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

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1. ADMINISTRATIVE INFORMATION

1.1. Identification of the Applicant

Organization Name:	Parexel International
Address Details:	*Please see section 1.1 of the confidential annex*
Contact Person:	*Please see section 1.1 of the confidential annex*
Telephone Number:	*Please see section 1.1 of the confidential annex*
Email Address:	*Please see section 1.1 of the confidential annex*

1.2. Identification of the Sponsor

Organization Name:	Sarepta Therapeutics
Address Details:	*Please see section 1.2 of the confidential annex*
Contact Person:	*Please see section 1.2 of the confidential annex*
Telephone Number:	*Please see section 1.2 of the confidential annex*
Email Address:	*Please see section 1.2 of the confidential annex*

1.3. Identification of the Manufacturer of the Clinical Vector

Organization Name:	*Please see section 1.3 of the confidential annex*
Manufacturing Location:	*Please see section 1.3 of the confidential annex*

2. INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT SRP-9001

SRP-9001 is an AAV vector-based gene therapy designed to treat the proximate cause of Duchenne Muscular Dystrophy (DMD) by replacing dysfunctional or missing dystrophin protein with a functional shortened dystrophin, called SRP-9001-dystrophin, in cardiac, respiratory, and skeletal muscle, the key tissues affected in this lethal degenerative disease. SRP-9001 vector is a non-replicating, recombinant adeno-associated virus (AAV) serotype rh74 (AAVrh74) vector containing the SRP-9001-dystrophin expression cassette construct, under the control of the MHCK7 promoter.

As SRP-9001 lacks 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.

2.1. Description of the Production System

SRP-9001 drug substance is manufactured by transient transfection of the human embryonic kidney cell line (HEK293) cells by three plasmids containing necessary genes for assembly of recombinant AAV and assembly of the vector. This process utilizes DNA-containing plasmids including: the “transgene plasmid” which contains the therapeutic gene of interest (GOI) - pAAV.MHCK7.Micro-Dystrophin, and the “rep/Cap” plasmid - pNLREP2-Caprh74.

The non-replicating, recombinant adeno-associated virus (rAAV) contains a human micro-dystrophin gene (SRP-9001 dystrophin) under the control of the MHCK7 promotor/enhancer that has been optimized for driving expression in cardiac and skeletal muscle (Rodino-Klapac, 2013). Please refer to section 2.1 of the confidential annex for further details.

2.2. Demonstration of Absence of Formation of Replication-Competent Virus

The packaging and purification of recombinant DNA into viral vectors for gene therapy studies carries the theoretical risk of contamination by wild type AAV or the initiation of a recombination event resulting in the production of replication-competent AAV (rcAAV). As part of the overall safety testing strategy for SRP-9001, the final product samples from each production batch are analyzed for the presence of replication competent virion (rcAAV) .

In cell culture, rcAAV genome can be rescued and replicated by superinfection with wtAAV and a helper virus. However, in vivo rescue experiments failed except in one case, in which very large doses of wtAAV and adenovirus were administered in a particular setting. However, given the high stability of AAV particles for a short period of time, the presence of even very low amounts of rcAAV should be identified.

Please refer to section 2.2 of the confidential annex for additional details.

2.3. Map of the Clinical Vector

The diagrams of the clinical vector showing all the constituent parts are considered confidential and/or business sensitive and are provided in section 2.1 of the confidential annex. Please also refer to section 2.4 for further details.

2.4. Molecular characterization of the clinical vector

SRP-9001 vector genome is comprised of a promoter, a transgene encoding functional domains of the human dystrophin gene and a polyadenylation signal, flanked by AAV inverted terminal repeats (ITRs). The aims of each functional element are listed below:

- **Promoter:** Intended to drive skeletal and heart muscle specific gene expression.
- **Functional domains of the human dystrophin gene retained in SRP-9001 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 the SRP-9001-dystrophin gene.
- **AAV ITRs**: Inverted Terminal Repeat (ITR) sequences required for second strand DNA synthesis to facilitate gene expression

Further details regarding the molecular characterization of the clinical vector are considered confidential and are provided in section 2 of the confidential annex.

2.5. Description of the insert

The description of the insert is considered confidential and/or business sensitive and is provided in section 2.5 of the confidential annex.

2.6. Biodistribution and Shedding

2.6.1. Biodistribution

Biodistribution has been an important component of multiple nonclinical studies performed with SRP-

9001 during development. Biodistribution of SRP-9001 has been evaluated in studies in adult DMD^{MDX} mice, adult C57BL/6J mice, neonatal C57BL/6J mice, NHP and in juvenile and adult DMD rats. Available data from these studies confirm SRP-9001 biodistribution to the skeletal muscle, heart, and liver while vector copy numbers were lower in other non-target tissues. Biodistribution is generally similar between WT, DMD^{MDX} mice and rats, as well as NHP. Biodistribution of non-muscle cells should not result in transgene expression due to the use of a skeletal and cardiac specific promoter.

2.6.2. Shedding

SRP-9001 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.

Non-clinical study data and interim viral shedding data from Study SRP-9001-103 are summarized in section 2.6.2 of the confidential annex.

3. INFORMATION RELATING TO THE CLINICAL TRIAL

3.1. General Information about the Clinical Study

EudraCT-number (where available):	2020-002372-13
Deliberate release reference number (where available and applicable):	Not applicable / Not available
Title of the clinical trial:	A Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 in Non-Ambulatory and Ambulatory Subjects With Duchenne Muscular Dystrophy (ENVISION)
Name of principal investigator:	*Please see section 3.1 of the confidential annex.*
Objective of the study:	Primary Objective: To evaluate the effect of SRP-9001 on physical function in Part 1 as assessed by the Performance Upper Limb (PUL) (Version 2.0 [V2.0])
Intended start and end date:	• Globally - Start: Q2 2023; End: Q2 2026 • In Belgium - Start Q3 2023; End: Q2 2026
Number of trial subjects that will take part in the study:	Approximately 116 (globally); 2 in Belgium
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:	Belgium, France, Germany, Italy, Spain, and Sweden.

3.2. Intended Location(s) of the Study

Organization Name:	Universitair Ziekenhuis Gent
Address Details:	*Please see section 3.2 of the confidential annex*
Contact Person:	*Please see section 3.2 of the confidential annex*
Telephone Number:	*Please see section 3.2 of the confidential annex*

Email Address:	*Please see section 3.2 of the confidential annex*
Planned Activities:	Receipt/Storage / dose preparation/ transport (on site) / destruction
Containment Level:	Risk Group 1 (RG1) agents, capable of handling at Biosafety Level 1 (BSL-1)
Name and Contact Details of the Responsible Person:	*Please see section 3.2 of the confidential annex*

3.3. Storage of the Clinical Vector at the Clinical Site

SRP-9001 will be shipped frozen on dry ice in a temperature-controlled shipment container managed by a specialty courier. Immediate attention should be given to receipt of the temperature sensitive contents.

SRP-9001 vials will arrive held in a white, rigid transport box enclosed in a sealed plastic bag.

The white, rigid transport boxes in which the SRP-9001 vials arrived may be used to house the vials during storage.

SRP-9001 vials should be stored in an access-controlled, locked room under the responsibility of the Investigator or other authorized persons (e.g., delegated pharmacists) in accordance with local regulations, policies, and procedures. Storage temperature excursions should be reported immediately to the monitor. SRP-9001 will be removed from storage only when ready to use. It is recommended not to remove SRP-9001 from storage until the subject is confirmed to be on site for the infusion visit. Thawed vials cannot be refrozen for future use.

3.4. Logistics for On-Site Transportation of the Clinical Vector

SRP-9001 will be transported to the infusion room in a sealable leak-proof biohazard bag.

3.5. Information about Reconstitution, Finished Medicinal Product and Administration to Patients

Reconstitution (where applicable, summarize reconstitution steps):	Not Applicable
Pharmaceutical form and strength:	Solution for infusion. *Please refer to section 3.5 of the confidential annex.*
Mode of administration:	IV infusion
Information on dosing and administration schedule (in case of repeated dosing):	Single dose
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):	None known and no literature has reported concomitant medications influencing vector shedding or enhancing replication of clinical vectors.

3.6. Measures to Prevent Dissemination into the Environment

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

Reconstitution:
SRP-9001 does not require reconstitution prior to administration.

Handling:
Refer to section 3.3 of the public CAF.

Administration:
SRP-9001 will be administered in treatment centers (i.e. hospitals) supervised by a physician experienced in the management of patients with DMD. The infusion will be prepared and administered to patients by specialized healthcare professionals including pharmacists and nurses. The administration room will be disinfected according to local standard institutional procedures after the administration of SRP-9001 to the patient to minimize the environmental spread of the recombinant organism before preparing the final volume required based on the patient weight. It is not expected that SRP-9001 will be deliberately released into the environment outside the administration site.

All involved personnel on the site will be trained in best biosafety practices to be applied during preparation in the pharmacy, transport to the administration room, precautions during administration and disposal of any biological waste. Such training involves, among other things, wearing adapted protective clothing, gloves and goggles, the constant presence of a spill kit and the decontamination of waste prior to disposal.

Any spills and accidents (e.g. accidental needle stick injury) resulting in potential exposure of AAV to individuals will be reported to the Principal Investigator and the site Occupational Health Services equivalent within 24 hours. More details are described in the pharmacy manual.

b. Personal protective equipment

The following personal protective equipment should be used while handling or administering SRP-9001:

- Gloves
- Safety goggles
- Disposable isolation gown
- Appropriate PPE should also be used for lower arms such as sleeve covers or securing gloves over the sleeves of laboratory coat.

c. Personnel should not work with SRP-9001 if skin is cut or scratched. Accidental exposure to SRP-9001 must be avoided. Advice will be provided in the event of exposure to skin or eyes as reflected in the Pharmacy Manual. 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.

In case of accidental spillage of SRP-9001 during the dose preparation and administration to the patient at the health-care provider, instructions provided by the Sponsor´s pharmacy manual will be followed to contain and immediately disinfect the spill to prevent further spread. All spills of SRP-9001 must be wiped and the spill area decontaminated with the disinfectant in use at the administration site. All cleaning materials must be double bagged and disposed of per local guidelines for handling of biological waste. All contaminated materials will be disposed of locally by incineration or autoclaving.

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

All vials, both used and unused, must be sealed in leak-proof containers and should be retained until the monitor has completed drug accountability and the sponsor has provided permission for destruction either at site or returned to depot for destruction.

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.

Any waste material should be disposed of in accordance with local guidelines on handling of biological waste.

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

Family members and caregivers will be instructed to practice good hand-hygiene after the product administration for up to 4 weeks after SRP-9001 administration. This requires washing hands with soap regularly and using appropriate protective gloves if coming into direct contact with bodily fluids and waste of the treated individual. Infant waste such as dirty diapers should be double-bagged before disposal. Further hygiene guidance is provided to clinical trial subjects through patient-facing materials (e.g.: participant study guide). Blood donation 6 months after SRP-9001 infusion is considered to represent minimal and acceptable risk.

The risk and benefit of a potential organ donation needs to be carefully evaluated with the responsible physician.

g. Other measures (where applicable).

None.

4. OTHER DATA REQUIREMENTS

4.1. Plan of the Site(s) Concerned

Please see section 4.1 of the confidential annex

4.2. Other Information

Please see section 4.2 of the confidential annex

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 □

6. REFERENCES (AVAILABLE UPON REQUEST)

1. Rodino-Klapac, L. R., P. M. Janssen, K. M. Shontz, B. Canan, C. L. Montgomery, D. Griffin, K. Heller, L. Schmelzer, C. Handy, K. R. Clark, Z. Sahenk, J. R. Mendell, and B. K. Kaspar. 2013. 'Micro-dystrophin and follistatin co-delivery restores muscle function in aged DMD model', Hum Mol Genet, 22: 4929-37.