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

FOR PUBLIC

For Belgium

Investigational Medicinal Product: SRP-9003

Study: SRP-9003-301

EU CT: 2022-503112-17-00

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:	PPD Belgium
Address Details:	Lozenberg 19, 1932 St-Stevens-Woluwe, Belgium
Contact person:	Regulatory Specialist
Telephone No:	N/A
Email Address:	PPDBelgiumECSubmissions@ppd.com

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

Organisation Name:	Sarepta Therapeutics, Inc.
Address Details:	215 First Street, Cambridge, MA 02142, United States
Contact person:	Patient Recruitment
Telephone No:	+18887273782
Email Address:	SareptAlly@sarepta.com

1.3 Identification of the manufacturer of the clinical vector.

Organisation Name:	*Confidential.*
Manufacturing location:	*Confidential.*

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1 Description of the production system

Bidridistrogene xeboparvovec (also known as SRP-9003) is a nonreplicating, recombinant AAV-based gene therapy. The vector contains the hSGCB gene under the control of the MHCK7 promoter, a regulatory cassette based on enhancer/promoter regions of murine muscle CK and myosin heavy-chain genes. SRP-9003 is an investigational gene therapy designed to treat the underlying cause of LGMD2E/R4 by delivering the corrected gene to the affected tissues.

As SRP-9003 lacks all the wild-type AAV genes with the exception of the inverted terminal sequences, it is incapable of replicating itself, which therefore does not present a potential risk associated with transmission to third parties, animals or to the environment.

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

Adeno-associated viral vectors are engineered to be replication defective, however, generation of replication competent AAV (rcAAV) can occur during vector manufacturing by means of recombination events within the producer cells. Manufacturing efforts have been made to develop non-replicative vectors to lower the probability of contact between the viral vector and the WT parental virus, thereby reducing the probability of recombination.

SRP-9003 vector production systems currently in use have been optimized to reduce this probability to undetectable levels. The method has been validated in accordance with ICH Q2(R1). Through validation the assay has been shown to be specific as it did not detect unrelated viral serotypes. Additional details are considered confidential and/or business sensitive and are provided in Section 2.2 of the confidential annex.

2.3 Map of the clinical vector

The vector contains minimal elements required for gene expression including the full-length human sarcoglycan beta (hSGCB) gene insert under the control of the MHCK7 promoter. The diagrams of the clinical vector showing all the constituent parts are considered confidential and/or business sensitive and are provided in Section 2.3 of the confidential annex.

2.4. Molecular characterisation of the clinical vector

SRP-9003 (scAAVrh74.MHCK7.hSGCB) is a self-complementary, nonreplicating, recombinant adeno-associated virus (AAV) serotype rhesus 74 (rh74) vector containing full-length WT β-SG complementary DNA (cDNA) under the control of the myosin heavy chain/muscle creatine kinase promoter (MHCK7).

The genetic stability of DNA viruses such as AAV is well characterized and in general, they are highly stable when compared to the RNA viruses. This may be attributed to factors such as (a) DNA being more thermodynamically stable than RNA, (b) replication of DNA being much less error-prone process than the replication of RNA and (c) more mechanisms exist in the host cell for repairing errors in DNA than in RNA. Homologous genomic recombination may occur spontaneously in nature between the

viral genomes of AAV strains only under circumstances where a cell of the host organism is infected simultaneously by two different strains of AAV and a helper virus.

Further details regarding the molecular characterization of the clinical vector are considered confidential and are provided in Section 2.4 of the confidential annex.

2.5. Description of the insert

The insert is full-length human sarcoglycan-beta (SGCB) cDNA. The detailed description of the insert is considered confidential and/or business sensitive and is provided in Section 2.5 of the confidential annex.

The viral vector does not contain any viral sequences that would lead to the production of viral particles or DNA replication. No genes for toxins, potential oncogenes, growth factors or other genes that could be potentially harmful have been inserted into the viral vector. There is no basis to consider that addition of the hSGCB transgene to the viral vector would promote any post-release selection or increased invasiveness or any other selective advantage.

2.6. Biodistribution and shedding

2.6.1 Information on the administered dose and route of administration

SRP-9003 is administered as a single IV infusion at a dose of 7.41×10^{13} vg/kg.

2.6.2 Immune Status of the participants

In general patients are expected to be immunocompetent. All patients in the clinical trials will be administered a prophylactic glucocorticoid to dampen the host immune response to AAV. This does not pose a risk in the setting of gene therapy administration. Rather, it has become common practice across multiple disorders for which gene therapy is used to provide glucocorticoids for several months following gene therapy administration to mitigate the observed immune reactions.

2.6.2.1 Immunology

In the clinical experience gained to date, it was observed that SRP-9003 did not elicit any concerning immune responses. As expected, AAVrh74 antibodies were detected. No antibodies to the transgene were detected, and no significant T cell responses were observed to either the transgene or AAVrh74; therefore, the risk that immune-mediated decrease of expression would occur remains extremely low.

Subjects are excluded from the clinical study if AAVrh74 antibody titres are above the threshold as determined by an AAVrh74 Antibody enzyme-linked immunosorbent assay (ELISA).

Blood samples for antibody and T-cell monitoring will be obtained at the time points specified in the clinical study protocol. Testing for antibodies against rAAVrh74 will occur prior to infusion to confirm eligibility.

Subjects will be administered a prophylactic glucocorticoid (prednisone or equivalent) to dampen the host immune response to AAV therapy, starting approximately 24 hours prior to SRP-9003 infusion. A prophylactic glucocorticoid (prednisone or equivalent) regimen will continue for approximately 60 days, with a tapering period.

2.6.3 Biodistribution

Non-clinical biodistribution study data is considered confidential and/or business sensitive and are provided in Section 2.6.3 of the confidential annex.

Biodistribution following SRP-9003 administration has been evaluated in rodent models. Across studies, SRP-9003 was shown to effectively transduce skeletal and cardiac muscle. The highest levels of vector DNA were observed in the liver – a known location of systemically administered adeno-associated viral gene therapies, including AAVrh74. Biodistribution in non-muscle cells (liver) should not result in transgene expression due to the use of a skeletal and cardiac specific promoter (MHCK7) within the SRP-9003 construct.

2.6.4 Shedding

SRP-9003 is replication-incompetent and is not expected to survive, multiply or disperse if it were to be eliminated intact from the treated patient; therefore, there is a minimal risk of transition by viral shedding. 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.

Vector shedding data is being collected in the ongoing clinical studies (SRP-9003-101 and SRP-9003-102). Interim viral vector shedding data from these studies are summarized in Section 2.6.4.2 of the confidential annex. Additional vector shedding data will be collected in the Phase 3 clinical study SRP-9003-301.

Non-clinical study data and interim viral vector shedding data are considered confidential and/or business sensitive and are summarized in Section 2.6.4 of the confidential annex.

References

Chen CL, Jensen RL, Schnepp BC, Connell MJ, Shell R, Sferra TJ, Bartlett JS, Clark KR, and Johnson PR. Molecular characterization of adeno-associated viruses infecting children. 2005. J. Virol. 79:14781-14192.

Penaud-Budloo M, François A, Clément N, Ayuso E. Pharmacology of Recombinant Adeno-associated Virus Production. 2018. Mol Ther Methods Clin Dev. 8:166-180.

Salva MZ, Himeda CL, Tai PW, Nishiuchi E, Gregorevic P, Allen JM, Finn EE, Nguyen QG, Blankinship MJ, Meuse L, Chamberlain JS, Hauschka SD. Design of tissue-specific regulatory cassettes for high-level rAAV-mediated expression in skeletal and cardiac muscle. 2007. Mol Ther. 15(2):320-9.

Schnepp BC, Jensen RL, Chen CL, Johnson PR, Clark KR. Characterization of adeno-associated virus genomes isolated from human tissues. 2005. J. Virol. 79(23):14793-803.

Sondergaard PC, Griffin DA, Pozsgai ER, Johnson RW, Grose WE, Heller KN, Shontz KM *et al*. AAV. Dysferlin overlap vectors restore function in dysferlinopathy animal models. 2015. Ann Clin Transl Neurol 2(3): 256–270.

SECTION 3 –INFORMATION RELATING TO THE CLINICAL TRIAL

3.1 General information about the clinical trial.

EU CT-number (where available):	2022-503112-17-00
Deliberate release reference number (where available and applicable):	Not available
Title of the clinical trial:	A Phase 3 Multinational, Open-label, Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9003 in Subjects with Limb Girdle Muscular Dystrophy 2E/R4
Name of principal investigator:	*Confidential.*
Objective of the study:	- Primary: To evaluate the effect of SRP-9003 on β-sarcoglycan (β-SG) expression at Day 60 post-dose as measured by immunofluorescence (IF) percent β-SG positive fibers (PβSGPF) - Secondary: To evaluate the effect of SRP-9003 on β-SG expression at Day 60 post-dose as measured by IF percent fluorescent expression (PFE) and Western of biopsied muscle tissue - Secondary: To evaluate the effect of SRP-9003 on physical function through Month 60 in all cohorts, as assessed by: o North Star Assessment for Dysferlinopathy (NSAD) score o Performance of Upper Limb (PUL) 2.0 score - Secondary: To evaluate the effect of SRP-9003 timed function tests for subjects in Cohort 1 (ambulatory) through Month 60 - Secondary: To evaluate the safety of SRP-9003 - Secondary: To evaluate the effect of SRP-9003 on creatine kinase (CK) level - Secondary: To evaluate the effect of SRP-9003 on disease milestones (e.g., loss of ambulation (LOA))
Intended start and end date:	Start: May 2024 End: January 2031
Number of trial subjects that will take part in the study:	Approximately 15 subjects 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:	2022-503112-17-00 Belgium, Germany, Italy, Spain

3.2 Intended location(s) of the study.

Organisation Name:	UZ Leuven
Address Details:	*Confidential.*
Contact person:	*Confidential.*
Telephone No:	*Confidential.*
Email Address:	*Confidential.*
Planned activities:	Administration of IMP, Sampling, Preparation and storage of IMP in the site pharmacy
Containment level:	IMP is classified as Risk Group 1 (RG1) agents, capable of handling at Biosafety Level 1 (BSL-1)
Name and contact details of the responsible person[10]:	*Confidential.*

Organisation Name:	UZ Gent
Address Details:	*Confidential.*
Contact person:	*Confidential.*
Telephone No:	*Confidential.*
Email Address:	*Confidential.*
Planned activities:	Administration of IMP, Sampling, Preparation and storage of IMP in the site pharmacy
Containment level:	IMP is classified as Risk Group 1 (RG1) agents, capable of handling at Biosafety Level 1 (BSL-1)
Name and contact details of the responsible person[10]:	*Confidential.*

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

Not applicable. All samples shall be stored on site and sent to central lab for testing.

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 at the site pharmacy at the same address.

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. All samples are stored on site, until being sent to central lab for analysis.

3.3 Storage of the clinical vector at the clinical site.

1. Site UZ Leuven

Storage location: hospital pharmacy. See annex "Floorplans".

Condition of storage: SRP-9003 must be stored in a secure freezer and segregated from commercial and other investigational products. The SRP-9003 vials may be stored within the white, rigid transport boxes in which the SRP-9003 vials were packaged in during shipping. SRP-9003 vials should be stored in an access-controlled, locked room under the responsibility of the delegated pharmacist in accordance with local regulations, policies, and procedures.

Maximum storage duration of IMP on site: as per expiration date on the label

2. Site UZ Gent

Storage location: hospital pharmacy, see section 4 and annex "Floorplans".

Condition of storage: the same as outlined above.

Maximum storage duration of IMP on site: as per expiration date on the label

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

The IMP (SRP-9003) will be placed in a sealable leak-proof biohazard bag and delivered to the procedure room/area for infusion

The infusion set and dosing syringe used for delivery of SRP- 9003 must be placed in a biohazard bag and destroyed per site pharmacy and institutional policy.

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

Reconstitution (where applicable, summarise reconstitution steps):	Not applicable
Pharmaceutical form and strength:	Solution for infusion. Please refer to Section 3.5 of the confidential annex for additional details
Mode of administration:	Intravenous infusion
Information on dosing and administration schedule (in case of repeated dosing):	Not applicable, only one dose will be administered
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

3.6 Measures to prevent dissemination into the environment.

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

Reconstitution:

All materials used for preparation and administration of SRP-9003 injection, including sterile drapes and needles in contact with SRP-9003, must be sealed in leak-proof primary and secondary containers. All waste must be double bagged in bags bearing the biohazard symbol and sealed with tape. The bag must then be disposed of in a biohazard waste container.

Handling:

Handling of SRP-9003 will follow compliance standards for Biosafety Level 1 (BSL-1) vectors following the NIH Guidelines, Centers for Disease Control and Prevention (CDC) Biosafety in Microbiology and Biomedical Laboratories (BMBL) for Risk Group 1 agents in the United States, and the World Health Organization (WHO) Laboratory Safety Manual outside the United States. Belgium is following the Sciensano SBB Guidelines for Risk Group 1 agents.

Administration:

The infusion set and dosing syringe used for delivery of SRP- 9003 must be placed in a biohazard bag and destroyed per site pharmacy and institutional policy.

All study staff handling the investigational agent must have documentation of Biosafety training on
the handling of AAV agents. The research coordinator will ensure that these training records are in
place for all study staff handling the agent. Institutional policies for assigning personnel to work with BSL-1 agents such as SRP-9003 must be followed.
Individuals manipulating the vector will be required to wear adequate PPE.

All materials used for preparation that come in contact with the IP will be sealed in leak-proof primary and secondary containers. These containers will then be placed in red biohazard waste for
incineration. All surfaces will be decontaminated with appropriate agents, such as a 1:10 dilution of 5.25% sodium hypochlorite (bleach) solution, per policy

b) Personal protective equipment.

Individuals manipulating the vector will be required to wear adequate Personal Protective Equipment (PPE) for handling of a Biosafety Level 1 agents.

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.

1. Evacuate area, remove contaminated PPE and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure.
2. Cover the spill with absorbent material. Starting at the edges and work towards the centre.
3. Carefully pour disinfectant (bleach solution followed by alcohol wipes) over the absorbed spill, again starting at the edges. Saturate the area with disinfectant.
4. Allow sufficient contact period to inactivate the material in the spill. Non-viscous spills require 15-20 minutes: viscous spills require 30 minutes.

5. Use paper towels to wipe up the spill, working from the edge to centre. Use tongs or forceps to pick up broken plastics, glass or other sharps that could puncture gloves.
6. Discard absorbent material in chemical waste bags.
7. Clean the spill area with fresh paper towels soaked in disinfectant. Thoroughly wet the spill area, allow to disinfect for 15-20 minutes longer, and wipe with towels.
8. Discard all cleanup materials (soaked with disinfectant) in Chemical bag/ container, and any contaminated PPE in a biohazard bag. Close and secure the bags.
9. Place bag in a second biohazard bag, secure and dispose of in a biohazardous waste container.

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

All materials used for preparation that come in contact with the IP will be sealed in leak-proof primary and secondary containers. These containers will then be placed in red biohazard waste for incineration. All surfaces will be decontaminated with appropriate agents, such as a 1:10 dilution of 5.25% sodium hypochlorite (bleach) solution, per pharmacy policy.

In the event there is an extra unopened vial remaining after entire dose was drawn, the thawed/unused vial should be retained for accountability by the CRA. The thawed/unused vials will need to be destroyed locally or returned to the depot, pending authorization from CRA.

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.

All waste will be considered as medical waste (UN 3291)
UZ Leuven: Transport: Veolia
Incineration of the biohazard waste: Indaver

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

IMP will be administered intravenously at the site. Patients and those around him/her will be reminded to practice good hygiene.

- Washing hands with soap and warm water often.
- Avoid crowded situations; when appropriate, wear personal protective equipment such as masks or gloves.
- Others should use appropriate protective gloves if coming into direct contact with bodily fluids and waste of the treated patient or potentially contaminated materials, such as tissues or masks.
- Parents and caregivers will be provided with a supply of gloves, masks, and hand sanitizer when the patient is treated.
- Put potentially contaminated materials in a sealable bag; double-bag them before throwing them away.
- Use a disinfectant to clean hard surfaces you touch, such as tables, counters, and doorknobs.
- Wash clothing, linen, pillows, blankets, and towels with laundry detergent in hot water.
- Contact with materials or surfaces commonly used by others needs to be limited. When the treated patient's bodily fluids are in contact with surfaces (e.g. handkerchiefs, toys that may be shared with others), these need to be thoroughly decontaminated using the above instructions.

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

Subjects are prohibited from donating blood for 2 years following the vector injection.

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

a) 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.

Not applicable

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

Not applicable

c) If samples are stored at the clinical site, describe storage location and storage conditions.

Not applicable

d) Explain if there is any non-routine[12] testing of the samples and indicate whether the clinical vector is generated *de novo* during the testing.

Not applicable

SECTION 4 – OTHER DATA REQUIREMENTS

4.1. Plan of the site(s) concerned

UZ Gent

Confidential.

UZ Leuven

Confidential.

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.