

Public Information

1. Title of the clinical study

« 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)»

2. Name and address of the sponsor

Sarepta Therapeutics, Inc.
215 First Street Cambridge, MA 02142 USA

3. Information on the GMO

Recombinant Adeno Associated Virus (AAV) serotype rh74 (isolated from Rhesus macaque) containing human micro-dystrophin (hMicro-Dys) gene for the treatment of Duchenne Muscular Dystrophy.

The cellular assembly of SRP-9001 facilitated via the process of transfection. This process utilizes three DNA-containing plasmids: the “transfer vector” which contains the therapeutic gene of interest (GOI) - pAAV.MHCK7.Micro-Dystrophin, the “rep/Cap” plasmid - pNLREP2-Caprh74, and a “helper plasmid” which generally contains several critical (adenovirus) genes

4. Description of the clinical study

The release of the GMO is made in the context of the SRP-001-303 clinical trial study

The primary objective of this study is 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]).

To date, there are limited treatment options for patients suffering from DMD, none of which reverse the course of this debilitating and ultimately fatal disease.

SRP-9001 is a gene therapy designed to treat the underlying biological cause of DMD by replacing dysfunctional or missing dystrophin protein with a functional truncated dystrophin, called micro-dystrophin, in cardiac and skeletal muscle; the key tissues affected in this lethal degenerative disease. Thus, micro-dystrophin would address the root cause of DMD, alter the course of the disease, and address a significant unmet medical need.

This is a Phase 3, randomized, double-blind, placebo-controlled 2-part study of systemic gene transfer therapy of SRP-9001 in approximately 116 Duchenne Muscular Dystrophy (DMD) subjects across 2 cohorts:

- Cohort 1 consists of approximately 88 male DMD non-ambulatory subjects.
- Cohort 2 consists of approximately 28 male DMD ambulatory subjects who are ≥ 8 to < 18 years of age.

The total duration of each subject's participation in the study is expected to be approximately 128 weeks

The study start in Belgium is expected for the first quarter of 2023 (Q1 2023) and the end of study is expected in second quarter 2026 (Q2 2026). In Belgium, one study hospital center "UZ-Gent Neurologie" will participate to the study with 10 planned patients.

5. Summary of the assessment of the effects and environmental risks

5.1. Property of Reducing other Microorganisms

There are no reports that the AAV, used to produce SRP-9001 possesses any property of reducing other microorganisms. Animals or plants are not affected by the property of reducing other microorganisms. Consequently SRP-9001 would not be expected to cause any risk of Adverse Effect on Biological Diversity attributable to the property of reducing other microorganisms.

5.2. Pathology

Adeno-associated viruses (AAV) are single stranded DNA viruses that have not been found to cause pathology in humans.

5.3. Productivity of Harmful Substances

The recombinant virus expresses micro-dystrophin protein and does not produce any harmful substances.

5.4. Property of Transmitting Nucleic Acid Horizontally

Genetically altered AAV used to deliver SRP-9001 has been shown to shed a very small proportion of the total number of viral genomes injected, and its ability to transmit nucleic acid horizontally is considered to be substantially degraded compared to wtAAV which is the taxonomical species to which the altered organism belongs. Additionally, no evidence of nonhuman animals or plants, which may be impacted through "horizontal" transmission of nucleic acid have been described.

As a result, SRP-9001 would not be expected to pose any appreciable risk of Adverse Effect on Biological Diversity attributable to the property of transmitting nucleic acid horizontally

5.5. Overall Assessment

Recombinant AAV technology is distinct from that of wild type (wt) AAV. The rAAV vectors do not contain viral coding sequences and do not express Rep proteins which play a key role not only for DNA replication but also for site-specific integration and cellular growth inhibitory effects. Human gene therapy recombinant products are used to deliver (and ultimately express) a therapeutic "transgene" in somatic cells for the purposes of treating genetically inherited diseases. Somatic cells contribute to the various tissues of the body but not to the germline. The effects of changes made to somatic cells are limited to the treated individual and would not be inherited by future generations. Therefore, the biosafety assessment of rAAV must rely on studies performed directly with the vectors in relevant animal and cellular models. Recent data has further elucidated specific biological properties of rAAV such as integration specificity and efficiency ([Tenenbaum, 2003](#)).

6. The proposed measures to limit the potential risks, to control and to ensure follow-up of the deliberate release

SRP-9001 will be shipped frozen on dry ice in a temperature-controlled shipment container managed by a specialty courier.

The following procedures are proposed to avoid and/or minimize the spread of the GMO based

on the risk assessment.

- The transportation is performed under sealed conditions.
- Administration site will be disinfected to minimize the environmental spread of the recombinant organism.
- Family members and caregivers will be instructed to practice good hand-hygiene after the product administration. This require washing hands with soap regularly and using appropriate protective gloves if coming into direct contact with bodily fluids and waste of the treated individual.
- Samples of urine, stool and saliva may be collected at safety visits to test the viral shedding.

Duration of the Treatment

The complete administration procedure including preparation of the infusion system is expected to take less than 2 hours.

Methods and Procedures to avoid and/or Minimize the Spread of the GMOs

Beyond the Site of the Release:

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.

Personal Protective Equipment (PPE) Used for the Procedure

- Gloves (double gloving)
- Safety goggles
- Lab coat
- Appropriate PPE should also be used for lower arms such as sleeve covers or securing gloves over the sleeves of laboratory coat.
- Personnel should not work with AAV, if skin is cut or open sores.

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 contaminated materials will be disposed of locally by incineration or autoclaving. All other places will be cleaned, according to normal decontamination procedures as per the NIH/CDC guidance for handling of biosafety level 1 agents and the Pharmacy Manual.

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 center.
3. Carefully pour disinfectant (fresh 10% 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 center. Use tongs or forceps to pick up broken plastics, glass or other sharps that could puncture gloves.
6. Discard absorbent material in biological 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 as per institutional guidelines for biohazardous waste.

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.

The quantities that will be released into the environment by shedding will be a very small proportion of the total number of viral genomes injected, of which the majority, if not all, is not considered “infectious”. Preliminary studies have shown that some vector can be excreted from the body for up to a few weeks after IV infusion. Vector shedding can be found in the blood, urine, saliva, and stool for up to a few weeks following injection. The risks associated with the vector shedding is very minimal and unlikely to result in clinically significant adverse effects because of the non-pathogenic nature and replication deficiency of the vector.