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| **Application form** **for clinical research with genetically modified adeno-associated viral vectors conform article 39a of the Regeling ggo[[1]](#footnote-1)**   * This application form can only be used for genetically modified viral vectors derived from Adeno-associated dependoparvovirus A or B without harmful inserted sequences where the proposed work is conform article 39a of the Regeling ggo. It follows that there is no risk of formation of replication competent virus. * This application form serves to provide the necessary information in accordance with article 40a of the Regeling ggo. In this application form, a number of questions that follow from the *Common Application form for investigational medicinal products for human use that contain or consist of AAV vectors,* do not apply. These fields are indicated with N/A (not applicable). A number of questions are already answered in accordance with Bijlage 10, Deel B Artikel B:5 – B:8 of the Regeling ggo. * In accordance with the GDPR ((EU) 2016/679), a separate general personal data form (*Algemene persoonsgegevens*) is used for personal information (see website Loket Gentherapie). * The granting of a GMO-permit is a public procedure and therefore all information provided in the application is public. Information about keeping data confidential and how this must be requested can be found on the website (see website Loket Gentherapie). * For a clarification of the necessary substantive information, a “tips & tricks” is available on the website Loket Gentherapie. * The application form must be accompanied by a Part B Summary Notification Information Format (SNIF B) (online via E-submission Food Chain platform) * Contact:   + Internet: [www.ggo-vergunningverlening.nl](http://www.ggo-vergunningverlening.nl) / www.loketgentherapie.nl   + Email: [bggo@rivm.nl](mailto:bggo@rivm.nl)   + Telephone: 0031 (0)88-689 7099 | | |
| **Document**  **history** | **Publication**  **Date** | **Description of main changes** |
| Version 1.1[[2]](#footnote-2) | September 2021 | English translation of Dutch application form version 1.1 |
| Version 1.2 | December 2022 | Change in SNIF submission procedure |
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**APPLICATION FORM FOR CLINICAL RESEARCH WITH GENETICALLY MODIFIED ADENO-ASSOCIATED VIRAL VECTORS CONFORM ARTICLE 39a OF THE REGELING GGO MILIEUBEHEER 2013**

# ADMINISTRATIVE INFORMATION

**1.1 Identification of the applicant.**

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| **Organisation Name:** | *Fill in the name of the legal entity* |
| **Address Details:** | *Fill in the address of the legal entity* |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |

* 1. **Identification of the sponsor (to the extent that is different from the applicant).**

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| **Organisation Name:** | N/A |
| **Address Details:** | N/A |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |

* 1. **Identification of the manufacturer of the clinical vector.**

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| **Organisation Name:** |  |
| **Manufacturing location:** |  |

# INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

* 1. **Description of the production system.**

*Clear maps of the vectors used for recAAV production (e.g. plasmids, baculoviruses) showing all the constituent parts of the AAV clinical vector should be provided (i.e. in addition to the “transgene vector”, all other vectors such as helper, packaging and pseudotyping vectors should be described).*

*The characteristics of all cell lines used and eventual modifications of the cell genome should be explained. Describe the cell type(s) concerned as well as their origin (e.g. human kidney, epithelial cells, insect cells).*

*The possibility of the genetic material in the cells/cell lines causing a certain interaction with the clinical vector, such as by complementation or recombination should be discussed. In particular, the tests applied to identify possible contamination of the cell line by wild-type AAV viruses and/or any virus identified as helper virus for AAV should be explained..*

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  *Describe the production system of the adeno-associated viral vector.* |

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

*The risk of generation of a replication competent AAV through recombination of the constituent parts of the viral vector system should be minimised. Test methods for detection of replication-competent virus should be described including information on the specificity and sensitivity thereof. Data from RCV testing at different manufacturing steps should be provided (e.g. virus seed bank, final product). Release criteria with regard to RCV testing should be specified*.

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  Provide information indicating that no replication-competent adeno-associated virus is present in the medical product to be administered to the subject. |

# Provide a diagram (‘map’) of the clinical vector.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers

should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

*Describe the viral vector genome and the molecular characterization of the adeno-associated viral vector.*

# Molecular characterisation of the clinical vector.

*Provide the annotated sequence of the genome (i.e. indicate the location of the sequences encoding the transgene expression cassette(s) and its regulatory elements).*

*Describe in what way the clinical vector deviates from the parental virus at the level of molecular characterisation.*

*Available data supporting genetic stability of the clinical vector should be provided. Deviations should be discussed, in particular the biological significance thereof.*

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  Describe the molecular characterization of the adeno-associated viral vector and the method how the identity of the vector is verified. |

# Description of the insert.

*The expression cassette e.g. transgene, including regulatory and coding sequences, should be described. In particular, it should be explained if the expressed product is toxic or otherwise harmful to humans (other than the clinical trial subject) or other hosts. Additionally, if the applicant considers that the transgene could confer any advantage for replication/survival of the clinical vector (vis-à-vis the parental virus), this should be explained.*

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  Describe the insert. |

# Biodistribution and shedding.

*Detailed data on clinical vector shedding (including information on the administered dose, the route of administration, and –where available- immune status of the treated subjects) from previous clinical trials with the clinical vector should be provided. Where available and if relevant for the environmental risk assessment, biodistribution data should be provided.*

*If there is no prior clinical experience with the same clinical vector, the potential for shedding should be discussed based on non-clinical data and/or clinical experience from related clinical vectors. If the applicant relies on data from related clinical vectors, the relevance of the data to the product that isthe object of this application should be explained considering, in particular, the dose and route of administration.*

*When shedding occurs, the estimated duration should be specified.*

*The methods used for detection of viral shedding, including information on the specificity and*

*sensitivity thereof, should be provided..*

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  Provide a brief summary on the biodistribution and shedding (reference to source is not required). |

# INFORMATION RELATING TO THE CLINICAL TRIAL

# General information about the clinical trial

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| **EudraCT-number (where available):** | N/A |
| **Deliberate release reference number (where available and applicable):** |  |
| **Title of the clinical trial:** | *Provide a title that covers the proposed work.* |
| **Name of principal investigator:** | ***This information should be provided in the annex with confidential information.*** |
| **Objective of the study:** | *Provide the objective(s) of the proposed work.* |
| **Intended start and end date:** | N/A |
| **Number of trial subjects that will take part in the study:** | N/A |
| **Indicate if an application related to the same investigational medicinal product has been submitted -or is planned to be submitted- to other EEA Member States. In the affirmative, please identify the countries concerned:** | N/A |

* 1. **Intended location(s) of the study.**

The applicant should provide information about the sites located in the country of submission of the application. Besides the location of the clinical activities, information should be provided about the location of laboratories where work with the GMO will be performed under the preset conditions of this application (e.g. location of storage of the GMO, location of storage of patient samples that may contain the GMO).

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| **Organisation**  **Name:** | *Fill in the place(s) where the work will be performed. This is the location(s) (i.e. location name and visiting address) where the work, under responsibility of the applicant, will be performed.* |
| **Address Details:** |  |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |
| **Planned Activities:** | N/A |
| **Containment**  **level:** | N/A |
| **Name and**  **contact details of**  **the responsible**  **person:** | N/A |

* 1. **Storage of the clinical vector at the clinical site:**

The applicant should provide information about the storage location, conditions of storage (including restrictions of access), and the maximal storage duration.

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| *The genetically modified AAV vector is stored in a closed, break-proof, leak-proof double container in a room with limited access.* |

* 1. **Logistics for on-site transportation of the clinical vector.**

The applicant should provide information about the logistics for in-house transportation.

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| *In-house transport of the genetically modified AAV vector takes place in a closed, break-proof, leak-proof packaging.*  *In-house transport of samples from the test subjects that may contain the genetically modified AAV vector is performed conform the transport of regular patient samples.* |

* 1. **Information about reconstitution, finished medicinal product and administration to patients.**

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| **Reconstitution**  **(where applicable,**  **summarise reconstitution**  **steps):** |  |
| **Pharmaceutical form and**  **strength:** |  |
| **Mode of administration:** |  |
| **Information on dosing and**  **administration schedule (in case of repeated dosing):** |  |
| **Information on concomitant**  **medication that may affect**  **the shedding of the clinical**  **vector/ environmental risks**  **(e.g. administration of laxatives, administration of**  **a medicinal product that**  **could enhance the**  **replication activity of the**  **clinical vector,**  **administration of a plasmid-based medicinal product):** |  |

* 1. **Measures to prevent dissemination into the environment.**

1. **Control measures during reconstitution (if applicable), handling and administration.**

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| *Preparation and administration of the genetically modified AAV vector takes place conform standard hospital hygienic measures.* |

1. **Personal protective equipment.**

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| *Medical personnel will follow standard hospital hygienic measures.* |

1. **Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e. decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector.**

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| *Non-disposable materials are disinfected with appropriate validated disinfection detergents or autoclaved. In case of spilling, contaminated surfaces are disinfected with a suitable validated disinfectant.* |

1. **Elimination or inactivation of left-overs of the finished product at the end of the clinical trial.**

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| *Waste that has been in contact with the genetically modified AAV vector during preparation and administration will be disposed of as specific hospital waste or as waste containing GMO’s.* |

1. **Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management.**

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| *All disposable waste that has been in contact with the genetically modified AAV vector during preparation and administration will be disposed of as specific hospital waste or as waste containing GMO’s.*  *Waste from samples, from sampling and from processing of samples from the test subjects that may contain the genetically modified AAV vector, is disposed of as specific hospital waste or as waste containing GMOs.* |

1. **Recommendations given to clinical trial subjects to prevent dissemination (where applicable).**

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1. **Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject.**

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| N/A |

1. **Other measures (where applicable).**

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* 1. **Sampling and further analyses of samples from study subjects.**

*This Section should be filled in where samples are being taken from patients which may contain*

*GMOs in the context of the clinical trial.*

1. **Describe how samples will be handled/stored/transported.**

*To the extent that handling/ storage and transport of samples are treated under same procedures as the clinical vector, cross-reference can be made as appropriate.*

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| *Standard hospital hygienic measures will be effective during sampling and further analyses. In-house transport of samples from the test subjects that may contain the genetically modified AAV vector is performed conform transport of regular patient samples. Samples from the test subjects that may contain the genetically modified AAV vector will be stored conform the storage of regular patient samples.* |

1. **Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects.**

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| *Indicate the range of the sampling time(s).* |

1. **If samples are stored at the clinical site, describe storage location and storage conditions.**

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| *Samples from the test subjects that may contain the genetically modified AAV vector will be stored conform the storage of regular patient samples.* |

1. **Explain if there is any non-routine testing of the samples and indicate whether the clinical vector is generated de novo during the testing.***Standard clinical tests that are required for (long-term) follow-up of test subjects does not need to be included here.*

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# ENVIRONMENTAL RISK ASSESSMENT

**Specific environmental risk assessment:**

Considering the specific characteristics of the investigational medicinal product (as described in Section 2), the applicant considers that investigational medicinal product falls under the provisions of article 39a of the Regeling ggo, and that the standardized environmental risk assessment as described in Bijlage 1 to the explanation of the regulation to amend the Regeling ggo[[3]](#footnote-3) and the associated conditions described in Bijlage 10, Deel B (article B:1 – B:10) apply:

Yes □

No □

If the answer to the above is “No”, the work cannot be applied for under article 3.26a of the Besluit ggo[[4]](#footnote-4) and the applicant should apply for a GMO-permit conform the regular procedure for GMOs under article 3.10 of the Besluit ggo.

1. Regeling genetisch gemodificeerde organismen milieubeheer 2013 (Regeling ggo) [↑](#footnote-ref-1)
2. This form follows the structure of the questions as established in the *Common application form for investigational medicinal products for human use that contain or consist of AAV vectors*, Version 1, October 2019. This form applies to applications that are in accordance with article 3.26a of the Besluit ggo and they are dealt with in accordance with article 3.24 of the Besluit ggo. [↑](#footnote-ref-2)
3. [Staatscourant 2020 nr. 63350 14 december 2020](https://zoek.officielebekendmakingen.nl/stcrt-2020-63350.pdf) [↑](#footnote-ref-3)
4. Besluit genetisch gemodificeerde organismen milieubeheer 2013 [↑](#footnote-ref-4)