - *Ref. SC/1510/BAC/2022_0677*
[2] Advice of the Belgian Advisory Council on the notification B/BE/22/BVW5 – Ref. SC/1510/BAC/2023_0693_

Summary of the scientific evaluation

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

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-9001 is accomplished via the cellular transfection using three DNA-containing plasmids: the “transfer vector” which contains the therapeutic gene of interest (GOI) - pAAV.MHCK7.Micro-Dystrophin, the “Rep/Cap” plasmid, and a “helper plasmid” which contains some adenovirus genes. These three plasmids are well described in the confidential documents.

3. The conditions of the release

The study consists of two parts. In Part 1, approximately 58 subjects will receive intravenous (IV) one-single dose of SRP-9001 and approximately 58 subjects will receive matching infusion volumes of placebo. In Part 2, subjects who received placebo in Part 1 will receive IV SRP-9001, and subjects who received SRP-9001 in Part 1 will receive placebo. All patients will stay approximatively 4-6h at the hospital to allow the trial nurses and trial staff to collect vital signs. Thereafter, patients can leave the hospital.

No shedding analysis will be planned during this clinical trial because biological samples for saliva, urine and stool for the monitoring of the GMO is currently being collected in Sarepta study SRP-9001-103 which is using the same IMP at the same dose. Preliminary results from shedding analysis obtained so far during the clinical trial SRP-9001-103 on children treated with the same single dose of microdystrophin vector SRP-9001 as for the current study have been described in the confidential CAF document.

4. The risks for the environment or human health

SRP-9001 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 only a remote possibility of homologous recombination between the ITR-sequences of AAVrh74 in the IMP and wild-type AAV, in case a triple infection by SRP-9001, wild type AAV (providing the rep and cap functions) and a helper virus occurs in exposed persons. Such recombination event would result in gain of functional genes of AAVrh74 required for replication and encapsidation but would in turn lead to the loss of the current abbreviated version of the human dystrophin transgene. Moreover, the genetic material from rep and cap genes together with the micro-dystrophin transgene would be too large in size to be packed in AAV capsid, making it impossible to package this information, and thus to form a replication competent viral particles that would contain the transgene and the rep and cap genes necessary for multiplication.

In the case of transfer of vector to an unintended immune-competent human recipient, the risks are expected to be considerably reduced as compared to any potential risk for the participant, since the vector cannot replicate and the 'dose' that may conceivably be transferred (from e.g. aerosol, splashing or fomites) will be orders of magnitude lower than that received by patients. Worst case, the receiver will develop an immune response to the AAVrh74 capsid.

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

After injection, patients and patient's family will be provided with detailed instructions in order to avoid potential transmission of the virus to other people or to the environment when patients are leaving the hospital setting. Following BAC's request, the notifier clarified that diapers will be sealed in plastic bags and then double-bagged before being disposed of in household waste. In addition to having to wear protective gloves when handling bodily fluids/waste and when disposing of potentially contaminated materials, gloves will also have to be worn when handling potential contaminated cloth and launderable materials, such as clothing, linens, pillow, and blankets. These gloves together with other potentially contaminated materials will be placed in a sealable bag before being placed in the household trash.

All these instructions for the patients and patient's family with respect to good hygiene practices have been detailed in a short, readable format document that will be provided to each patient.

With respect to the instructions regarding blood, organs, tissues and cells donation, the BAC remarks that proposed instructions were either missing or differ from instructions given in the product information document (EPAR) of EU registered medicinal products containing AAV. In its response, the notifier took due account of the remark and updated relevant text in the ICF, the SNIF and the public CAF by stipulating that 'Patients treated must not donate blood, organs, tissues, and cells for transplantation'. The notifier further commits to implement the text in the same way in a protocol version for Belgium and to distribute a protocol clarification letter to all sites immediately following the approval of the clinical trial.

In addition to the Pharmacy manual, the medical personnel will be received an Addendum to Pharmacy Manual giving an overview of all relevant handling instructions, detailed instructions in case of spill, waste management and other risk management measures.
Upon BAC's request, the notifier adequately improved this instruction sheet for the site personnel by detailing the procedure to prevent and deal with exposure to blood, urine, vomit or other bodily fluids from subjects for a period of 4 weeks post infusion.

The notifier also appropriately implemented the remarks addressed by the BAC regarding the procedure to be followed in case of accidental spills or breakage of a GMO containing vial in the Pharmacy Manual and other relevant documents.

The notifier clearly indicates throughout the different documents that the personal protective equipment consists of lab coats, safety goggles, gloves, hair covers and overshoes, and that the use of double gloves will be considered as a standard.

Regarding the clean-up disinfectant to be used, the notifier clarified that freshly prepared hypochlorite solution will be used. Alcohol wipes in combination with bleach will be avoid since bleach solution and alcohol can react and can produce toxic vapors as chloroform. The notifier also provided a list of adequate decontamination/disinfection solutions.

Beside the Addendum to the Pharmacy Manual, these instructions to site personnel have also be appropriately implemented in a revised version of the SNIF, the Public CAF, the CAF confidential, the Dose Administration Manual and the Pharmacy Manual when applicable.

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

Given the assessment of the likelihood of further propagation of SRP-9001, 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.

Conclusion

Based on the scientific assessment of the notification made by the Belgian expert, the Biosafety Advisory Council concludes that it is unlikely that SRP-9001 developed as a gene therapy approach for the treatment of Duchenne Muscular Dystrophy disease will have 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 as described in the following updated documents:

- Addendum to Pharmacy Manual_Belgium_15June2023 to be updated
- BE Hygiene Guidance 3.1 20230801
- BEL Main ICF update 21June 2023
- Dose Administration Manual v5.0 update 02August2023
- BEL_Public CAF-update Aug 2023
- BEL_Confidential Annex_CAF June 2023
- BEL_SNIF_August 2023
- Participant Study Guide 20230801 3.1

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 2, and all the safety instructions as described in the dossier and the updated and new documents listed here above. Regarding the instruction for patients with respect to donation of blood, organs, tissues, and cells for transplantation, and referring to the notifier's commitment, relevant text in the protocol needs to be adapted, an upcoming Belgium-specific protocol addendum will be written and protocol clarification letter shall be distributed to all sites immediately following the approval clinical trial.

- Regarding the study specific instructions for caregivers that will visit patients at home, and referring to the notifier's commitment to incorporate BAC's comments in an updated document, the notifier shall distribute an instruction sheet for caregivers at patients' home to in the Belgium site

immediately following the approval of the clinical trial. Furthermore, if possible, samples should be taken in an area that is readily cleanable (hard floor for example) instead of a bedroom.

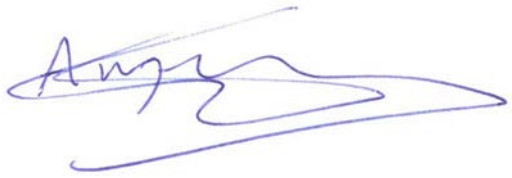
- Any protocol amendment has to be previously approved by the Competent Authority.

- The notifier is responsible to verify that the 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.

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

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

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report shall at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;
    - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - A report on the accidental releases, if any, of SRP-9001;
    - The BAC would genuinely appreciate to receive an update of the shedding results upon completion of the SRP-9001-103 study.



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/22/BVW6 (ref. SC/1510/BAC/2023_0396 and SC/1510/BAC/2023_0736)*

Annex II: *Answers to the public reaction to dossier B/BE/22/BVW6 in NL (ref. SC/1510/BAC/2023_0825) and FR (ref. SC/1510/BAC/2023_0824)*

Compilation of comments of experts in charge of evaluating the dossier B/BE/22/BVW6
And comments submitted to the notifier

05 May 2023
Ref. SC/1510/BAC/2023_0396

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 20 October 2022.
Coordinator: Anton Roebroek (KULeuven)
Experts: Rik Gijsbers (KULeuven), Willy Zorzi (ULiège)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/22/BVW6** 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 21 October 2022 and concerns a clinical trial entitled "A Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 in Non-Ambulatory and Ambulatory Subjects With Duchenne Muscular Dystrophy (ENVISION)". The investigational medicinal product, also known as SRP-9001, is a AAV rh74-derived recombinant replication deficient vector carrying a truncated dystrophin encoding gene.

♦ 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 04-05-2023 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

Additional coordinator's comment:

The first sentence in the document B_BE_22_BVW6_Part 1A_BEL_Public CAF (v4.1) is in fact not correct. Dysfunctional dystrophin protein will not be replaced. Expression of dysfunctional dystrophin will still be possible. Furthermore, strictly spoken something that is missing (and was never present) cannot be replaced. Consider rephrasing using '….. by adding (or by expression of) a functional shortened dystrophin, ……, in order to compensate for dysfunctional or missing dystrophin.' or similar.

SBB's Comment:

This request has been added in the list of questions to the notifier.

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.

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

On p7/17 of B_BE_22_BVW6_Dose Administration Manual_V3.0_20220527.pdf: NIH classification is indicated, does this apply for Belgium? Also, it is indicated that serotypes 1-4 are BSL1, this is not relevant for the rh74 serotype since this is rhesus derived. I'm convinced the rh74 will be fine to use, but the current info is not correct.

SBB's comment:

The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) identify AAV types 1-4, and rAAV constructs, in which the transgene does not encode either a potentially tumorigenic gene product (for example, an oncogene) or a toxin molecule, and are produced in the absence of a helper virus as risk group 1 (RG1) agents, which are not associated with disease in healthy adult humans.

According to the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors, that has been endorsed by Belgium, clinical trials with AAV clinical vectors, in accordance with the requirements in the ERA (the applicant demonstrates absence of formation of replication competent virus and the transgene is not harmful) can be conducted under BSL-1.

AAV is non-pathogenic and has not been classified under Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work. AAV has no known pathogenic effects, even though the estimated seroprevalence of some common human serotypes is ~80% (European Parliament and of the Council 2000). Consequently, AAV fulfils the definition of a risk group 1 biological agent according to the Directive 2000/54/EC “a biological agent that is unlikely to cause human disease”.

Coordinator’s comment:
The comment by the expert is strictly spoken correct. A rhesus derived AAV cannot simply be classified in a classification system used for human AAVs. Like the expert, the coordinator is convinced that rh74 will be fine to use. The risk for using rh74 will be similar or likely less as for using human AAV types 1-4 because of the NHP origin. No need to ask the notifier to address this further.

Comment 2
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
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.

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.

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

In p2/4 in B_BE_22_BVW6_Addendum to Pharmacy Manual_BE_20230217.PDF, the applicant indicates 'results from several previous clinical trials indicate that inadvertent exposure to recombinant replication-defective AAV vectors does not result in significant disease. Also, the vector DMD transgene is not expected to change the overall biosafety profile for this vector.' The text is misleading in my opinion. Are there a lot of inadvertent exposures reported? What is significant disease? Does the applicant mean 'exposure to rAAV does not result in disease'? Further, the rAAV vector does not contain a DMD transgene (this is not scientifically correct), but a microdystrophin cDNA.
Also, this info is not in line with the info in the CAF (p3/13 B_BE_22_BVW6_Part 1A_BEL_Public CAF (v4.1).pdf). I would suggest to adapt the txt to the one indicated in the CAF.

SBB's comment:

This point could be reported as a "Typos and other errors/omissions".
Proposed wording for question :
In the section "Management and procedure due to inadvertent exposure of human to SRP-9001 as a result of formation of aerosols in case of bag rupture" on page 2/4 of the Addendum to Pharmacy Manual, the following has been reported: *'results from several previous clinical trials indicate that inadvertent exposure to recombinant replication-defective AAV vectors does not result in significant disease. Also, the vector DMD transgene is not expected to change the overall biosafety profile for this vector.*' However, this text is misleading and requires some clarification. Are there a lot of inadvertent exposures reported? What is meant with "significant disease"? Does the applicant mean 'exposure to rAAV does not result in disease'? Further, the rAAV vector does not contain a DMD transgene (this is not scientifically correct), but it contains a microdystrophin cDNA. The notifier is requested to revised this section in accordance with the information included in the CAF_Public document page 3/13.

Coordinator's comment:

Agreed with the SBB comment.

On p2/4 in B_BE_22_BVW6_Addendum to Pharmacy Manual_BE_20230217.PDF (bottom), the "Procedure to prevent and deal with exposure to blood, urine, vomit or other bodily fluids from subjects in the initial period where there are high numbers of transduced cells after infusion" is mentioned. What is meant by initial period? This is subjective wording. It would be better to provide a specific time-frame. Also, there will be high number of transduced cells indeed, but these do not readily 'spread'. I would reckon that here the high number of rAAV particles that can potentially shed via bodily fluids are meant. Please adapt to the period indicated in B_BE_22_BVW6_BE Hygiene Guidance 2.0 20230217 EN.pdf.

SBB's comment:

Proposed wording for question :
According to the Addendum to Pharmacy Manual page 2/4, the procedure to prevent and deal with exposure to blood, urine, vomit or other bodily fluids from subjects should be followed in the initial period where there are high numbers of transduced cells after infusion. However, the term "initial period" is not precise. The notifier could be requested to update the title by providing a specific time-frame based on the period of time indicated in the BE Hygiene Guidance 2.0 (4 weeks).

Coordinator's comment:

The Addendum mentioned refers to measures to be taken by the hospital personnel during IMP administration, during patient hospitalization and during sample collection from the patient:

According to the Addendum to Pharmacy Manual page 2/4, the procedure to prevent and deal with exposure to blood, urine, vomit or other bodily fluids from subjects should be followed in the initial period where there are high numbers of transduced cells after infusion. However, the use of "initial period where there are high numbers of transduced cells after infusion" is unprecise and such period is anyhow difficult to determine. The procedure should simply be followed during IMP administration, during patient hospitalization and during sample collection from the patient. The notifier should indicate the timepoint after the hospitalization period after which special measures are no longer necessary during sample collection, presumably similar as stated in the BE Hygiene Guidance 2.0 (4 weeks).

On p5/37 in B_BE_22_BVW6_BEL Main ICF V1.1 20230125 EN.pdf it is indicated "You are not allowed to get someone pregnant during the trial and for some time after it". Best also to indicate blood (as in 6.4 p14/37). What about organ donation, this should also be indicated in this document. Also, what if somebody would become pregnant, the patient should know where to go for advice.

SBB's comment:

Since the section "The trial at a glance" in the Main ICF (p5/37) aimed at providing a clear summary of the trial including the points that are not allowed, the notifier could be requested to add in this section that patients are prohibited from donating blood following the vector injection. The period during which the prohibition runs must be specified.

According to the SNIF p14/22 and the CAF_Public p10/13, patients are prohibited from donating blood for 6 months following the vector injection. However, according to the ICF p14/37, participants are prohibited from donating blood for 2 years following the infusion. No information can be found in the protocol regarding blood restriction.

Furthermore, no instructions are made with respect to the donation of tissues, organs and cells.

The notifier could be requested to revise the instructions regarding blood, organs, tissues and cells and to align these with the instructions given in the product information document (EPAR) of EU registered medicinal products containing recombinant AAV (Glybera, Zolgensma, Roctavian, Luxturna, Upstaza, Hemgenix): 'Patients treated must not donate blood, organs, tissues, and cells for transplantation'.

Alternatively, the notifier is requested to give a rationale why instructions could deviate from measures commonly taken for current EU marketing authorized medicinal products containing recombinant AAV.

With respect to the question related to becoming pregnant during the trial, it can be considered that this event falls within the assessment of patient's safety considerations and go beyond the scope of the environmental risk assessment of SRP-9001.

Coordinator's comment:

Agreed with the SBB comment

Additional coordinator's comment:

Information on how to handle in case of sexual intercourse and to prevent pregnancy during the trial period is described in detail in page 14/37 of the Main ICF. Since all patients will be male, it makes no sense to refer to breastfeeding in the title of this section 6.5 (and not to discuss this in any way).

SBB's Comment:

This request has been added in the list of questions for the notifier.

On p7 and 10/37 in B_BE_22_BVW6_BEL Main ICF V1.1 20230125 EN.pdf it is indicated “The vehicle is a viral vector called adeno-associated virus (AAV). It is different from a normal virus. It has been changed in the laboratory so that it is not likely to reproduce or cause an infection once it is in your body. Doctors call this altered virus a “vector””. This information is confusing, refer to the viral vector as recombinant AAV viral vector.
Also on p10 (top of page, and one but last paragraph: “spread of virus or micro-dystrophin gene” and “However, recent research studies testing somewhat higher doses of adeno-associated virus (AAV)”, this is not correct. Virus should be viral vector (rAAV).
Also, somewhat is subjective wording (indicate exact dose?). Somewhat anyway sounds like an understatement to me (when referring to a study, indicate the study nr).
I would like to advice to replace viral by viral vector to make all documents more uniform. Also in B_BE_22_BVW6_Part 5_Public_information_EN.pdf (@ p2-4/4), ‘viral genomes injected’ and ‘viral coding sequences’, this should be “viral vector”. The same goes for the FR and NL version of this document.
The same information is provided to the patient in B_BE_22_BVW6_Participant Study Guide 20220824 1.0 EN.PDF. I would propose to adapt section “How does SRP-9001 work?”. The drug product does not contain a virus, this should be ‘rAAV viral vector’.

SBB comment:

All these points could be reported as “Typos and other errors/omissions”.
Proposed wording for questions :
In order to improve the wording in some documents by making the text scientifically correct, the notifier could be requested to adapt the documents as follow:

1- On p7/37 of the BEL Main ICF V1.1 20230125 EN.pdf : it is indicated that “The vehicle is a *viral vector* called adeno-associated virus (AAV). It is different from a normal virus. It has been changed in the laboratory so that it is not likely to reproduce or cause an infection once it is in your body. Doctors call this altered virus a “*vector*””. A correction should be made by changing the term “viral vector” into “recombinant AAV viral vector”.
2- On p10/37 in BEL Main ICF V1.1 20230125 EN.pdf : it is indicated that “One of the blood tests you will have will test for the body’s reaction to the *vector*”. A correction should be made by changing the term “vector” into “recombinant AAV viral vector”.
3- On p10/37 in BEL Main ICF V1.1 20230125 EN.pdf : in both sentences “complications from spread of *virus* or micro-dystrophin gene to other body parts in animal studies have not shown the development of cancer in treated animals.” and “recent research studies testing somewhat higher doses of adeno-associated *virus*”, the word “virus” should be corrected into “viral vector (rAAV)”. Furthermore, “somewhat” should be replace by the exact dose.
4- In the SNIF, pages 3/22, 13/22 and 14/22 when speaking about “*viral* shedding” or “*viral* load shed”, the notifier could be requested to change the wording “viral” into “viral vector”.
5- In the Public_CAF page 5/13, in both sentences “The *viral* load shed in bodily fluids is expected to be low” and “Non-clinical study data and interim *viral* shedding data”, the notifier could be requested to change the wording “viral” into “viral vector”.
6- In the Public_information_EN, “viral” should be replaced by “viral vector” in the sentences “‘viral genomes injected’, “viral shedding” and ‘viral coding sequences’. These corrections should also be done in the French and Dutch versions of the document.
7- In the Participant Study Guide v1.0, page 7/19, in section “How does SRP-9001 work?”, since the drug product does not contain a virus, the word “virus” should be replaced by ‘rAAV viral vector’.

Coordinator's comment:
Agreed with the SBB comment.

On p11/37 in B_BE_22_BVW6_BEL Main ICF V1.1 20230125 EN.pdf it is indicated "It is possible that the trial drug vector containing the micro-dystrophin gene could interact with other viruses with which you could come into contact, like cold viruses. If this happens, the trial drug vector might form a virus that makes you sick." This information is not correct. How would the trial drug generate a virus that makes you sick? One would require AAV and AdV, but mostly AAV does not make you sick.

SBB comment:
This point could be reported as "Typos and other errors/omissions".
Proposed wording for question :
According to page 11/37 of the BEL Main ICF V1.1, "it is possible that the trial drug vector containing the micro-dystrophin gene could interact with other viruses with which you could come into contact, like cold viruses. If this happens, the trial drug vector might form a virus that makes you sick.". However, this information is not correct since the trial drug is unable to generate a virus that makes you sick. The notifier could be requested to adapt this sentence by clarifying that only in the case of an extremely unlikely event of triple infection by SRP-9001, wild type AAV (providing the *rep* and *cap* functions) and a helper virus, there could be a remote possibility of homologous recombination between the viral vector and the wt AAV. However, such recombination event could only result in the exchange of the micro-dystrophin transgene expression cassette with the *rep* and *cap* genes of the wt AAV as it is not possible for the AAV genome to contain both *rep* and *cap* genes and the micro-dystrophin transgene, due to the limited packaging capacity of AAVs. Moreover, the regions of homology between SRP-9001 and a potential co-infecting wild-type AAV would be limited to the ITRs, since the *rep* and *cap* genes are not present in SRP-9001. This further decreases the possibility of recombination leading to replication competent viral particles. Furthermore, adeno-associated virus is not known to be pathogenic.

Coordinator's comment:
Agreed with the SBB comment.

On p14/37 in B_BE_22_BVW6_BEL Main ICF V1.1 20230125 EN.pdf paragraph 6.4. Also indicate how to handle organ, plasma donation?

SBB's comment:
Please refer to SBB's comment reported here above.

Coordinator's comment:
Agreed with the SBB comment.

P4/12 in B_BE_22_BVW6_Part 1A_BEL_Public CAF (v4.1).pdf point 2.6.1 Biodistribution, could also describe the results obtained in men? This is a Phase3 trial. See also info provided in SNIF (p3-4).

SBB's comment:
Biodistribution studies with SRP-9001 have been performed in multiple non-clinical studies in adult DMD^{MDX} mice, adult C57BL/6J mice, neonatal C57BL/6J mice, NHP and in juvenile and adult DMD rats.

Preclinical data in animal models have the disadvantage that these cannot be readily extrapolated to human beings. Biodistribution studies with SRP-9001 have not been performed in human. No biodistribution results have been reported in the SNIF.

Coordinator's comment:
Agreed with the SBB comment.

Comment 2
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.

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
Handling of spill as described in p9/17 in B_BE_22_BVW6_Dose Administration Manual_V3.0_20220527.pdf: "Evacuate area, remove contaminated PPE and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure." This may be standard, but in case of a spill, I reckon it would be more sensible to start directly with point2, instead of spreading the spill by evacuating the area.

SBB's comment:
In order to provide clear and concise instruction to health care personnel, the notifier could be requested to adapt the procedure in case of accidental spill or breakage in the SNIF p21/22, in the Dose Administration Manual p8/17 and in the Pharmacy Manual p15/27 by adding the following points:

1- In case of spill, before evacuating the area, contaminated PPE like labcoat, shoes, and others clothing, should be removed as they should not leave the area
2- A message "DO NOT ENTER" should be posted on the door
3- When the area can be entered again, a clean lab coat, disposable gloves, glasses, disposable shoe covers and a mask should be worn
4- Since bleach solution and alcohol can react and can produce toxic vapors as chloroform, the notifier should include this note in the procedure
5- The medical staff should report the incident to the responsible of the site
6- 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, shoe covers, mask), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.

Furthermore, Since there is only one site in Belgium where this clinical trial will be performed, the procedure should be detailed in the document “Addendum to Pharmacy Manual”.

Coordinator’s comment:
Agreed with the SBB comment.

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

Additional SBB’s comment:
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 9/13 of the Public_CAF and on page 21/22 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-9001 during the dose preparation and administration to the patient […] *immediately* disinfect the spill to prevent further spread”.

Coordinator’s comment:
Agreed with the SBB comment.

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.

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
In 3.6.b in B_BE_22_BVW6_Part 1A_BEL_Public CAF (v4.1).pdf PPE are discussed. Hair covers are not included, whereas these were earlier discussed in B_BE_22_BVW6_Addendum to Pharmacy Manual_BE_20230217.PDF p3/4. Information is not consistent.

SBB’s comment:
According to the Addendum to Pharmacy annual and to the CAF confidential document p18/38, the personal protective equipment consists of lab coats, safety goggles, gloves, hair covers and overshoes. However, hair covers and overshoes are not reported in the list of PPE mentioned in the SNIF p17/22, in the Dose Administration Manual p7/17 and in the CAF_Public p9/13. The notifier could be requested to adapt the documents where applicable in order to render the different documents consistent.

Coordinator's comment:
Agreed with the SBB comment.

In point 6.4 in B_BE_22_BVW6_BEL Main ICF V1.1 20230125 EN.pdf it is indicated that no blood can be donated for two years following trial drug infusion. Still at p10/13 in the CAF states 'Blood donation 6 months after SRP-9001 infusion is considered to represent minimal and acceptable risk'. This is conflicting information and should be clarified (same for organ donation). Also the SNIF indicates 6 months (@ p14/22).

SBB's comment:
This point has been included in section 2.6 under comment 1.

Coordinator's comment:
Agreed with the SBB comment.

Further on in the SNIF (p17/22) also PPE are not complete. Haircovers are again omitted (inconsistent info throughout the different files), please make uniform.

SBB's comment:
This point has been included in section 3.6 under comment 1.

Coordinator's comment:
Agreed with the SBB comment.

Comment 2
In the document : Sarepta Therapeutics, Inc. SRP-9001-303 EMBARK Dose Administration Manual, Version 3.0 27-May-2022. Page 8 of 17 point 4.2. Handling Spills, it is writting that :

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

Comment :
Bleach solution and alcohol can react and can produce toxic vapors such as chloroform. The combination of bleach and the use of alcohol wipes should be avoided (cfr step 3 of procedure of handling spills : 'Carefully pour disinfectant (bleach solution followed by alcohol wipes) over the absorbed spill, again starting at the edges. Saturate the area with disinfectant). The notifier is also requested to specify the disinfectant. Hypochlorite solution 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. A list of adequate of decontamination / disinfection solutions should be provided.

SBB's comment:

Some clarifications regarding the clean-up disinfectant to be used are missing in SNIF p21/22, in CAF_Public, in the 3 Public Information documents and in the Pharmacy Manual p15/26. The notifier could be requested to improve these documents by clarifying:

1- Hypochlorite concentration in household bleach solutions varies by manufacturer. All decontamination procedures involving the use of sodium hypochlorite solution should thus specify the precise mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution.
2- Whenever hypochlorite solution is used (e.g. for the decontamination of work areas), attention should be given to the use of freshly prepared hypochlorite solution.
3- Bleach solution and alcohol can react and can produce toxic vapors as chloroform. The notifier should include this note in the cited here above or should avoid suggesting the use of alcohol wipes in combination with bleach
4- Hypochlorite solution 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. A list of adequate of decontamination / disinfection solutions is required

Coordinator's comment:

Agreed with the SBB comment.

Page 3 / 4 Sarepta Therapeutics, Inc. / SRP-9001-303 / Public Information / 22 September 2022

Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e. decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector.

In case of accidental spillage of SRP-9001 during the dose preparation and administration to the patient at the health-care provider, instructions provided by the Sponsor´s pharmacy manual will be followed to contain and immediately disinfect the spill to prevent further spread. All contaminated materials will be disposed of locally by incineration or autoclaving. All other places will be cleaned, according to normal decontamination procedures as per the NIH/CDC guidance for handling of biosafety level 1 agents and the Pharmacy Manual.

1. Evacuate area, remove contaminated PPE and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure.
2. Cover the spill with absorbent material. Starting at the edges and work towards the center.
3. 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.

Comment : same comment as previously

SBB's comment:

This point has been included in the SBB comment here above.

Coordinator's comment:

Agreed with the SBB comment.

Page 15 of 26 Sarepta Therapeutics, Inc.SRP-9001-303 ENVISION Pharmacy Manual, Version 3.0 27-May-2022
Handling Spills
1. Evacuate area, remove contaminated PPE and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure.
2. Cover the spill with absorbent material. Starting at the edges and work towards the center.
3. Carefully pour disinfectant (bleach solution followed by alcohol wipes) over the absorbed spill, again starting at the edges. Saturate the area with disinfectant.

Comment : same comment as previously

SBB's comment:
This point has been included in the SBB comment here above.

Coordinator's comment:
Agreed with the SBB comment.

Additional SBB's comment:
A few remarks could be done regarding the BE_Hygiene guidance in order to improve this document:

1- The name and title of the study should be added on the first page in order to help the participant to easily recognise the document.
2- In point 1 regarding the "Hand hygiene", a reference is made to page 6. But it is not mentioned from which document.
3- Since there is no age limit for subjects enrolled in Cohort 1, this Cohort may include patients older than 18 years and also younger than 8 years old. Meaning that young children still using diapers could be included in the study. Therefore, the notifier could be requested to add an instruction to the patient and family regarding how diapers should be disposed of. According to SNIF p21/22 and CAF-Public p10/13 documents, diapers should be sealed in plastic bags and then double-bagged and disposed of in household waste.
4- Since gloves should be used when disposing of potentially contaminated materials, the notifier could be requested to mention in point 2 that when handling potential contaminated cloth and launderable materials, such as clothing, linens, pillow, and blankets, gloves should also be worn.

Coordinator's comment:
Agreed with the SBB comment.

Additional SBB's comment:
Instruction for study nurse during remote visits are missing and could be requested as follow:
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 could be requested to detail the instructions that will be given to the caregivers either on the Addendum to Pharmacy Manual document or as a separate instruction sheet. Among others, these following instructions will be mentioned: Which personnel protective equipment will be required for the study nurse? Disinfectant to be used ? How to handle in case of accidental spillage ? How will the waste be collected during the visit? How will the collected samples be transported back to the hospital?

Coordinator's comment:
Agreed with the SBB comment.

Additional SBB's comment:
According to the Addendum to Pharmacy Manual page 3/4, the personnel should follow existing site procedures to manage an exposure to blood, urine, vomit or other bodily fluids. Since there is only one site in Belgium where the clinical trial will be performed, the notifier could be requested to detail the procedures to prevent and to deal with exposure to blood, urine, vomit or other bodily fluids from patients in the initial period where there are high numbers of transduced cells after infusion directly in the Addendum to Pharmacy Manual, so as to have all information on the same document.

Coordinator's comment:
Agreed with the SBB comment, but see also comment by coordinator with respect to Addendum to Pharmacy Manual page 2/4 (point 2.6)

SBB's Comment:
This additional query has been combined with previous query reported in point 2.6.

Additional SBB's comment:
Since the use of double gloves should be standard, the notifier could be requested to update this information in the CAF confidential p18/38, the CAF Public p9/13, the Pharmacy Manual p14/27 and the Dose Administration Manual p7/17 (p7/18?). Furthermore, in the Pharmacy Manual p14/27 and the Dose Administration Manual p7/18, the word "consider" should be deleted in the sentence "Gloves (consider double gloving)".

Coordinator's comment:
Agreed with the SBB comment.

Additional coordinator's comment:
In CAF-Public p8/13, the second last sentence in Administration seems incomplete. After/before? Please rephrase.

SBB's Comment:
This query has been added as "Typos and other errors/omissions" in the list of questions to the notifier.

Additional coordinator's comment:
In CAF confidential p19/38 and p20/38, where appropriate, a box should be checked in column 'Incineration by'

SBB's Comment:
Query has been added in the list of questions to the notifier.

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.

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
None

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Sarepta Therapeutics, Inc. on the list of questions for dossier B/BE/22/BVW6

26 July 2023
Ref. SC/1510/BAC/2023_0736

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

INTRODUCTION

Dossier **B/BE/22/BVW6** concerns a notification from Sarepta Therapeutics, Inc. for a clinical trial entitled "A Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 in Non-Ambulatory and Ambulatory Subjects With Duchenne Muscular Dystrophy (ENVISION)".

On 4 May 2023, based on a list of questions prepared by the BAC (SC/1510/BAC/2023_0391), 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 18 July 2023. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 26-07-2023 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.

Evaluation Rik Gijsbers

I read through the replies of the applicant, and considered the majority of answers and adaptations to be sufficient.
Still, I indicate below some comments (and typo's) that could be considered, or at least advised to the applicant.

- Q1, Q3-9, Q11-12 are answered and/or mitigated satisfactory for me.
- As to Q2: even though the BE Hygiene Guidance described a period of 4 weeks, I wonder whether this time-frame is sufficient. As far as I know the dose provided to these patients is amongst the highest currently applied (>1.33 x 10^14 vg/kg). Are there data available on the presence of viral vector sequences in these bodily fluids at 4 weeks from other trials, and are these data then confirming that a 4 week period is sufficient? In 5.3a SRP-9001-303_Addendum to Pharmacy Manual_Belgium_15Jun2023_TC.pdf the applicant states *'As SRP-9001 lacks the wild-type AAV genes with the exception of the inverted terminal sequences, it is incapable of replicating itself, which therefore does not present a potential risk*

associated with transmission to third parties, animals or to the environment.' This is not correct. Please state which 'risk' is considered here. For example, if a family member or other patient with DMD would be exposed to the drug product, an immune response would be elicited, which would render this person resistant to the DP. Also further on in the text, it would be best to indicate that also family members should adhere to these measures (or is this redundant in the Pharmacy Manual?)? "*Therefore, personnel should study participants should be isolated and refrain from any contact with other patients. All personnel who are in contact with the study participants should use personal protective equipment follow existing site procedures to manage an exposure to blood, urine, vomit or other bodily fluids*."

- As to Q10: it is not clear to me what the specific document will now advise to study nurses.

- In p3/6 in 4.4.2a SRP-9001-303 BEL Public Information Form (June 2023 - Track Changes)_FR-BE_tracked changes.pdf the applicant indicates "Les cellules infectées par le virus recombinant". This should be 'transducées' instead and 'vecteurs vireaux' instead of 'virus'.
- Similar for the Dutch version in 4.4.3a SRP-9001-303 BEL Public Information Form (June 2023 - Track Changes)_NL-BE_tracked changes_M.pdf
- At p14/30 in 5.1a SRP-9001-303_Pharmacy Manual_V4.0_23Jun2023_TC_BEL.pdf: 'siet' should be 'site'
- At p2/5 in 5.3a SRP-9001-303_Addendum to Pharmacy Manual_Belgium_15Jun2023_TC.pdf: 'it's' should be 'its'. Also, the applicant states 'As SRP-9001 lacks the wild-type AAV genes with the exception of the inverted terminal sequences, it is incapable of replicating itself, which therefore does not present a potential risk associated with transmission to third parties, animals or to the environment.' This is not correct. Please state which 'risk' is considered here. For example, if an family member or other patient with DMD would be exposed to the drug product, an immune response would be elicited, which would render this person resistant to the DP.
- In document 3.4a 252376 Belgium Hygiene Guidance 3.0 20230615 English TC.pdf, it is indicated 4 weeks/30 days. This is not clear.

SBB's comment :

As to the expert's comment to Q2:

The use of SRP-9001 in a clinical trial has already been assessed by the BAC in the framework of notification B/BE/21/BVW5 (EMBARK study,SC/1510/BAC/2022_0677, submitted by Sarepta Therapeutics) and B/BE/22/BVW5 (ENVOL study, SC/1510/BAC/2023_0693, submitted F. Hoffmann – La Roche Ltd.).

Data on vector genome DNA in saliva, urine, feces have been included in a SRP-9001 vector shedding report presented 20 Dec 2022 in the context of a substantial amendment of dossier B/BE/21/BVW5 (EMBARK study), which has been assessed by the coordinator and the secretariat of the Biosafety advisory Council (BAC). Following this assessment, the proposal to limit the period to apply post-injection hygiene measures for caregivers to only 4 weeks was agreed upon. This period of 4 weeks was also deemed sufficient for the other studies with the SRP-9001 Vector (handled in the context of B-BE-22-BVW5). The dose administered intravenously in all of the three studies is the same, yet stratified by weight (1,33 x 10E14 vg/kg). The age of the trial subjects differ, as indicated in the table below :

	B-BE-21-BVW5	B-BE-22-BVW5	B-BE-22-BVW6
Protocol	SRP-9001-301	BN43881 (SRP-9001-302)	SRP-9001-303
Trial name	EMBARK	ENVOL	ENVISION
Notifier	Sarepta therapeutics, Inc.	F. Hoffman-La Roche Ltd	Sarepta therapeutics, Inc.
Phase	Phase 3	Phase 2	Phase 3
Age	≥ 4 to <8 (4 to 7 included)	Under the age of 4	Cohort 1 : non-ambulatory; Cohort 2: ambulatory ≥ 8 to < 18 year of age
Dose	1,33 x 10e14 vg/kg	1,33 x 10e14 vg/kg	1,33 x 10e14 vg/kg (if <70kg), if >70 kg , max 9,31 x 10e15 vg

With respect to the remainder of the comments and typo's, these could be addressed to the notifier under section '*Typo's and other errors/omissions'*.

As to last remark of the expert with respect to the duration of post-infusion measures, it is remarked that the same comment applies to the BEL participant study (it is indicated 4 weeks/30 days), whereas in the ICF parental document it is indicated 4 weeks. In order to have univoquity in the duration of measures post infusion, the notifier could be invited to align the documents to 4 weeks.

Coordinator's comment:
Agreed with the SBB comment.

Additional: instructions to study nurses when providing care at the patient's home should be worked out in detail and communicated to the BAC (Q10) (as suggested in the proposal for a second list of questions)

Evaluation Willy Zorzi

In the file « 4.3a SRP-9001-303 Belgium SNIF Track Changes (June 2023) », p21, it will be better to change the line :
"In the event of spills, chlorine (0.58g of sodium hypochlorite per 100mL) neutralized with 3% sodium thiosulfate solution is used with attention given to the use of freshly prepared hypochlorite solution " as follows :
In the event of spills, chlorine (0.58g of sodium hypochlorite per 100mL) ~~neutralized with 3% sodium thiosulfate solution~~ is used with attention given to the use of freshly prepared hypochlorite solution. After 15-30 min of sodium hypochlorite chlorine application on the spills, the chlorine solution could be neutralized with 3% sodium thiosulfate solution.

The same comment applies to the files
'4.4.1a SRP-9001-303 BEL Public Information (June 2023 - Track Changes)', p5
' 5.1a SRP-9001-303_Pharmacy Manual_V4.0_23Jun2023_TC_BEL ', p16

SBB's comment :

The same comment could be given for the CAF public (p9 of the Track changes doc), public information (p4 of the Track changes doc, in version FR and NL) and dose administration (p9 of the Track changes doc).

Coordinator's comment:
Agreed with the SBB comment.

In the file '4.4.2 SRP-9001-303 BEL Public Information Form (June 2023 - Track Changes)_FR-BE', p5, it is better to change the line :
'Du chlore (0,58 g d'hypochlorite de sodium pour 100 ml) neutralisé avec une solution de thiosulfate de sodium à 3 % sera utilisé en veillant à employer une solution d'hypochlorite fraîchement préparée' as follows :
'*Une solution de javel (0,58 g d'hypochlorite de sodium pour 100 ml) sera utilisée en veillant à employer une solution d'hypochlorite fraîchement préparée. Après 15-30 min d'application de cette solution en contact avec l'éclaboussure, la solution de javel peut éventuellement être neutralisée avec une solution de thiosulfate de sodium à 3 %.*

SBB's comment :

The same comment could be given for the NL-BE version of the BEL Public Information Form.

Coordinator's comment:
Agreed with the SBB comment.

SBB's additional comment on the notifier's response on question 3 :

The revised instructions for blood, organ, tissue and cell donation in the ICF, SNIF and public CAF are acknowledged. The notifier informs not to revise the instructions in the protocol by arguing that the protocol is not a facing document and that instructions within the protocol are limited in scope to the duration of the trial. One could remark that we do not concur with this reasoning for not adapting the protocol and request the notifier to at least commit to adapt relevant text in the next update of the protocol and to distribute a protocol clarification letter to all sites immediately following the approval of the clinical trial.

Coordinator's comment:
Agreed with the SBB comment.

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/22/BVW6 de Sarepta Therapeutics, Inc. pour l'introduction volontaire dans l'environnement, à des fins de recherche et développement, d'organismes génétiquement modifiés autres que les plantes supérieures

Adopté le 25/08/2023
Ref. SC/1510/BAC/2023_0824_FR

Contexte

La notification B/BE/22/BVW6 a été soumise en septembre 2022 par Therapeutics, 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 21 octobre 2022, après que le notifiant aie suffisamment répondu aux questions de validation.
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_2023_0823). 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: Nous constatons qu'aucune mesure concernant l'excrétion n'est décrite dans le dossier public ou technique, bien qu'une dissémination du transgène dans l'environnement ne soit pas exclue (mais peu probable). Les dossiers précédents décrivaient souvent une forme de quarantaine ou de protection du site d'administration. L'absence de telles mesures constitue-t-elle un problème à vos yeux?

Commentaire du SBB :
La section 3.6 du CAF public intitulée « Mesures pour prévenir la dissémination dans l'environnement » décrit les mesures de contrôle à appliquer lors de la manipulation et de l'administration de SRP-9001, les équipements de protection individuelle (PPE) recommandés pour le personnel médical, la procédure en cas de déversement accidentel, la procédure d'élimination et d'inactivation du SRP-9001 résiduel et les recommandations aux patients pour prévenir la dissémination lorsqu'ils sont à la maison.

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De plus, le dossier contient un "Guide d'étude du participant" qui sera fourni à tous les patients de l'essai clinique, décrivant et résumant les mesures que le patient doit lui-même appliquer.
SRP-9001 est un vecteur viral recombinant adéno-associé (AAV) sérotype rh74 (AAVrh74) déficient en réplication et non pathogène contenant la cassette d'expression de la dystrophine SRP-9001. Il n'y a pas de données indiquant un danger ou des effets indésirables pour le non-patient, car le virus parent dont le vecteur viral est dérivé est non pathogène (et omniprésent dans la population) et le transgène codant pour une protéine de micro-dystrophine humain ne présente pas de propriétés toxiques. Bien que l'exposition des contacts étroits à l'excrétion du patient ne puisse être exclue, il n'existe pas de données suggérant un risque réel pour les contacts étroits. Par conséquent, les mesures de quarantaine ne sont pas nécessaires pour ces patients.

Question 2: Nous notons que des informations manquent dans le dossier concernant l'immunogénicité et la tumorigénicité, alors que des informations à ce sujet étaient disponibles dans des dossiers similaires de Duchenne utilisant l'AAV comme vecteur. S'agit-il de la négligence d'un demandeur et, si oui, est-ce problématique ?

Commentaire du SBB:
Dans le premier dossier de Sarepta Therapeutics (B/BE/21/BVW5), le demandeur avait rempli un document complet d'évaluation des risques pour l'environnement. Dans la section 5 « Informations relatives aux risques pour l'environnement et la santé humaine » de ce document, il faut compléter des informations sur l'immunogénicité et la tumorigénicité.
Pour le dossier actuel, le demandeur a rempli le document spécifique Formulaire Commun de demande pour les vecteurs cliniques d'AAV (un CAF_AAV) dans lequel les données sur l'immunogénicité et la tumorigénicité n'ont pas besoin d'être détaillées.

Afin de faciliter l'application des études cliniques utilisant des vecteurs AAV en Europe, les autorités nationales compétentes de l'Union européenne et la Commission ont préparé un document intitulé "Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors". Ce document (Good Practice) correspond à une évaluation ERA (Environmental Risk Assessment) spécifique pour les AAV et accompagne le formulaire commun de demande CAF (Common Application Form) spécifique pour les vecteurs cliniques AAV. Cet ERA spécifique ne peut être appliqué aux vecteurs AAV cliniques que si le demandeur démontre l'absence de formation de virus capables de se répliquer et que le transgène n'est pas nocif. Dans ce document Good Practice, les risques potentiels pour la santé humaine associés à l'utilisation d'un vecteur AAV et de son insert sont caractérisés et analysés.

En répondant « oui » à la question de la section 5 « Évaluation des risques environnementaux » du document CAF_AAV, le notifiant indique que l'évaluation des risques environnementaux spécifiques telle que décrite à la section 2 du document de bonnes pratiques précité a été réalisée. Dans ce cas, les différents aspects de l'évaluation des risques pour l'environnement ne doivent plus être décrits dans le document CAF_AAV.

References:
Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors (2019) https://health.ec.europa.eu/system/files/2022-01/aavs_gp_en.pdf

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Antwoorden van de Adviesraad voor Bioveiligheid op opmerkingen gekregen tijdens de publieksraadpleging over de kennisgeving B/BE/22/BVW6 van Sarepta Therapeutics, Inc. voor doelbewuste introductie in het leefmilieu van genetisch gemodificeerde organismen met uitzondering van hogere planten voor onderzoek en ontwikkeling

Goedgekeurd op 25/08/2023
Ref. SC/1510/BAC/2023_0825_NL

Contexte

De kennisgeving B/BE/22/BVW6 werd in september 2022 door Sarepta Therapeutics, 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 21 oktober 2022 nadat de kennisgever de validatievragen voldoende beantwoord had.
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_2023_0823). 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: We merken dat er geen maatregelen rond shedding beschreven staan in het publieke of het technische dossier, hoewel een vrijgave van het transgen naar het milieu niet uitgesloten is (maar onwaarschijnlijk). In voorgaande dossiers was een vorm van quarantaine of bescherming van de plaats van toediening vaak wel beschreven. Is het ontbreken van zulke maatregelen een probleem wat jullie betreft?

SBB's Comment:
Sectie 3.6 van de openbare CAF met als titel " Measures to Prevent Dissemination into the Environment" beschrijft de controlemaatregelen die moeten worden toegepast tijdens de behandeling en toediening van SRP-9001, de aanbevolen persoonlijke beschermingsmiddelen (PPE) voor het medisch personeel, de procedure in geval van accidenteel morsen, de procedure voor de eliminatie en het inactiveren van restanten van SRP-9001 en de aanbevelingen aan de patiënten om de verspreiding te voorkomen als ze thuis zijn. Bovendien, is er een " Participant study guide" in het dossier die aan

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alle patiënten van de klinische proef zal worden verstrekt en die de maatregelen, die de patiënt zelf moet toepassen, beschrijft en samenvat.
SRP-9001 is een replicatie-deficiënte, niet-pathogene recombinant adeno-geassocieerd virus gebaseerde vector (AAV) met serotype rh74 (AAVrh74) die het SRP-9001- micro-dystrophine - expressiecassetteconstruct bevat. Er zijn geen gegevens die wijzen op enig gevaar of schadelijke gevolgen voor de niet-patiënt, aangezien het moedervirus waarvan de virale vector is afgeleid niet pathogeen is (en bovendien alomtegenwoordig in de bevolking) en het transgen dat codeert voor een humaan micro-dystrophine-eiwit, geen toxische eigenschappen vertoont. Hoewel blootstelling van naaste contacten aan uitscheiding door patiënten niet kan worden uitgesloten, zijn er geen gegevens die wijzen op een reëel risico voor naaste contacten. Daarom zijn quarantainemaatregelen voor deze patiënten niet nodig.

Vraag 2: We merken dat informatie ontbreekt in het dossier wat betreft immunogeniciteit en tumorigeniciteit, terwijl hier wel informatie over beschikbaar was in soortgelijke Duchenne-dossiers met het gebruik van AAV als vector. Is dit een nalatigheid van de aanvrager, en zo ja, is dit problematisch?

SBB's Comment:
In het eerste dossier B/BE/21/BVW5 van Sarepta Therapeutics, had de aanvrager een volledig Environmental Risk Assessment document ingevuld. In sectie 5 "Information related to the risks for the environment and human health" van het ERA, moesten ze informatie over immunogeniciteit en tumorigeniciteit toevoegen.
Voor het huidige dossier, heeft de aanvrager de specifieke Common Application Form voor klinische vectoren van AAV (CAF_AAV) document ingevuld waar gegevens over immunogeniciteit en tumorigeniciteit niet in detail moeten weergegeven worden.

Om de toepassing van studies met klinische AAV-vectoren in Europa te vergemakkelijken, hebben de nationale bevoegde autoriteiten van de Europese Unie en de Commissie een document opgesteld met de titel " Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors ". Dit Good Practice document is gelijk aan een specifieke ERA (Environmental Risk Assessment) voor AAV en hoort bij het specifieke gemeenschappelijke aanvraagformulier (CAF) voor klinische vectoren van AAV. Deze specifieke ERA kan alleen op klinische AAV-vectoren worden toegepast als de aanvrager aantoont dat er geen replicatie-competent virus wordt gevormd en dat het transgen niet schadelijk is. In deze specifieke ERA worden de potentiële gevaren voor de menselijke gezondheid in verband met het gebruik van een AAV-vector en de insert gekarakteriseerd en geanalyseerd.
Door "Ja" te antwoorden op de vraag in sectie 5 "Environmental risk assessment" van het CAF_AAV document geeft de kennisgever aan dat de beoordeling van specifieke milieurisico's zoals beschreven in sectie 2 van het bovenvermelde Good Practice document is uitgevoerd. In dat geval moeten de verschillende aspecten van de ERA niet meer worden beschreven in de CAF_AAV.

References:

Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors (2019) https://health.ec.europa.eu/system/files/2022-01/aavs_gp_en.pdf