Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/21/BVW3 of the company Prevail Therapeutics, for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

12/11/2021
Ref. SC/1510/BAC/2021_1036

Context

The notification B/BE/21/BVW3 has been submitted by Prevail Therapeutics to the Belgian Competent Authority in July 2021 for a request of deliberate release in the environment of genetically modified organisms (GMOs) other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

The planned activity concerns a clinical trial and the title of the notification is: ***"A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)".***

The purpose of this study is to assess the safety, tolerability, immunogenicity and effects of the investigational medicinal product (IMP) PR006A on progranulin protein (PGRN) levels in plasma and/or cerebrospinal fluid (CSF).

Fronto-temporal dementia (FTD) is a devastating dementia syndrome encompassing a heterogenous group of clinical syndromes characterized by progressive deficits in behavior, executive function, and language. Disease progression is typically more aggressive than Alzheimer's Disease with death occurring within 3 to 10 years after diagnosis. No disease-modifying therapies are available for patients with FTD. FTD-GRN patients carry a single mutation in the GRN gene, which encodes the progranulin protein (PGRN), resulting in haploinsufficiency and an approximately 50% reduction in PGRN levels. GRN mutation carriers have an approximately 90% risk of developing FTD by age 75.

Progranulin is a secreted glycoprotein broadly expressed in the central nervous system (CNS) and periphery in a variety of cells and has been implicated in several physiological functions and roles including an activator of lysosome function, an anti-inflammatory, a neurotrophic factor and a growth factor.

The IMP is an adeno-associated virus serotype 9 (AAV9) viral vector developed to deliver a functional copy of the wild type *GRN* gene, which encodes the wild type PGRN, to a patient's cells. The cassette containing the human gene coding for progranulin is flanked by AAV2 inverted terminal repeats (ITRs).

No other viral sequences are present in the final GMO. The GMO does not contain any antibiotics resistance genes.

The 15 study subjects will be divided over three escalating-dose cohorts each consisting of 5 subjects who will be administrated a one-time dose with a maximum of 1.4×10^{14} vector genomes (vg) of PR006A. PR006A will be administered as a single dose via a radiographically guided sub-occipital injection into the cisterna magna by an interventional radiologist or neurosurgeon. The procedure will be performed with the patient under general anaesthesia or deep sedation and using imaging guidance.

In Belgium, an estimated number of two patients will be included at one clinical site located in the Flemish Region. Vector shedding will be monitored at several time points in urine, stool and saliva after patient dosing utilizing qPCR.

The dossier has been officially acknowledged by the Competent Authority on 23 July 2021 and forwarded to the Biosafety Advisory Council (BAC) for advice.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Four experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. One expert from the SBB took part in the evaluation of the dossier.
The experts assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the genetically modified organism would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments from the expert.

The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.

The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

On 20 August 2021, 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 10 September 2021 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 28 September 2021. The answers of the notifier were received on 29 October 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 abovementioned Royal

Decree. The Competent Authority received four reactions from the public of which some were related to biosafety issues. According to Article 16 §2 of the Royal Decree of 21 February 2005, the comments that are relevant for biosafety received in the framework of the public consultation, have been taken into account in the preparation of the advice below.

Summary of the scientific evaluation

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

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

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

The notifier was requested to further substantiate the description of the PR006A vector since the provided confidential data showing the DNA sequence of the vector was unclear on the origin and function of an element located in the vicinity of one of the ITR, thereby hampering a correct assessment of recombination possibilities.
In its answer the notifier complemented its description of the vector as requested and the BAC had no further remarks with respect to the molecular characteristics of the vector.

3. The conditions of the release

All patients receiving the single dose of 1.4×10^{14} vg of PR006A by intra cisterna magna injection will be hospitalised for at least 24h after dosing and will then leave the reference hospital. The notifier was asked to detail in the main Informed Consent Form (ICF) and in a short, readable format what exactly is requested from the patient with respect to good hygiene practices. Given the preliminary results on the shedding, the notifier was also asked to adapt the ICF so that the patient will be recommended to wear a face-mask made of disposable material and to keep social distancing when in contact with immunocompromised human or children whose immune system is not mature, as long as significant levels of viral vector are present in the saliva of the patient. Furthermore, the BAC also advised to consider restriction on blood donation.

The notifier agreed with the additional exclusion criteria and adequately implemented the remarks and requests addressed by the BAC in a revised version of the informed consent form and the study protocol.

4. The risks for the environment or human health

PR006A is a recombinant, replication deficient adeno-associated virus-based vector not harbouring any antibiotic or other resistance genes. Although its parental strain is not known to be pathogenic, some non-clinical studies with *Grn* KO mouse or NHP animals treated with PR006A described a few toxicities such as mononuclear cell inflammation, neuronal degeneration, spinal cord degeneration, axonal degeneration, neuronal necrosis or gliosis. The BAC is of the opinion that these observations are not considered to impact the environmental risk assessment of PR006A for the reasons outlined here below.

The route of administration will possibly limit peripheral exposure to the AAV and therefore possibly limit shedding. Furthermore, in the case of transfer of vector to an unintended human recipient, the risks are expected to be considerably reduced, 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.

Several *in vitro* and *in vivo* preclinical studies performed with *Grn* KO mouse model of FTD-GRN and in Non-Human Primate model have evaluated the dose-dependent biodistribution of the transgene and production of progranulin mRNA and protein in the CNS. Following BAC's request, sufficient clarification has been provided by the notifier regarding these studies.

Viral vector excretion/secretion was first proposed to be monitored in stool, urine and saliva at day 14, month 1, 2, 3 and 6 compared with results obtained at baseline. Taking into account the first preliminary data on shedding from the first patient already involved in the Phase 1/2a, the BAC was of the opinion that further efforts to characterize the 'shedding window' at time points earlier than D14 would further inform the environmental risk assessment. In its response, the notifier committed to add an extra timepoint at Day 7 for collecting urine, stool and saliva samples to complete the evaluation of the vector shedding and provided an update of the study protocol. Following the inclusion of this additional timepoint and in order to ensure consistency between the different documents making part of the Biosafety dossier, the applicant is suggested to further adapt the SNIF accordingly. The text in the SNIF regarding the limit of quantification of the detection of shed particles achieved by a qPCR assay has been adapted and the notifier committed to further detail the results related to the shedding analysis in the next amendment of the Investigational Brochure as requested by the BAC.

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

While non-replicating, it is anticipated that PR006A, 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, the notifier further explained that 0.07 – 0.09 M sodium hypochlorite in freshly prepared solution (1:10 dilution of 5-6% sodium hypochlorite bleach) will be used to decontaminate any surface area exposed to the GMO.

Upon request, the notifier also adapted the SNIF and the CAF by improving the description of the procedures for the management of accidental spills. In order to be consistent between the different documents, the same procedure for the management of accidental spills could be added in the 'IMP Handling Instructions for study staff personal' technical sheets as follows:
Larger spills will require the removal of non-essential personnel from the affected area. Reporting of emergency situations immediately. Clean up operations should only be undertaken by trained personnel.
In case of accidental spills, the medical staff should alert people in the area of the spill, remove contaminated clothes and leave the area for 30 min. He/she should close the area and post "DO NOT ENTER". After 30 min, he/she must wear a clean lab coat and wear gloves, glasses and a FFP2 mask. He/she must cover the spill with towels and other absorbent material starting from the edge toward the center. He/she must carefully pour the appropriate disinfectant over the absorbent material starting from the edge to the center. It must allow a sufficient contact time for the disinfectant to inactivate the GMO.

After that, he/she must remove the paper towels and broken vials with tongs or forceps and discard in a biohazard waste bag. The PPE should be discarded in the biohazard bag.
Consumables used in the preparation and administration of the GMO that may have come into contact with PR006A will be decontaminated prior to disposal as biohazardous waste (either by autoclaving or by treatment with an appropriate chemical disinfectant with effectiveness against AAV, and/or incinerated). Liquid waste will be decontaminated using an appropriate chemical disinfectant or autoclaved.

Upon BAC's request, the notifier provided a 2-4 pages technical sheet 'IMP Handling Instructions for study staff personal' including all relevant handling instructions, detailed PPE, detailed instructions in case of accidental spill or breakage of a vial containing the GMO, clean-up procedure, waste management.

Given the assessment of the likelihood of further propagation of PR006A, 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 PR006A developed as a gene therapy approach for the treatment of Fronto-Temporal Dementia with Progranulin mutations 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:

- IMP Handling Instructions for Study Staff Personnel – taking into account the additional text adaptations provided by the BAC
- Protocol Amendment Version 5.2 (Belgium), dated 07 October 2021
- Main ICF Belgium, v4.3.0 dated 28 September 2021 (ENG, DUT, FRE), taking into account the text adaptation provided by the BAC for Main ICF – French[1]
- Participating Partner ICF Belgium, v4.3.0 dated 28 September 2021 (ENG, DUT, FRE)

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

- The notifier and the investigators must strictly apply the clinical trial protocol version 5.2 (Belgium), and all the safety instructions as described in the dossier and the updated and new documents listed here above.

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

- The 'IMP Handling Instructions for study staff personal' technical sheets are improved by adding information related to the procedure for the management of accidental spills as mentioned in paragraph 5 of this advice. Furthermore, eye protection should be worn as a standard PPE while performing manipulations that may create aerosols with highly concentrated rAAV and not solely in

[1] p8 (3) 'en ne partageant pas les verres, la vaisselle, les ustensiles ou autres objets qui son ten contact avec la bouche' should read ' sont en contact avec la bouche '

case of spills. Therefore, “(in case of spills)” reported near “Eye protection” in Personal protective equipment (PPE) section should be deleted. Finally, since eyes and wounds will not be washed with soap, in section “Management of inadvertent exposure to a gene therapy product”, it is recommended to adapt the following sentence “the affected area should be washed with soap and water” as follows: “the affected area should be washed with soap and/or water for at least 15 min”.

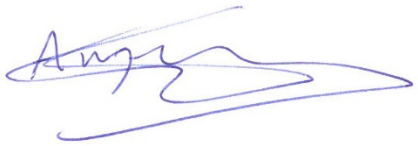
- The SNIF is improved by adding the additional timepoint at Day 7 for vector shedding monitoring.

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

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

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

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report shall at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;
    - A report of the shedding data obtained from the clinical trial (monitoring of viral vector excretion/secretion in stool, urine and saliva at day 7, 14, month 1, 2, 3 and 6 compared to baseline)
    - 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 PR006A.



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/21/BVW3 (ref. SC/1510/BAC/2021_0808, SC/1510/BAC/2021_0921)
Annex II: Answers to the public reaction to dossier B/BE/BVW3 in NL (ref. SC/1510/BAC/2021_1035) and FR (ref. SC/1510/BAC/2021_1034)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/21/BVW3 And comments submitted to the notifier

20 August 2021
Ref. SC/1510/BAC/2021_0808

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 28 May 2021.
Coordinator: Jozef Anné (KULeuven)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Aline Baldo (SBB), Willy Zorzi (ULiège)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/21/BVW3** concerns a notification from Prevail Therapeutics 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 July 2021 and concerns a clinical trial entitled "A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)". The investigational medicinal product is a AAV9 derived recombinant replication deficient vector carrying the human Progranulin (GRN) 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 20-08-2021 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 common application form for AAV vectors – Confidential annex of this application mentions in the plasmid map of PRO06A, the schematic PRO06A vector genome and the PRO06A vector annotated sequence a TRY element immediately downstream of the 5'-end ITR. The significance of this element is not explained in the text nor in the tables describing the functional elements present in the PRO06A plasmid and vector genome. What is the function of this element? Should this apparently AAV2-derived sequence be considered as part of the 5'-end ITR? If not, then the statement that in the final GMO besides the ITRs no other viral sequences are present, is not correct.

SBB Comment:
Agreed. It is important to know exactly what the different sequences of the plasmid PRO06A are.
Proposed question:
The "Common Application Form – Confidential annex" of this application mentions in the plasmid map of PRO06A, in the schematic PRO06A vector genome and in the PRO06A vector annotated sequence, a TRY element immediately downstream of the 5'-end ITR. The significance of this element is not explained neither in the text nor in the tables describing the functional elements present in the PRO06A plasmid and vector genome.
What is the function of this element? Should this apparently AAV2-derived sequence be considered as part of the 5'-end ITR or not? If not, then the statement that in the final GMO besides the ITRs no other viral sequences are present, could be not correct. In order to correctly assess the risk of recombination with other viruses, the notifier should be required to clarify the origin of this sequence.

Comment 4

Map of the vector- Figure 1: the TRY sequence is not described.

All other regulatory elements present in the vector are commonly used elements which do not present safety concerns.

SBB Comment:
A related question regarding the TRY sequence was also raised in comment 3. Both questions have been combined under comment 3.

Comment 5

Has not evaluated this item.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5

Has not evaluated this item.

2.3. Diagram (map) of the clinical vector

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

See 2.1

Comment 4

The TRY sequence is not defined.

SBB comment
See above SBB combined comment in section 2.1

Comment 5

Has not evaluated this item.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

See 2.1

Comment 4

Although the sequence of the "TRY" element is given, no clue is given concerning its role. In order to assess the risk of recombination with other viruses, it is important to know the origin of this sequence.

SBB comment
See above SBB combined comment in section 2.1

Comment 5

Has not evaluated this item.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

It is claimed that "no toxic effects of the expressed transgene are expected" since GRN is a "codon-optimised version of a naturally occurring human gene". However, one publication describes a transgene-specific toxicity with T cells infiltration in the hippocampus after intracerebroventricular injection to mice (Amado DA et al., 2019 https://doi.org/10.1016/j.ymthe.2018.11.013). Furthermore, in the "Investigator brochure, the applicants repeatedly describe a "minimal mononuclear cell inflammation", "minimal neuronal degeneration", "gliosis" etc,) but not absent toxicity" (see Investigator brochure pp 14,55, 62,66 etc..)…
Even though the doses that could inadvertently infect untargeted individuals are expected to be lower than those administered to patients, if the codon-optimised transgene causes neuroinflammation in the brain- either by local overexpression or by recognition of a foreign DNA sequence, for example- the risk of a peripheral inflammatory response for inadvertently infected untargeted individuals should be envisaged

SBB Comment:
A publication describes a transgene-specific toxicity with T cells infiltration in the hippocampus after intracerebroventricular injection to mice (Amado DA et al., 2019). Several studies described in the Investigational Brochure (PRV-2019-006, PRV-2018-027, PRV-2018-021, PRV-2018-028) with Gm KO mouse or NHP animals describe mononuclear cell inflammation, neuronal degeneration, spinal cord degeneration, axonal degeneration, neuronal necrosis or gliosis. These toxicities were presented as minimal. 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. However, the notifier could be requested to develop the risk for inadvertently infected non-targeted individuals and the measures that will be put in place in order to avoid any exposure of non-target individuals at the hospital and when the patient come back home. Careful surveillance will be needed to monitor the shedding of rAAV.

Comment 5

Has evaluated this item and has no questions/comments.

2.6. Biodistribution and shedding

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

Comment 1

In page 3 of «20 of B_BE_21_BVW3_Part 2_SNIF_v2_Sep2020» file,

it is written that : « Minimal risk of transmission by vector shedding: Viral shedding was assessed in faeces and urine in the GLP NHP study PRV-2018-028. There was no detectable PR006A DNA in any of the treatment groups at either timepoint. »
It would be interesting to precise that « the result of no-trace of PR006A DNA in any of the treatment groups at either timepoint » was obtained in the limits and the sensitivity of detection of the in-house qPCR test.

SBB Comment:
Viral shedding was assessed in faeces and urine in the GLP NHP study PRV-2018-028. The value of the lower limit of quantification of the detection of shed particles achieved by a qPCR assay has been reported on page 22 of the B/BE/21/BVW3 - Part 1B_Confidential annex to CAF document. In order to be consistent in the SNIF regarding the limit of quantification of the test, the SBB could suggest that the notifier specifies on page 3 of the SNIF_v2 that "the result of no-trace of PR006A DNA in any of the treatment groups at different time point was obtained in the limits and the sensitivity of detection of the in-house qPCR test."

Furthermore, according to table 8 of the Investigational Brochure on p64, Vector Shedding (urine/faeces) was achieved at sacrifice. No result of the viral shedding assessment has been reported in the Investigational Brochure. The notifier could be suggested to clarify in section 4.4.1.2.2 of the IB the results of the viral shedding assessment as it has been mentioned in the Confidential annex to CAF document (page 22).

Comment 2

In Fig13 at p44 in B_BE_21_BVW3_Investigator Brochure_v5.0.pdf, the applicant indicates significant presence of rAAV vector genomes in the kidney and gonads of mice. Even though the specific timing of sampling after administration was not clear to me, was it tested whether the sperm and urine were similarly high? Was vector transmitted between mice?

I agree with the applicant that NHP studies will be more relevant (p58 in B_BE_21_BVW3_Investigator Brochure_v5.0.pdf). Still, these animals are young and do not compare to the age of the target population. In how far can the biodistribution and shedding be compared? Is it correct that the doses /g brain were here lower than those that will be used in the human study?

SBB Comment:
Several NHP studies have been described in the Investigational Brochure. Doses used in the NHP studies were either lower or higher than the doses that will be used in the human study.

On p21/23 in B_BE_21_BVW3_Part 1B_Confidential Annex to CAF.pdf the applicant indicates that all male NHP showed measurable expression of the DP in the gonads. Even though the term 'gonads' is rather broad (what is meant exactly?), the fact that signal was detected in the high dose condition, should raise attention (in the end the doses used in the NHP are lower than the highest dose that will be used in patients). Was the sperm also assessed, and if not, shouldn't this be done in the study to assess shedding through intercourse (in as far as this is possible for the group of patients considered)?

Coordinator Comment:
See Investigator brochure p86/100

Additionally, the risk of exposure to PR006A through semen is unknown. In current and future clinical studies of PR006A, the clinical study protocol guidance regarding use of effective contraception and avoidance sperm donation restrictions for male subjects should be followed to minimize the risk of exposure to PR006A through semen to female partners with reproductive potential.

Vector shedding is only assessed at sacrifice (p64 in B_BE_21_BVW3_Investigator Brochure_v5.0.pdf)? The study also indicates that the gonads in the high dose treated males express the gene of interest (p70 in B_BE_21_BVW3_Investigator Brochure_v5.0.pdf _ the applicant indicated it was measurable, but no data were shown – was this only near LLOQ?). The latter would imply that the viral vector is present in the gonads. Was semen assessed to be positive for vector particles?

Remark:

1. Doses in animals are expressed as vg/g brain, where all patients will receive the same dose, irrespective of the body weight or brain volume/weight (3.5×10^{13} total vg dose (the "low dose"), 7.0×10^{13} total vg dose (the "mid dose"), or 1.4×10^{14} total vg dose (the "high dose")). In how far does this affect the shedding potential?
2. The section Warnings and Precautions (p81 in B_BE_21_BVW3_Investigator Brochure_v5.0.pdf) does not provide a complete overview: recent reports are not included such the August2020 report on the Audentes trial on the death of two additional patients in the high dose arm of a study for AAV based GT for a rare neurological disease (AT132) (see https://www.nature.com/articles/s41587-020-0642-9 and https://www.fiercebiotech.com/biotech/astellas-audentes-reports-third-death-gene-therapy-trial). It is not clear to me in how far the current dose may present a risk for the current patients.

SBB comment:

Agreed with Comments 2 and 5. We kept the questions raised by the experts and compiled their comments. The second remark concerning the omission of a reference has been added to the list of 'typos and other errors/omissions' here below:

It is agreed that any shedding data collected from previous studies will contribute to a proper environment risk evaluation. These data will need to be evaluated in light of the observed quantity of shed viral vector material, the period of time during which shedding is observed. It will be important to answer the question whether the observed shed PR006A 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 of remaining or rescued replication-deficient viral vector particles. Therefore, the notifier is requested to provide, if available, any clarification regarding the following points:

1- In the *in vivo* non-clinical dose-ranging study (PRV-2019-004) in the Adult Grn KO Mouse Model (IB p40): Why has the biodistribution analysis been performed at Month 3 after injection. Also, has the presence of the vector genome and the protein levels been tested in the sperm and urine. If yes, were these results similarly high as in the kidney and the gonads? Was vector transmitted between mice?
2- Although, the brain of the NHP is most similar to that of humans and therefore, NHP studies are the most relevant, the notifier should clarify if the difference of age between the animals (2-4 years old) and the target population could influence the biodistribution and shedding analysis in the toxicology studies (PRV-2018-021, PRV-2018-028 and PRV-2019-006) and if this difference has been taken into account in the analysis?

3- Since the highest dose that will be administrated to patients in the study is higher than most of the doses administrated in the NHP, the notifier could also be asked to discuss any anticipated impact on biodistribution and shedding in humans.
4- Since expression of PR006A was measurable in the male gonads at the high dose only (6.5×10^{10} vg/g brain), in the non-human primates studies, the notifier is requested to clarify if expression of PR006A has also been assessed in the sperm of the cynomolgus monkeys. Since the doses used in NHP are lower than the highest doses that will be used in human, the SBB suggests the notifier to assess the expression of PR006A in the semen during the study.
5- Vector shedding was evaluated in faeces and urine in the GLP NHP study PRV-2018-028. There was no detectable PR006A in any of the treatment groups at both necropsy time points (D30, D183). One NHP (F) who received $6.5x10^{10}$ vg/g was euthanized at Day 7. The notifier is requested to clarify if any data related to vector shedding in the NPH euthanized at Day 7 has been collected?

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5

Vector shedding was evaluated in faeces and urine in the GLP NHP study PRV-2018-028. There was no detectable PR006A in any of the treatment groups at either of the necropsy timepoints (D30, D183). One NHP (F) who received $6.5x10^{10}$ vg/g was euthanized at day 7. Have data related to vector shedding in the NPH euthanized at day 7 been collected?

SBB Comment:
Agreed with this comment. It has been included in the SBB comment for expert 2 (point 4).

Additional SBB Comment:
In addition to the expert's comment, the notifier could be requested to give some clarification regarding the viral shedding assessment:

First, according to the SNIF, page 3, section A7: Viral shedding will be assessed in saliva, urine, and stool samples and will be assessed on Days -1 (baseline), and 14, and at Months 1, 2, 3, and 6.
Same is reported in the Confidential annex of the CAF (section 2.6, page 22).
However, according to the protocol, in the synopsis page 26 and the Study objectives and Endpoint page 51: Viral vector shedding will be evaluated at Day 14 and at Months 1, 2, 3, and 6 only.
Data in the documents and/or in the protocol need to be updated in order to correct this incoherence between the documents.

Second, In the "Information for the public", page 2, the notifier reported that "Viral vector shedding, i.e., excretion/secretion of recombinant viral particles that could be transmitted to other individuals, will be assessed in saliva, urine, and stool samples. Analysis of samples will continue until 3 consecutive data

points are obtained at or below the limit of detection of the shedding assay. If the level of shedding does not reach the limit of detection of the assay but there is a continual decreasing trend, collection should continue until the results demonstrate that a plateau has been reached in at least 3 consecutive data points."
The latter prerequisite has not been reported in the other documents. If this condition will be applied, the documents should be updated in order to reflect this condition on the shedding analysis.

Third, the notifier could be requested to justify the choice of limited number of time points for sample collection as the question whether shedding is expected earlier than D14 after administration still remains. Since the PR006A vector is replication incompetent, release of the vector following administration is limited to environmental release of the vector by subject shedding during a limited time period following administration. Therefore, any shedding data obtained in a short time period after injection could greatly contribute to the evaluation of the environmental risk assessment. Furthermore, any potential risk for close contacts related to the viral shedding by clinical participants still remains to be investigated. Therefore, the notifier could be recommended to increase the number of sample time points, at least earlier than D14.

Finally, the Investigational brochure mentions on page 79 (section 5.1) an ongoing Phase 1/2 study (PRV-FTD101) in patients with FTD-GRN. The notifier could be requested to clarify whether any shedding analysis has been performed on the first patient already included in this study.

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

In the « B_BE_21_BVW3_Part 1A Common Application Form _Confidential Sections Removed » file, point 3.3. Storage of the clinical vector at the clinical site.
In this paragraph, there is no information about the total number and maximal (stored together in the freezer) number of PR006A vector 2 mL polypropylene tubes <with 1 mL extractable volume>.

SBB Comment:
In section 3.3 of the Common Application Form _Confidential Sections Removed, the applicant provided information about the storage location, conditions of storage (including restrictions of access), the maximal storage duration and whether the clinical dose has been prepared in the hospital pharmacy as requested by the section. Information related to the IP and buffer packaging has been described in the Pharmacy Manual v5 on page 4: "PR006A will be supplied in cartons containing sterile, single-use vials. Each vial consists of frozen sterile solution for injection with 1 mL extractable volume in single-use 2 mL pre-sterilized, polypropylene, gasketed micro-centrifuge tubes or 1 mL extractable volume in single-use 2 mL pre-sterilized, glass vials with 13 mm stoppers and flip-off seals. A label will be affixed to the outside of the carton, and individual product labels will be affixed to each vial."

Comment 2

In B_BE_21_BVW3_Facility Plans.pdf it is indicated that the viral vector and the samples will be stored and manipulated at BSL1 (see also p4 in B_BE_21_BVW3_Pharmacy Manual_v5.0.pdf). Is this level

sufficient? In research settings, where significantly lower concentrations of AAV vectors are stored, a BSL2 safety level is required with limited access.

SBB Comment:

According to the Common Application Form with confidential sections removed, preparation of IMP, administration of IMP and sampling will be performed in BSL1. Whereas, in the laboratory, analysis of a subset of samples will be carried out at BSL2 since untested human samples have to be treated as potentially infectious with harmful viruses. In the Facility Plans and on page 4 of the Pharmacy Manual, BSL-1, handling and storage of biosamples will be done at BSL1.

Clarification should be provided by the notifier regarding the biosafety level during the handling and the storage of the samples.

According to the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors that has been endorsed by Belgium, clinical trials with AAV clinical vectors in accordance with the requirements in the ERA in Section 2 can be conducted under BSL-1. The requirements as reported in section 2 of the ERA are the absence of formation of replication competent virus and a harmful transgene. Both requirements are met. As demonstrated in the Confidential annex to CAF (page10), each batch of PR006A has been tested for the presence of replication competent vector and no rcAAV could be detected, which confirms that PR006A is a non-replicating recombinant vector derived from AAV9. This vector contains a gene encoding for the human progranulin GRN.

Coordinator Comment:

The National Institutes of Health (NIH) classifies all serotypes of AAV-based vectors produced by helper-virus free methods as Risk Group 1, but depending on the transgene being expressed (e.g., oncogenes, toxic genes, etc.), the classification may be elevated.

https://ec.europa.eu/health/sites/
health/files/files/advtherapies/docs/aavs_gp_en.pdf
Clinical trials with AAV clinical vectors in accordance with the requirements in the ERA in Section 2 can be conducted under BSL-1. applicable to AAV clinical vectors if the applicant demonstrates absence of formation of replication competent virus and that the transgene is not harmful

Coordinator Comment:

In common application form

P17: PR006A is a RG1 agent and will be prepared for administration in a Biological Safety Cabinet Class II Type A2 or better

P14: Storage location: IMP will be stored in an ultra-freezer within the clean room facility, with controlled access limited to the staff working in that facility
P16 The IMP must only be thawed and diluted before use.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5

Has evaluated this item and has no questions/comments.

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

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5

Any surfaces contaminated with PR006A will be decontaminated using an appropriate virucidal agent, such as 1:10 dilution bleach, for 10 minutes. Could the applicant provide the final concentration of sodium hypochlorite? Sodium hypochlorite is unstable, diluted solutions should be prepared extemporaneously, dated and used rapidly (within the week). It should be stored in the dark and protected from heat.

SBB Comment:

See below SBB comment regarding the comment 3 in section 3.6

Additional SBB Comment:

The notifier reported in the Confidential Application Form with Confidential sections removed, on page 12, section 3.2, that "Most samples will be sent to central lab".

The notifier should be requested to update the form by reporting the address of the Central lab. Furthermore, the notifier could clarify whether the Central lab is aware or will be informed on the precautions to be taken when manipulating the GMO based samples.

Coordinator Comment

Address is mentioned: Herestraat 49; 3000 Leuven; Belgium (p12)

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.

Comment 5

Has evaluated this item and has no questions/comments.

3.6. Measures to prevent dissemination into the environment
(e.g. control measures, PPE, decontamination/cleaning measures after administration or in the case of accidental spilling, waste treatment, recommendation given to clinical trial subjects, …)

Comment 1

In the "B_BE_21_BVW3_Part 1A Common Application Form _Confidential Sections Removed" file, point 3.6.b) Personal protective equipment.
To reduce the risk for inadvertent exposure during handling of PR006A, site personnel and all those present during preparation and administration must wear standard Personal Protective Equipment (PPE) for handling of a RG1 agents, as described in the pharmacy manual. The following are recommended: gowns (preferably disposable), chemotherapy gloves, shoe covers, hair covers and, in the case of spills, facial mask, eye protection and respiratory protection.
We would like to ask for precision for PPE in the case of spills : the proposal to wear facial mask <or/and/with> respiratory protection should be clarified.

SBB Comment:
The dilution and the retrieve of vaccine from the vial are manipulations that could create aerosols. AAV (wt and rAAV) are resistant to some disinfectants, dehydration and are known to persist in aerosols or aqueous solutions. Therefore, as it has been previously mentioned in the Advices for the dossiers B/BE/19/BVW2 and B/BE/18/BVW4, the SBB would recommend that facial mask and eye protection should be worn as a standard PPE while performing manipulations that may create aerosols with highly

concentrated rAAV and not solely in case of spills. Furthermore, the notifier could be requested to clarify what kind of facial mask or/and/with respiratory protection they will use. As requested in a previous advice, the medical staff should wear a FFP2 mask for the infusion of the IMP to the patients.

Comment 2

On p17 in B_BE_21_BVW3_Part 1A Common Application Form _Confidential Sections Removed.pdf the dossier states 'The following are recommended: gowns (preferably disposable), chemotherapy gloves, shoe covers, hair covers and, in the case of spills, facial mask, eye protection and respiratory protection.' Eye protection should be included as a standard PPE when working with these highly concentrated rAAV preps, and not solely 'in case of spills'. (see also p4 in B_BE_21_BVW3_Pharmacy Manual_v5.0.pdf).

SBB Comment:

See above SBB comment regarding comment 1 in section 3.6

On p4 in B_BE_21_BVW3_Pharmacy Manual_v5.0.pdf it is stated that BSL1 level would be sufficient. In the framework of ERA (minimizing spill into the environment), I would not agree, and at least a BSL2 level should be used. BSL1 laboratory setting typically consists of research taking place on benches without the use of special contaminant equipment, and is not required to be isolated from surrounding facilities.

SBB Comment:

See SBB comment regarding comment 2 in section 3.3

Also, patients should be requested as well to refrain from blood/organ donation as a clinical trial subject. (p18 - B_BE_21_BVW3_Part 1A Common Application Form _Confidential Sections Removed.pdf).

SBB Comment:

Given the highly concentrated rAAV preparations, the notifier could be requested to clarify which recommendations on donation of blood/cells/tissues/organs by the clinical trial subject will be received.
The notifier could be recommended to refrain patients from blood/cells/tissues/organs donation for the duration of the clinical trial.
If any specific recommendation will be added, the notifier should also be requested to update the protocol accordingly.

Coordinator Comment

Only to abstain from blood donation should be further highlighted since already mentioned (p18) "Male participants of the study must agree to abstain from sperm donation for the duration of the study, including long-term follow-up and women must agree to abstain from egg donation for the duration of the study including long-term follow-up."

Comment 3

The disinfection procedure describes the use of a 1:10 dilution of bleach as an appropriate viricidal agent. The precise mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution should be mentioned, because bleach is usually already a dilution which can have variable concentrations of sodium hypochlorite.

SBB Comment:

In the SNIF page17, section I1 and J2 and in the Common Application Form_Confidential sections removed, p15, section 3.4 and p17, section 3.6.d, the applicant proposes that any surface area exposed to the GMO will be decontaminated using an appropriate virucidal agent, such as a 1:10 dilution of bleach, for 10 minutes.

Firstly, the notifier should be requested to mention in the text the precise mass concentration (g/100 ml) or molar concentration (M or mol/l) of sodium hypochlorite in the final solution.

Secondly, it should be specified that, whenever hypochlorite solution is used (e.g. for the decontamination of work areas), special attention should be given to the use of freshly prepared hypochlorite solution.

Finally, as it was previously raised in the context of dossier B/BE/20/BVW4, the use of a 1:10 dilution of bleach may be effective to inactivate the AAV vector, but is not always suitable since surfaces will be corroding. On top, bleach will precipitate the proteins/vectors and removal from the surface may even be more difficult. The SBB 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. So, the notifier could be requested to adapt the procedure as requested for previous dossier.

Coordinator Comment

Disinfection: 10% bleach is a standard procedure (followed by an alcohol wipe to lessen the corrosive nature of the bleach)

Last paragraph should not be taken into account because:

1. Bleach contains sodium hypochlorite, an extremely corrosive chemical that can break the hydrogen bonds between DNA base pairs and thus degrade or “denature” a DNA sample.
2. Bleach denaturates proteins.
3. Corrosion is not a biosafety issue
4. In none of previous dossiers, besides the attention to use freshly prepared bleach, Wescodyne has been mentioned. For Wescodyne: some organic and inorganic substances neutralize effect

Comment 4

Has evaluated this item and has no questions/comments.

Comment 5

The patients who received PR006A must agree to abstain from blood donation during the clinical trial.

SBB Comment:

See SBB comment regarding to comment 2 in section 3.6

In case of accidental spills, the medical staff should alert people in the area of the spill, remove contaminated clothes and leave the area for 30 min. He/she should close the area and post "DO NOT ENTER". After 30 min, he/she must wear a clean lab coat and wear gloves, glasses and a FFP2 mask. He/she must cover the spill with towels and other absorbent material starting from the edge toward the center. He/she must carefully pour the appropriate disinfectant over the absorbent material starting from the edge to the center. It must allow a sufficient contact time for the disinfectant to inactivate the GMO. After that, he/she must remove the paper towels and broken vials with tongs or forceps and discard in a biohazard waste bag. The PPE should be discarded in the biohazard bag. The lab coat should be decontaminated before disposal.

SBB Comment:

The same comment was formulated in the final advice of the Council for dossiers B/BE/18/BVW4, B/BE/18/BVW9 and B/BE/19/BVW2. Agreement to include this comment in the final advice of the Council as a recommendation to update the "Safety Data Sheet".

Liquid waste will be decontaminated using an appropriate chemical disinfectant or autoclaved. Is the waste disposed as biohazard waste after decontamination or discharged to the sewer system?

Could the applicant provide instructions in case of accidental splash into the eyes and needle stick?

SBB Comment:

The notifier could be asked to provide a 2-4 page 'instructions for study staff personal' that can be provided as a plasticized document to personnel preparing and administering the MP detailing. This sheet should include all relevant handling instructions, detailed instructions in case of spill, waste management and other risk management measures:

- risk management procedures used in case of needle-stick injury or the formation of aerosols in case of bag rupture
- the use of personal protective equipment for health care workers (e.g. which PPE are mandatory)
- procedure in the event of accidental occupational exposure through a splash in the eyes or mucous membrane
- procedures for treatment of accidental spill (concentration of disinfectant, contact time)
- procedures to prevent and to deal with exposure to blood, urine, vomit or other bodily fluids from patients in the initial period where there are high numbers of transduced cells after infusion

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

The AAV GP document concerns AAV vectors which only retain the 145 bp ITRs from the AAV genome. The origin and role of the TRY sequence should be provided in order to determine whether the PR006A vector falls into this description of AAV vectors.

SBB comment
See above SBB comment related to combined comment in section 2.1

Comment 5

Has evaluated this item and has no questions/comments.

6. OTHER INFORMATION

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

Comment 1

None.

Comment 2

In the B_BE_21_BVW3_Main ICF_Belgium Dutch_v4.1.0_19Apr2021 (and also in the other languages) the brochure specifies the use of AAV virus. Even though this is outside of the scope of the ERA, I reckon it is important to use the word viral vector instead, since rAAV9 based vectors are not viruses. It is key to provide information using the proper wording to facilitate the general understanding and to support the development of gene therapeutic approaches, without stimulating the emergence of fake stories.

SBB comment:
A remark concerning the incorrect use of "AAV virus" has been added in a list of "typos and other erros/omissions".

Comment 3

None.

Comment 4

None.

Comment 5

None.

References

D.A. Amado, J.M. Rieders, F. Diatta, P. Hernandez-Con, A. Singer, J.T. Mak, J. Zhang, E. Lancaster, B.L. Davidson, and A.S. Chen-Plotkin, AAV-Mediated Progranulin Delivery to a Mouse Model of Progranulin Deficiency Causes T Cell-Mediated Toxicity *Molecular Therapy* Volume 27, ISSUE 2, P465-478, February 06, 2019 DOI: https://doi.org/10.1016/j.ymthe.2018.11.013

Astellas' Audentes reports 3rd death in gene therapy trial (Nick Paul Taylor | Aug 21, 2020)

High-dose AAV gene therapy deaths (Nature Biotechnology volume 38, page 910 (2020)) DOI: https://doi.org/10.1038/s41587-020-0642-9

Typos and other errors/omissions

Main ICF_Belgium Dutch/French/English_v4
Throughout the documents, the words 'AAV virus' are used when 'viral vector' should be used. For example in section 1.3, page 10. But also further on in the documents.

Investigational Brochure on page 63:
According to the title of table 8, study PRV-2018-028 corresponds to a Non-GLP NHP, while, throughout the document, the PRV-2018-028 study is clearly mentioned as a GLP study. The notifier should clarify or correct this point.

SNIF on page 12, section E2b:
It is said that "Safety results for PR006A evaluated in nonclinical efficacy and toxicology models have shown no adverse effects at the highest doses administered to date". In order to confirm this statement, the notifier should provide, in the text, the reference of these preclinical studies.

SNIF on page 14, section F6
It is said that: "PR006A has been well tolerated and no significant safety signals have emerged in Mouse and NHP studies". In order to confirm this statement, the notifier should provide, in the text, the reference of these preclinical studies.

CAF Confidential Annex on page 19, section 2.5:
The toxicology studies were mentioned but the references of these studies were not provided. In order to confirm this statement, the notifier should provide, in the text, the reference of these studies.

SNIF on page 12, section F2
it is said that "shed AAV-based vector have been shown to be non-infectious".
The notifier should be more moderate by saying that : "as no toxic/harmful properties have been identified related to the expression of the transgene, the risk associated to latent infection in case of exposure to clinical vector particles shed from the trial subject is considered **negligible**." As proposed in the ARE for AAV section 2.3.2 (risk characterisation).

Coordinator Comment:
The highlighted sentence is different from the meaning "shed AAV-based vector have been shown to be non-infectious"

SNIF on page 12, section E2b + Protocol section 6.2.2.5 on page 94 + CAF_confidential on page 20 section 2.6:
It is said that "Since FTD-GRN patients are heterozygous mutation carriers and express a certain amount of normal PGRN, the potential risk to develop an immune response to the "wild type" PGRN produced by the transduced cells may be considered as null".
In order to be consistent with the risk analysis, the notifier should correct "null" into "negligible".

Coordinator Comment
In my opinion null is correct in this case, because negligible means "very small but possible" or "so small in size that it can be discarded" while "null" is zero.
Furthermore, this is not a biosafety concern

Investigational Brochure on page 81:
The section Warnings and Precautions does not provide a complete overview: recent reports are not included such as the August 2020 report on the Audentes trial on the death of two additional patients in the high dose arm of a study for AAV based GT for a rare neurological disease (AT132).

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of Wageningen Bioveterinary research on the list of questions for dossier B/BE/21/BVW3

30 september 2021
Ref. SC/1510/BAC/2021_0921

Coordinator: Jozef Anné (KUleuven)
Experts: Rik Gijsbers (KULeuven), Anton Roebroek (KULeuven), Willy Zorzi (ULiège), Aline Baldo, Liliane Tenenbaum
SBB: Sheela Onnockx and Katia Pauwels

INTRODUCTION

Dossier **B/BE/21/BVW3** concerns a notification from Prevail Therapeutics for a clinical trial entitled "A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)".

On 20 August 2021, based on a list of questions prepared by the BAC (SC/1510/BAC/2021_0807), 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 10 September 2021. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

The expert has read through the replies of the applicant and appreciated the detailed answers and thorough report.

The expert stipulates below specific comments for each individual question (Q) that was replied to.

Q1
The applicant has provided sufficient additional info in response to the question asked.

Q2
The applicant mentions in the Sponsor Response 2 that 'low amounts of viral particles are shed' and that 'the virus is inactive'. I presume that 'viral vector particles', and 'viral vectors' is meant, respectively.

Q3-4 & 5.1
The applicant has provided sufficient additional info in response to the question asked.

Q5.2
It is not entirely clear how the calculus works for the statement that animals of 2-4 years old (maximally reaching 25-30) would be representative for a target population of 45 years in human.

Still, I understand that this NHP are a model, and that costs and animal welfare are key issues to be considered. For sure, it is the best possible model available to provide information on shedding, prior to going to the patients themselves. In addition, this topic lies outside the ERA (in my opinion).

Q5.3-5.5
The applicant has provided sufficient additional info in response to the question asked.

Q6-7-8
The applicant has provided sufficient additional info in response to the question asked.

Q9
I understand the reasoning that when samples would be positive at D14, that earlier time points would be positive as well as was stipulated in Sponsor Response 8 (even though the titers of the viral vector particles would probably be significantly higher at earlier time points). Still, in Sponsor Response 9, it is indicated that for the first treated patient urine and saliva samples were negative at all-time points, except saliva which was positive at D14.
In my opinion, the latter calls for additional time-points to be included earlier than D14, to pinpoint a 'shedding window' that is as narrow as possible.

SBB's and coordinator's Comment:
Given that preliminary results indicate that significant levels of viral vector are present in the saliva of patient at D14 and given that virus / vector shedding in cases of replication incompetent virus vectors would be of a much shorter duration, we would strongly encourage the notifier to consider the conduct of the proposed clinical trial as an opportunity to further characterize the shedding window by adding timepoints <D14 for urine, stool and saliva samples.
Timepoints earlier than D14 have been included in the context of two other clinical trials evaluated by the BAC (cfr B/BE/20/BVW4 (Pfizer) and B/BE/19/BVW2 (Biomarin) using an AAV viral vector, albeit by a different route of administration (intravenous injection).
Furthermore, BAC would strongly encourage the notifier to recommend the patient to wear a face-mask made of disposable material and to keep his/her distant when in contact with immunocompromised human or children whose immune system is not mature, as long as significant levels of viral vector are present in the saliva of the patient.

Q10-15
The applicant has provided sufficient additional info in response to the question asked.

Typos-Errors
The applicant has provided sufficient additional info in response to the question asked.

Evaluation Expert 2

Concerning the answers of the notifier for the dossier B/BE/21/BVW3, it could be considered as satisfactory.
The expert has no additional request or advice.

Evaluation Expert 3

The expert has evaluated the answers and changes in the dossier by the notifier. In his opinion the notifier answered adequately to the raised questions and concerns. The dossier is OK in its present form.

Evaluation Expert 4

With respect to the notifier's answer on question 10 stating that
The pharmacy manual does not specify the type of mask needed to allow flexibility in compliance with local institutional guidelines in this global trial. If required, the Sponsor commits to providing an additional guidance document to the local site with the recommendation of using facial mask and eye protection during sample manipulation, it can be remarked that chirurgical mask are medical devices rather than personal protective equipment (PPE). Personnel must wear a particle filtering half mask FFP2/KN95 during sample manipulation.

With respect to the notifier's answer on question 14 it is remarked that the notifier's commitment to provide a brief instructions document for study staff personnel can be verified in the context of the notification requirement according to the regional decrees implementing Directive 2009/41/EC on the contained use.

SBB's and coordinator's Comment:
The BAC genuinely appreciates the willingness of the notifier to provide a brief instruction document for study staff personnel. As a response to the question, and before the clinical trial may start, the notifier should be asked to provide a 2-4 page technical sheet for investigational medicinal product (IMP) handling that can be provided as a plasticized document to personnel preparing and administering the MP detailing. This sheet should include all relevant handling instructions, detailed personal protective equipment (among other things, use of FFP2/KN95 mask during sample manipulation), detailed clean-up procedure, detailed instructions in case of spill, waste management and other risk management measures.

Evaluation Expert 5

In general, the expert was satisfied by the answers of the applicant except concerning the TRY sequence. Indeed the applicant did not explain the reasons for introducing this AAV sequence in their vector. Presumably, it enhances the recombinant virus production?
However, an analysis or discussion on the potential influence of this sequence on AAV recombination with natural viruses neither on AAV integration is provided.

Coordinator's Comment:
What possible recombinant could result from this, given also the limited packaging capacity of AAV? Moreover, for this recombination to take place, both PR006 and a WT AAV would have to infect the same cell with a helper virus such as HSV1. Is there any chance of this happening? The coordinator would not include this question.

SBB's and coordinator's additional comment on the notifier's response Q2:

The SBB and the BAC are of the opinion that, in order for the patients to adhere and practice good hygiene, it is important to explain why measures are taken and what are the likely sources of contaminated material. The notifier is requested to complement the instructions for good hygiene and the rationale in the informed consent form (ICF) as appropriate and to make sure that the information for the patients can be consulted in a readable format whenever they want. A small take home summary would be considered very helpful.