Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/20/BVW4 of the company Pfizer Inc. for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

05/02/2021
Ref. SC/1510/BAC/2021_0105

Context

The notification B/BE/20/BVW4 has been submitted by Pfizer Inc. to the Belgian Competent Authority in September 2020 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 entitled “A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy”. This multicentric clinical trial aims at investigating whether the investigational medicinal product (IMP) can safely alter the clinical phenotype of ambulatory male participants, ages ≥4 to <8 years, with a genetic diagnosis of Duchenne Muscular Dystrophy (DMD) who are on a stable daily regimen of glucocorticoids.

DMD is an X-linked muscular dystrophy which predominantly affects boys. It is caused by a mutation in the gene coding for the protein dystrophin. The lack of fuctional dystrophin protein results in the degredation of skeletal muscle. Ultimately heart and respiratory muscles are affected, causing premature death of DMD patients.

The experimental gene therapy approach planned with this study aims at delivering a shortened version of the dystrophin gene (mini-dystrophin), which has been designed on the basis of the mutant form of the gene carried in a mildly affected patient.

The IMP PF-06939926 is a disabled version of a non-pathogenic wild-type adeno-associated virus (AAV), modified by deletion of the *rep* and *cap* genes rendering it unable to replicate, even in the presence of a helper virus. The vector genome contains a synthetic promoter intended to drive skeletal and heart muscle specific gene expression, mini-dystrophin, a polyadenylation signal, flanked with AAV2 inverted terminal repeats and it is encapsidated within AAV9 capsid.

Overall, aproximately a hundred patients will be included in this Phase III study and three patients will be included in Belgium, each receiving a single dose of 2.10^{14} vector genome/kg weight. Vector shedding will be monitored at several time points after administration utilizing qPCR.

Biosafety Advisory Council - Secretariat • Service Biosafety and Biotechnology (SBB)
Sciensano • Rue Juliette Wytsmanstraat 14 • B-1050 Brussels • Belgium
T + 32 2 642 52 93 • bac@sciensano.be • www.bio-council.be

This study should be conducted in three clinical sites located in Flanders and Wallonia. The national territory is considered as the potential release area of PF-06939926.

The dossier has been officially acknowledged by the Competent Authority on 18 September 2020 and forwarded to the Biosafety Advisory Council (BAC) for advice.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Three experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The SBB also took part in the evaluation of the dossier. The experts and the SBB 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 (GMO) would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments from the experts.
The GMO laboratory (Transversal activities in applied genomics) of Sciensano evaluated the analytical procedure for the detection of PF-06939926.

The scientific evaluation has been performed considering the 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.
- Good practice document on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors developed by the national competent authorities and the Commission services available at https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/aavs_gp_en.pdf

The pure medical aspects concerning the efficacy of the IMP 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 30 October 2020, 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 04 December 2020 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the BAC and resulted in a second list of questions, which was transmitted to the notifier on 18 December 2020. The answers of the notifier were received on 27 January 2021 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 six reactions from the public of which none were related to biosafety issues.

Summary of the scientific evaluation

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

Upon assessment of the production protocol, the BAC asked the notifier to provide further clarification on the detection limit and the methodology of the assays for detection of replicating competent AAV (rcAAV) and the extent of homology between vector and helper plasmids. More explanation was also asked on how the rcAAV concentration was estimated on the basis of statistical analysis of historical PF-06939926 data set. The additional information provided in this context along with the use of PF-06939926 in the context of the proposed clinical trial and implementation of management measures (see below) adds to the consideration that potential exposure of non-target individuals (e.g. accidental exposure of heath care professionals at clinical trial site; exposure of close contacts because of shedding) would occur with much lower amounts of the drug product compared to the clinical dose.

The donor, recipient and parental organisms were found to be adequately described in the dossier.

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

The molecular characteristics of PF-06939926 including phenotypic and genetic stability of the transgene were found to be adequately described in the dossier.

3. The conditions of the release

In this study, comprising of two cohorts, two single intravenous infusions will be administered to each patient, one with PF-06939926 as a dose of 2.10^{14} vector genome/kg body weight and one with placebo. The first cohort will first receive a dose of PF-06939926 followed by a dose of placebo at Day 390, the second cohort will first receive a dose of placebo followed by a dose of PF-06939926 at Day 390. All participants will be followed for a duration of five years after administration of the IMP.

The BAC takes notice that no shedding data from study subjects are made available yet and that the current study will investigate viral vector shedding in whole blood, saliva and urine, at several time points after administration using polymerase chain reaction (PCR). Testing will be continued until two consecutive results are at or below the limit of detection as determined for each of the matrices.

According to the information provided by the notifier all involved personnel on the sites during preparation and administration are required to wear disposable back closing gown, safety glasses, goggles or mucous splash protector, gloves, hair coverage, and shoe covers. The preparation of the IMP for administration will be conducted in a biological safety cabinet.

While non-replicating, it is anticipated that PF-06939926, like any other AAV, is stable in a wide pH range (3-9) and like other non-enveloped viruses, is quite resistant to alcohol disinfectants. Following a remark of the BAC with respect to the decontamination procedure upon completion of PF-06939926 or placebo preparation in the biological safety cabinet, the notifier provided additional justification for the proposed procedure and, after a second question, provided more detailed instructions with respect to the use of appropriate disinfectans[1].
The notifier was also asked to detail in a short, readable format what exactly is requested from the

[1] IP Manual v.4.0 dd.07Jan2021forC3391003

patient and family/friends with respect to good hygiene practices.
The notifier adequately implemented the remarks and requests addressed by the BAC in a revised version of documents including the revised patient information note [2] and informed consent[3]. With respect to the Patient and Guardian Special Instructions Summary, the BAC has one last remark on the handling of piece of cloth, tissue or any other material that has been in contact with bodily fluids from the patient (such as blood, urine, saliva, etc.).

4. The risks for the environment or human health

PF-06939926 is a recombinant, replication deficient adeno-associated virus-based vector not harbouring any antibiotic or other resistance genes. Like its parental strain, it is not known to be pathogenic. The genetic modification introduced in this AAV2/9-derived vector does not 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 AAV2 in the IMP wild-type AAV in case a triple infection by PF-06939926, 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 AAV2 required for replication and encapsidation but would in turn lead to the loss of the transgene. Moreover, the genetic material from *rep* and *cap* genes together with the transgene would be too large in size to be packed in AAV capsid, making it impossible to form a viral particle that would contain the transgene and the *rep* and *cap* genes necessary for multiplication.

In the case of transfer of vector to an unintended human recipient, the risks are expected to be considerably reduced as compared to any potential risk for the participant, since the vector is not able to 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.

The BAC wants to emphasize that shedding data collected form the Phase 1b and the proposed phase III study will further contribute to a proper environmental risk evaluation. These data will need to be evaluated in light of the observed quantity of shed viral material, and the period of time during which shedding is observed. It will be important to answer the question whether the observed shed PF-06939926 is only vector DNA or a remnant thereof, whether or not it is present in shed cells, whether it reflects integrated vector DNA in shed cells or whether it consists out of remaining or rescued replication-deficient viral vector particles. In its response to the question of the BAC, the notifier informed that complete shedding profiles of patients enrolled in the Phase 1b clinical study (C3391001) are not available yet and that these will be complemented by additional viral vector shedding assessments undertaken in the Phase 3 pivotal (C3391003) clinical study.

The BAC concludes that, based on the non-pathogenic and non-replicative nature of PF-06939926 and the assumed lower amounts of shed and intact viral particles of PF-06939926 as compared to the therapic dose, the overall risk associated to exposure and transmission to other individuals can be considered negligible.

[2] 2019-002921-31_Patient and Guardian Special Instructions Summary v.1.0.dd.22Jan2021-studyC3391003
[3] (2019-002921-31_C3391003_Belgium_English_ICD_Main_V3.3.0_22Jan_2021)

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

While the instructions for staff were found sufficiently detailed for how the IMP should be prepared, the BAC remarked that the clarity of information to be provided to health care workers could be improved and benefit from a Technical Sheet with Personnel Instructions that summarizes precautions, biosafety procedures and details specific steps in regards the decontamination of spills, disposal of contaminated material, and accidental exposure for use in the pharmacy and treatment room. The format of such a Technical sheet (1-2 pages) facilitates the health care workers to have it on hand. The BAC also made specific remarks with respect to clear instructions on the use of appropriate disinfectant.
The notifier implemented the suggestion of providing a technical sheet and also implemented the remarks of the BAC in the corresponding revised documents [4], [5].

Given the assessment of the likelihood of further propagation of PF-06939926, 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 experts, the Biosafety Advisory Council concludes that it is unlikely that PF-06939926 developed as a gene therapy approach for the Treatment of Duchenne Muscular Dystrophy, 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 new or updated documents:

- Investigational Product Manual Protocol Number C3391003, Version 4.0
- PF-06939926 Technical Sheet for Investigational Product (IP) Handling, Version 3.0, dated 08 January 2021
- 2019-002921-31_Patient and Guardian Special Instructions Summary v.1.0.dd.22Jan2021-studyC3391003 , taking into account the text adaptation provided by the BAC[6]
- 2019-002921-31_C3391003_Belgium_English_ICD_Main_V3.3.0_22Jan_2021)

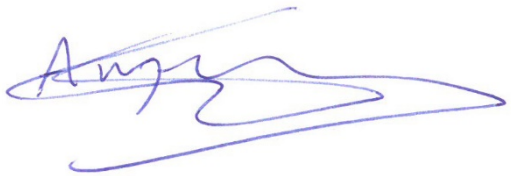
[4] PF-06939926 Technical Sheet for Investigational Product (IP) Handling, Version 3.0, dated 08 January 2021

[5] Investigational Product Manual Protocol Number C3391003, Version 4.0

[6] Proposal for text modification 'Patient and Guardian Instructions Summary' : To prevent the potential spread of participles of study drug, especially for the month before and during the first 2 months after receiving study drug, any piece of cloth, tissue or any other material that has been in contact with bodily fluids from you/your child (such as blood, urine, saliva, etc.) should be thoroughly washed with a disinfectant detergent (Dettol or something similar) for at least 30 minutes at 90 degrees Celsius, or, if 90 degrees Celsius is not possible, use the maximum temperature of your machine with a disinfectant detergent. Spills on surfaces that cannot be washed should be cleaned with a washable cloth in combination with detergent or if possible a commercial disinfectant (Dettol, eau de Javel, etc.).

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

- The notifier and the investigators must strictly apply the clinical trial protocol and the safety instructions as described in the dossier and the updated and new documents listed here above.
- The notifier takes due account of its commitment to report shedding data obtained from the planned clinical trials in view of any further step in the clinical development of PF-06939926.
- Any protocol amendment has to be previously approved by the Competent Authority.
- The notifier is responsible to verify that each study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorisations 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 the contained use of genetically modified micro-organisms.
- The BAC 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 the competent authority for the attention of the BAC a report with details concerning the biosafety aspects of the project. This report shall contain at least:
  - 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 PF-06939926.



Prof. Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex I: *Compilation of comments of experts in charge of evaluating the dossier B/BE/20/BVW4 (ref. SC/1510/BAC/2021_0084, SC/1510/BAC/2020_1198, SC/1510/BAC/2021_0091)*

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/20/BVW4
And comments submitted to the notifier

30 October 2020
Ref. SC/1510/BAC/2021_0084

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 18 September 2020.
Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Aline Baldo (Sciensano, SBB)
SBB: Katia Pauwels

INTRODUCTION

Dossier **B/BE/20/BVW4** 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 18 September 2020 and concerns a clinical trial entitled “Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy”. The investigational medicinal product is a AAV9- 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 30 October 2020 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

List of comments/questions received from the experts

2. INFORMATION RELATED TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1. Description of the production system

(e.g. maps of the vectors used, characteristics of the cell lines used, possibility of complementation or recombination….)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

The adenovirus helper plasmid (pXX680) contains sequences coding for the adenoviral late genes L3, L4 and L5.(page 63 of the IMPD) The only genes necessary for AAV helper effects are E1A (expressing by the 293 cells), E2, E4orf6 and VA (Grimm *et al.,* 2002). Additional sequences could code for immunogenic proteins. Are L3,L4,L5 or portions of it expressed by the plasmid?
The notifiers specifiy that they will later on modify the production protocol and use another adenoviral helper plasmid (Ad-Helper2; page 2-in 1b_EudraCT_2019-002921-31_Common Application Form_Confidential Annex) which does not carry sequences coding for late genes. However, in the planned Phase III clinical trial, the rAAV batches were still produced using pXX6-80. The purity of the viral batches raises > 98% . However, around 1-2 % of high molecular weight proteins are present in the final product (see IMPD Page 205, 221, 265 and 289). The notifier does not show a characterization of these contaminating proteins. A SDS-page gel showing the purity of the final product would be useful. Neither do they report an evaluation of the potential immune response that adenoviral contaminant proteins (if present) could induce.
However, if a care personal is exposed, the amount of virus to which he/she will be in contact with, is presumably low and the probability that a toxic immune response will be elicited is negligible.

SBB comment :

The evaluation of the purity of the viral batches, such as a characterization of contaminating proteins, are relevant for the quality assessment of the drug product but goes beyond the environmental risk assessment of PF-06939926. Also, it should be remarked that the inclusion of the IMPD into the biosafety dossier is not mandatory. From the perspective of the environmental risk assessment and as pointed out by the expert, exposure of non-target individuals (e.g. accidental exposure of heath care professionals at clinical trial site; exposure of close contacts because of shedding) will be exposed to much lower amounts of the drug product compared to the clinical dose.

Coordinator comment :
Agreed

Comment 4
Has not evaluated this item.

2.2. Demonstration of absence of formation of replication-competent virus
(e.g. assessment of risk of generation of replication competent AAV, test methods and test data, ….)

Comment 1

p208/466 - 10_2019-002921-31_IMPD.pdf: the infectious virus titer is determined. Maybe I'm mistaken, but I guess, the applicant discusses viral vector titers, and transduction of cell lines using the drug product, and not contaminating AAV virus in the AAV vector prep. For clarity, it would be better to replace the word 'virus' by 'viral vector'.
Further on the same page, the applicant writes 'The assay involves infection of myotubes by PF-06939926', here, transduction is meant.
On p209, results are reported as picograms (pg) HCP/1E9 viral genomes (vg), this should be (AAV) vector genomes. See also, p22/28 in 1b_EudraCT_2019-002921-31_Common Application Form_Confidential Annex.pdf.

p221 & 224/466 - 10_2019-002921-31_IMPD.pdf: the applicant indicates that rcAAV is detected in their assay. Detection limit is indicated to be 10 IU of wild type AAV2 in 1E10 vg PF-06939926. With two instances of rcAAV detected (even though this was not shown for all test flasks) in the production, can it be overall considered to be safe? Should the sensitivity of the test be improved? Was this really a rcAAV, or an external AAV2 infection of the flasks?

SBB comment:
In addition to the expert's comment : Table S.2.6-26 (p158 of IMPD) on release testing summary for Drug substance also reveals that rcAAV was detected in process 2 reference material, though it is remarked that Phase 2 reference material was not used for clinical trials.

On p221 (bath analysis for process 1 non clinical toxicology and references standard) it is stated that the detection limit is 1 IU of wild type AAV2 in 1E10 vg PF-06939926 for two of the tested batches.

Proposal question to be addressed to applicant :

With two instances of rcAAV detected (even though this was not shown for all test flasks) in the production (p221 & 224/466 - 10_2019-002921-31_IMPD.pdf) and one instance of rcAAV detected in process 2 reference material (Table S.2.6-26, p158 of 10_2019-002921-31_IMPD.pdf), the applicant is asked to discuss the probability of rcAAV into more detail.
The applicant is asked to clarify why detection limit was not 1 IU of wild type AAV2 over all tested flasks?
Could the applicant confirm there was no external AAV2 infection of the flasks ?

p265 Table P.5.1-1. PF-06939926 Drug Product Specifications rcAAV is not included. Also further on in this section (p275-277/466 - 10_2019-002921-31_IMPD.pdf) the applicant provides the Justification of acceptance criteria for PF-06939926 drug product in Table P.5.6-1, however, formation of rcAAV is not included in this Table. I would consider this to be an intrinsic part of the batch control and drug product analysis. Why is this not monitored?

SBB comment:
A copy of certificate analysis is provided at page 312 and 313, which contains a conclusion on rcAAV formation.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has not evaluated this item.

2.3. Diagram (map) of the clinical vector

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has not evaluated this item.

2.4. Molecular characterisation of the clinical vector

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

Comment 1

The applicant thoroughly tested the presence of contaminating DNA in the different drug substance badges (p198/466 - 10_2019-002921-31_IMPD.pdf) and shows presence of a segment of E1A DNA in all instances, which is presumably protected by the AAV capsid. Between 9 - 320 copies/1E9 vg are detected in clinical preps. Considering doses of >1E14 to be used, these numbers increase substantially in the final product applied to the patient. It is difficult to judge the importance of this assay. Is the E1A DNA functional; can it transform cells in culture for example?

SBB comment :
The evaluation of the purity of the viral batches, such as presence of segment E1A DNA , may be relevant for the quality assessment of the drug product but goes beyond the environmental risk assessment of PF-06939926.

Coordinator comment :
Agreed

P70/89 in document 7_EudraCT_2019-002921-31_Investigator-Brochure.pdf the applicant reports "3 subjects in Cohort 1 (all received 1E14 vg/kg per ITR assay) and 8 subjects in Cohort 2 (6 received 3E14 vg/kg per ITR assay and 2 received 2E14 vg/kg per TG assay)."
AAV vector titers are calculated based on PCR analysis of vg. However, depending on the ratio of full and empty AAV particles (AAV particles without, or with incomplete genomes contaminate all AAV preps - these ratios vary between different preps), the effective number of particles injected will differ. In the end it is this what may result in adverse events. The applicant indicates later in the same document (p81/89): "The ongoing first-in-human (FIH)/first-in-patient (FIP) clinical study C3391001 will explore ascending single doses of PF-06939926; (1) 1E14 vector genomes/kilogram (vg/kg), and (2) 3E14 vg/kg, with the option to de-escalate to 2E14 vg/kg in case of a suspected dose-limiting toxicity at the highest dose level.". Since the full/empty ratio will differ between preps, I wonder whether this should/could be taken into account to determine the effective drug concentration of the product.

SBB comment:
These comments relate to patient's safety considerations and go beyond the environmental risk assessment.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has 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

The patients are screened for pre-existing immunity by assessing NAb for AAV9. However, a study by Flanigan, 2013 reported on pre-existing T cell responses to dystrophin in DMD patients. This will also jeopardise the effectiveness of the gene therapy, and may result in adverse events for the patient. Flanigan and co-workers showed a higher prevalence of anti-dystrophin T cell responses with age and that corticosteroids treatment modulated that risk. Are the patients also evaluated for dystrophin Ab, and if so, how does this affect their inclusion criteria?

SBB comment:
These comments relate to patient's safety considerations and go beyond the environmental risk assessment.

Coordinator comment :
Agreed

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has not evaluated this item.

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

P25/28 in 1b_EudraCT_2019-002921-31_Common Application Form_Confidential Annex.pdf: biodistribution is described for dogs and rats, however, distribution largely depends on the dose applied. Since this study applies high doses of rAAV vectors one should consider that biodistribution may be different from the one described in dogs and rats. In addition, the higher doses will also affect the shedding characteristics.

P3/466 of 10_2019-002921-31_IMPD.pdf: PF-06939926 doses range from 1E+14 vg/kg (low) to 3E+14 vg/kg (high). No safety concern has arisen in studies for systemic AAV delivery at various dose ranges in mouse models of neuromuscular diseases studies. However, toxic responses were reported when high-dose (>7.5x10e13 vg/kg) AAV was delivered intravenously in large mammals. Kornegay *et al*. (2010) reported severe adverse events upon delivery of AAV-9 vector expressing mini-dystrophin to three 4-day-old dystrophin null dog puppies at the dose of 1.5x10e14 vg/kg. In two recent studies also the Wilson lab reported on adverse events elicited by high dose AAV treatments (Hinderer *et al*., 2018; Hordeaux et al., 2018). Additionally, recently the US FDA halted a phase2 gene therapy trial of Audentes

Therapeutics for a rare neuromuscular disease following the death of three patients receiving the higher dose of the investigational treatment AT132, a gene therapy vector (AAV8) in a Phase I trial for X-linked myotubular myopathy (MTM) (see weblinks below).
In how far can the high doses applied in the current study result in adverse events? The applicant already reports on two serious adverse events (p15/19 - 2a_EudraCT_2019-002921-31_SNIF.pdf and p10/20-1a_EudraCT_2019-002921-31_Common_application_form_Belgium.pdf): '*PF-06939926 is currently being investigated in a Phase I FIH study (C3391001) in up to 12 patients. Two serious adverse events have been reported after receipt of the drug but could be resolved*'. Was this in the higher dose patients, and was the dose believed to be the underlying cause (mentioned only p87/89 in 7_EudraCT_2019-002921-31_Investigator-Brochure.pdf). Also in other trials high doses of AAV have been linked to adverse events (e.g. Table6 in Duan,, 2018).

SBB comment :
Whether high doses of AVV are at the origin of reported adverse events observed in treated patients is predominantly relevant from the viewpoint of patients' health after treatment. Form an environmental risk assessment point of view, hazards associated to high amounts of the drug product should be balanced against the likelihood of accidental exposure of non-target individuals to such high doses of the drug product (during preparation of an injection sample for example).

Coordinator comment :
Agreed

Shedding is discussed on p10/20-1a_EudraCT_2019-002921-31_Common_application_form_Belgium.pdf. In my opinion it is not correct to consider the risk to humans and the environment associated with viral shedding of PF-06939926 as negligible. The applicant indicates that shedding data will be collected with the Phase 3 study (C3391003) of PF-06939926 in DMD, which is anticipated to provide definitive characterization of the viral shedding profile. Until those data are collected, the risk should at least be considered low.

SBB comment :
It is agreed that shedding data collected form the Phase 1b and the proposed phase III study will contribute to a proper environmental risk evaluation. These data will need to be evaluated in light of the observed quantity of shed viral material, the period of time during which shedding is observed. It will be important to answer the question whether the observed shed PF-06939926 is only vector DNA or a remnant thereof, whether or not present in shed cells, whether it reflects integrated vector DNA in shed cells or whether it consists out of remaining or rescued replication-deficient viral vector particles.
Given the route of administration and dose, the likelihood of shedding can be low to moderate. However, given the low infectivity rate of recombinant AAV's and the likelihood of non-target to be exposed to sufficient amounts to enable efficient transduction, it can be argued that the risk are expected to be negligible (see specific ERA document developed under the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors[1]).

Coordinator comment :
Agreed

[1] https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/aavs_gp_en.pdf

P93/139, section 8.4 in 6_EudraCT_2019-002921-31_Protocol-Amendment-1.pdf the applicant indicates that “For this study, any dose of PF-06939926 greater than a single administration of 2E+14 vg/kg within a 24-hour time period will be considered an overdose.” This is contradictory to what is mentioned in P3/466 of 10_2019-002921-31_IMPD.pdf: PF-06939926. The specific method used to determine titers should also be included.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

I did not find shedding data from the Phase I clinical trial. A phase I clinical trial consisting in minidystrophin gene transfer for DMD has been completed (Bowles *et al*., 2012) but it was using intramuscular injections of AAV2.5 whereas in the planned Phase III clinical trial, they will use AAV9 injected intravenously.

SBB comment :

A shedding plan for both the ongoing phase 1b study (C3391001 study - treatment of boys to 2 years of age) and the proposed Phase 3 study is described in 1a_EudraCT_2019-002921-31_Common_application_form_Confidential Annex.pdf. It is likely that shedding data were not available yet at the time of the current biosafety dossier submission.

Coordinator comment :

I think that this is an absolute necessity in order to be able to truly evaluate the risk and they should be required to provide updated information.

Question to be addressed to the notifier :

Shedding data collected form the Phase 1b and the proposed phase III study will contribute to a proper environmental risk evaluation. These data will need to be evaluated in light of the observed quantity of shed viral material, the period of time during which shedding is observed. It will be important to answer the question whether the observed shed PF-06939926 is only vector DNA or a remnant thereof, whether or not present in shed cells, whether it reflects integrated vector DNA in shed cells or whether it consists out of remaining or rescued replication-deficient viral vector particles. It is likely that shedding data were not available yet at the time of the current biosafety dossier submission. However, the notifier is requested to provide an update shedding data from the Phase 1b if available.

Comment 4

Has evaluated this item and has no questions/comments.

3. INFORMATION RELATED TO THE CLINICAL TRIAL

3.3. Storage of the clinical vector at the clinical site

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

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

See 3.6

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

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.

Comment 4

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

On p16/37 in 10_EudraCT_2019-002921-31_Instructions-for-staff-IB-Manual.pdf, the applicant proposes decontamination measures upon completion of PF-06939926 or Placebo preparation: "all internal hood surface areas must be thoroughly decontaminated using 10% bleach. The 10% bleach minimum required contact time is 20 minutes. Upon completion of this contact time, the hood should be cleaned using the local standard cleaning solution (e.g. 70% alcohol, etc.) to remove any remaining decontamination solution from surfaces."
This may be effective to inactivate the AAV vector, but is not feasible since surfaces will be corroding. On top, bleach will precipitate the proteins/vectors and removal from the surface may even be more difficult. I would propose to use a detergent/EtOH70% to clean the surface of possible contamination (knowing that this does not inactivate the vector, but rather cleans the surface), and subsequently inactivate the cloth in bleach 10% solution for appropriate time. Also for a spill, first contain the spill and inactivate afterwards. Wescodyne or detergent-based disinfectant are good suggestions, but provide working solutions that have proven effective. Please adapt procedure.

Coordinator comment :

Agreed.

In addition, the 10_EudraCT_2019-002921-31_Instructions-for-staff-IB-Manual is very detailed for how they want the drug product to be prepared but rather thin on what happens in case of an accidental spill, needle stick injury or other event.

AAV (wt and rAAV) are resistant to some disinfectants, dehydration and are known to persist in aerosols or aqueous solutions. For this reason, it is CRITICAL that clear information be provided to the health care workers involved in preparing and administering the drug product that detail the correct procedures to follow after accidental exposure. A 1-2 pg plasticized Technical Sheet that summarizes precautions, biosafety procedures, decontamination of spills, disposal of contaminated material, and accidental exposure for use in the pharmacy and treatment room is indispensable for the health care workers to have on hand.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

In the common application form, the applicant says that “patients and those around him will also be reminder to practice good hygiene, especially for the month prior to and during the first 2 months after each IMP administration.” Could the applicant explain what means ‘good hygiene’ in this context and give more details?

Coordinator comment :

Agreed, if the patient and family/friends are required to be careful in some way then it is necessary to provide a Patient Instruction sheet that explains simply in a short, readable format what is necessary.

Furthermore, there are detailed instructions for the correct preparation and administration of the drug product but no Biosafety Manual or Personnel Instructions describing procedures that reduce accidental exposure through spills or needle stick injuries, and what the specific steps are that should be taken in the event of an accident. While the centers involved are experienced in handling biohazardous materials it is the responsibility of the company to provide details on a clear and concise plan of action to be followed in the event of accidental exposure, including necessary medical follow up. Every drug product will be different and may require modifying standard approaches to insure full containment.

Could the applicant consider the breaking of a hold vial containing the IMP and the disinfection procedures in this case?

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.

Comment 4

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

Comment 4

None

References

Bowles DE, *et al*. Phase 1 gene therapy for Duchenne muscular dystrophy using a translational optimized AAV vector. Mol Ther. 2012;20(2):443-55.

Duan D. Systemic AAV Micro-dystrophin Gene Therapy for Duchenne Muscular Dystrophy. Mol Ther. 2018 Oct 3;26(10):2337-2356. doi: 10.1016/j.ymthe.2018.07.011. Epub 2018 Jul 1

Flanigan KM *et al*. Anti-dystrophin T cell responses in Duchenne muscular dystrophy: prevalence and a glucocorticoid treatment effect. Hum Gene Ther. 2013 Sep;24(9):797-806. doi: 10.1089/hum.2013.092.

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Hordeaux J, The Neurotropic Properties of AAV-PHP.B Are Limited to C57BL/6J Mice. Mol Ther. 2018 Mar 7;26(3):664-668. doi: 10.1016/j.ymthe.2018.01.018. Epub 2018 Feb 2
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Kornegay JN *et al*.Widespread muscle expression of an AAV9 human mini-dystrophin vector after intravenous injection in neonatal dystrophin-deficient dogs. Mol Ther. 2010 Aug;18(8):1501-8. doi: 10.1038/mt.2010.94. Epub 2010 Jun 1.

Weblinks

https://www.nature.com/articles/s41587-020-0642-9 ;
https://myotubulartrust.org/wp-content/uploads/23JUNE2020-Letter-to-Patient-Community_Sent.pdf
https://www.fiercebiotech.com/biotech/astellas-audentes-reports-third-death-gene-therapy-trial.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/20/BVW4
And comments submitted to the notifier

18 December 2020
Ref. SC/1510/BAC/2020_1198

Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital)
SBB: Katia Pauwels

INTRODUCTION

Dossier **B/BE/20/BVW4** concerns a notification from Pfizer, inc. for a clinical trial entitled "Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy".

On 30 October 2020, 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 04 December 2020. This complementary information (C3391003 DR Response document) was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

QUESTION 1

Comment

The reply is heavily based on the Wright publication (compare txt to the section in the paper on rcAAV). From an ERA point of view it is essential to ensure that the prep does not contain rcAAV, but also for the patients safety.
In the end the question is not answered in sufficient detail. What is meant by 'a statistical analysis concordant with the results'? What was the analysis, which results were used, what result was obtained? The concern lies in my opinion in the fact that high vg are supplied to the patient. Considering <10 IU rcAAV/1E10 vg PF-06939926 and finally doses of >1E14 to be used, the numbers of rcAAV increase substantially in the final product applied to the patient, and thus also affect the chance of shedding (not only of rcAAV viruses, but potentially also viral vector particles – see Song et al.)

Ref:
Song L, Samulski RJ, Hirsch ML. Adeno-Associated Virus Vector Mobilization, Risk Versus Reality. Hum Gene Ther. 2020 Oct;31(19-20):1054-1067. doi: 10.1089/hum.2020.118. PMID: 32829671

Comment

The applicant mentions that homologous or non-homologous recombination could be the source of appearance of rcAAV in their viral production.
Is homologous recombination possible? Are there homologous sequences in the 3 plasmids? Why didn't the applicant use a system without homology between the vector and helper plasmids?
To avoid that homologous or non homologous recombination could generate rcAAV, helper plasmids have been described which use large heterologous promoters to express rep/cap so that even if a viral DNA harboring ITRs, rep and cap is generated, it will be too large to be encapsidated. Thus, theoretically no rcAAV viral particle could appear.
Could the applicant describe whether there are homologous regions in their 3 plasmids and comment this issue?

In any case, rcAAV would still need a helper virus to infect the same cell in order to replicate, which is very unlikely as regard to the extremely amount of rcAAV present in some (and not all) batches. It is also very unlikely that such a low contamination with rcAAV could have any adverse effect, such as e.g., an immune response against rep cap which could trigger the elimination of transduced cells.
Finally, this extremely low amount of rcAAV, will not possibly be accidentally transferred to a person other than the patient, since even in the case of accidental injection, the recipient will be exposed to a much lower dose than the patient.

Comment

Has no further questions, the response of the notifier is considered adequate and sufficient.

QUESTION 2

Comment

Even though complete shedding profiles are not available, can the applicant report on the incomplete ones?

SBB comment:
It is proposed to mention in the advice of the BAC that 'the notifier informed that complete shedding profiles of patients enrolled in the Phase 1b clinical study (C3391001) are not yet available and that these will be complemented by additional viral vector shedding assessments undertaken in the Phase 3 pivotal (C3391003) clinicals study' . In the conditions of the advice it can mentioned that the BAC took note notifier's commitment to report shedding data obtained from the planned clinical trials in view of any further step in the clinical development of PF-06939926.

Comment

Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

QUESTION 3

Comment

To me the use of 10% bleach still does not make sense in the hoods. Inactivation would require the bleach to be left there for at least 20'. However, I'm not aware of the European regulation (here the applicant refers to USP regulation).

SBB comment :

SBB colleagues were consulted as to whether it is preferable to first clean the hood with detergent /EtOH 70% and subsequently to inactivate with 10% bleach (expert's view) or to first inactivate with 10% bleach and to subsequently clean with detergent /EtOH 70%. There was a preference for the first approach, which is in line with expert's view. However, we are not aware of European standards that specifically addresses the sequence at which cleaning and inactivation should occur in a biological safety cabinet.

Coordinator comment :

AAV is stable in a wide pH rang (3-9) and like other non-enveloped viruses, is quite resistant to alcohol disinfectants. Therefore, decontaminants such as bleach 0.5% (5000 ppm sodium hypochlorite – this needs to be specified as various commercial sources have different concentration) or virusolve (recommended for equipment), 2% glutaraldehyde or 0.25% sodium dodecyl sulfate are recommended for 30 minutes followed by rinsing with water. I am afraid that saying the surface can be cleaned with 70% alcohol will lead to some places using this and not decontaminating first – it needs to be a protocol that people follow even when they might be a bit distracted. This needs to be changed in the investigational sheet.

SBB comment :

Indeed, one should avoid terminology such as % bleach as different commercial available bleach have different % of active Chloor (in weight). For clarification 0,5 % NaOCl (5000 ppm sodium hypochlorite) corresponds to a 1 to 10 dilution of bleach at 5% active Cl in weight and a 1 to 5 dilution of bleach at 2,5 active Cl in weight.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

QUESTION 4

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Coordinator comment :
With regards the 1-2 pg Technical sheet more precise details on the disinfectants are important for this virus – hospitals tend to think 70% alcohol kills everything.

QUESTION 5

Comment

The information provided to the patient is only poorly supported. In order for the patients to adhere (or the parents to understand), I reckon it is important to explain why these measures are taken.
If these measures are installed to limit the shedding, or when shedding takes place, limit the spread of the particles, just washing the hands is not sufficient. What about other routes of shedding (now only the mouth is considered)? Parents and care-takers should be informed on possible other sources of contaminated material when possible.

Coordinator comment :

Agreed with the expert that the patient information is a bit lite and will rely on how much of an explanation the doctor or nurse provides. I think a small take home summary sheet could really be helpful here.

I did not find anything revised for family and friends…

SBB comment :
The instructions found in the Informed Consent Document state that patients and contacts should thoroughly washing hands with soap and water after using the bathroom, before preparing or touching food, or after blowing the nose, coughing, or sneezing. With these instructions it can be considered that possible routes of shedding by urine, faeces, saliva or nasal secretions are not neglected.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

QUESTION 6-7

Comment

I do not understand why the document will not be updated about these wrongly used terms. It is not because the reviewer re-interprets the meaning correctly, that it should not be corrected. The correct use of terminology is essential, especially in pharmaceutics, but more importantly, when using ATMPs. These new products will be new to the market, and it is important that doctors, parents, but also (less-informed) parents and other personnel are aware of the fact that here no viruses are applied, and thus no virus-genomes are present, or infection is taking place, whereas for other therapies there are (e.g. oncolytic virus preps).

Coordinator comment :
Agreed with the expert that Pfizer took a rather arrogant approach (Q6-7) to updating the terminology saying they would not change it.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Comment
Has no further questions, the response of the notifier is considered adequate and sufficient.

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Pfizer, Inc on the second list of questions for dossier B/BE/20/BVW4

03 February 2021
Ref. SC/1510/BAC/2021_0091

Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital)
SBB: Katia Pauwels

INTRODUCTION

Dossier **B/BE/20/BVW4** concerns a notification from Pfizer, inc. for a clinical trial entitled "Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy".

On 18 December 2020, based on a second 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 27 December 2020. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation expert 1

I reviewed the replies of the notifier to the second round of questions.

As to Q1 and Q2 and their response.
In response to Q1 the applicant provides additional info on the conservation of the bp sequence, which is not longer than 10bp between the respective plasmids used for production.
However, in Q2 information is provided on the potential generation of rcAAV due to recombination events. These are considered very low, notwithstanding the fact that during production virus was detected. It is not clear to me how recombination can be the cause of the generation of rcAAV if there is not homology between the sequences that extends 10bps.

The additional info on the assay used to determine the rcAAV (provided in document 2019-002921-31 CONFIDENTIAL INX100430448 Informal QRM-2020 For Replication Competent AAV (rcAAV) DMD GT (PF-06939926) Oct 2020.pdf) shows that AAV virus is amplified in several steps by additional Adenovirus infection on adherent 293 HEK cells. The resulting qPCR assays for Rep2 cDNA. This implies that the resulting rcAAV only contains Rep2 for sure. AAV9 encapsidated particles are quite bad in transducing 293HEK cells, whereas AAV2 capsid is much better. This possibly indicates that the viral vector prep is contaminated with AAV2-virus (consisting of Rep2-Cap2) and not of rcAAV resulting from recombination (Rep2-Cap9).
Together this implies that this rather relates to patient safety, or product safety, rather than ERA.

SBB comment
The last sentence is an important conclusion with respect to ERA and remit of tasks of BAC.

Coordinator comment
Agreed, the concerns relate to patient/product safety rather than ERA.

The response to remark1
As long as this info is not available, we cannot judge the risks for the environment in my opinion.

SBB comment :
see draft advice – conditions : 'The notifier takes due account of the notifier's commitment to report shedding data obtained from the planned clinical trials in view of any further step in the clinical development of PF-06939926. '

The response to Q5
The applicant added the following txt, *"To prevent the potential spread of participles of study drug, any piece of cloth, tissue or any other material that has been in contact with bodily fluids from you/your child (such as blood, urine, saliva, etc.) should be thoroughly washed for at least 30 minutes at 90 degrees Celsius."*
There is no timing provided to the patient/parents/care-givers. If this sentence is added, also provide information on how spills can be properly taken care of on materials that cannot be washed (floor, wheelchair?, …). These patients are disabled I reckon, and special care should be given to inform supporting personnel.

SBB comment :
With respect to timing , In Patient and Guardian Instructions Summary' it is specified : 'To help your child stay healthy during the study, and prevent infections, practice good hygiene, especially for the month before and during the first 2 months after receiving study drug, ….
See also comment of expert 2 .

As a result, the following text could be added to Patient and Guardian Instructions Summary'

'To prevent the potential spread of participles of study drug, especially for the month before and during the first 2 months after receiving study drug,any piece of cloth, tissue or any other material that has been in contact with bodily fluids from you/your child (such as blood, urine, saliva, etc.) should be thoroughly washed with detergent for at least 30 minutes at 90 degrees Celsius, or, if not possible at 90 degrees Celsius at the maximum temperature. Spills on surfaces that cannot be washed should be cleaned with an washable textile in combination with detergent.

Comment coordinator :
With the ready availability of commercial disinfectant (Dettol, bleach solution, etc.) due to COVID, I think we should specify this as opposed to just detergent. If they treat these things the same way as recommended for COVID it will be exactly right. One of the few advantages of this pandemic is that people are more educated on how to protect from viruses! And I think that the hygiene habits are here to stay – so the products will remain available.

The following text is proposed (adapted from the proposal of SBB) :

To prevent the potential spread of participles of study drug, especially for the month before and during the first 2 months after receiving study drug, any piece of cloth, tissue or any other material that has been in contact with bodily fluids from you/your child (such as blood, urine, saliva, etc.) should be thoroughly washed with a disinfectant detergent (Dettol or something similar) for at least 30 minutes at 90 degrees Celsius, or, if 90 degrees Celsius is not possible, use the maximum temperature of your machine with a disinfectant detergent. Spills on surfaces that cannot be washed should be cleaned with a washable cloth in combination with detergent or if possible a commercial disinfectant (Dettol, eau de Javel, etc.).

The reply to remark1 on applicant's rebuttal Q6-7, is in my opinion not valid.
As mentioned in my reply early December 2020, I do not understand why the document will not be updated replacing wrongly used terms.
It is not because the reviewer re-interprets the meaning correctly, that it should not be corrected. The correct use of terminology is essential, especially in pharmaceutics, but more importantly, when using ATMPs.
It is appreciated that the documents for the patients will use precise terminology. However, also study personnel, and physicians taking care of patients require correct information, as do experts that review the files. If in the end, wrong information can be retained in a reviewed file, just because the applicant does not feel like updating the documents involved, one can wonder why we do all the reviewing.

By the way, in the consent form 2019-002921-31 C3391003 Belgium English ICD_Main_V3.3.0_22 Jan_2021_Clean.pdf (and the track changes version) the word 'virus' is still used where 'viral vector' should be used (eg p3/27 and p14/27 (shedding of virus)).

Comment Coordinator :
The expert does make a point but without some strict guidelines in place for the initial submission, I think this is hard to require at this late date. Maybe we need to think of how to insure the language is standardized in the future?

Evaluation expert 2

In my opinion, the notifier addressed correctly and satisfactorily the remaining comments/questions that were raised in December. Except the added washing instructions at 90 degrees Celsius seem to be partly impractical and overdone:

"To prevent the potential spread of participles of study drug, any piece of cloth, tissue or any other material that has been in contact with bodily fluids from you/your child (such as blood, urine, saliva, etc.) should be thoroughly washed for at least 30 minutes at 90 degrees Celsius."

- Most modern cloths and textiles are not suitable for thoroughly washing for at least 30 minutes at 90 degrees Celsius. Thoroughly washing at the maximum temperature for a particular textile should be sufficient.
- Since shedded viral particles in faeces and urine are discharged and diluted via sewage, also discharge of contaminated washing machine water should not be considered as problematic.
- What about "other material" e.g. surfaces? Cleaning with a washable textile in combination with cleaning agent is probably the most practical solution.

SBB comment :
See previous SBB comment on text proposal for 'Patient and Guardian Instructions Summary'

Evaluation expert 3

To my opinion, the applicant addressed satisfactorily our comments.