Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/24/BVW5 of the company Pfizer Inc., for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Final version : 31/05/2024
Ref. SC/1510/BAC/2024_0752

Context

The notification B/BE/24/BVW5 has been submitted by Pfizer, Inc. 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: ***"Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2)".***

The purpose of this study is to assess the safety and the efficacy of the investigational medicinal product (IMP) PF-06838435 (generic name: fidanacogene elaparvovec; formerly known as SPK-9001 or rAAV Spark100-hFIX-R338L) in male adults with hemophilia B resulting from a deficiency of the blood coagulation Factor IX (FIX).

Factor IX, a serine protease, is an essential factor in the blood coagulation cascade. Various mutations in this gene can impair the functioning of the FIX protein, resulting in an X-linked recessive bleeding-disorder hemophilia B. Individuals with moderately severe to severe hemophilia B frequently experience bleeding and recurrent spontaneous bleeding events into muscle, soft tissue, and joints (hemarthroses) starting from infancy and throughout adulthood.

Fidanacogene elaparvovec is a non-replication recombinant adeno-associated virus (rAAV) serotype Rh74 vector containing an expression cassette encoding a naturally occurring human FIX (hFIX) variant (FIX-R338L) under the control of a liver-specific promoter driving sustained hepatic production of FIX in hemophilia B study participants.

Overall, approximately fifty patients will be included in this Phase III study and approximately two patients will be included in Belgium, each receiving one single intravenous infusion. This study will be conducted at one clinical site located in Brussels.

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The dossier has been officially acknowledged by the Competent Authority on 23 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. Two experts, from the common list of experts and one expert from the SBB drawn up by the BAC answered positively to this request.
The experts assessed whether the information provided in the notification was sufficient and accurate to state that the deliberate release of the genetically modified organism would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments 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 25 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 9 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 24 April 2024. The answers of the notifier were received on 21 May 2024 and transmitted to the BAC, after which the BAC concluded 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

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 PF-06838435 is accomplished via a triple transfection using three different plasmid DNA construct: the "transfer vector" which contains the therapeutic gene of interest - phFIX39v2, the "AAV Rep/Spark 100 Cap" plasmid, and an "Ad helper" plasmid which contains some adenovirus genes.

Following BAC's request, some inconsistencies within the composition of the three plasmids have been clarified and adequately amended in the updated confidential documents.

3. The conditions of the release

In this study, all patients will receive one-single intravenous dose of PF-06838435 that will be administrated on Day 1. All patients will remain at the hospital for a limited time duration 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, patients can be discharged from the hospital.

Shedding analysis is planned during this clinical trial in semen, saliva and urine samples collected at baseline and every week after IMP administration until three consecutive measurements are obtained at or below the lower limit of detection of the shedding assay. Preliminary results from shedding analysis obtained from the Phase 1/2a study C0371005 and the pivotal Phase 3 study C0371002 with the same IMP have been described in the confidential CAF document.

4. The risks for the environment or human health

PF-06838435 is a recombinant, replication deficient adeno-associated virus (rAAV)-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 AAVSpark100 (bioengineered rAAV vector derived from a naturally occurring AAV serotype (Rh74)) 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 AAV Spark100 in the IMP and wild-type AAV, if a triple infection by PF-06838435, wild type AAV (providing the rep and cap functions) and a helper virus occurs simultaneously 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 human factor FIX transgene. Moreover, the genetic material from rep and cap genes together with the factor FIX transgene would be too large for packaging in AAV capsid, making it impossible to form replication competent viral particles containing the transgene and the rep and cap genes necessary for replication.

In the case the AAV vector was accidentally transferred through shedding to an immune-competent human recipient, the risks are expected to be considerably lower than for the patient participant because the vector is non-replicative and the 'AAV dose' that could be inadvertently transferred (from e.g. aerosol, splashing or fomites) will be orders of magnitude lower than that administered to patients. Even under the worst-case scenario, the recipient's immune response should clear the AAVSpark100 capsid.

The BAC concludes that, based on the non-pathogenic and non-replicative nature of PF-06838435, the expected lower amounts of PF-06838435 shed and intact AAV vector particles compared to the therapeutic dose, and the strict implementation of the precautionary measures for preventing 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 PF-06838435, patients and patient's family will be provided with detailed instructions with respect to good hygiene practices to avoid any potential transmission of the AAV viral vector to other people or to the environment outside the hospital setting. Resulting from the BAC's request, the notifier provided one single page with all the relevant information and instructions that patients and patient's family easily can consult whenever needed.

With respect to the instructions regarding blood, organs, tissues and cells for transplantation donation, the notifier aligned the instructions reported in the different documents (Patient's instruction summary, SNIF, CAF) by clarifying that patients are prohibited to donate blood, organs, tissues, and cells following PF-06838435 administration.

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

The notifier has also taken into consideration and answered the remarks and requests addressed by the BAC regarding the clean-up procedure for usual work and in case of accidental spill or breakage of a GMO containing vial. 10% bleach (0.53% or ~5000 PPM sodium hypochlorite solution) can be used with a minimum contact time of at least 20 minutes. Thereafter, area should be thoroughly rinsed with water and dried before cleaning with an appropriate cleaning solution (e.g. 70% alcohol). The notifier also clearly indicated in the documents that 70% alcohol is not an acceptable decontamination solution for this gene therapy product.

The waste contaminated with IP from handling, preparation, and administration will be disposed of per local standards for biohazardous materials in a manner that prevents cross contamination with other supplies.

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 follow to avoid any potential dissemination of the recombinant virus to the environment during such visits.

Given the assessment of the likelihood of further propagation of PF-06838435, 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 PF-06838435 developed as a gene therapy approach for the treatment of Hemophilia B 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:

- IP Manual for staff_v7 (14May2024)
- SDS Fidavec (28 June 2023)
- Main ICD V1_28Nov2023
- CAF Public_BE (16 May 2024)
- CAF Confidential Annex_BE (04 April 2024)
- SNIF_Belgium (16 May 2024)
- Patient Special Instructions Summary (17 May 2024)
- Technical Sheet for Investigation Product (IP) Handling_v2.0 (06 May 2024)
- Addendum 2 GMO_V1.0 (16 May 2024)

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

- The notifier and the investigators must strictly apply the approved clinical trial protocol, and all the safety instructions as described in the dossier and the updated/new documents listed here above.

- The notifier makes sure patients are well informed about the instructions to be applied regarding blood, organs, tissues and cells for transplantation or donation. Furthermore, 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 Informed Consent Document at the next substantial amendment.

- The study specific instructions for caregivers that will visit patients at home must be updated by detailing the PPE to be used during the visit and by specifying the minimum contact time of the decontamination solution with the spill in case of accidental spill (section III).

- Any protocol amendment must 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;

- o A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
- o A report on the accidental releases, if any, of PF-06838435;

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/BVW5 (ref. SC/1510/BAC/2024_0451 and SC/1510/BAC/2024_0595)*

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/24/BVW5
And comments submitted to the notifier

26 March 2024
Ref. SC/1510/BAC/2024_0451

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 25 January 2024.
Coordinator: Rik Gijsbers (KULeuven)
Experts: Anton Roebroek (KULeuven), Willy Zorzi (ULiège), Amaya Leunda Casi (SBB)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/24/BVW5** concerns a notification from Pfizer Inc. for the deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 23 February 2024 and concerns a clinical trial entitled “A Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2).” The investigational medicinal product is an AAV serotype Rh74-derived recombinant replication deficient vector carrying the FIX-R338L variant of the human factor IX (hFIX) gene, for the potential treatment of patients with Haemophilia B.

♦ 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 25-03-2024 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

Based upon info provided in the confidential CAF annex the following questions should be addressed:
Table 1: Functional Elements of phFIX39v2: The size of the AAV2 ITR sequences (130 bp each) differs from the size of these ITRs in the final clinical vector genome (145 bp each, Table 5). This difference should be explained.
Table 2: Functional Elements of pSpark100PK: Spark100 Cap gene: provide information on the serotype origin of these sequences (like for the Rep gene: AAV2): AAV-serotype Rh74?
Table 3: Functional Elements of pAd2-Helper: the origin of the adenovirus type-2 derived sequences is mistakenly indicated as AAV2!

SBB's comment :

The expert's comment is supported and could be forwarded to the notifier

Coordinator's comment:

Agreed. While reading through the document, I also noticed that in Figure5 the ITR sequences (italic according to the legend) are 145bp long for the 5' end, but the italicized sequence at the 3' end is much longer and interspersed with non-italic sequence. I reckon this is an overlooked detail, but it could be mentioned to the notifier to be updated.

SBB's comment :

This remark for the applicant has been added in the list of questions

Comment 3

Has evaluated this item and has no questions/comments.

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

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

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

Comment 3
Has not evaluated this item.

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

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

Comment 2
See 2.1: first question about the size difference in ITRs

According to the detailed sequence data in the confidential CAF and Table 5 the clinical vector has a size of 4245 nucleotides. However, in the text on page 17 of 28 also a figure of 4204 nucleotides is mentioned.

SBB's comment :
According to figure 4 of the confidential CAF document, representing a schematic of fidanacogene elaparvovec vector genome (p13/28) and to Table 5 detailing the Fidanacogene elaparvovec vector genome functional elements (p14/28), the full vector genome sequence has a size of 4245 nucleotides. However, on page 17/28 of the same document, the notifier mentioned that "the fidanacogene elaparvovec vector is derived from the wt AAV using recombinant DNA techniques and contains a single-stranded DNA genome of 4,204 nucleotides". The notifier could be requested to correct the data where applicable to be consistent throughout the document.

Coordinator's comment:
Agreed.

Comment 3
Has not evaluated this item.

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

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

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

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

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

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

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

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

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

By comparison of the requirements indicated in the file 8 C0371002_SNIF Belgium_11Jan2024.pdf, p19 point J.1. concerning « Information on emergy response plans »

Table 1: Management of incidents related to fidanacogene elaparvovec:

Incident	Procedure
Accidental spillage	All spills of fidanacogene elaparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean up materials must be double bagged and disposed of per local guidelines for handling of biohazardous waste.

with the requirements indicated in the 6.3.1 point (p19) of the file B_BE_24_BVW5_IP Manual for staff_v6_04Apr2023 :

Upon completion of PF-06838435 preparation, all internal hood surface areas must first be thoroughly decontaminated using 10% bleach [0.53% or ~5000 parts per million (PPM) sodium hypochlorite solution]. The decontamination solution must be left in contact with the interior surface of the hood for an appropriate duration according to the manufacturer's specifications. The 10% bleach (0.53% or ~5000 PPM sodium hypochlorite solution) minimum required contact time is at least 20 minutes but may vary based on the manufacturer's specifications.

Upon completion of this decontamination contact time, rinse away residual decontamination solution with water, the hood should then be cleaned using the local standard cleaning solution (e.g., 70% alcohol, etc.) to remove any remaining decontamination solution from surfaces. Please note that 70% alcohol is not an appropriate decontamination solution for this gene therapy product.

1) It seems to exist a confusion in the procedure described in the Table 1 here above, when alcohol wipes are used after disinfection using bleach solution, while in 6.3.1 point (p19) of the file B_BE_24_BVW5_IP Manual for staff_v6_04Apr2023, it is clearly indicated that 70% alcohol is not appropriate decontamination solution for this gene therapy product.

2) Please note that the use of 70% alcohol to remove any remaining decontamination solution from surfaces as here proposed is not recommended if the first standard decontamination solution is bleach. The principal reason is that bleach reacts with alcohols (currently used to

disinfect hood surfaces) and could give chloroform and eventually other toxic derivatives vapours.
Ex: reaction between Ethanol and Bleach:
CH3CH2OH + 4 NaOCl + 2 NaCl + H2O —>2CHCl3 + 6NaOH

3) Considering these previous remarks, the notifier is invited to modify and synchronise in all the documents of this dossier, all the protocols of disinfection/decontamination for the gene therapy product (for the usual work and for the accidental spillage cases).

SBB's comment :

Based on the comment from the expert about the disinfectant and based on questions that have already been raised in the past in previous similar applications, the following questions could be sent to the applicant for this trial:

According to table 1 of the SNIF (p18/19) and to the public CAF document pages 12 and 13/16, in case of accidental spill, the spill area must be disinfected using a bleach solution followed by alcohol wipes. According to section 6.3.1 of the IP Manual for staff_v6 (p19/44), upon completion of PF-06838435 preparation, all internal hood surface areas must first be thoroughly decontaminated using 10% bleach. After time contact of minimum 20 minutes with the decontamination solution, the hood should then be cleaned up using the local standard cleaning solution (e.g., 70% alcohol, etc.) to remove any remaining decontamination solution from surfaces.

The notifier is requested :

- To adapt the clean-up procedure for usual work and for accidental spillage cases in order to be consistent between the different documents.
- To clearly indicate in all documents that 70% alcohol is not an appropriate decontamination solution for the AAV gene therapy product
- Sodium hypochlorite used with alcohol can cause a reaction that produces toxic vapors and eventually other toxic derivatives 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 all the documents or should avoid the suggestion of using alcohol following sodium hypochlorite decontamination.
- Whenever bleach solution is used (e.g. for the decontamination of work areas), it must be stated that a freshly prepared solution should be used.
- To indicate the mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution as the concentration of sodium hypochlorite in standard bleach solutions varies between manufacturers.

Coordinator's comment:

Agreed.

Comment 2

The response of the Sponsor to question 4 (see document "B_BE_24_BVW5_Response to validation questions_09Feb2024") is not considered to be adequate and sufficient.

The suggested update of the local ICD with information on good hygiene practices is insufficient to deal with the concern of the BAC. The local ICD will be discussed with the patient and signed weeks in advance of the actual administration of vector. Furthermore, this ICD contains a lot of information and special instructions on good hygiene practices might not get the proper attention at the right moment, when the patient leaves the hospital. Patients and patient's family should be reminded about the good hygiene practices. A small take home summary (preferably one-page, plasticized document) could ensure that patients and patient's family easily can consult the information and all the instructions.

SBB's comment :

During the validation period of the dossier, the notifier has been suggested to provide a patient information sheet that would collect 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. The notifier commits to have all these recommendations reported in the informed consent document (ICD) instead of on a separate document. However, as the local ICD will be discussed with the patient and signed weeks in advance of the actual administration of vector and as the ICD contains a lot of information, special instructions on good hygiene practices might not get the proper attention at the right moment (when the patient leaves the hospital). For some patients it will be easier to have all the relevant information summarized on one single page rather than having to search for information in a multi-page document. Therefore, the notifier could be requested to provide a small take home summary (preferably one-page, plasticized document) that could ensure that patients and patient's family easily can consult the information and all the instructions in an understandable format whenever needed.

The following information (with their duration) should be reported in this instruction sheet for the patient:

- Which bodily fluids are anticipated to contain viral vector genome (albeit very low levels)
- Instruction on good hygiene to be practiced
- Instructions aimed at limiting contact with materials or surfaces frequently contaminated with bodily fluids (e.g. handkerchiefs, toys that may be shared with brothers/sisters of the trial participant).
- Effective solutions to decontaminate possible contaminated areas, tissues, skin, …
- Restriction on blood, organs, tissue and cells for transplantation donation
- The obligation to use contraceptive methods

According to the public CAF document, section 3.6.6, page 13/16, information on restriction on blood, organs, tissue and cells donation will be provided in the patient card that will be given to the patient after treatment. What information is included on this card? We would like to propose these different recommendations for the patient to be mentioned on this card as well.

Coordinator's comment:

Agreed. As viral vector present in body fluids will be very low this can be added. I guess the notifier also does not want to scare patient/caregivers

The response of the Sponsor to question 5 (see document "B_BE_24_BVW5_Response to validation questions_09Feb2024") is not considered to be adequate and sufficient.

The Sponsor has the opinion that comprehensive information on the raised issues is already included in the Investigational Product (IP) Manual (Version 6 dated 04 April 2023), Safety Data Sheet (dated 28 June 2023) and Study C0371002 protocol (Amendment 5 dated 09 May 2023). Thus the Sponsor proposes that no additional technical sheet is required. These three documents are large in size and the relevant information is in many instances present in different sections of the documents and as such not as easily accessible as in a requested hands-on technical sheet (2-4 page), intended to be given as an hands-on document for study staff. Furthermore, not all three documents work out necessary information to the same detailed level: e.g. detailed instructions how to handle in case of a spill.

SBB's comment :

During the validation period of the dossier, the notifier has been suggested to provide a technical sheet (2-4 page), intended to be given as an hands-on document for study staff. As all the requested

information is already present in different documents, listed in his response, the notifier does not plan to provide an additional technical sheet. However, these documents are lengthy and the relevant information is in many instances distributed over different sections of the documents and sometimes with different level of detail. As a result, the required information is not as easily accessible as in a hands-on technical sheet (2-4 page). The notifier could therefore be requested to provide a hands-on technical sheet (2-4 page), intended to be given as an hands-on document for study staff.
This sheet should include all relevant handling instructions, detailed procedures to handling a spill including appropriate disinfectants, waste management and other risk management measures:
- the use of personal protective equipment for health care workers (e.g. specify which PPE are mandatory)
- procedure in the event of accidental occupational exposure through a splash in the eyes, mucous membrane, needle-stick injury or contact with skin and clothing
- procedures for treatment of accidental spill (disinfectant, concentration of disinfectant, contact time)
- procedures to prevent and to deal with direct exposure to blood, urine, vomit or other bodily fluids from patients in the initial period after administration of the IMP
- waste management

Coordinator's comment:
Agreed. I understand the hesitation of the notifier, but I do agree that we should aim to provide all required info in such a way that the environmental risk is minimized. On the other hand, we should also not provide too much information. Still, in this case I'm convinced that this document provides substantial information for the healthcare staff, and allows them in case of a spill accident to act swiftly.

With respect to the instructions how to handle in case of a spill the SNIF and the common CAF even mentions the use of alcohol wipes after disinfection using a bleach solution. Use of alcohol in combination with bleach show be avoided.

SBB's comment :
This point has been included within the SBB's comment for "Comment to expert 1" here above in the same section 3.6.

Only the common CAF document mentions restrictions to donate blood, cells, organs, tissue after treatment with the vector. The sponsor should be requested to update the ICD and possibly other documents (SNIF?) with restrictions to donate blood, organs, tissues, and cells.

SBB's comment :
Referring to section 3.6.6 of the public CAF document (p13/16), patients treated with this medicinal product should not donate blood, organs, tissue and cells for transplantation. No period (minimal period) for prohibition has been indicated for donation of blood, tissues or cells. The notifier could be requested to report in the CAF the duration of this restriction (for example, two negative tests?). Furthermore, the notifier could also be requested to report this restriction regarding blood, organs, tissue and cells for transplantation donation in the Main ICD and in the SNIF document.

Coordinator's comment:
Agreed. The indication of the period would be most essential in my opinion.

Comment 3

I suggest to include in the IP-manual for staff clear instructions for disposing of all waste contaminated with the IMP and generated during preparation and administration of the AAV-based IMP. This waste should be disposed of as a biohazard material and should be incinerated.

SBB's comment :

In the IP-manual for staff, no clear instructions have been reported for disposing of all waste contaminated with the IMP and generated during handling, preparation and administration of the AAV-based IMP. According to the SNIF and the CAF documents, all materials that may have come in contact with fidanacogene elaparvovec (eg, vial, all materials used for injection, including needles and any unused product) must be double bagged in bags. These bags should bear the biohazard symbol and sealed with tape. The bag must then be disposed of per local guidelines for handling of biohazardous waste, such as being placed in a biohazard waste container, before being incinerated. The notifier could be requested to align the waste management procedure in the IP-manual with that in the SNIF and CAF documents.

Coordinator's comment:

Agreed. I presumed that the collected material would be incinerated since it would be treated as clinical waste after being double sealed. If that is not a given, I would indeed suggest to align the procedures.

Additional SBB's comment:

In the SNIF, Table 1 "Management of incidents related to fidanacogene elaparvovec" (p18/19), no procedure has been reported in case of "contact with mucous membrane". The notifier could be requested to update this table by reporting the procedure to be followed in case of contact with mucous membrane.

Coordinator's comment:

I'm not sure whether this will add much to the overall procedure. Personally, I reckon it would be best to apply a uniform approach. If this topic (mucous membrane exposure) is included in other management of incidents instructions, it would be best to include it now as well.

SBB's comment :

Procedure to be followed in case of unexpected contamination of clinical site personnel by contact with IMP that involves a mucous membrane such as the mouth is not described repeatedly through the different dossiers.

Additional SBB's comment:

According to the response of the notifier to the validation question number 4, it is defined by the study protocol, that only male participants who meet study eligibility and agree to the following vertical transmission mitigations will receive study medication. However, it is not clear from the inclusion/exclusion criteria in the protocol, that women cannot participate to this clinical trial. As women can also have hemophilia, although very rarely, the notifier could be requested to clearly indicate in the protocol whether women may or may not participate to this clinical trial.

Coordinator comment:

Here I do not agree. The title of the trial (as indicated higher up in this document) states: *"A Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435*

(rAAV-Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2)." Accordingly, the latter comment does not hold.

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

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

Comment 3

None

References

/

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Pfizer Inc. on the list of questions for dossier B/BE/24/BVW5

23 April 2024
Ref. SC/1510/BAC/2024_0595

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

INTRODUCTION

Dossier **B/BE/24/BVW5** concerns a notification from Pfizer Inc. for a clinical trial entitled "A Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2)".

On 25 March 2024, based on a list of questions prepared by the BAC (SC/1510/BAC/2024_0420), the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions were received by the Competent Authority on 09 April 2024. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

In my view the applicant addressed the comments/questions 1-5 correctly and satisfactorily. The reply to the comment/question 6 is not addressed correctly. Instead of adding the requested info to the dossier, the applicant decided to delete the item 'Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject' completely from the dossier. This is not acceptable.

SBB's comment:
The expert's comment is supported and could be forwarded to the notifier as follows:
Recommendation on blood, organs, tissue and cells for transplantation donation should be provided to the patient and should therefore be mentioned in the different documents. The notifier is requested to provide 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.

Evaluation Expert 2

By this email, we would like to let you know that the notifier did not address correctly and satisfactorily the comments/questions that have been raised in March especially concerning the question n°3 to the applicant in the “1 C0371002_Belgium CTA_GMO Queries Response_05Apr2024” document.

We don’t agree with the applicant answer because the Belgian BAC suggested:
-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 all the documents or should avoid the suggestion of using alcohol following sodium hypochlorite decontamination.

Otherwise, the applicant proposed this following modification :
Upon completion of this decontamination contact time, rinse away residual decontamination solution with water, the hood should then be cleaned using the local standard cleaning solution (e.g., 70% alcohol, etc.) to remove any remaining decontamination solution from surfaces. Please note that 70% alcohol is not an appropriate decontamination solution for this gene therapy product.

By this way, the applicant proposed to rinse away the residual decontamination solution by dilution in water without neutralization before using alcohol solution to remove any remaining decontamination solution from surfaces.

We would like to invite the applicant to clearly indicate that:
1) the sodium hypochlorite solution should first be neutralized with a 3% sodium thiosulfate solution to avoid the potential interaction with alcohol if alcohol is used after, as local standard cleaning solution. The dilution of the residual decontamination solution in water is here, not sufficient and not appropriated before using 70% alcohol as local standard cleaning solution.
2) the 70% alcohol is not an appropriate solution to remove any remaining decontamination solution from surfaces when sodium hypochlorite solution is used as the standard decontamination solution for this gene therapy product.

SBB’s comment:
The expert’s comment is supported and could be forwarded to the notifier.

Evaluation Expert 3

Étant donné qu’ils ont fourni un document clair regroupant toutes les procédures de préparation, administration et élimination des déchets issus de ces manipulations, destiné au personnel, c’est acceptable.

SBB’s additional question

According to page 33/162 of the protocol, “semen samples can be collected at home the night before a clinic or mobile phlebotomy/ home health service visit and stored in the participant’s freezer until the clinic or mobile phlebotomy/home health service visit”. 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

Coordinator's comment
I would not include this.

SBB's comment:
As it is not sure whether home visits will be performed or not, it has been decided, following discussion with FAMHP, to ask the applicant whether home visits will be performed in Belgium. As for a previous clinical trial with a recombinant AAV serotype rh74, an instruction sheet for caregivers who will visit patients at home was requested, such an instruction sheet will also be requested here to be consistent between the different dossiers.

Coordinator's comment
Agreed.

SBB's comment on question 4

Semen samples can be collected at home the night before a clinic or mobile phlebotomy/ home health service visit and stored in the participant's freezer until the clinic or mobile phlebotomy/home health service visit (see protocol page 33/162). As these samples could potentially contain viral vector genome, clear instructions for the patients regarding semen samples collection and storage in the freeze should be provided. The notifier is therefore requested to include these instructions on the "Instruction sheet for the patient".

Coordinator's comment
I would not include this.

SBB's comment:
Instructions for patients who will collect semen samples at home has never been provided in previous biosafety dossiers and will not be requested for this dossier either.

Coordinator's comment
Agreed.