Common application form for investigational medicinal products for human use that contain or consist of AAV vectors[1]

Note 1: This application form can be used for submissions in the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania, and Spain.

Note 2: The application form must be accompanied by the SNIF (summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market)[2] in the case of submissions that are made under Directive 2001/18/EC.

Document history	Publication date	Description of main changes
Version 1	October 2019	

[1] This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

[2] Council Decision 2002/813/EC establishing, pursuant to Directive 2001/18/EC of the European Parliament and of the Council, the summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market (OJ L 280,18.10.2002, p.62).

1. Introduction

Clinical trials conducted in the EU with investigational medicinal products that contain or consist of genetically modified organisms ("GMOs"[3]) must comply with the legislation governing the authorization of clinical trials.[4]

Clinical trials with medicinal products that contain or consist of GMOs must also comply with applicable requirements under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms[5] ("deliberate release framework") and/or under Directive 2009/41/EC on the contained use of genetically modified micro-organisms ("contained use framework").[6]

This application form implements the requirements of the Directive 2009/41/EC and of the Directive 2001/18/EC, as adapted to the specific characteristics of adeno-associated viral vectors ("AAVs") contained in investigational medicinal products for human use.

This is an application form for investigational medicinal products for human use that contain or consist of AAVs (hereafter referred to as "clinical vectors"). However, if the application concerns an investigational medicinal product that contains or consist of AAVs that has already been granted a marketing authorisation, the *submission form for use in case of clinical trials with authorised medicinal products* should be used (provided that the submission form has been endorsed by the competent authorities in the relevant jurisdiction).

The application form has been endorsed by Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania, and Spain.

2. Explanatory notes

The common application form is without prejudice to consultation requirements that exist under Directive 2001/18/EC.

In addition, certain national requirements may need to be considered by developers of medicinal products before they submit the application form to the relevant competent authorities:

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[3] Throughout this document, the term "GMO" should be understood as covering both genetically modified organisms as defined under Article 2(2) of Directive 2001/18/EC, and genetically modified micro-organisms within the meaning of Article 2(b) of Directive 2009/41/EC.

[4] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1). Until the Regulation applies, Directive 2001/20/EC is applicable (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121,1.5.2001, p.34).

[5] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

[6] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75).

Austria:

Applicants should send separate submissions in case there are multiple sites concerned in Austria (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs).

Further information is available at:
https://www.sozialministerium.at/site/Gesundheit/Gentechnik/Rechtsvorschriften_in_Oesterreich/

Belgium:

The common application form should be part of a biosafety dossier submitted by each of the clinical sites where the investigational medicinal product will be administered. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites to submit all the necessary notifications, provided that the person responsible for the activity is clearly indicated in the form.

More information on procedural requirements and forms for the three regions is available at:
https://www.biosafety.be/content/contained-use-gmos-andor-pathogenic-organisms-notification-procedures.

Czech Republic:

Each clinical site as well as other institutions where the activities with GMOs will take place (*e.g.* laboratories that are not premises of one of the clinical sites) should submit a separate notification for deliberate release or for contained use, as appropriate. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

France:

For investigational medicinal products that are assessed under the contained use framework, applicants should send separate submissions in case there are multiple sites concerned in France.

Italy:

For investigational medicinal products that are assessed under the contained use framework, each clinical site (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs) should submit a separate notification. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

It is stressed that, in case the submission is made by a third party on behalf of the site, the responsibilities of the site holders and users concerned (as set out under Legislative Decree n. 206/2001) remain unchanged.

The Netherlands:

More information on national procedural requirements and forms is available at: https://www.loketgentherapie.nl/en/aav

COMMON APPLICATION FORM FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE THAT CONTAIN OR CONSIST OF AAV VECTORs

SECTION 1 – ADMINISTRATIVE INFORMATION

1.1. Identification of the applicant.

Organisation Name:	Pfizer, Inc.
Address Details:	235 East 42nd Street, New York, NY 10017, USA
Contact person:	Natalie Schmidt
Telephone No:	
Email Address:	CTABeLux@pfizer.com

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

Organisation Name:	Not applicable
Address Details:	-
Contact person:	-
Telephone No:	-
Email Address:	-

1.3 Identification of the manufacturer of the clinical vector.

Organisation Name:	Wyeth Pharmaceutical Division of Wyeth Holdings LLC
Manufacturing location:	4300 Oak Park Rd. Sanford, NC 27330 USA Chapel Hill, NC 27517

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1. 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.

Public summary:

PF-06939926 is manufactured using human cell line that is transfected with set of plasmids containing necessary genes for assembly of recombinant AAV and assembly of the vector.
The intended outcome of the transfection of the cell line is a recombinant AAV vector lacking viral genes so that the vector would be replication incompetent and serve only to introduce the transgene and to include the sequence coding for mini-dystrophin to cause replacement of the absent dystrophin and thus enable the treatment of patients with Duchenne Muscular Dystrophy.
PF-06939926 contains a gene encoding a shortened, but functional variant of the human dystrophin gene. Expression is driven by a skeletal- and cardiac muscle-specific promoter. Biodistribution in animal studies of PF-06939926 demonstrated predominant gene transfer to skeletal muscle, heart and liver tissue.
It is expected that administration of PF-06939926 will result in the expression of the mini-dystrophin transgene and improve the condition of study subjects.

2.2. 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.

Public summary:

PF-06939926 is a non-pathogenic recombinant AAV vector that lacks all AAV viral genes and cannot replicate without AAV-specific helper functions and helper virus activities. PF-06939926 replication could only occur in the extremely unlikely event of a host cell being infected by wild-type AAV and a helper virus such as human adenovirus or herpes simplex virus. If replication occurred, the only expected products would be PF-06939926 and WT AAV, both intrinsically non-pathogenic viruses.
Each batch of PF-06939926 are tested for presence of replication comment assay.

2.3. Provide a diagram ('map') of the clinical vector.

The diagram is considered confidential, please refer to section 2.4 for further details.

2.4. 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.

Public summary:

The vector genome comprises a synthetic promoter, a transgene encoding the essential functional domains of the human dystrophin gene and a polyadenylation signal, flanked by AAV inverted terminal repeats (ITRs).
The aim of each functional elements are listed below:

- *Synthetic promoter: Intended to drive skeletal and heart muscle specific gene expression.*
- *Essential functional domains of the human dystrophin gene (mini-dystrophin): Gene transfer may be effective for the treatment of patients with Duchenne Muscular Dystrophy, given that the disease is caused by mutations within the dmd gene that affect the expression or activity of dystrophin.*
- *Polyadenylation signal: terminate transcription of mini-dystrophin gene.*
- *AAV ITRs: Inverted Terminal Repeat (ITR) sequences required for second strand DNA synthesis required for gene expression.*

2.5. 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.

Public summary:

Please refer to the section above.

2.6. 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 is the 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.

Previous releases:

PF-06939926 has been administered to mice, rats (WT and DMD knock-out) and dogs.

PF-06939926 is currently being investigated in a Phase I FIH study (C3391001) in up to 12 patients. Two serious adverse events have been reported after receipt of the drug but could be resolved.

Shedding

PF-06939926 is replication-incompetent and is not expected to survive, multiply or disperse if it were to be eliminated intact from the treated patient. AAV-based gene therapies are known to shed via bodily fluids. It has been shown consistently that vectors are shed for a short period of time, but then become undetectable in bodily fluids. The viral load shed in bodily fluids is expected to be low, compared to the necessary dose required to achieve detectable gene expression in humans. The subjects treated in study C3391003 will be aged 4 to ~9 when receiving PF-06939926. Therefore, they are not sexually matured and it can be safely assumed that any traces of vector will have disappeared from semen, when the subjects reach sexual maturity. Vector shedding will be assessed for a maximum of 6 years or until 2 consecutive negative readings (at or below the limit of detection of the assay) for an individual are obtained for a given sample matrix (saliva, whole blood, urine).

Minimal exposure, such as environmental exposure, of persons other than study participants would not be of sufficient dose to result in significant gene expression in humans. Other than potential human hosts, exposure to PF-06939926 is not expected to affect any non-target organisms, either directly or indirectly. The risk to humans and the environment associated with viral shedding of PF-06939926 is thus negligible.

Shedding data will be collected with the Phase 3 study (C3391003) of PF-06939926 in DMD, which is anticipated to provide definitive characterization of the viral shedding profile. In this study samples will be collected from 3 matrices (whole blood, saliva, and urine) from approximately the first 45 randomized participants.

Safety and efficacy assessments will be conducted throughout the duration of the study.

SECTION 3 –INFORMATION RELATING TO THE CLINICAL TRIAL

3.1. General information about the clinical trial.

EudraCT-number (where available):	2019-002921-31
Deliberate release reference number (where available and applicable):	Not available
Title of the clinical trial:	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate The Safety And Efficacy Of PF-06939926 For The Treatment Of Duchenne Muscular Dystrophy
Name of principal investigator:	*This information may be provided in the annex with confidential information.*
Objective of the study:	Primary Objective: To demonstrate superior efficacy of treatment with PF-06939926 as compared to placebo based on change from baseline in the North Star Ambulatory Assessment (NSAA) total score.
Intended start and end date:	Q3 2020 – Q3 2027
Number of trial subjects that will take part in the study:	Approximately 99 participants globally.
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, identify the countries concerned:	Submissions are planned for 2020 in these EU countries: France Germany Greece Italy Spain United Kingdom

3.2. Intended location(s) of the study.

The applicant should provide information about the sites located in the country of submission of the application.

In some jurisdictions, the following additional information should be provided:

- *the location(s) of laboratories (in the country of submission) in which activities with the GMO are carried out under the framework of the clinical trial application should be stated.*[7]
- *information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the clinical site).*[8]
- *information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site).*[9]

Information on study sites:

Organisation Name:	UZ Gent
Address Details:	Corneel Heymanslaan 10, 9000 Gent, Belgium
Contact person:	Nicolas Deconinck
Telephone No:	+32 9 332 19 54
Email Address:	Nicolas.deconinck@huderf.be
Planned activities:	Administration of IMP, Sampling, Preparation and storage of IMP in the site pharmacy
Containment level:	IMP is Risk Group 1. Work will be carried out at BSL2 per sponsor request.
Name and contact details of the responsible	Same as Contact person

Organisation Name:	UZ Leuven
Address Details:	Herestraat 49, 3000 Leuven, Belgium
Contact person:	Liesbeth De Waele
Telephone No:	+32 16 34 38 45
Email Address:	liesbeth.dewaele@uzleuven.be
Planned activities:	Administration of IMP, Sampling, Preparation and storage of IMP in the site pharmacy
Containment level:	IMP is Risk Group 1. Work will be carried out at BSL2 per sponsor request.
Name and contact details of the responsible	Same as Contact person

Organisation Name:	CHR de la Citadelle
Address Details:	Boulevard du XIIème de Ligne 1, 4000 Liège, Belgium
Contact person:	Aurore Daron
Telephone No:	+32 4 321 85 15
Email Address:	aurore.daron@chrcitadelle.be
Planned activities:	Administration of IMP, Sampling, Preparation and storage of IMP in the site pharmacy
Containment level:	IMP is Risk Group 1. Work will be carried out at BSL2 per sponsor request.
Name and contact details of the responsible	Same as Contact person

Information on laboratories (in the country of submission) in which activities with the GMO are carried out:

Organisation Name:	Laboratorium voor Klinische Biologie – UZ Gent
Address Details:	Corneel Heymanslaan 10, 9000 Gent, Belgium
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	Analysis of patient samples
Containment level:	Untested human samples have to be treated as potentially infectious with harmful viruses. Therefore, work will be carried out at BSL2.
Name and contact details of the responsible person[10]:	Nicolas Deconinck; +32 9 332 19 54; Nicolas.deconinck@huderf.be

Organisation Name:	Laboratoriumgeneeskunde – UZ Leuven
Address Details:	Herestraat 49, 3000 Leuven, Belgium
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	Analysis of patient samples

Containment level:	Untested human samples have to be treated as potentially infectious with harmful viruses. Therefore, work will be carried out at BSL2.
Name and contact details of the responsible person[10]:	Liesbeth De Waele; +32 16 34 38 45; liesbeth.dewaele@uzleuven.be

Organisation Name:	Laboratoire - Centre Hospitalier Régional de la Citadelle SCRL
Address Details:	Boulevard du XIIéme de Ligne 1, 4000 Liège, Belgium
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	Analysis of patient samples
Containment level:	Untested human samples have to be treated as potentially infectious with harmful viruses. Therefore, work will be carried out at BSL2.
Name and contact details of the responsible person[10]:	Aurore Daron; +32 4 321 85 15; aurore.daron@chrcitadelle.be

Information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the clinical site):
Not applicable. IMP is stored on site.

Information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site):
Not applicable. Samples are stored on site, until being sent for analysis.

[7] Information about the location of laboratories is required for applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Portugal and Spain. In case of submissions to these jurisdictions, fill in the relevant table for laboratories that conduct specialised analysis referred in the protocol of the clinical trial only; laboratories that perform standard laboratory diagnostics analysis need not be listed.
[8] This information should be provided for applications submitted to Croatia, Germany, Ireland and Spain. This information should be provided for applications submitted to Belgium, Czech Republic and Finland, unless there is a contained use notification covering the storage of the product.
[9] This information should be provided for applications submitted to Germany and Ireland.
[10] The responsible person is either the person responsible for supervision and safety as provided for under Annex V of Directive 2009/41/EC, or the responsible scientist as provided for under Annex IIIA of Directive 2001/18/EC.
(Applicant should complete as many tables as necessary)

3.3. 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.[11]

Site 1: UZ Gent
Storage location: Pharmacy, Corneel Heymanslaan 10, 9000 Gent, Belgium
Condition of storage: As per IP Manual
Maximum storage duration of IMP on site: as per expiratory date on Label
Preparation of IMP in hospital pharmacy: **Yes**/~~No~~

Site 2: UZ Leuven
Storage location: Activity Center Biobanking, Herestraat 49, 3000 Leuven, Belgium
Condition of storage: as per IP Manual
Maximum storage duration of IMP on site: as per expiratory date on Label
Preparation of IMP in hospital pharmacy: ~~Yes/~~**No – Will be prepared at Activity Center Biobanking**

Site 3: CHR de la Citadelle
Storage location: Pharmacy, Boulevard du XIIème de Ligne, 4000 Liège, Belgium
Condition of storage: as per IP Manual
Maximum storage duration of IMP on site: as per expiratory date on Label
Preparation of IMP in hospital pharmacy: **Yes**/~~No~~

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

The applicant should provide information about the logistics for in-house transportation (i.e. transfer of the clinical vector from storage to the administration site and –where applicable- site where dose is prepared). The applicant should provide information about the characteristics of the containers used addressing also disinfection procedures applied and labelling of the containers.

Shipping:

Vials are shipped to the site in the following configuration: individual vials are packed into cartons with appropriately sized insert to hold vials. Cartons are placed in an inner core which can hold up to 12 single labelled cartons. The inner core is then placed in a sealed biohazard bag that is placed in the shipper. The shipper is filled with dry ice.

Preparation:

As per Pharmacy manual, manipulated aseptically in a biological safety cabinet Class II (of types A2, B1, or B2) or Class III.

On site transport:

PF-06939926 is stored in a clear 10 mL closed vial that must be stored upright. Local institutional practice for the transportation of biohazardous material is being followed.

Characteristics of the containers:

The containers need to fulfil requirements per local guidelines pertaining to the transport of BSL2 agents (IMP is Risk Group 1. All manipulation will be carried out at BSL2 per sponsor request). At a minimum must include the placement of IP in a sealed zip-top bag which is then placed within a second zip-top bag and placed in a hard-sided spill-proof container marked with a biohazard symbol.

Labelling of the containers:

The containers will be labelled according to local guidelines for BSL2 agents (IMP is Risk Group 1. All manipulation will be carried out at BSL2 per sponsor request). Also see point above.

Disinfection procedures:

Any surfaces contaminated with PF-06939926 will be decontaminated using an appropriate disinfectant, such as 10% chlorine bleach, Wescodyne, or detergent-based disinfectant. The required minimum contact time with PF-06939926 is 20 minutes for 10% bleach or as otherwise stated in the label information of an alternative equivalent decontamination solution. Upon completion of this contact time, the area may be cleaned according to standard local procedures. This process should be discussed with the local environmental health and safety officer and/or biosafety committee before receipt of any PF-06939926 product on site so that an appropriate plan and supplies are in place.

Consumables used in the preparation and administration of the GMO that may have come into contact with PF-06939926 will be decontaminated prior to disposal (either by autoclaving or by treatment with an appropriate chemical disinfectant with effectiveness against AAV, and/or incinerated). Liquid waste will be decontaminated using an appropriate chemical disinfectant or autoclaved. All used consumables and liquid waste must be treated as biohazardous waste.

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

Reconstitution (where applicable, summarise reconstitution steps):	Not applicable. The IMP must only be thawed before use.
Pharmaceutical form and strength:	PF-06939926 Solution for Infusion, 5 mL/vial, (concentration will be lot-specific)
Mode of administration:	Intravenous infusion
Information on dosing and administration schedule (in case of repeated dosing):	Not applicable. IMP will be administered as one single infusion.
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):	Not applicable.

[11] In case of applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Ireland, Italy, the Netherlands and Spain, the applicant should specify if the dose is being prepared in the hospital pharmacy. If the clinical dose is prepared at a location other than the hospital pharmacy, this should be explained.

3.6 Measures to prevent dissemination into the environment.

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

PF-06939926 is a RG1 agent and will be prepared for administration in a Biological Safety Cabinet (Class II (of types A2, B1, or B2) or Class III, as per sponsor request) by medical professionals. The IMP will be administered to study subjects under controlled conditions within a hospital.

b. Personal protective equipment.

To reduce the risk for inadvertent exposure during handling of PF-06939926, site personnel and all those present during preparation and administration must wear standard Personal Protective Equipment (PPE) for handling of a Biological Safety Level 2 (BSL2) agents per sponsor request. At a minimum, PPE must include disposable back closing gown, safety glasses, goggles or mucous splash protector, gloves, hair coverage, and shoe covers.

c. 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.

Any surfaces contaminated with PF-06939926 will be decontaminated using an appropriate disinfectant, such as 10% chlorine bleach, Wescodyne, or detergent-based disinfectant. The required minimum contact time with PF-06939926 is 20 minutes for 10% bleach or as otherwise stated in the label information of an alternative equivalent decontamination solution. Upon completion of this contact time, the area may be cleaned according to standard local procedures. This process should be discussed with the local environmental health and safety officer and/or biosafety committee before receipt of any PF-06939926 product on site so that an appropriate plan and supplies are in place.

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

Prior to study start up, the site should inquire with their local Biosafety officer / Environmental Health and Safety committee about local destruction requirements. Used, unused or partially used vials MUST NOT be kept for accountability purposes. Vials will be destroyed after completion of dose preparation according to the process agreed upon locally and will not be shipped back to the study Sponsor. All unused vials need to be kept in the required storage conditions (-90°C to -60°C); used/partly-used vials will be destroyed after dosing is complete following local requirements for biohazardous waste.

e. 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.

Consumables used in the preparation and administration of the GMO that may have come into contact with PF-06939926 will be decontaminated prior to disposal (either by autoclaving or by treatment with an appropriate chemical disinfectant with effectiveness against AAV, and/or incinerated). Liquid waste will be decontaminated using an appropriate chemical disinfectant or autoclaved. Disinfectants that are effective against AAV include 10% chlorine bleach, Wescodyne, or detergent-based disinfectant.

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

Patients and those around him will also be reminded to practice good hygiene, especially for the month prior to and during the first 2 months after each IMP administration.

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

Not applicable due to age range of subjects (subjects treated at age 4 to 9).

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

Not applicable.

3.7. 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 and the application is submitted to the following jurisdictions: Croatia, Czech Republic, Germany, Ireland, the Netherlands, Spain

SECTION 4 – OTHER DATA REQUIREMENTS

4.1. Plan of the site(s) concerned

Applicants should provide a copy of the plan of the site where the clinical trial takes place if the application is submitted to the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Finland, France, Hungary, Ireland and Italy.

[12] Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.

4.2 Other information

Submissions to Austria:

In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Belgium:

In addition to the plan of the site, a description of the location of the autoclave and the biosafety cabinet should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

The applicant is also asked to provide an overview (table) of the rooms involved in the CT activity by indicating for each of those the number of the room, the type of handling carried out (e.g. storage, administration of the IMP, reconstitution of the IMP) and the containment level.

Submissions to Czech Republic:

In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Denmark:

- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*
- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*
  - *Whether and for how long the waste will be stored (or frequency of waste disposal),*
  - *Storage location,*
  - *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
  - *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*

Submissions to France:

The plan of the site should indicate clearly the location of a PSMII, or an equivalent device.

Submissions to Germany:

- *The applicant is not required to provide further information in Section 3(6)(c) if he/she confirms that the disinfectant and decontamination procedure are included in the list of the Robert Koch Institute of currently approved disinfectants and disinfectant procedures or the VAH (Verbund für Angewandte Hygiene e.V) list of disinfectants.*
- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*

- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*
  - *Whether and for how long the waste will be stored (or frequency of waste disposal),*
  - *Storage location,*
  - *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
  - *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7 (c).*
- *The applicants is required to provide emergency response plans.*

Submissions to Ireland:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7(c).*

Submissions to Italy:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If the manufacturer of the clinical vector is located in Italy, the authorisation issued to the premises should be declared in Section 1.3.*

SECTION 5- ENVIRONMENTAL RISK ASSESSMENT

Specific environmental risk assessment

Considering the specific characteristics of the investigational medicinal product (as described in Section 2 of the application form), the applicant considers that 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 vectors is applicable:

Yes X

No ☐

If the answer to the above is NO, the following information should be provided:

- *For submissions made under Directive 2001/18/EC*: an environmental risk assessment is required in accordance with Annex II thereof.

- *For submissions made under Directive 2009/41/EC*: an assessment of the risks to human health and the environment in accordance with Article 4 thereof.