Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/25/BVW7 of the company AbbVie Deutschland GmbH & Co. KG for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

FINAL version : 09/01/2026
Ref. SC/1510/BAC/2026_0033

Context

The notification B/BE/25/BVW7 has been submitted by AbbVie Deutschland GmbH & Co. KG to the Belgian Competent Authority in September 2025 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 with the title : *"Randomized, Controlled, Partially Masked, Phase 3b Study to Assess the Injection Burden, Efficacy, Safety, and Long-Term Preservation of Visual Acuity of Surabgene Lomparvovec (ABBV-RGX-314) in a Real-World Context in Subjects with Neovascular Age-Related Macular Degeneration (nAMD)".*

Neovascular (wet) Age-Related Macular Degeneration (nAMD) is the less common but more serious form of AMD. Unlike dry AMD, which is marked by yellow retinal deposits, wet AMD occurs when abnormal blood vessels grow within the retina due to excess vascular endothelial growth factor (VEGF). These vessels leak fluid into the retinal tissue, damaging the macula, the area responsible for sharp clear vision. This fluid in the retina can destroy photoreceptor cells, causing significant and sometimes sudden vision loss. Because these cells cannot regenerate, early treatment that limits the effects of VEGF is essential to preserve vision and limit disease progression.

The primary objective of this phase IIIb study is to assess anti-VEGF injection burden and long-term efficacy after one single administration of subretinal surabgene lomparvovec (ABBV-RGX-314) compared to intravitreal injections of ranibizumab, an anti-VEGF treatment already authorised in European Union.
The active substance of ABBV-RGX-314 consists of an adeno-associated virus serotype 8 (AAV8) viral vector containing the expression cassette for human anti-vascular endothelial growth factor (VEGF) antigen-binding fragment (Fab).

Compared to the wild-type AAV virus, the AAV vector lacks the *rep* and *cap* viral sequences rendering it unable to replicate, even in the presence of a helper virus. The vector will therefore persist as episome.

Overall, up to 561 subjects with previously treated nAMD will be included in this Phase IIIb study, wherefore, eight are expected in Belgium. ABBV-RGX-314 will be administered at two different dose levels (low and high doses) as a single subretinal injection. A third group of subjects will receive PRN intravitreal ranibizumab injection. This study will be conducted at two clinical sites located in Flanders. The national territory is considered as the potential release area of ABBV-RGX-314.

The dossier has been officially acknowledged by the Competent Authority on 10 October 2025 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 and one expert from the SBB answered positively to this request. The experts assessed whether the information provided in the notification was sufficient and accurate to state that the deliberate release of the genetically modified organism would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments from the experts.

The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.
The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patients, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

On 12 November 2025, 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 28 November 2025 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts, and resulted in a second list of questions, which was transmitted to the notifier on 05 December 2025. The answers of the notifier were received on 16 December 2025 and reviewed by the coordinator, after which a third list of questions was transmitted to the notifier on 18 December. The answers of the notifier were received on 24 December 2025, 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 with the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the above mentioned Royal Decree. The Competent Authority didn’t receive any reactions from the public.

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.

The ABBV-RGX-314 drug substance is manufactured in a controlled environment, by a triple plasmid DNA transfection of the vector genome plasmid carrying the transgene, an AAV trans plasmid encoding the AAV *rep* and *cap* genes required for the encapsidation and an adenovirus helper plasmid containing essential adenoviral helper genes required for rAAV replication into human embryonic kidney (HEK) 293 cells.
Although, it is known that during rAAV viral vector production, illegitimate encapsidation of contaminant DNA from the bacterial backbone, helper plasmids or producer cell line (Lecomte et al. 2019) or truncated genomes resulting from partial replication of vector genomes occurs, the applicant ensures that the levels of packaged illegitimate DNA are controlled within acceptable limits.
Given that the transgene plasmid contains the ampicillin resistance (AmpR) gene, the applicant was asked to provide further details on the monitoring of bacterial backbone sequences in the vector production batches and on the structure and composition of the plasmids used. As confirmed by the applicant, to maintain the integrity and safety of the clinical rAAV vector lots, a ddPCR assay is performed on every batch produced and results were within acceptable limits.

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

Information related to the molecular characteristics of ABBV-RGX-314 were adequately described in the dossier.

3. The conditions of the release

This phase IIIb study will consist of three treatment groups (low or high dose ABBV-RGX-314 (rAAV) or ranibizumab). The GMO will be administered via a single subretinal injection into the eye, in hospital centres. After administration, subjects will stay in the unit for observation. Subjects will be monitored for 54 weeks to assess treatment outcomes. Afterwards, all the subjects will continue the study for long-term follow-up for a total of five years after ABBV-RGX-314 administration.

Given that ABBV-RGX-314 vector shedding in tears, urine and serum has been investigated in subretinal administration of surabgene lomparvovec in two other similar studies investigating the same doses, no viral shedding analysis will be performed during this Phase IIIb trial.

As a safeguard against potential vector transmission to other people or release into the environment once patients leave the hospital setting, the notifier committed to update the Patient Information and Informed Consent Form for Belgium at the earliest opportunity by explaining and summarizing all the critical information and instructions for patients and their families. So, clear instructions on proper disposal of waste material generated from dressings, tears and nasal secretion will be provided to the patients and medical personel, which may include storage of waste material in sealed bags prior to disposal. Disposal will be performed in accordance with site-specific instructions. These handling precautions should be followed for 14 days after administration.

Taken together, the information related to the conditions of the release were found to be adequately described in the dossier.

4. The risks for the environment or human health

The GMO is a recombinant, replication-deficient adeno-associated virus-based vector not harbouring any antibiotic resistence genes. Like the wild-type AAV virus, a rAAV vector is not known to be pathogenic. The genetic modification introduced in the AAV-based vector does not confer the GMO any properties that could pose risks to the human population or the environment.

There is only a remote possibility of homologous recombination between the ITR-sequences of ABBV-RGX-314 and wild-type AAV in case a triple infection by ABBV-RGX-314, 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 AAV required for replication and encapsidation but would in turn lead to the loss of the transgene. It was also remarked that the genetic material from *rep* and *cap* genes together with the transgene size would be too large to be packaged in AAV capsid, making it impossible to form a replication competent viral particle that would contain the transgene and the *rep* and *cap* genes necessary for multiplication.

Following BAC's request, the applicant confirmed that non-human germline transmission was evaluated using a stepwise approach in non clinical studies, that found no vector DNA in ovarian germline cells and no biodistribution to the testes in animal models. According to the protocol, female subjects must be postmenopausal or surgically sterilized and male subject must agree to use highly effective methods of birth control for at least 3 months after ABBV-RGX-314 administration.

In order to align with the instruction given in the product information document (EPAR) of EU registered medicinal products containing recombinant AAV, a lifelong restriction on donating blood, organs tissues and cells for transplantation is recommended.

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

The BAC concludes that, based on the non-pathogenic and non-replicative nature of ABBV-RGX-314 and the assumed lower amounts of shed and intact viral particles of ABBV-RGX-314 as compared to the therapic dose, the overall risk associated to exposure and transmission to other individuals can be considered negligible.

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

As liquids containing GMOs are injected under pressure into the patient's eye by the vitrectomy device, and although the risk of liquid micro-splashes is low, it cannot be completely ruled out. Therefore, alongside other PPE, personnel will be requested to ensure adequate facial protection (mask and protective eyewear) against potential splashes of the IMP during its preparation and administration, as well as when manipulating patient samples.

In the event a spill of the IP occurs, the spill will be contained, and the area will be decontaminated with an approved disinfectant such as freshly prepared 6,000 ppm (mg/L) sodium hypochlorite solution. To maintain chlorine strength and ensure bleach effectiveness, it is essential to prepare the solution just

before use to prevent loss of effectiveness over time. The Pharmacy Manual containing all specific handling instructions for the personnel, has also been adapted as requested by the BAC.

Since propagation of ABBV-RGX-314 is very unlikely, 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 provided that the additional requests as outlined in the conditions here below are met.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that ABBV-RGX-314 developed to treat patients with Neovascular Age-Related Macular Degeneration (nAMD), by means of endogenous production of anti-VEGF antigen binding fragment (Fab) protein, will have any 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.

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 all the safety instructions as described in the following documents :
    - Latest version of the ICF
    - Latest version of the Protocol
    - SNIF v2.1
    - CAF_v1.2_non confidential
    - CAF_confidential
    - M24-528 – Investigative Site Pharmacy Manual_v3.0

- As commited by the applicant, some documents still need to be updated as follows in the next amendment opportunity:
    - IB (Investigator Brochure) section 11.3 : since shedding has only been assessed in a very limited number of bodily fluids (serum and urine), the statement “short-term shedding is not likely to have clinical relevance” is incorrect and should be updated to clearly state that this is true only for the tested samples.
    - IB page 71 : as the term “infect” refers to viruses, it is not appropriate to use it when describing the activity of viral vectors. The term “transduce” should be used instead. Therefore, the following sentence should be corrected accordingly : “release of vectors that did not infect the target cells”.
    - ICF for Belgium will be implemented with details about care instructions related to preventing dissemination of study product as mentioned in the Agency response to second and third RFI from Belgium (28 november 2025 and 30 december 2025). Furthermore, to limit potential environmental spread, patients should be advised to dispose of waste material arising from dressings, tears and nasal secretions in sealed bags prior to disposal. Disposal will be performed in accordance with site-specific instructions. These handling precautions should be followed for 14 days following ABBV-RGX-314 administration.

- Protocol and ICF will be updated by clarifying that ‘The long-term safety of recombinant AAV gene therapies including Sura-Vec remains uncertain. Therefore, a lifelong restriction on donating blood, organs, or cells for transplantation is recommended’

- 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 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.

- 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 will at least contain:
  - The total number of patients included in the trial and the number of patients included in Belgium;
  - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
  - A report on the accidental releases, if any, of ABBV-RGX-314.

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

Annex I: Compilations of comments of experts in charge of evaluating the dossier B/BE/25/BVW7 (ref. SC/1510/BAC/2025_1320 and SC/1510/BAC/2025_1388)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/25/BVW7
And comments submitted to the notifier

17 November 2025
Ref. SC/1510/BAC/2025_1320

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 03 October 2025.
Coordinator: Rik Gijsbers (KULeuven)
Experts: Willy Zorzi (ULiège), Anton Roebroek (KULeuven), Liliane Tenenbaum (Lausanne University Hospital), Amaya Leunda Casi
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/25/BVW7** concerns a notification from AbbVie Deutschland 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 10 October 2025 and concerns a clinical trial entitled "*Randomized, Controlled, Partially Masked, Phase 3b Study to Assess the Injection Burden, Efficacy, Safety, and Long-Term Preservation of Visual Acuity of Surabgene Lomparvovec (ABBV-RGX-314) in a Real-World Context in Subjects with Neovascular Age-Related Macular Degeneration (nAMD)"*. The investigational medicinal product is a AAV8- derived recombinant replication deficient vector carrying an anti-VEGF Fab transgene expression cassette.

♦ 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 12-11-2025 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
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

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

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

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

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

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

Comment 4
Has evaluated this item and has no questions/comments.

2.3. Diagram (map) of the clinical vector

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

Comment 2

Has evaluated this item and has no questions/comments.

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

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

Comment 3
• The sentence below (from CAF confidential: 2.4. Molecular characterization of the clinical vector) seems to assume that the sequence of the rAAV final product, matches 100% the sequence of the transgene expression cassette". This sentence is misleading. Indeed, it is known that during viral production, illegitimate encapsidation of i) contaminant DNA from the bacterial backbone, helper plasmids or producer cell line (doi: 10.1007/978-1-4939-9139-6_5) or ii) truncated genomes resulting from partial replication of vector genomes occurs. These illegitimate single-stranded DNA genomes were presumably not revealed by the Ion Torrent technology method used but were shown by others to represent a non-negligible proportion (up to 20% of encapsidated DNA) using Multiplex digital PCR sequencing. The authors have demonstrated that encapsidated DNA is highly heterogeneous. (DOI: 10.1371/journal.pone.0293277). Moreover, in contrast to applicant's statement, single base substitutions were evidenced.

In conclusion, evidencing the unmodified transgene sequence using next generation sequencing does provide a full description of the capsids content and does not exclude that contaminants are present.
The authors should either provide data from a multi-probe digital sequencing method allowing to evidence DNA contaminants and amounts of truncated genomes or re-phrase their conclusion.

From CAF confidential: 2.4. Molecular characterization of the clinical vector:
"The sequence of the GMO's genome was confirmed by the next generation sequencing utilizing Ion Torrent technology. This assay provided confirmation of the GMO transgene genome sequence directly from AAV products, in addition to sequence confirmation of plasmids in the release testing of plasmids by Sanger sequencing. The obtained sequences match 100% the sequence of the transgene expression cassette in the anti-VEGF Fab transgene plasmid."

SBB's comment:
Given the importance of accurate molecular characterization of the clinical vector during the evaluation of its potential impact on human health and the environment, the applicant could indeed be asked to either provide data from a multi-probe digital sequencing method allowing to evidence DNA contaminants and amounts of truncated genomes or re-phrase their conclusion.

Coordinator comment:
I agree with the SBB comment. Still, the wording used is to me correct. The fact that contaminants may be present and packaged is intrinsic to the platform (and probably also occurring in wtAAV viral infection). We could ask to be cautious and indicate that it is known that other sequences may be packaged as well.

Comment 4
Has not evaluated this item.

Additional SBB's comment:
Usually, AAV GMO vectors are manufactured by triple plasmid transfection of human cells (eg. HEK 293) : the vector genome plasmid carrying the transgene, an AAV trans plasmid encoding the AAV rep and cap genes required for the encapsidation and an adenovirus helper plasmid containing essential adenoviral helper genes required for rAAV replication. However, according to page 8 of the SNIF, HEK 293 cells will be transfected only with a transgene vector and a helper vector. The applicant could be requested to clarify whether this description in the SNIF is accurate, or should the document be corrected. If information is confirmed, please update the SNIF to include an explanation of how the GMO production will be carried out.

Coordinator comment:
I agree with this comment and the SNIF info should be amended. In B_BE_25_BVW7_Part 2_CAF_CONFIDENTIAL.pdf p2/14 the applicant states "The GMO is manufactured by triple plasmid transfection of human embryonic kidney (HEK) 293 MCB cells with: (i) the human anti-VEGF Fab vector genome plasmid, pAAV.CB7.CI.amd42.RBG.KanR, (ii) an AAV trans plasmid, pAAV28KanRGX, containing the AAV rep genes of AAV2 and the AAV cap genes from AAV8, and (iii) a helper adenovirus plasmid, pAdDeltaF6, containing adenoviral sequences necessary for recombinant AAV generation."

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
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
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.

Additional SBB's comment:
Based on data from shedding analysis from the NHP studies developed in the CAF ANNEX and on the preliminary results from the clinical study, the applicant could be requested to clarify if there were any biological samples other than urine and blood analysed for vector shedding (such as tears, saliva, nasal swaps…) during Study RGX- 314-001 and were any human shedding assessments conducted prior to Week 14, particularly within the first 7 days post-administration, given that non-clinical NHP studies demonstrated the presence of ABBV-RGX-314 DNA in certain sample up to 7 days after dosing ? The applicant is requested to provide further details and justification regarding this aspect. If no other samples and no other timepoints were analysed during this study, the applicant could be requested to justify his choices with supporting results or to consider including shedding analysis on different samples (tears, nasal secretion, saliva) at different timepoints before Week 14.

Coordinator comment:
I agree with SBB.

Additional coordinator comment:
- Biodistribution to the ovaries has been observed with other AAV8 therapeutics delivered to rats or NHPs (see refs 37,38) however, without distribution to oocytes. Even though levels are very low, and knowing that biodistribution is very species specific, this should be followed with caution (effect in human may even be more outspoken). Since the DP expresses an antiVEGF FAb, toxicity in other regions in the body should be considered (beyond ERA). Still, doses used in human would be 1-2 log lower (Table2, p38/122).
- At B_BE_25_BVW7_IB_ABBV-RGX-314.pdf p71/122 paragraph: "short-term shedding is not likely to have clinical relevance" => statement is not correct, shedding is only assessed in very limited bodily fluids, and would be best that that is specifically indicated. I would request for more samples to be assessed like tears, nasal swaps, saliva.
- Further on the same page "Male subjects with female partners of childbearing potential must be willing to use condoms plus a highly effective form of partner contraception from the Screening visit until at least 4 weeks or up to 3 months, per local requirement, after vector administration. Cessation of birth control after this point should be discussed with a responsible physician." To me this should be defined better and more uniform. The current advise is open to very different interpretation. What is meant by "at least 4 weeks or up to 3 months, per local requirement, after vector administration"? Is the decision open to the person being treated?

SBB's comment:
- The following request could be sent to the applicant:
Biodistribution to the ovaries has been observed with other AAV8 therapeutics administered to rats or non-human primates; however, no distribution to oocytes was reported. Although the detected levels are very low, and given that biodistribution patterns are highly species-specific, this finding should be interpreted with caution, as effects in humans could potentially be more pronounced. Since the drug product expresses an anti-VEGF Fab, potential toxicity in other tissues should also be evaluated. Nevertheless, the doses intended for human administration are expected to be 1–2 logs lower.

It is therefore requested that the applicant further evaluates and discusses the potential environmental implications of ovarian biodistribution observed in non-human primates, considering the persistence of vector DNA and transgene expression in reproductive tissues. The applicant should address whether such findings could influence the potential for germline transmission, shedding, or secondary exposure in the environment.
- The following request has been added to the additional SBB's comment here above:
Furthermore, since shedding has only been assessed in a very limited number of bodily fluids (serum and urine), the following statement in section 11.3 of the IB; "short-term shedding is not likely to have clinical relevance" is incorrect and should be updated to clearly state that this is true only for the tested samples.
- The following question could be sent to the applicant:
According to section 11.3 of the IB (Germ line transmission), it is reported that "Male subjects with female partners of childbearing potential must be willing to use condoms plus a highly effective form of partner contraception from the Screening visit until at least 4 weeks or up to 3 months, per local requirement, after vector administration". This requirement should be defined more clearly and applied uniformly across study sites. As currently worded, the statement allows for wide variation in interpretation. It is unclear what is meant by "at least 4 weeks or up to 3 months, per local requirement, after vector administration." The applicant should define a duration and clarify whether the duration is determined by regulatory guidance, clinical judgement, or participant choice.

Coordinator comment:
I agree with the SBB amended 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
In the CAFs (common and confidential, page 7 and 8) in the section "3.2 Intended location(s) of the study" no details are given about the location of the laboratories involved in the administration the product etc. Are more details like a plan of the site(s) concerned not required for Belgium?

SBB's comment
The list of the rooms at the site involved in the clinical trial and their location within the site is requested and analysed during the contained used procedure

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
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.

3.5. 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
In the CAFs (common and confidential, page 6) regarding germ line transmission reference is made to the non-clinical IMPD section 2.2.3 attached. This section was not found attached. Thus it is not clear whether additional information exists other than mentioned in the investigator brochure (IB) on pages 34 and 35 “Reproductive and Developmental Toxicity”.

SBB’s comment
A discussion on the risk for germline transmission and insertional mutagenesis can be found in the non-clinical IMPD. The information contained in the IB is developed in greater detail in the IMPD, and additional references are also included.

In the CAFs (common and confidential, page 11) in the section “f) Recommendations given to clinical trial subjects to prevent dissemination (where applicable)” it is mentioned that care instructions will be given to the patients to ensure dissemination of the product is being prevented at all times. These instructions are not described the available documents and consequently cannot be evaluated.

SBB's comment

The following question could be sent to the applicant:

According to the CAF document, page 11/14, care instructions will be given to the patients to ensure dissemination of the product is being always prevented. However, only a few details are presented on how clinical trial subjects should avoid dissemination of the product.

For patients and patient's family to adhere to and practice good hygiene, it is important to explain why measures are taken and what are the likely sources of contaminated material. Therefore, it is strongly recommended to develop a small take home summary (preferably one-page, plasticized document) which would bring together all information and instructions for patients and patient's family to avoid potential transmission of the viral vector to other people or to the environment, if any, when patients are leaving the hospital setting.

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

- Which bodily fluids are anticipated to contain viral vector genome (albeit very low levels)
- Instructions aimed at limiting contact with materials or surfaces frequently contaminated with bodily fluids
- If applicable, at which time points eye pads may be removed and how these eye pads should be disposed of.
- Instruction on good hygiene to be practiced
- Instruction and effective solutions for decontaminating potentially contaminated areas, tissues, skin…
- Restriction on blood, organs, tissue and cells for transplantation donation
- The obligation to use contraceptive methods

On the same page in the CAFs in the section" g) Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject" it is mentioned that no recommendations are applicable. This is not correct. Recommendations are surely necessary for an initial period after administration. It seems also in contradiction with the recommendations in the section "4.3. Contraception, pregnancy and breast-feeding" (Main ICF, page 11-13).

SBB's comment

The following question could be sent to the applicant:

According to the Public CAF document p 11, no recommendations on donations of blood/cells/tissues/organs by the clinical trial subject are planned or considered necessary. However, since there is a lack of experience with donation of blood or organs, tissues and cells for transplantation following AAV vector-based gene therapy, the notifier is requested to revise the instructions regarding blood, organs, tissues and cells and to align these with the instruction given in the product information document (EPAR) of EU registered medicinal products containing recombinant AAV (Glybera, Zolgensma, Roctavian, Luxturna, Upstaza, Hemgenix) : 'Patients treated must not donate blood, organs, tissues, and cells for transplantation'.

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

In the documents several times (personal) protective equipment is mentioned in detail. The use of eye protection by the healthcare professional should be added to this detailed information.

SBB's comment

This recommendation has been included in the proposed question in the comment 2 here below

Comment 2
Considering the point a) and the point b) of section 3.6 of the CAF document (p10/14):

1)For staff administering the GMO, the applicant could be recommended to clearly include in the PPE, laboratory goggles in order to protect the eyes from the risk of liquid micro-splashes (GMO liquids are injected under pressure by the vitrectomy machine into the patient's eye).

2)Please clarify the standard PPE for administration without loss of a part of equipment: ex: in point b), the mask has disappeared from the list.

3) To ensure clear and consistent guidance for healthcare personnel, the PPE has been aligned across all relevant documentation of this dossier, as follow: gloves, mask and protective eyewear should be worn.

SBB's comment:
The following question could be sent to the applicant:
According to the SNIF page 15 and the CAF document page 10, section 3.6.b, the required protective equipment includes laboratory coats and gloves. However, the CAF document (pages 10, section 3.6.a, and 12) and the pharmacy manual (page 6) additionally specify the use of a mask alongside the laboratory coat and gloves. The applicant is requested to update the relevant document(s) as necessary to ensure consistency across all submitted materials. Furthermore, liquids containing GMOs are injected under pressure into the patient's eye by the vitrectomy device. Although the risk of liquid micro-splashes is low, it cannot be completely ruled out. Personnel should ensure adequate facial protection against potential splashes of the IMP during its preparation and administration, as well as when manipulating patient samples. The applicant is therefore requested to include a mask and protective eyewear to the list of personal protective equipment PPE.

Considering the point c) of section 3.6 of the CAF document (p10/14):

1) Please complete the information for the bleach solution preparation by indicating that this solution must be freshly prepared. To maintain chlorine strength and ensure bleach effectiveness, it is crucial to prepare the solution just before use to avoid loss of effectiveness over time.

2) Please consider that 10% bleach solution is not the usual concentration for treating all the spill-contaminated aera because, at this concentration, its can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns. This treatment at this concentration must be only reserved for minor aera spill treatment.

3) The usual concentration for the decontamination of Adenovirus is 6000 ppm (cf.ref 1). The ready to use solutions can contain in Belgium between 5 and 36 °Chl. So the dilution (1:10 or 10%) of the Household Bleach (for the "USA") is depending of this initial concentration. We invite the notifier to change the ambigous terms "10% Bleach solution" in "6000 ppm (mg/L) Bleach solution".

Ref 1 :
Antimicrob Agents Chemother. 2006 Apr;50(4):1419–1424. doi: 10.1128/AAC.50.4.1419-1424.2006

Efficacy of Hospital Germicides against Adenovirus 8, a Common Cause of Epidemic Keratoconjunctivitis in Health Care Facilities. William A Rutala [1,2,*], Jeffrey E Peacock [3], Maria F Gergen [1], Mark D Sobsey [3], David J Weber [1,2]

Ref 2 :

For the “USA” :

Expected Chlorine Concentrations by Various Dulitions of Household Bleach (5.25-6.15% sodium hypochlorite)

Dilution	Chlorine (ppm)
None	52,500–61,500
1:10	5,250-6,150
1:100	525-615
1:1000	53-62

source :

Accessible version: https://www.cdc.gov/infection-control/hcp/disinfection-and-sterilization/index.html

Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008

Update: June 2024

William A. Rutala, Ph.D., M.P.H.[1,2], David J. Weber, M.D., M.P.H.[1,2], and the Healthcare Infection Control Practices Advisory Committee (HICPAC)[3]

4)Although the Bleach solution at concentration 6000 ppm is available for eliminating non-enveloped RNA viruses, its use should not be considered “universal” because its corrode or damage stainless steel, aluminium and the most rubbers components of surfaces.

5) In the event of a biological spill treatment using Bleach solution, to protect the eyes and the face from the risk of bleach (splashes) and to ensure clear and consistent guidance for healthcare personnel, the PPE has been aligned across all relevant documentation of this dossier as follow: In the event of a biological spill treatment, protective eyewear, lab coat, overshoes, gloves, mask and protective eyewear should be worn.

SBB’s comment

The recommendations proposed by the expert could be summarize as follow :

According to section 3.6.c of the CAF document (page 10/14), in the event a spill of the IP occurs, the spill will be contained, and the area will be decontaminated with a 10% bleach solution.

- Given that to maintain chlorine strength and ensure bleach effectiveness, it is crucial to prepare the solution just before use to avoid loss of effectiveness over time, the notifier could be requested to complete the information by indicating that this sodium hypochlorite solution must be freshly prepared.
- As 10% bleach solution may cause ocular and mucosal irritation, it is not suitable for general spill decontamination. The effective concentration for Adenovirus decontamination is 6000 ppm (mg/L) available chlorine. As household bleach concentrations vary (between 5 and 36 °Chl in Belgium), the expression “10% bleach solution” is ambiguous and should be replaced by “6000 ppm (mg/L) bleach solution.”
- Although the Bleach solution at concentration 6000 ppm is available for eliminating non-enveloped RNA viruses, its use should not be considered “universal” because it can corrode or damage stainless steel, aluminium and the most rubbers components of surfaces.

Point 5 to be included in the additional SBB's comment requesting the instruction sheet for personnel

Coordinator comment:
I align with the replies of SBB

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

Comment 4
In the CAF document
- PPE: In addition to wearing gloves and a laboratory coat, personnel should also ensure adequate facial protection against potential splashes of the IMP during its preparation and administration, as well as when manipulating patient samples. The recommended personal protective equipment (PPE) includes a mask and protective goggles.
- Recommendation given to CT subjects to prevent dissemination:
Clinical trial participants may also receive guidance on the appropriate procedures for disposing of the patch and protective shield in the event of an incident or loss of the eye patch at home. A designated hazardous waste disposal bag could be provided to patients for the safe elimination of the patch or for returning it to the investigators.
- Waste: It may be specified that the final disposal method for contaminated waste and unused vectors should be incineration. This requirement is mentioned when unused vectors are returned to the sponsor, but not when they are managed directly at the clinical site.

SBB's comment
First point has been included in previous comment 2 in this section (3.6)
Second point has been included in previous comment 1 in this section (3.6)
Recommendation reported in point 3 could be rewritten as follows:
According to section 3.6.e of the CAF document (page 10/14), "all equipment used during the procedure will either be disposed of in line with current biological hazard procedures or decontaminated with virucidal agents as dictated by the local biological hazard waste management plan". However, as with unused vectors, all equipment should also be destroyed by incineration. Therefore, the applicant could be requested to complete these instructions.

Coordinator comment:
I would assume that all biological waste is incinerated, but for sure fine to include more explicit mentioning.

Additional SBB's comment:
According to the CAF document, page 10, a Safety Data Sheet (SDS) is available in the Pharmacy Binder and includes further handling instructions. The applicant could be requested to amend the SDS sheet to make sure this document contains all relevant instructions for study staff personal as detailed here:

- Personal Protective Equipment (PPE)
    - o For the IMP preparation
    - o For the administration to the patients
    - o For the samples collection from the patient

- o In the event of a biological spill treatment, protective eyewear, lab coat, overshoes, gloves, mask and protective eyewear should be worn when using freshly prepared bleach

- Management of inadvertent exposure of human to the vaccine
  - o Eye exposure from splash or aerosol
  - o Mouth exposure from splash or aerosol
  - o Needlestick, sharps exposure or non-intact skin exposure
  - o Contact with skin and clothing
- Management of inadvertent exposure to blood, urine, vomit or other bodily fluids from patients in the initial period at the hospital
- Clean-up procedure
  - o After IMP preparation (specify decontamination solution, concentration and minimum contact time)
  - o In case of accidental spill or breakage (specify decontamination solution and minimum contact time)
- Waste Management
  - o During IMP preparation
  - o During IMP administration

Coordinator comment:
I would suggest the applicant to include this information in the SDS sheet, but does not seem necessary to have the document provided to SBB again?

SBB's comment:
Since we haven't received the SDS document (it's mentioned in the CAF, but it wasn't included with the other documents in the dossier), we would recommend asking them to provide it to us so that we can ensure the information contained in the document is complete and accurate.

Coordinator comment:
Agreed.

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
See comment 3.6. With correct recommendations and compliance to these recommendations the overall environmental risk will be negligible.

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

Comment 3
The environmental risk assessment is dependent on the accurate characterization of encapsidated DNA sequences. For example, the presence of the kanR gene in the final products, which could possibly represent a safety concern, has not been determined or provided.

SBB's comment

According to section 2.1 of the CAF confidential document, the GMO is manufactured by triple plasmid transfection of HEK cells in which the transgene plasmid carries the kanamycin resistance (kanR) gene. Although, transfer of the kanR gene to the environment following accidental spillage or shedding has not been reported, it is important to verify its presence in the final products. The applicant could therefore be requested to clarify if these measurements have been performed and provide the corresponding results.

Coordinator comment:

I agree that PCR technology will allow detection of KanR (fragments) sequences. All depends on the transfer plasmid design. While present in small percentages, contamination can be problematic as ITR-flanked bacterial DNA can be transcribed by the cell and translated, especially in high-dose treatments. To mitigate the problem clever plasmid design may help, such as to design plasmids with significantly longer "stuffer" DNA sequences between the genes of interest and the bacterial sequences, placing them outside the packaging range of the AAV ITRs (at least 2kb). Based on the plasmid info provided this is not possible for us to judge.
The applicant could be asked to provide more info on the plasmid make-up as well.

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

In the SNIF several mistakes and omissions are present:

Page 2, point 5: Yes should be ticked.
Page 2, point 6: Only Yes should be ticked.
Page 8, point 4b and 4f(vi): also the transfer plasmid providing rep and cap should be mentioned.
Page 9, point 6 d: except for the ITRs.

SBB's comment:

These points could be reported as "Typos and other errors/omissions":

- SNIF Page 2 : No has been reported for the question "Has the same GMO been notified for release elsewhere in the Community by the same notifier?" (question 5), whereas Yes should have been reported
- SNIF Page 2 : both Yes and No have been reported for the question " Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?"
- SNIF Page 9 : According to section 6.d, "the described insert is recombinant and completely replaces the genome of the parental organism - wild-type AAV". This statement is not entirely accurate as the parental ITRs are still present, and the text should be updated to reflect this.

Page 8 : this comment has been included in the additional SBB's comment in section 2.4. "Molecular characterisation of the clinical vector"

Coordinator comment:

- B_BE_25_BVW7_IB_ABBV-RGX-314.pdf p71/122 paragraph: 'infect' (=virus) should be 'transduce' (AAV vector)

Comment 2

Has no further comment

Comment 3

Has no further comment

Comment 4

Has no further comment

References

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Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of the expert's evaluations of the answers of AbbVie Deutschland on the list of questions for dossier B/BE/25/BVW7

04 December 2025
Ref. SC/1510/BAC/2025_1388

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

INTRODUCTION

Dossier **B/BE/25/BVW7** concerns a notification from the AbbVie Deutschland o for a clinical trial entitled "A Randomized, Controlled, Partially Masked, Phase 3b Study to Assess the Injection Burden, Efficacy, Safety, and Long-Term Preservation of Visual Acuity of Surabgene Lomparvovec (ABBVRGX-314) in a Real-World Context in Subjects with Neovascular Age-Related Macular Degeneration (nAMD)".

On 12 November 2025, based on a list of questions prepared by the BAC (SC/1510/BAC/2025_1301), 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 28 November 2025. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation 1

According to my evaluation, the notifier addressed correctly and satisfactorily the comments/questions that have been raised.

Evaluation 2

The notifier addressed correctly and satisfactorily the comments/questions that have been raised by the Biosafety Council.

Evaluation 3

I noted that the applicant modified the conclusion in Section 2.4 in the CAF by writing that:
« Presence of other sequences that may be packaged within the GMO cannot be excluded. Therefore, an orthogonal technique, ddPCR assay is used to measure encapsulated vector genomic DNA in GMO. This assay ensures that Presence of other sequences that may be packaged within the GMO cannot be excluded. Therefore, an orthogonal technique, ddPCR assay is used to measure encapsulated vector genomic DNA in GMO. This assay ensures that the levels of packaged plasmid DNA and host cell HEK-293 DNA are controlled within acceptable limits using digital PCR-based technology.

However, the results of the ddPCR assay are not shown and the applicant's conclusion that " the levels of packaged plasmid DNA and host cell HEK-293 DNA are controlled within acceptable limits " is vague. What are the limits that the applicant considers acceptable?.

SBB's comment:

Details on the results of the ddPCR assays are reported in the "Investigational Medicinal Product Dossier Quality Section" document. Quality, manufacturing, and GMP compliance will be further evaluated by the competent authority.

Evaluation 4

I have reviewed the applicant's responses. To me, they are satisfactory.

Additional SBB comment

On answer to question 7:

According to the applicant, details about care instructions related to preventing dissemination of study product will be provided to subjects in the Patient Information and Informed Consent Form for the study, as follow:

"*The type of vector used as part of ABBV-RGX-314 is widely present in humans and monkeys and is not known to cause disease, nor is it believed to be a health hazard. In this trial, treatment with ABBV-RGX-314 may result in some vector being present in body fluids for a short period of time. Although there could be a small chance of passing the vector to others, it is not considered likely to present a health risk to them. You should practice good hygiene, and you should always wash your hands with soap and clean running water if you come into contact with bodily fluids for at least 4 weeks after ABBV-RGX-314 injection.*"

Given that non-clinical NHP studies demonstrated the presence of ABBV-RGX-314 DNA in certain samples (tears, nasal secretions, saliva, serum, urine, and feces) up to 7 days after dosing (ANNEX to CAF) and given that no shedding analysis seems to have been performed in human before Day 8 (AbbVie response on question 4), it is therefore key to explain to patients why specific measures are taken and what are the likely sources of contaminated material.

Therefore, the following information should also be specified in the document :

- Which body fluids are anticipated to potentially contain viral vector genome (albeit at very low level)
- Proposition of effective solutions for decontaminating potentially contaminated areas, tissues, skin and procedure to be followed
- If applicable the time points when eye patch may be removed and instruction on how these eye patches should be disposed of

According to the CAF document, section 3.6.f, a patch and shield are applied to cover the operated eye and will be removed "typically" by the investigator, according to clinical site's local procedures. The word "typically" ("meestal" for "mostly" in the Dutch translation) is not appropriate. Please rephrase.

Also, the timing of eye pad removal is not specified. Please clarify how long the patient must wear the eye pad. If it must remain in place for several days, specify how often it should be changed and who is responsible for changing it. If patients are expected to remove or replace the pad themselves, they must

receive complete and clear instructions, and these instructions must be implemented in the local ICF too.

Coordinator's comment:
I agree with the additional comment of the SBB, and briefly elaborated based on my personal comments.

Additional Coordinator's comment:
Further in the same paragraph, at 3.6g, it is now indicated that patients cannot give blood, organs, cells for transplantation. Please clarify a time-frame (assuming this is not a life-long ban).

SBB's comment:
This comment is related to question 8.

Within the EPARs of EU-authorized medicinal products containing recombinant AAV (e.g. Glybera, Zolgensma, Roctavian, Luxturna, Upstaza, Hemgenix), no specific time frame is specified for the restriction on donating blood, organs, or cells for transplantation.

Therefore, if it is deemed applicable, the following question could be sent to the applicant:
Although within the EPARs of EU-authorized medicinal products containing recombinant AAV (e.g. Glybera, Zolgensma, Roctavian, Luxturna, Upstaza, Hemgenix), no specific time frame is specified for the restriction on donating blood, organs, or cells for transplantation, please clarify on whether the same approach will apply for this clinical trial or not. If a specific time frame will be implemented, please ensure that all relevant documents are updated accordingly.