PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) Member State of notification : BELGIUM
(b) Notification number N/A
(c) Date of acknowledgement of notification N/A
(d) Title of the project
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 (ABBV-RGX-314) in a Real-World Context in Subjects with Neovascular Age-Related Macular Degeneration (nAMD)
(e) Proposed period of release
First Subject First Visit 05Feb2026
Last Subject Last Visit 06Apr2033

2. Notifier

Name of institution or company: AbbVie Deutschland GmbH & Co. KG

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(X)
bacterium	(.)
fungus	(.)
animal	
mammals	(.)
insect	(.)
fish	(.)
other animal	(.)
specify phylum, class	…

(b) Identity of the GMO (genus and species)
Family: *Parvoviridae*

Genus: *Dependoparvovirus*
Species: Adeno-associated virus (recombinant AAV-derived-replication-deficient viral vector)

(c) Genetic stability – according to Annex IIIa, II, A(10)

The GMO is an adeno-associated virus serotype 8 (AAV8) viral vector containing the expression cassette for human anti-vascular endothelial growth factor (VEGF) antigen-binding fragment. The AAV8 vector is a DNA viral vector. DNA viruses are genetically stable due to intrinsic thermodynamic stability of the DNA molecule. The frequency of errors during the replication of DNA is relatively low; and host cells have molecular mechanisms that can repair replication errors made by DNA polymerases.

The GMO was constructed by DNA recombinant technology which allowed the replacement of all viral genes by the transgene expression cassette. Deletion of all viral DNA, except for inverted terminal repeats, rendered the GMO replication incompetent and, therefore, genetically stable since no further genetic modifications or rounds of replications are possible even in the presence of a helper virus.

The manufacturing process further supports genetic stability of the produced GMO by using characterised and fully sequenced DNA plasmids released following GMP requirements.

Also, the vector-delivered DNA is maintained in the host cells without genome integration as episomal concatemers.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes (X) No (.)

If yes, insert the country code(s)

Austria (AT), Belgium (BE), Bulgaria (BG), Croatia (HR), Czech Republic (CZ), France (FR), Germany (DE), Greece (GR), Hungary (HU), Italy (IT), Spain (ES), , Portugal (PT), Slovakia (SK).

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes (.) No (X)

If yes:

- Member State of notification: Spain (ES) / Notification number: B/ES/23/23
- Member State of notification: Germany (DE) / Notification number : B/DE/23/PEI/P00672
- Member State of notification: Hungary (HU) / Notification number: B/HU/23/02
- Member State of notification: France (FR) / Notification number: 13859160 and 19376604
- Member State of notification: Italy (IT) / Notification number: Site level applications.

Please note these notifications for release were submitted in the context of a previous Clinical Trial using the same GMO product: ABBV-RGX-314-3101 / M23-409 / EU CT: 2023-503666-23-00.

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (X) No (X)

If yes: Member State of notification

United States (USA) Canada (CAN) Japan (JPN)

- Notification number United States (USA): IND and sequence number: 17280/SN0000 6/Jan/2017

- Notification number Canada (CAN): NSN-21105, 25/Jan./2022
- Notification number Japan (JPN): MHLW/PSEHB Notification No. 0603-49 MOE/NCB Notification No. 2106031 25/May/2023

Please note these notifications for release were submitted in the context of a previous Clinical Trial using the same GMO product: ABBV-RGX-314-3101 / M23-409 / EU CT: 2023-503666-23-00.

7. Summary of the potential environmental impact of the release of the GMOs.

The GMO is an adeno-associated viral vector of serotype 8 carrying an anti-VEGF Fab transgene expression cassette inserted by recombinant DNA technology. This GMO is completely devoid of all viral genetic material (except for inverted terminal repeats) and, therefore, the GMO is replication incompetent. The vector genome is a single stranded DNA genome with AAV2-derived inverted terminal repeats (ITRs) flanking the anti VEGF Fab expression cassette. Expression from the transgene cassette is driven by a CB7 promoter, a hybrid between a CMV immediate early enhancer and the chicken β-actin promoter, while transcription from this promoter is enhanced by the presence of the chicken β-actin intron (CI). The polyadenylation signal for the expression cassette is the RBG polyA.

The GMO is planned to be administered in study M24-528, a phase 3b clinical trial; the planned number of participants is 561. The GMO will be administered subretinally as a single dose. Participants who receive Surabgene Lomparvovec (ABBV-RGX-314) will be followed for approximately 5 years in study M24-528 (for participants randomized to one of the two Surabgene Lomparvovec (ABBV-RGX-314) arms as well as the control participants). Potential GMO release to the environment will be analysed in serum, urine and tears obtained from participants in the US only Phase 2 study RGX-314-2103 (who received the same doses as those being evaluated in RGX-314-3101). The samples will be analysed for GMO detection and quantification based on a specific qPCR. Given the transient and minimal vector shedding of ABBV-RGX-314 following subretinal administration observed in the Phase 1/2a Study RGX-314-001, vector shedding in humans is not further evaluated in the ongoing pivotal trials (RGX-314-2104 and RGX-314-3101).

For humans other than the clinical trial subjects, the infection likelihood with this GMO is negligible; shedding is expected to occur at very low levels for a limited time, if at all. In the event of transient shedding in humans, the GMO cannot confer any selective advantage other microorganisms because the GMO does not contain prokaryotic promoters, antibiotic or other types of resistance genes, which would enhance their growth. In the unlikely scenario that the GMO is transmitted from a participant to other humans, the severity of potential adverse effects is negligible because a transgene expression cassette contained in the GMO encodes a humanized anti-VEGF Fab, designed to bind and inhibit human VEGF.

The dissemination of the GMO in the environment is severely restricted since the GMO is rendered replication-incompetent by removing from the GMO's genome rep and cap genes required for replication and packaging.

In the event that ABBV-RGX-314 is detected in urine, the potential impact to the environment through wastewater release is de minimis. Fleischmann (2023) reports that shed recombinant adeno-associated virus (rAAV) particles do not remain stable and/or soluble once entering a typical wastewater treatment facility (WWTF) and therefore do not pose a threat to the natural environment.
Altogether, the risk for people, animals, microorganisms and the environment exposed to the GMO is negligible.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:
(select one only)

viroid	(.)
RNA virus	(.)
DNA virus	(X)
bacterium	(.)
fungus	(.)
animal	
mammals	(.)
insect	(.)
fish	(.)
other animal	(.)
(specify phylum, class)	…
other, specify	…

2. Name

(i)	order and/or higher taxon (for animals)	*Parvoviridae*
(ii)	genus	*Dependoparvovirus*
(iii)	species	Adeno-associated dependoparvovirus
(iv)	subspecies	N/A
(v)	strain	N/A
(vi)	pathovar (biotype, ecotype, race, etc.)	AAV2 (ITRs) /AAV8 (capsid)
(vii)	common name	Adeno-associated virus (wild type)

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (X) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (X)
If yes, indicate the type of ecosystem in which it is found:

Atlantic	X
Mediteranean	X
Boreal	X
Alpine	X
Continental	X
Macaronesian	X

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (X)

4. Natural habitat of the organism

(a) If the organism is a microorganism
water (.)
soil, free-living (.)
soil in association with plant-root systems (.)
in association with plant leaf/stem systems (.)
other, specify Human and non-human primates

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not applicable

5. (a) Detection techniques
Quantitative polymerase chain reaction (qPCR)

(b) Identification techniques
Quantitative polymerase chain reaction (qPCR)

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (X) No (.)
If yes, specify
Wild-type AAVs (wt AAVs) are not known to be a pathogenic virus in humans. While wt AAVs have not been classified under Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from the risks related to exposure to biological agents in the working environment, wt AAVs do meet the definition of a group 1 biological agent under this directive (i.e., a biological agent that is unlikely to cause disease in humans).

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes () No (X) Not known (.)
If yes:

(a) to which of the following organisms:
humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC
N/A

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
After entry into the host cell nucleus, *wt* AAV can follow either one of two distinct and interchangeable pathways of its life cycle: the lytic or the latent phase. For entry into a lytic phase, a latently infected cell needs to be co-infected with a helper virus, inducing genome rescue of the provirus DNA followed by replication and packaging of the viral genome. Finally, upon helper virus-induced cell lysis, the newly assembled virions are released.

(b) Generation time in the ecosystem where the release will take place:
Not applicable

(c) Way of reproduction: Sexual .. Asexual ..
Not applicable

(d) Factors affecting reproduction:
Wild type AAV requires a helper virus (adenovirus or herpesvirus) for effective replication.

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (fungi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	Not applicable

(b) relevant factors affecting survivability:
Wt AAV does not form survival structures but can remain infectious for at least a month at room temperature following simple desiccation or lyophilisation.
Wt AAV is susceptible to appropriate virucidal disinfectants with activity for non-enveloped viruses, such as Softa-Man acute for disinfecting the hands and Incidin PLUS, alkaline solutions at pH >9,5% phenol, heat (>80°C for 60 minutes), UV radiation and extreme pH (<2 and >12). Effective disinfectants require a minimum of 20 minutes contact time to be effective.

10. (a) Ways of dissemination
Dissemination of wild type adeno-associated viruses can occur through inhalation of aerosolized droplets, mucous membrane contact, parenteral injection, or ingestion and co-infection with a helper virus.

(b) Factors affecting dissemination
Factors affecting wtAAV dissemination include dose, formation of aerosols, and closeness of contacts. However, wtAAVs are not able to replicate unless a co-infection with a helper virus occurs.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
None

C. Information relating to the genetic modification

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(X)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification

The intended outcome is a GMO, which is a recombinant adeno-associated virus serotype 8 (AAV8) vector encoding humanized anti-VEGF Fab transgene protein. Other than the AAV serotype 2 inverted terminal repeat sequences (ITR) at each end of the single-stranded DNA virus genome, all other viral sequences, including the rep and cap genes from the Wt AAV genome, have been removed and replaced with the humanized anti-VEGF Fab expression cassette and control elements necessary to drive transgene expression. The viral genome is packaged in an AAV8 capsid, resulting in a recombinant viral vector that can drive expression of the anti-VEGF Fab in transduced human cells, but is not able to replicate in host cells in the absence of a helper virus and wild type AAV.

3. (a) Has a vector been used in the process of modification?

Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (X) No (.)

If no, go straight to question 5.

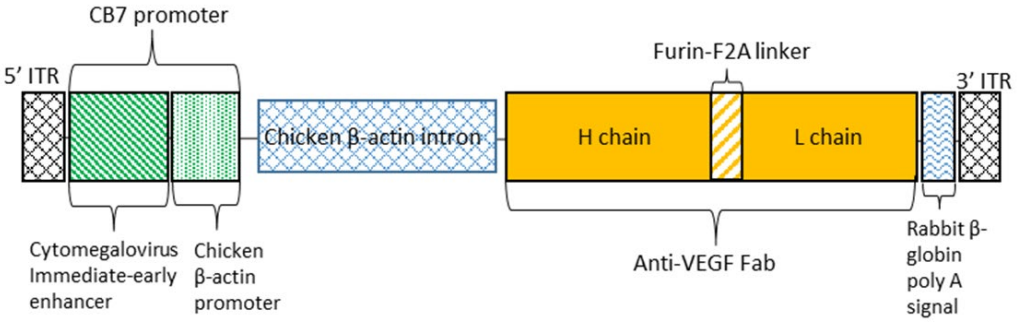
4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(X)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify …	

(b) Identity of the vector

Plasmids are used to construct the vector by transfecting the human embryonic kidney (HEK) 293 MCB cells:
- the human anti-VEGF Fab vector genome plasmid,
a helper adenovirus plasmid, containing adenoviral sequences necessary for recombinant AAV generation



(c) Host range of the vector

The vectors (plasmids) replicate in *E.coli*

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (X) No (.)

antibiotic resistance (X)
other, specify …

Indication of which antibiotic resistance gene is inserted

The kanamycin resistance gene is inserted in the vectors (plasmids). This gene confers kanamycin resistance to bacterial cells used for plasmid production.

(e) Constituent fragments of the vector

The necessary components to make the vector are provided by the plasmids. These plasmids contain the transgene cassette flanked by ITRs, the rep genes (for replication and packaging of the transgene cassette), the cap gene (required to make the capsid), and adenoviral helper genes.

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify

Transfection of the HEK293 cell line with vectors (plasmids):
transgene vector – a plasmid containing the AAV clinical vector genome with the transgene flanked by ITRs,

helper vector – a plasmid with adenoviral helper genes.

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify …Not applicable

6. Composition of the insert

(a) Composition of the insert

The expression cassette comprises:

- 3' and 5' AAV2 inverted terminal repeats (ITRs)
- CAG (CB7) promoter:
  - Cytomegalovirus immediate-early enhancer,
  - Chicken β-actin promoter,
- Chicken β-actin intron
- Humanized anti-VEGF Fab
- Polyadenylation signal

(b) Source of each constituent part of the insert

- 3' and 5' AAV2 inverted terminal repeats (ITRs): Adeno-associated virus serotype 2
- CAG (CB7) promoter:
  - Cytomegalovirus immediate-early enhancer: Cytomegalovirus,
  - Chicken β-actin promoter: Chicken,
- Chicken β-actin intron: Chicken,
- Humanized anti-VEGF Fab: Human
- Rabbit β-globin polyadenylation signal: Rabbit

(c) Intended function of each constituent part of the insert in the GMO

- 3' and 5' ITR sequences: cis acting sequences required for vector genome replication and packaging
- Humanized anti-VEGF Fab: therapeutic part of the GMO
- Chicken β-actin intron: Common feature for increased gene expression, shown to enhance accumulation of steady level of mRNA for translation
- Enhancer/promoter: enhance the expression of the transgene
- Polyadenylation signal: provides cis sequences for efficient polyadenylation of the mRNA

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify

The described insert is recombinant and completely replaces the genome of the parental organism – wild-type AAV.

(e) Does the insert contain parts whose product or function are not known?

Yes (.) No (X)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

	viroid	(.)
	RNA virus	(.)
	DNA virus	(.)
	bacterium	(.)
	fungus	(.)
	animal	
-	mammals	(X)
-	insect	(.)
-	fish	(.)
-	other animal	(.)
	(specify phylum, class) …	
	other, specify …	

2. Complete name

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	…
(iii)	genus	Homo
(iv)	species	*sapiens*
(v)	subspecies	*sapiens*
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	Human

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)
If yes, specify the following:

(a) to which of the following organisms: N/A

humans	(.)
animals	(.)
plants	(.)
other	(.)

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
…N/A

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (.) No (X)

If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (X) No (.) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (.) No (X) Not known (.)
Specify …

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (X) No (.) Unknown (.)
Specify - The GMO is unable to replicate, even in the presence of required helper virus.

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (X) No (.) Not known (.)
Specify - The GMO is unable to replicate. Therefore, though it has the capacity to infect cells, the lack of replicative capacity will severely restrict dissemination.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (X) Not known (.)
Specify …

2. Genetic stability of the genetically modified organism
Generally, DNA viruses like AAVs are stable. It is replication incompetent even in the presence of a helper virus, which even further minimizes the likelihood of genetic variation as result of replication Additionally, the long-term therapeutic activity of the GMO is not dependent on replication.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?
humans (.)
animals (.)
plants (.)
other …

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)
Point II(A)(11)(d) of Annex III (pathological, ecological and physiological traits): Recombinant AAV viruses are not pathogenic to human and non-human primates, although they can infect cells from humans and non-human primates and may persist within infected cells as episomal form. Recombinant AAV viruses are not toxic, virulent, allergenic, or carriers (vectors) of a pathogen. They do not replicate or activate other latent viruses and cannot colonise other organisms.
Point II(C)(2)(i) of Annex III (considerations for human health and animal health, as well as plant health): Recombinant AAV viruses and/or their metabolic products do not have toxic or

allergenic effects on humans, animals or plants. Recombinant AAV viruses are not pathogenic and do not have colonisation capacity.
Moreover, it cannot replicate, even in the presence of a helper virus.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
The GMO can be detected by different PCR techniques using specific primer/probes against anti-VEGF Fab coding region.

(b) Techniques used to identify the GMO
PCR based techniques with primers/probes specific to anti-VEGF Fab coding region.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

Clinital trial M24-528: 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 (ABBV-RGX-314) in a Real-World Context in Subjects with Neovascular Age-Related Macular Degeneration (nAMD)

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (.) No (X)

If yes, specify …

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

The GMO will be administered to patients in Austria (AT), Belgium (BE), Bulgaria (BG), Croatia (HR), Czech Republic (CZ), France (FR), Germany (DE), Greece (GR), Hungary (HU), Italy (IT), Spain (ES), Portugal (PT), Slovakia (SK).

Sites in Belgium:

Organisation Name:	UZ Leuven
Address Details:	Herestraat 49 3000 Leuven Belgium
Contact person:	Prof Julie Jacob (Principal Investigator), Lies Prové (Study Coordinator)
Organisation Name:	UZ Gent
Address Details:	Corneel Heymanslaan 10 9000 Gent Belgium
Contact person:	Dr Julie De Zaeytijd (Principal Investigator), Amber De Freyne (Study Coordinator)

(b) Size of the site (m^2): Not applicable m^2

(i) actual release site (m^2): Not applicable m^2

(ii) wider release site (m^2): Not applicable m^2

(a) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

Not applicable.

(b) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not applicable

4. Method and amount of release

(a) Quantities of GMOs to be released:

The GMO is administered to humans enrolled in a clinical trial in a controlled hospital setting and is not intended to be released into the environment. Based on the intended route of administration, none to minimal release in the form of shedding (e.g. in tears) in quantities unable to cause significant infection is expected (European Commission - Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors).

(b) Duration of the operation:

The GMO will be administered subretinally by a trained retinal surgeon. It is a routine retina surgery that can usually be performed safely as an outpatient procedure in approximately 30 minutes.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the releaseThe GMO will be administered to patients in a hospital operating room or ambulatory surgical center. Participant samples (aqueous humor, urine, and serum) will be drawn in the clinic and analysed by a qualified laboratory (for transgene protein concentrations and routine lab assessments). During GMO administration and sample draws, established routine practices for dealing with potentially biohazardous materials are in place as well as protective equipment including laboratory coats and gloves. Instructions for collection, processing and transportation of the clinical samples are provided in the Laboratory Manual. Standard practices for the disposal of biohazardous materials in the healthcare setting cover accidental breakages during blood draws.

5. Short description of average environmental conditions (weather, temperature, etc.)

Not applicable: given that the GMO is prepared for administration and given to subjects in a clinical environment, it is not anticipated that the GMO will be released into the environment.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.

Not applicable.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	Homo
(iv)	species	*sapiens*
(v)	subspecies	*sapiens*
(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	Human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
It is anticipated that delivery of the gene encoding for anti-VEGF Fab via a one-time administration of the GMO provides a durable source of anti-VEGF Fab activity in the retina for the treatment of nAMD.

3. Any other potentially significant interactions with other organisms in the environment
No potentially significant interactions with other organisms in the environment are predicted.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (X) Not known (.)
Give details
…

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
The GMO is a replication-incompetent virus derived from AAV2 (ITRs) and AAV8 (capsid). The genetic modifications do not affect its survival outside the host or probable mode of dissemination. The lack of replicative ability prevents multiplication and therefore severely limits its ability to disseminate. Shedding of AAV vectors has been monitored in both humans and animals; the shedding is transient and is at the low level. It is not anticipated that the GMO can establish or persist in any known ecosystem.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…

(ix) common name …

Not applicable

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
Negligible

(b) from other organisms to the GMO:
Negligible

(c) likely consequences of gene transfer:
Negligible

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
The GMO is a replication-incompetent virus derived from AAV2 (ITRs) and AAV8 (capsid). The genetic modifications do not affect its natural host and tissue tropism.
No specific studies have been conducted regarding transmission of the GMO between humans or animals and on the ecological impact of the vector in simulated natural environments.
Fleischmann (2023) reports that shed recombinant adeno-associated virus (rAAV) particles do not remain stable and/or soluble once entering a typical wastewater treatment facility (WWTF) and therefore do not pose a threat to the natural environment. In the event that ABBV-RGX-314 is detected in urine, the potential impact to the environment through wastewater release is de minimis.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None known or predicted

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Potential GMO release to the environment will be analyzed in serum, urine and tears obtained from participants in the US only study RGX-314-2103 (who received the same doses as those being evaluated in RGX-314-3101). The samples will be analyzed for GMO detection and quantification based on a specific qPCR. Given the transient and minimal vector shedding of ABBV-RGX-314 following subretinal administration observed in the Phase 1/2a Study RGX-314-001, vector shedding in humans is not further evaluated in the ongoing pivotal trials (RGX-314-2104 and RGX-314-3101). In the pivotal studies, participants will be monitored clinically.

2. Methods for monitoring ecosystem effects

The chance of ecosystem effects is considered negligible, and monitoring is not planned.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Co-infection of GMO and a helper virus is a scenario for potential exchange of genetic material between the GMO and the helper virus to generate a replication-competent AAV. The replication competent AAV assay (rcAAV) will be used to detect any competent replication virus during GMO manufacturing. However, active helper virus infection is not expected to be common in the eye where the GMO will be injected, so the risk of generating replication competent virus is extremely low.

4. Size of the monitoring area (m^2)

Not applicable.

5. Duration of the monitoring

Not applicable.

6. Frequency of the monitoring

Not applicable.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

In general terms, decontamination or site management will be performed according to local biosafety guidelines or procedures and BSL-I. 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. The bleach solution shall be in contact with the area for at least 20 minutes. The destruction of all material used for GMO manipulation will be performed following internal clinical site's procedures and depends on what is in the waste. For GMO waste only, BSL-I procedures for management of biological agents as biohazardous waste are followed since it is not known to cause human disease.

2. Post-release treatment of the GMOs

In general terms, 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.

3. (a) Type and amount of waste generated

Vials, injection device (subretinal cannula, MicroDose syringe & viscous fluid injection tubing), general hospital waste (gloves, gowns, and related accessories, etc.).

3. (b) Treatment of waste

Following GMO administration, used vials as well as the used delivery system components will be disposed of in a manner consistent with the standard practice of the institution for biohazardous materials. In addition, any disposable surgical instruments or other materials used during the administration procedure or collection of body fluids will be disposed of according to standard biosafety practice of the institution.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

   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. The bleach solution shall be in contact with the area for at least 20 minutes. A Safety Data Sheet (SDS) is provided in the Pharmacy Binder with further handling instructions. Sites may also follow their institutional procedures for infectious agent spills.

2. Methods for removal of the GMO(s) of the areas potentially affected

   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. The bleach solution shall be in contact with the area for at least 20 minutes. A Safety Data Sheet (SDS) is provided in the Pharmacy Binder with further handling instructions. Sites may also follow their institutional procedures for infectious agent spills.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

   Not applicable since exposure of animals and plants etc. is not anticipated.

4. Plans for protecting human health and the environment in the event of an undesirable effect

   Considering the negligible risk for human health and the environment, no specific plans are deemed necessary.