

Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine

Office of Clinical Evaluation

Office of Therapeutic Products, CBER, FDA

BLA	125781/0
Applicant	Sarepta Therapeutics, Inc.
Product	Delandistrogene moxeparvovec-rokl (SRP-9001) Suspension for Infusion (Intravenous), 1.33E+13 vector genome (vg)/mL
Proprietary Name	ELEVIDYS
Proposed Indication	Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the <i>DMD</i> gene
Date Received	September 28, 2022
Reviewer	Xiaofei Wang, PhD Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation General Medicine
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1 EXECUTIVE SUMMARY

Sarepta Therapeutics, Inc. (The Applicant) seeks accelerated approval of its Biologics License Application (BLA) for delandistrogene moxeparvovec-rokl (also known as SRP-9001; proprietary name: ELEVIDYS) for the proposed indication of treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. SRP-9001 is an adeno-associated virus (AAV) vector-based gene therapy designed to treat DMD by expressing a novel, engineered shortened dystrophin (ELEVIDYS micro-dystrophin or Sarepta’s micro-dystrophin) consisting of select domains of the full-length dystrophin protein present in normal muscle cells. The proposed surrogate endpoint for accelerated approval is expression of Sarepta’s micro-dystrophin measured at Week 12 after SRP-9001 administration. SRP-9001 is a suspension with a nominal concentration of 1.33×10^{13} vg/mL and supplied in a single-dose 10 mL as a single-use, preservative-free, sterile, aqueous liquid. The proposed dose of SRP-9001 is 1.33×10^{14} vector genome per kilogram of body weight (vg/kg) for patients with body weight of 10 to 70 kg and 9.31×10^{15} vg for patients with body weight of ≥ 70 kg. SRP-9001 is administered as a single-dose intravenous infusion over 1 to 2 hours.

The clinical pharmacology evaluation of this BLA is based on data from 3 clinical studies using SRP-9001 from two manufacturing processes: Study SRP-9001-101 (Study 101, Process A Product) and Study SRP-9001-103 (Study 103, Process B Product/To-be-Commercialized Product) are two open-label studies. Study SRP-9001-102 (Study 102, Process A Product) Part 1 is randomized, double-blind, placebo-controlled study, while Study SRP-9001-102 Part 2 is an open-label study.

DMD results from mutation that causes disruption of the reading frame of the *DMD* (also known as *Dystrophin*) gene and subsequent deficiency of wild-type (normal) dystrophin protein. SRP-9001 is designed to express a shortened version of wild-type dystrophin in target muscle tissues. After one-time intravenous infusion, SRP-9001 distributes to target tissues, transduces into muscle fibers, and expresses transgene, Sarepta's micro-dystrophin consisting of selected domains of the wild-type dystrophin. The transgene is delivered to skeletal and cardiac muscle cells, as observed in nonclinical studies.

To support the accelerated approval of SRP-9001, the Applicant proposed to use Sarepta's micro-dystrophin protein expression in muscle biopsy tissue samples at Week 12 following administration of SRP-9001 as surrogate endpoint. To assess whether the proposed surrogate endpoint is "reasonably likely to predict clinical benefit" to be used for accelerated approval, correlation analysis was conducted to evaluate the association between Sarepta's micro-dystrophin at Week 12 post-infusion and the clinical outcome, North Star Ambulatory Assessment (NSAA) total score change at Year 1. NSAA is an effort-dependent and process-dependent clinical endpoint, and blinding and concurrent control are critical to ensure reliability of NSAA assessment and interpretability of NSAA data. Therefore, the correlation analyses were performed using Study 102 Part 1 data (randomized, double-blind, placebo-controlled study design) alone as well as pooled data from Studies 102 (Part 1 & 2) and Study 103.

Correlation analysis using Study 102 Part 1 data only:

Based on limited data available, results of partial Spearman analysis (adjusted for baseline age and NSAA total score) using Study 102 Part 1 data alone did not show clear association between Sarepta's micro-dystrophin expression and NSAA total score change. Exploratory correlation analysis suggested improved NSAA total score change with increased Sarepta's micro-dystrophin expression in younger subjects (4 – 5 years of age); however, there was no clear association between Sarepta's micro-dystrophin protein expression and NSAA total score changes in older subjects (6-7 years of age). Because of the very limited data, these results have to be interpreted with caution.

Correlation analysis using pooled data from Study 102 (Part 1 & 2) and Study 103:

There are concerns regarding correlation analysis using pooled data from Study 102 (Part 1 & 2) and Study 103: 1) the open-label Design may affect NSAA total score change; and 2) open-label design without concurrent control may confound association between micro-dystrophin and NSAA total score change. Results of partial Spearman analysis (adjusted for baseline age and NSAA total score) using pooled data suggested Sarepta's micro-dystrophin accounts for 11% of variation in NSAA total score change. These results were not sufficiently persuasive to consider expression of Sarepta's micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit" to support accelerated approval.

Sarepta's micro-dystrophin is a novel, engineered protein that contains selected domains of the dystrophin expressed in normal muscle cells. No epidemiologic or pathophysiologic evidence of function of Sarepta's micro-dystrophin is available. The protein differs in important ways from both the endogenous shortened forms of dystrophin in patients with BMD, and the internally truncated dystrophins expressed through exon-skipping drugs. Measurement of levels of Sarepta's micro-dystrophin in muscle tissue therefore provides information only about expression of the transgene product in cells transduced by SRP-9001, rather than insight into a pharmacologic effect on a known biomarker in the pathway of the disease. In addition, results from correlation analysis were not sufficiently persuasive to consider expression of Sarepta's micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit." Therefore, the submitted clinical pharmacology information is not sufficient to support the use of Sarepta's micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit" for accelerated approval of SRP-9001. Clinical pharmacology reviewer does not recommend granting accelerated approval for SRP-9001 based on data provided in current submission.

2 INTRODUCTION

Duchenne muscular dystrophy (DMD) is a degenerative, neuromuscular disease. DMD results from mutation of the *DMD* (also known as *Dystrophin*) gene, the largest known human gene, which is carried on the X chromosome. Patients with DMD have a mutation that causes disruption of the reading frame of the *DMD* gene; subsequently there is a deficiency of this structural protein, Dystrophin. Dystrophin is expressed in multiple tissue types including skeletal muscle, smooth muscle, and cardiac muscle. In a normal muscle cell dystrophin serves as a flexible structural protein linking the intracellular space with the sarcolemma (muscle cell membrane) in a complex comprised of several proteins called the dystrophin-associated protein complex (DAPC), which then link to the extracellular matrix via laminin. This link helps transmit and dissipate force related to muscle contraction and to maintain sarcolemma integrity during muscle use preventing muscle and membrane damage. Without this structural link, normal muscle contraction in DMD patients results in chronic muscle breakdown and loss of function and translates to a loss of sarcolemma integrity, leakage (including that of creatine kinase), and undesired permeability.

Although histologic and laboratory evidence of myopathy may be seen at birth, the clinical onset of skeletal muscle weakness usually does not become evident until early childhood. The average age at diagnosis is approximately 5 years.

SRP-9001¹ is an AAV vector-based gene therapy. SRP-9001 drug substance is a non-replicating, recombinant AAV serotype rh74 (AAVrh74) vector containing the SRP-9001 micro-dystrophin expression cassette construct, under the control of the MHCK7 promoter

¹ In this review, delandistrogene moxeparvovec is referred to as SRP-9001.

(rAAVrh74.MHCK7.micro-dystrophin). SRP-9001 consists of a 4.7 Kb codon-optimized DNA vector genome encapsidated in a simian AAV serotype rh74 capsid. Each virion potentially contains a single copy of the vector genome. The vector genome expresses Sarepta's micro-dystrophin, a novel, engineered protein that contains selected domains of the dystrophin in normal muscle cells). It is about 138 kDa in size (dystrophin in normal muscle cells: 427 kDa). Expression of Sarepta's micro-dystrophin protein is under the control of the chimeric MHCK7 (α -myosin heavy-chain creatine kinase 7) promoter to restrict expression to skeletal and cardiac muscle.

The purified SRP-9001 vector is formulated at nominal vector genome concentration of 1.33×10^{13} vg/mL, for intravenous infusion. It is supplied as a single-use, preservative-free, sterile, aqueous formulation buffer.

The goal of treatment with SRP-9001 is to change the disease trajectory of DMD into a milder, Becker muscular dystrophy (BMD)-like phenotype. In this BLA, the Applicant proposed to utilize a novel surrogate endpoint—expression of Sarepta's micro-dystrophin protein to support accelerated approval approach. Sarepta's micro-dystrophin protein expression at Week 12 after administration of SRP-9001 was used as primary evidence of effectiveness. This biomarker thus is intended to serve as the required surrogate endpoint considered “reasonably likely to predict clinical benefit” for accelerated approval of SRP-9001.

The clinical pharmacology of SRP-9001 was assessed in three clinical studies: Study SRP-9001-101 (Study 101), Study SRP-9001-102 (Study 102), and Study SRP-9001-103 (Study 103). Please refer to Section 6.1 and Section 7 for details.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

SRP-9001 is an AAV vector-based gene therapy designed to treat the proximate cause of DMD by replacing dysfunctional or missing dystrophin protein with a shortened wild-type dystrophin (Sarepta's micro-dystrophin) in cardiac and skeletal muscle. After one-time intravenous infusion, SRP-9001 distributed to target tissues, transduced into muscle fibers, and expressed transgene, Sarepta's micro-dystrophin.

Vector Biodistribution and Vector Shedding

Vector Biodistribution

- After IV administration, the ELEVIDYS vector genome copy (VGC) concentration-time profiles in serum showed a bi-phasic disposition characterized by a rapid distribution phase up to 10 days post-dose followed by a slow and nearly flat terminal elimination phase. The median (min, max) time to reach the first below limit of quantification (BLOQ) followed by 2 consecutive BLOQ samples was 55.3 (20.8, 252.0) days. The median time to achieve first below limit of quantification [BLOQ] sample followed by 2 consecutive BLOQ samples were 63 days post-dose for serum for Study 103 Cohort 1.
- At Week 12 (90 days for Study 101), ELEVIDYS VGCs were detected in all study subjects. ELEVIDYS muscle tissue exposure (VGC levels) increased with increasing ELEVIDYS dose. High inter-subject variability of VGC levels was observed.
- At the dose 1.33×10^{14} vg/kg, the VGC levels (change from baseline) to Week 12 in muscle tissue biopsy samples were similar for ELEVIDYS from manufacturing Process A and manufacturing from Process B. The mean (standard deviation [SD]) of VGC levels (change from baseline) at Week 12 in muscle tissue biopsy samples were 3.3 (SD: 2.4) VGCs per nucleus and 3.4 (SD: 2.4) VGCs per nucleus from ELEVIDYS Process A (n=33) product and Process B (n=20) product, respectively.
- For subjects aged 4 to 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS VGC levels (change from baseline) at Week 12 post-infusion were 3.18 (N=4, SD: 1.54) copies per nucleus in Study 2 Parts 1 and 2 (Process A Product) and 2.97 (N=11, SD: 2.15) copies per nucleus in Study 3 Cohort 1 (Process B Product).

Vector Shedding

- After administration, ELEVIDYS vector genome was detected in all treated subjects. The median (min, max) time to achieve peak levels were 0.3 (0.2, 13.7) days, 0.3 (0.2, 72.0) days, and 13.1 (0.3, 27.8) days in saliva, urine, and feces, respectively.
- SRP-9001 vector genome concentrations decreased rapidly. The median time (min, max) to reach the level below the limit of detection was 49.8 (27.8, 169.0) days, 78.2 (26.9, 257.0) days, and 162.0 (76.1, 251.0) days in saliva, urine, and feces, respectively. For Study 103 Cohort 1, the median time to achieve complete elimination as the first BLOD sample followed by 2 consecutive BLOD samples were 49.8 days, 123 days and 162 days post-dose for saliva, urine and feces, respectively.

Pharmacodynamics

After one-time IV infusion, ELEVIDYS is expected to be transduced to the target cells and lead to expression of the ELEVIDYS transgene, ELEVIDYS micro-dystrophin. Muscle biopsy samples were collected at baseline and Week 12 post-infusion to evaluate the quantity of expression of the ELEVIDYS transgene (ELEVIDYS micro-dystrophin levels by western blot assay, correct

localization of the expressed protein at the sarcolemma membrane by immunofluorescence (IF) staining assay (IF fiber intensity and IF percent ELEVIDYS micro-dystrophin positive fiber [PMDPF; %]).

Sarepta's Micro-dystrophin Expression Amount at Week 12 in Muscle Biopsy Tissue Samples (Western Blot Assay)

The absolute amount of ELEVIDYS micro-dystrophin in muscle biopsy tissue samples were measured by western blot assay, adjusted by muscle content, and expressed as a percent of control (levels of WT dystrophin in subjects without DMD or Becker muscular dystrophy [BMD]). High inter-subject variability was observed in ELEVIDYS micro-dystrophin expression in muscle tissues measured by western blot.

- In Study 102 part 1, subjects received three different dose levels of ELEVIDYS: 6.29×10^{13} vg/kg (SRP-9001-DL1), 8.94×10^{13} vg/kg (SRP-9001-DL2), and 1.33×10^{14} vg/kg (SRP-9001-DL3, intended dose). ELEVIDYS micro-dystrophin was expressed in a dose-dependent manner. The mean (SD) ELEVIDYS micro-dystrophin levels (percent of control) (change from baseline) at 12 weeks post-infusion were 3.6 (5.7), 28.2 (52.2), and 43.4 (48.6) for subjects receiving SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. ELEVIDYS micro-dystrophin levels were generally maintained until Week 12 Part 2, except for SRP-9001-DL2. In Study 102 Part 2, subjects who were in the Part 1 placebo group received ELEVIDYS at the intended dose (1.33×10^{14} vg/kg). At 12 weeks post-dosing of ELEVIDYS in Part 2, the mean (SD) level of ELEVIDYS micro-dystrophin (percent of control) was 40.8 (32.5), similar to Study 102 Part 1 SRP-9001-DL3.
- In Study 103 Cohort 1, all subjects received ELEVIDYS at the intended dose (1.33×10^{14} vg/kg). The mean (SD) level of ELEVIDYS micro-dystrophin was 54.2 (42.6) at Week 12.
- At the intended dose (1.33×10^{14} vg/kg), the mean (SD) ELEVIDYS micro-dystrophin levels (percent of control) in muscle tissue biopsy samples at Week 12 were 41.3 (35.4) and 54.2 (42.6) for ELEVIDYS Process A (n=27) product and ELEVIDYS Process B (n=20) product, respectively. For subjects aged 4 to 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS micro-dystrophin expression levels (change from baseline) at Week 12 following ELEVIDYS infusion were 95.7% (N=3, SD: 17.9%) in Study 102 Parts 1 and 2 (Process A product) and 51.7% (N=11, SD: 41.0%) in Study 103 Cohort 1 (Process B product), respectively.

ELEVIDYS Micro-dystrophin Expression at Week 12 in Muscle Biopsy Tissue Samples (Immunofluorescence Staining Assay)

Localization of ELEVIDYS micro-dystrophin at sarcolemma membrane was evaluated by IF staining assay (IF fiber intensity and IF PMDPF [%]). High inter-subject variability was observed for the IF fiber intensity (percent of control) and PMDPF (%) results.

- In Study 102 Part 1, both IF Fiber Intensity (percent of control) and PMDPF (%) increased with an increasing dose of ELEVIDYS. At Week 12, the mean changes from baseline of IF Fiber Intensity (percent of control) were 7.3 (SD: 7.0), 40.1 (SD: 73.3), and 36.2 (SD: 41.3) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. The mean (SD) increases of PMDPF (%) from baseline were 15.6 (14.8), 30.3 (32.9), and 26.7 (26.0) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. Both IF Fiber Intensity (percent of control) and PMDPF (%) continued to increase for all three dose levels except SRP-9001-DL2 (8.94×10^{13} vg/kg). Subjects in the Part 1 placebo group received ELEVIDYS (1.33×10^{14} vg/kg). At 12 weeks post-dosing (Study 102 Part 2, Week 12), the mean (SD) change of ELEVIDYS micro-dystrophin were 74.1 (47.7) and 77.6 (21.9) for IF fiber intensity (percent of control) and PMDPF (%), respectively.
- The mean (SD) changes of ELEVIDYS micro-dystrophin at Week 12 in Study 103 Cohort 1 were 66.5(64.1) and 48.3 (25.4) for IF fiber intensity (percent of control) and PMDPF (%), respectively.

Correlation Analysis Between ELEVIDYS Micro-dystrophin at Week 12 and NSAA Total Score Change at Year 1 (Clinical Efficacy Endpoint)

To support the accelerated approval of ELEVIDYS, the Applicant proposed to use ELEVIDYS micro-dystrophin protein expression in muscle biopsy tissue samples at Week 12 following administration of ELEVIDYS as surrogate endpoint. To assess whether the proposed surrogate endpoint is “reasonably likely to predict clinical benefit” to be used for accelerated approval, correlation analysis is conducted to evaluate the association between ELEVIDYS micro-dystrophin at Week 12 post-infusion and the clinical outcome, North Star Ambulatory Assessment (NSAA) total score change at Year 1.

Correlation Analysis Using Study 102 Part 1 Data Only

Based on limited data available, results of partial Spearman analysis (adjusted for baseline age and NSAA total score) using Study 102 Part 1 data only showed no clear association between ELEVIDYS micro-dystrophin expression and NSAA Total Score change. Correlation analysis at age-group level did not suggest clear association between ELEVIDYS micro-dystrophin expression and NSAA Total Score change either based on limited data. However, improved NSAA Total Score with increased ELEVIDYS micro-dystrophin expression was observed in younger subjects (aged 4-5 years), but not in those aged 6 years and older. Because of the very limited data and exploratory nature of NSAA assessment, the results in subjects aged 4 to 5 years need to be interpreted with caution.

Correlation Analysis Using Pooled Data From Study 102 (Part 1 & 2) and Study 103

There are concerns regarding correlation analysis using pooled data from Study 102 (Parts 1 & 2) and Study 103:

- The open-label design may affect NSAA Total Score change; and
- The open-label design without concurrent control may confound associations between ELEVIDYS micro-dystrophin and NSAA Total Score change. Results of partial Spearman analysis (adjusted for baseline age and NSAA Total Score) using pooled data suggested ELEVIDYS micro-dystrophin account for 11% of variation in NSAA Total Score change. The result is not sufficiently persuasive to consider expression of ELEVIDYS micro-dystrophin “reasonably likely to predict clinical benefit.”

Immunogenicity

- ***Anti-AAVrh75 Antibodies:*** All subjects had baseline anti-adenovirus vector rhesus serotype 74 (AAVrh74) total binding antibody titer <1:400 based on an investigational assay in all three clinical studies. Following administration of ELEVIDYS, elevated anti-AAVrh74 antibody titers were observed in all subjects. Anti-AAVrh74 antibody titers continued to increase over time, reaching peak levels during Week 8 to Week 24, and remained positive during the observation period in all three studies (up to Year 4, Year 2, Week 48, and Week 52 for Study 101, Study 102 Part 1, Study 102 Part 2, and Study 103, respectively). There is no dose-dependent relationship between ELEVIDYS dose and anti-AAVrh74 antibody response established. There is no evident impact of anti-AAVrh74 antibodies on muscle transduction or ELEVIDYS micro-dystrophin protein expression (western blot assay) observed.
- ***Anti-ELEVIDYS Micro-dystrophin Antibodies:*** Anti-ELEVIDYS micro-dystrophin antibodies were assessed in Study 103. All enrolled subjects were below assay threshold for positivity (<10) for anti-ELEVIDYS micro-dystrophin antibodies prior to ELEVIDYS infusion. Twenty-one of the 39 subjects developed anti-ELEVIDYS micro-dystrophin antibodies throughout the 52 weeks post-dosing.
- ***Cellular Immune Responses Against AAVrh74 Capsids:*** Cellular immune responses against AAVrh74 were inconsistently observed across all subjects treated with ELEVIDYS. In Study 101, all 4 subjects display a positive IFN γ cytokine release after ELEVIDYS infusion. At Week 4 post-dosing of ELEVIDYS, 4 out of 41 subjects (9.8%) and 23 out of 39 (59.0%) subjects displayed a positive cellular immune response against AAVrh74 for Study 102 and 103, respectively. No evident impact of T-cell mediated cellular response against AAVrh74 capsids on ELEVIDYS micro-dystrophin protein expression in muscle biopsy samples (Week 12) was observed.

- ***Cellular Immune Responses Against Sarepta's Micro-dystrophin:*** A total of 8 subjects (1 subject in Study 102 and 7 subjects in Study 103) had an elevated cellular immune response greater than threshold at 4 weeks post ELEVIDYS infusion. No evident impact of T-cell mediated cellular response against micro-dystrophin on ELEVIDYS micro-dystrophin protein expression in muscle biopsy samples (Week 12) was observed.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125781/0 and finds it acceptable pending the following revisions shown below.

Comments to Applicant:

1. Please change “ELEVIDYS dystrophin” to “ELEVIDYS micro-dystrophin”.
2. Please delete promotional languages.
3. Please only include Study 102 and Study 103 Cohort 1 information.
4. Please move ELEVIDYS micro-dystrophin protein expression information from Section 14 to section 12.2 Pharmacodynamics.
5. ELEVIDYS micro-dystrophin protein expression measured by immunohistochemistry assay should not be considered as fully quantitative assay. Therefore, please only include western blot assay results for ELEVIDYS micro-dystrophin protein expression amount information.
6. Please also include nonclinical data in Vector Distribution and Vector Shedding part.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Delandistrogene moxeparvovec-xxxx is the recombinant gene therapy product that is comprised of 3 components: 1) vector: a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) vector, 2) promoter: a MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α -myosin heavy chain enhancer, 3) transgene, contained in the ELEVIDYS dystrophin protein expression cassette.

Vector: Clinical and nonclinical studies have demonstrated AAVrh74 serotype transduction in skeletal muscle cells. Additionally, in nonclinical studies, AAVrh74 serotype transduction has been demonstrated in cardiac and diaphragm cells.

Promoter: The MHCK7 promoter/enhancer drives transgene expression and has been shown in animal models to drive transgenic ELEVIDYS dystrophin protein expression predominantly in skeletal muscle (including diaphragm) and cardiac muscle, with minimal to undetectable levels of ELEVIDYS dystrophin protein expression in other tissues. In clinical studies, muscle biopsy analyses have confirmed ELEVIDYS dystrophin expression in skeletal muscle.

Transgene: DMD is caused by a mutation in the DMD gene resulting in lack of functional dystrophin protein. Delandistrogene moxeparvovec-xxxx introduces a transgene encoding functional elements of the DMD gene in transduced skeletal cells, and cardiac cells as observed in nonclinical studies, with the goal of prolonged ELEVIDYS dystrophin protein expression in patients with a mutation in the DMD gene.

~~ELEVIDYS produces functional ELEVIDYS dystrophin protein in patients with a mutation in the DMD gene, regardless of mutation, sex, or stage of disease. ELEVIDYS dystrophin protein expressed by delandistrogene moxeparvovec xxxx provides a link between the intra and extracellular environments intended to stabilize the sarcolemma membrane during muscular contraction. Maintenance of sarcolemma membrane integrity is expected to protect muscle cells from contraction induced injury and preserve muscle function, with the treatment goal of improving or stabilizing DMD.~~

12.2. Pharmacodynamics

In 77 patients across three clinical studies (Study 1, 2, 3), ELEVIDYS dystrophin protein expression from muscle biopsies (gastrocnemius or biceps femoris) was quantified by Sarepta western blot and immunofluorescence staining (fiber intensity and percentage dystrophin positive fibers) [*see Clinical Studies (14)*].

Assessment of dystrophin levels can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, valid comparisons of dystrophin measurements obtained from different assays cannot be made.

12.3. Pharmacokinetics

Following IV administration, ELEVIDYS vector genome undergoes rapid distribution via the systemic circulation and widely distributes into target muscle tissues followed by elimination in the urine and feces. Extensive ELEVIDYS biodistribution and tissue transduction are detected in the target muscle tissue groups and quantified in the gastrocnemius or biceps femoris biopsies obtained from patients with mutations in the *DMD* gene. Evaluation of ELEVIDYS vector genome exposure in clinical muscle biopsies at Week 12 post-dose expressed as copies per nucleus revealed robust ELEVIDYS drug distribution and transduction with a mean observed value of 3.00 copies per nucleus at the recommended dose of 1.33×10^{14} vg/kg across studies 3 studies (Study 1, 2, and 3 [Cohorts 1,2, and 3]) [*see Clinical Studies (14)*].

As an AAV-based gene therapy that consists of a protein capsid containing the transgene DNA genome of interest, ELEVIDYS capsid proteins are broken down through proteasomal degradation following AAV entry into target cells. As such, ELEVIDYS is not likely to exhibit the drug-drug interaction potential mediated by known drug metabolizing enzymes (cytochrome P450-based) and drug transporters. The estimated elimination half-life of ELEVIDYS vector genome in the serum is approximately 12 hours, and majority of the drug is expected to be cleared from the serum by 1-week post-dose. In the excreta, the estimated elimination half-life of ELEVIDYS vector genome is 40 hours, 55 hours, and 60 hours in the urine, feces, and saliva, respectively.

Consistent serum and excreta PK profiles and characteristics were observed across a broad pediatric and adult DMD population (age 4 to 20 years old) and patients with ambulatory or non-ambulatory status.

12.6. Immunogenicity

The observed incidence of anti-AAVrh74 antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-AAVrh74 antibodies in the studies described below with the incidence of anti-AAVrh74 antibodies in other studies.

In ELEVIDYS clinical studies, patients were required to have baseline anti-AAVrh74 total binding antibodies of $\leq 1:400$, measured using an enzyme-linked immunosorbent assay (ELISA). The safety and efficacy of ELEVIDYS in patients with elevated anti-AAVrh74 total binding antibody titer ($>1:400$) have not been evaluated [*see Clinical Studies (14)*].

Across three clinical studies (Study 1, Study 2 and Study 3) evaluating a total of 84 patients, elevated anti-AAVrh74 total binding antibodies titers ($>1:400$) were observed in all patients following a one-time ELEVIDYS infusion. There was no identified clinically significant effect of the development of anti-AAVrh74 total binding antibodies post-infusion on the safety and/or efficacy of ELEVIDYS.

Re-administration of ELEVIDYS has not been evaluated [*Warnings and Precautions (5.4)*].

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA is inadequate to support a marketing approval for this product through accelerated approval pathway due to following reasons:

- Sarepta's micro-dystrophin is a novel, engineered protein that contains selected domains of the dystrophin expressed in normal muscle cells. No epidemiologic or pathophysiologic evidence of function of Sarepta's micro-dystrophin is available. The protein differs in important ways from both the endogenous shortened forms of dystrophin in patients with BMD, and the internally truncated dystrophins expressed through exon-skipping drugs. Measurement of levels of Sarepta's micro-dystrophin in muscle tissue therefore provides information only about expression of the transgene product in cells transduced by SRP-9001, rather than insight into a pharmacologic effect on a known biomarker in the pathway of the disease.
- The Applicant proposed to use Sarepta's micro-dystrophin protein expression at Week 12 post-dosing as surrogate endpoint to support its accelerated approval approach. However, the correlation between Sarepta's micro-dystrophin protein expression and the clinical outcome, North Star Ambulatory Assessment (NSAA) total score change was not sufficiently persuasive to consider expression of Sarepta's micro-dystrophin "reasonably likely to predict clinical benefit".

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 Overview of Clinical Pharmacology Evaluation of SRP-9001

Clinical Studies with Clinical Pharmacology Evaluation

The clinical pharmacology section of this BLA includes 3 clinical studies (Table 1):

- Study SRP-9001-101 (Study 101), an ongoing, open-label, first-in-human, proof of concept, single-arm, single-dose, Phase 1/2a study conducted at a single site in the United States (US) on subjects with DMD (**Process A / investigational product**);
- Study SRP-9001-102 (Study 102), an ongoing, randomized, double-blind, placebo controlled, Phase 2, 3-part study conducted at 2 sites in the US on ambulatory subjects with DMD aged ≥ 4 to < 8 years at time of screening (**Process A / investigational product**); and
- Study SRP-9001-103 (Study 103), an ongoing, open-label, single-arm, single-dose, Phase 1b study with 4 cohorts and a 2-part follow-up period conducted at 5 sites in the US (**Process B / to-be-commercialized product**)

Clinical Pharmacology Evaluations

Pharmacokinetics – Vector Biodistribution and Vector Shedding

SRP-9001 biodistribution and viral shedding was evaluated in serum, saliva, urine, feces and target muscle tissues. Muscle tissues were collected as biopsies of gastrocnemius from all ambulant subjects in Studies 101, 102 and 103 Cohort 1. Biopsies of bicep muscle were obtained for older ambulant and non-ambulant subjects in Cohorts 2 and 3 of Study 103. SRP-9001 biodistribution and viral shedding was determined by detection of SRP-9001 vector DNA and quantified using droplet digital polymerase chain reaction (ddPCR) assay. SRP-9001 vector DNA in target muscle tissues was the primary biodistribution endpoint and was characterized in all 3 clinical studies. SRP-9001 biodistribution in serum and viral shedding in saliva, urine and feces were exploratory endpoints and characterized in Study 103.

Pharmacodynamics Biomarker

The SRP-9001 pharmacodynamic endpoint, Sarepta's micro-dystrophin protein expression in the muscle tissue biopsy, served as biological efficacy endpoint following SRP-9001 treatment. Sarepta's micro-dystrophin protein expression is quantified by immunofluorescence (IF) staining and western blot (WB) assays. IF staining provides quantification on the percentage of SRP-9001-micro-dystrophin positive fibers (PMDPF) and fiber intensity in the tissues of interest. This quantification evaluates the biologically active and membrane-localized SRP-9001-dystrophin. The WB results provide quantification of total SRP- 9001 protein expressed as a percentage of full-length dystrophin in normal controls. The protocol includes normalization of muscle content for each of the tissue biopsies in Studies SRP-9001- 102 and SRP-9001-103.

Immunogenicity

Immunogenicity assessment of SRP-9001 included humoral and cellular immunogenicity against 1) vector AAVrh74 capsid and 2) transgene product, SRP-9001-micro-dystrophin.

Table 1. Clinical studies with SRP-9001 clinical pharmacology evaluation

Study No.	SRP-9001-101	SRP-9001-102	SRP-9001-103
Purpose	First in human and proof of concept	Efficacy and safety	Expression, safety, and vector shedding of intended commercial process SRP-9001
Primary endpoint	Safety	12-week SRP-9001-dystrophin expression by WB (Part 1), 48-week NSAA (Part 1), and safety	12-week SRP-9001-dystrophin expression by WB
Key secondary/exploratory endpoints	Day 90 (~12 weeks) SRP-9001-dystrophin expression by WB, NSAA, TFTs, safety	12-week (Part 2) SRP-9001-dystrophin expression by WB, IF, vector genome copies, NSAA (Part 2), TFTs, CK	Vector shedding, immunogenicity, IF, vector genome copies, NSAA, TFTs, CK, safety
Design	Open label	Part 1: Double blind, randomized, placebo controlled Part 2: blinded crossover in Part 2	Open label
Status	Ongoing; fully enrolled	Ongoing; fully enrolled	Ongoing, fully enrolled
Population	Ambulatory	Ambulatory	Ambulatory (Cohorts 1 and 2) and non-ambulatory (Cohort 3)
Age at study baseline for subjects dosed	≥ 4 to 7 years (n = 4)	≥ 4 to 7 years (n = 41)	Cohort 1: ≥4 to <8 years of age (n = 20) Cohort 2: ≥8 to <18 years of age (n = 7) Cohort 3: 9-20 years of age (n = 6)
Study duration	5 years	Up to 260 weeks	260 weeks

Source: Applicant with modification. Module 2, Section 2.7.2. Summary of Clinical Pharmacology Studies.

Reviewer Comment:

Study 102 Part 2 is essentially an open-label study as all subjects know they received SRP-9001 either at the beginning of Part1 or Part 2.

6.2 General Pharmacology and Pharmacokinetics — Vector Biodistribution and Vector Shedding

SRP-9001 vector biodistribution and vector shedding was assessed in Study 103. Subjects in Cohort 1 (ambulatory patients 4 to 7 years old, n = 20), Cohort 2 (ambulatory patients 8 to 12 years old, n = 7), Cohort 3 (non-ambulatory patients 9 to 20 years old, n = 6) of Study 103 were included in the analysis.

Serum for vector quantification was collected on the day of SRP-9001 administration (Day 1) at 4-6 hours following the end of infusion, and on Day 2 at 22 to 26 hours following the end of the infusion. Additional serum samples were collected at Weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 24, 36, and 52 following SRP-9001 administration. Vector shedding samples were taken on the day of administration (Day 1), Day 2, and at Weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 24, 36, 52, 78, and 104. SRP-9001 concentrations in serum, urine, and feces samples were determined by ddPCR. Results were reported in units of copies/mL (serum, urine, saliva) or copies/μg DNA (feces).

6.2.1 Vector Biodistribution

SRP-9001 Vector in Serum

After IV administration, the SRP-9001 vector genome concentration-time profiles in serum showed a bi-phasic disposition characterized by a rapid distribution phase up to 10 days post-dose followed by a slow and nearly flat terminal elimination phase. As of April 2022, all 30 subjects in Study 103 Cohorts 1, 2, and 3 had three consecutive below limit of quantification (BLOQ) levels of SRP-9001. The median (min, max) time to reach the first below limit of quantification (BLOQ) followed by 2 consecutive BLOQ samples was 55.3 (20.8, 252.0) days (Table 2). High levels of variability were observed in the terminal elimination phase, which exhibited a high proportion of observations below the limit of quantification. The median time to achieve first below limit of quantification [BLOQ] sample followed by 2 consecutive BLOQ samples were 63 days post-dose for serum for Study 103 Cohort 1.

Table 2. Summary of SRP-9001 vector genome biodistribution in serum (Study 103, Cohorts 1, 2, & 3)

		Time to First Detectable Sample (Days)	Peak Concentration (10^{13} copies/mL)	Time to Peak Concentration (Days)	Time to Achieve Clearance (First BLOQ Sample Followed by 2 Consecutive BLOQ Samples) (Days)	Number (%) of Subjects Achieved Viral Shedding Clearance as of April 2022
Serum	N	33 (100%)	33 (100%)	33 (100%)	30 (91%)	30 (91%)
	Mean (SD)	0.735 (2.74)	0.00547 (0.00265)	0.889 (2.72)	70.1 (56.7)	-
	Median	0.222	0.0053	0.242	55.3	-
	Min, Max	0.142, 15.9	5.03e-09, 0.013	0.142, 15.9	20.8, 252	-

Source: Applicant's response to FDA's Information Request (IR).

The exposure of SRP-9001 vector genome in serum was summarized in Table 3.

Table 3. Summary of SRP-9001 Serum Exposure (Study 103 Cohorts 1, 2, and 3)

Study Cohort	Parameter [Unit]	N	Mean [SD]	Geom. Mean [CV%]	Median [Min, Max]
Cohort 1	C_{max} [10^{14} vg/L]	20	0.561 (0.101)	0.553 (17.5)	0.56 [0.415, 0.827]
	dose-normalized C_{max} [vg/L/vg copies]	20	0.0201 (0.00153)	0.02 (7.87)	0.02 [0.016, 0.0226]
	AUC_{∞} [10^{14} vg/L*h]	20	10.7 (2.03)	10.5 (19.1)	10.5 [7.66, 15.4]
	dose-normalized AUC_{∞} [vg/L*h/vg copies]	20	0.382 (0.0202)	0.382 (5.16)	0.379 [0.35, 0.431]
	AUC_{0-130} [10^{14} vg/L*h]	20	10.7 (2.03)	10.5 (19.2)	10.5 [7.66, 15.4]
	dose-normalized AUC_{0-130} [vg/L*h/vg copies]	20	0.382 (0.0202)	0.382 (5.16)	0.379 [0.35, 0.431]
	$t_{1/2}$ [h]	20	12.4 (1.53)	12.4 (11.1)	12.1 [10.6, 17.9]
Cohort 2	C_{max} [10^{14} vg/L]	6	0.949 (0.153)	0.939 (15.8)	0.897 [0.774, 1.18]
	dose-normalized C_{max} [vg/L/vg copies]	6	0.0206 (0.00202)	0.0205 (10.6)	0.0212 [0.0166, 0.0221]
	AUC_{∞} [10^{14} vg/L*h]	6	18 (3.03)	17.8 (17)	17.5 [14.2, 21.5]
	dose-normalized AUC_{∞} [vg/L*h/vg copies]	6	0.388 (0.0222)	0.388 (5.8)	0.388 [0.352, 0.417]
	AUC_{0-130} [10^{14} vg/L*h]	6	18 (3.03)	17.8 (17)	17.5 [14.2, 21.5]
	dose-normalized AUC_{0-130} [vg/L*h/vg copies]	6	0.389 (0.0217)	0.388 (5.67)	0.388 [0.353, 0.416]

	$t_{1/2}$ [h]	6	12.4 (2.19)	12.2 (16.8)	11.8 [9.95, 16.4]
Cohort 3	C_{max} [10^{14} vg/L]	6	1.53 (0.295)	1.5 (20.6)	1.56 [1.08, 1.86]
	dose-normalized C_{max} [vg/L/vg copies]	6	0.02 (0.00224)	0.0199 (11.9)	0.0201 [0.0159, 0.0226]
	AUC_{∞} [10^{14} vg/L*h]	6	28.6 (6.08)	27.9 (24.1)	30.7 [18.3, 35.8]
	dose-normalized AUC_{∞} [vg/L*h/vg copies]	6	0.37 (0.0153)	0.369 (4.24)	0.373 [0.341, 0.384]
	AUC_{0-130} [10^{14} vg/L*h]	6	28.6 (6.08)	28 (24.1)	30.8 [18.3, 35.7]
	dose-normalized AUC_{0-130} [vg/L*h/vg copies]	6	0.37 (0.0151)	0.37 (4.19)	0.373 [0.342, 0.384]
	$t_{1/2}$ [h]	6	11.8 (1.08)	11.8 (9.03)	11.8 [10.6, 13.5]

Source: Applicant. Study 9001-103 Vector Shedding Report.

SRP-9001 Vector Genome Copy (VGC) Numbers in Muscle Tissues

To assess biodistribution (tissue vector genome exposure) and success of transduction, muscle tissue biopsy samples were collected at baseline and 12 weeks post-infusion, and the levels of SRP-9001 VGC were measured using droplet digital polymerase chain reaction assay (ddPCR) and expressed as genome copies per nucleus. Change in SRP-9001 VGC in muscle tissues from baseline to 12 weeks post-dosing (90 days for Study 101, 12 weeks for Study 102 and Study 103) was listed as one of the exploratory endpoints for all three clinical studies.

At Week 12 (90 days for Study 101), SRP-9001 VGCs were measured in all study subjects. The levels of VGC were summarized in Table 4 and Figure 1. In general, SRP-9001 muscle tissue exposure (VGC levels) increased with increasing SRP-9001 dose. High inter-subject variability of VGC levels was observed.

Table 4. Vector Genome Copies per Nucleus as Measured by ddPCR in Muscle Tissue Biopsy Post-infusion

Vector Genome Copies per Nucleus	101 (n=4)	101-P1-PLACEBO (n=21)	102-P1-SRP-DL1 (n=6)	102-P1-SRP-DL2 (n=6)	102-P1-SRP-DL3 (n=8)	102-P1-PLACEBO-P2-SRRP-DL3 (n=21)	102-Pooled-SRP-DL3 (n=29)	103-COH1 (n=20)
Mean (SD)	5.7 (4.1)	0.0 (0.0)	0.7 (0.2)	2.4 (2.2)	1.6 (1.2)	3.4 (2.0)	2.9 (2.0)	3.4 (2.4)
Median (Q1, Q3)	5.4 (2.3, 8.9)	0.0 (0.0, 0.0)	0.7 (0.5, 0.8)	1.6 (1.0, 2.7)	0.9 (0.7, 2.7)	3.5 (2.0, 4.6)	2.8 (1.0, 4.1)	2.7 (1.9, 3.9)
Min, Max	2.2, 9.9	0.0, 0.0	0.5, 0.9	0.8, 6.6	0.5, 3.3	0.3, 7.3	0.3, 7.3	0.7, 9.8

Source: FDA Clinical Pharmacology Reviewer

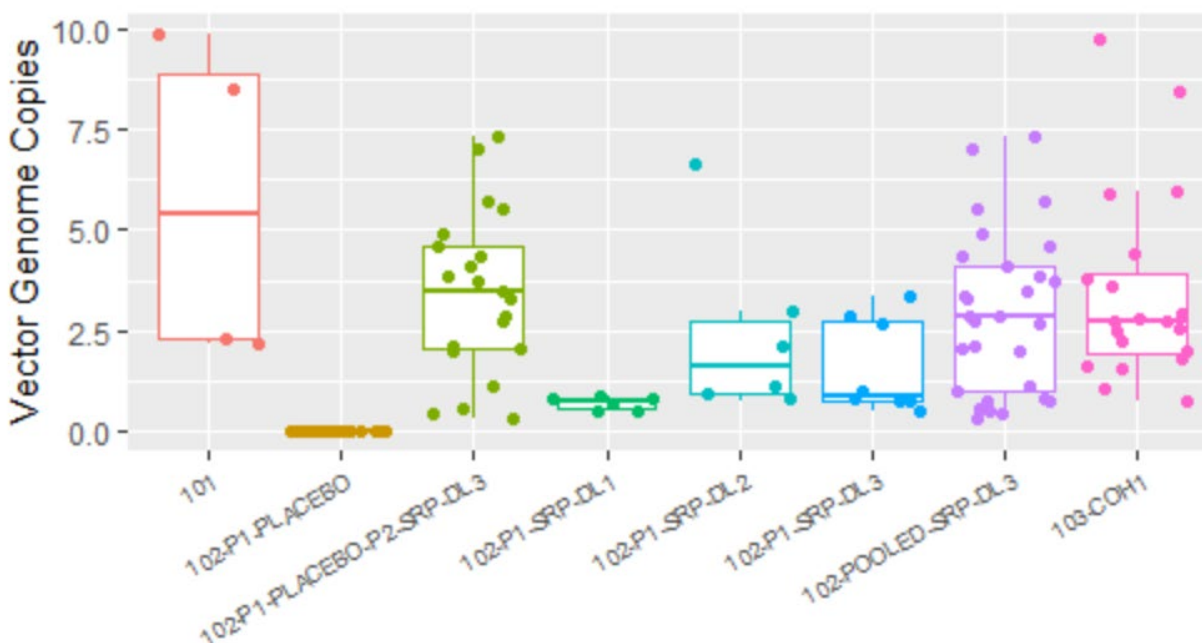
Note: Vector genome copy levels were measured at 90 days post-dosing in Study SRP-9001-101 (101) and at 12 weeks post-dosing in Study 102 and Study 103.

There were four subgroups in Study 102 Part 1: 3 subgroups of subjects received SRP-9001 treatment at three different dose levels respectively: 6.29×10^{13} vg/kg (102-P1-SRP-DL1), 8.94×10^{13} vg/kg (102-P1-SRP-DL2), and 1.33×10^{14} vg/kg (102-P1-SRP-DL3), and one subgroup of subjects who received placebo in Part 1 (102-P1-PLACEBO) and received SRP-9001 in Part 2 at a dose of 1.33×10^{14} vg/kg (102-P1-PLACEBO-P2-SRRP-DL3).

Pooled-102-SRP-DL3 subgroup includes subjects who received SRP-9001 at the dose of 1.33×10^{14} vg/kg in Part 1 (n=8) and Part 2 (n=21).

Abbreviation: ddPCR, droplet digital polymerase chain reaction; Max, Maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Figure 1. Boxplot of Vector Genome Copies per Nucleus as Measured by ddPCR in Muscle Tissue Biopsy Post-Infusion



Source: FDA Clinical Pharmacology Reviewer

Note: Vector genome copy levels were measured at 90 days post-dosing in Study SRP-9001-101 (101) and 12 weeks post-dosing in Studies SRP-9001-102 and SRP-9001-103.

There were four subgroups in Study SRP-9001-102 Part 1: 3 subgroups of subjects received SRP-9001 treatment at three different dose levels respectively: 6.29×10^{13} vg/kg (102-P1-SRP-DL1), 8.94×10^{13} vg/kg (102-P1-SRP-DL2), and 1.33×10^{14} vg/kg (102-P1-SRP-DL3), and one subgroup of subjects who received placebo in Part 1 (102-P1-PLACEBO) and received SRP-9001 in Part 2 at the dose of 1.33×10^{14} vg/kg (102-P1-PLACEBO-P2-SRRP-DL3).

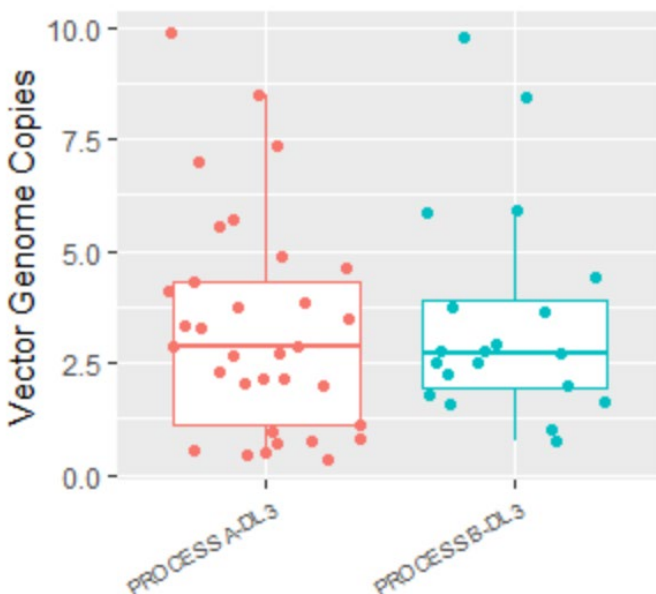
102-POOLED-SRP-DL3 includes two subgroups of subjects who received SRP-9001 at the dose of 1.33×10^{14} vg/kg in Part 1 (102-P1-SRP-DL3) and Part 2 (102-P1-PLACEBO-P2-SRRP-DL3).

Abbreviation: ddPCR, droplet digital polymerase chain reaction

Comparison of Muscle Tissue Exposure (VGC) of SRP-9001 Manufactured from Manufacturing Processes A & B

The mean (standard deviation [SD]) and median (min, max) of VGC levels (vector genome copies per nucleus) in muscle tissue biopsy samples from SRP-9001 Process A (n=33) product were 3.3 (2.4) and 2.8 (0.3, 9.9), respectively. The mean (SD) and median (min, max) of VGC levels (vector genome copies per nucleus) in muscle tissue biopsy samples from SRP-9001 Process B (n=20) product were 3.4 (2.4) and 2.7 (0.7, 9.8), respectively (Figure 2).

Figure 2. Boxplot of Vector Genome Copies in Muscle Tissue Biopsy of Process A SRP-9001 and Process B SRP-9001 Post-Infusion



Source: Reviewer.

Note: PROCESS A-DL3: subjects in Study 101 and Study 102 who received placebo in Part 1 (102-P1-PLACEBO) and received SRP-9001 in Part 2 at the dose of 1.33×10^{14} vg/kg

For subjects aged 4 to 5 years of age who received 1.33×10^{14} vg/kg of SRP-9001, the mean (SD) SRP-9001 VGC levels (change from baseline) at Week 12 post-infusion were 3.18 (N=4, SD: 1.54) copies per nucleus in Study 2 Parts 1 and 2 (Process A Product) and 2.97 (N=11, SD: 2.15) copies per nucleus in Study 3 Cohort 1 (Process B Product).

6.2.2 Vector Shedding

As shown in Table 5, compared to the administered dose of SRP-9001 (1.33×10^{14} vg/ kg of body weight), the amount of shedded vector was very low. The level of SRP-9001 vector genome peaked the first couple of days (saliva, urine) or weeks (feces) post dosing. The median (min, max) time to achieve peak levels were 0.3 (0.2, 13.7) days, 0.3 (0.2, 72.0) days, and 13.1 (0.3, 27.8) days in saliva, urine and feces, respectively.

Table 5. Summary of SRP-9001 vector genome vector biodistribution and vector shedding (Study 103, Cohorts 1, 2, & 3)

		Time to First Detectable Sample (Days)	Peak Concentration (10^{13} copies/mL for saliva and urine, 10^{13} copies/ug total cDNA for feces)	Time to Peak Concentration (Days)	Time to Achieve Clearance (First BLOD Sample Followed by 2 Consecutive BLOD Samples) (Days)	Number (%) of Subjects Achieved Viral Shedding Clearance as of April 2022
Saliva	N	31 (97%)	31 (97%)	31 (97%)	29 (91%)	28 (88%)
	Mean (SD)	0.766 (2.41)	7.86e-06 (1.24e-05)	1.01 (2.73)	60.6 (32.8)	-
	Median	0.281	2.31e-06	0.281	49.8	-
	Min, Max	0.184, 13.7	2.52e-08, 4.78e-05	0.184, 13.7	27.8, 169	-
Urine	N	33 (100%)	33 (100%)	33 (100%)	29 (88%)	26 (79%)
	Mean (SD)	1.13 (3.33)	2.78e-07 (9.92e-07)	3.75 (13.3)	102 (76.3)	-
	Median	0.267	2.07e-08	0.271	78.2	-
	Min, Max	0.184, 14.1	1.12e-10, 4.7e-06	0.184, 72	26.9, 257	-
Feces	N	31 (100%)	31 (100%)	31 (100%)	10 (32%)	3 (10%)
	Mean (SD)	6.31 (7.37)	4.87e-06 (1.05e-05)	10 (6.68)	156 (49.3)	-
	Median	0.997	1.7e-07	13.1	162	-
	Min, Max	0.167, 27.8	4.88e-10, 3.95e-05	0.292, 27.8	76.1, 251	-

Time to achieve clearance = First below-limit of detection (BLOD) (saliva, urine, stool) sample followed by 2 consecutive BLOD samples.

N (%) = number of subjects for which the metric could be determined, percentages are relative to the total number of subjects with available data at the date of data-cut.

BLOD (saliva, urine, stool) values were considered as zero for the calculation of mean and standard deviation.

MEAN, SD, MEDIAN, MIN, MAX rounded to 3 significant digits. N and percentages rounded to whole numbers.

Source: Applicant's IR response.

SRP-9001 vector genome concentrations decreased rapidly. At Week 4, the concentrations of SRP-9001 vector genome DNA decreased greater than 99% compared to the peak concentration for saliva, urine, and feces (Table 6). The median time (min, max) to reach the level below the limit of detection (BLOD) was 49.8 (27.8, 169.0) days, 78.2 (26.9, 257.0) days, and 162.0 (76.1, 251.0) days in saliva, urine and feces, respectively (Table 5). For Study 103 Cohort 1, the median time to achieve complete elimination as the first BLOD sample followed by 2 consecutive BLOD samples were 49.8 days, 123 days and 162 days post-dose for saliva, urine and feces, respectively.

Table 6. Mean vector genome DNA at peak compared to week 4

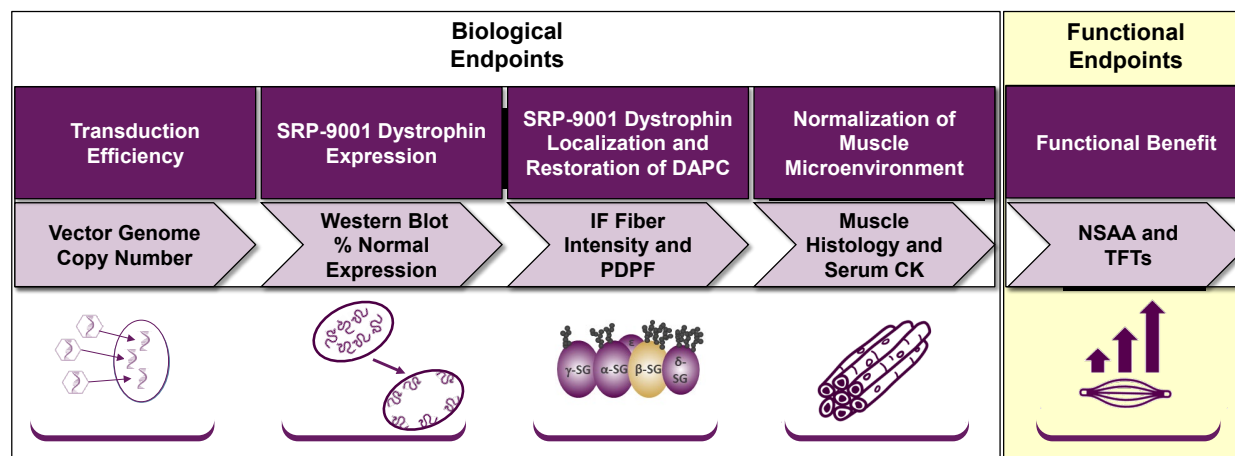
Sample	Mean Peak Concentration (vgc/ml)	Mean Week 4 concentration (vgc/ml)	Percentage Decrease from Peak to Week 4
Saliva	56,354,000.0 (Day 1)	14,440.8	99.97%
Urine	476,158.8 (Day 1)	1731.1	99.64%
Feces	133,000,000.0 (Week 1)	10,622.7	99.99%

Source: Applicant. Study 9001-103 Vector Shedding Report.

6.3 Pharmacodynamics Biomarker – Sarepta’s Micro-dystrophin (SRP-9001-Micro-Dystrophin) Expression in Muscle Biopsy Samples

As shown in Figure 3, after one-time intravenous infusion, SRP-9001 distributes to target tissues, transduces into muscle fibers, and expresses transgene, Sarepta’s micro-dystrophin. Expressed Sarepta’s micro-dystrophin is expected to be located on the sarcolemma membrane to restore dystrophin associated protein complex (DAPC), which helps to improve muscle function by stabilizing sarcolemma membrane, and normalizing muscle microenvironment. Sarepta’s micro-dystrophin protein expression in muscle biopsy samples (at baseline and Week 12 post-infusion) was evaluated as biological activity biomarker.

Figure 3. SRP-9001 biological cascade



Source: Applicant. Advisory committee briefing document.

Muscle biopsy samples were collected at baseline and Week 12 post-infusion. Sarepta’s micro-dystrophin protein expression from muscle biopsies (gastrocnemius or biceps femoris) was quantified by western blot and localized by immunofluorescence staining (immunofluorescence fiber intensity [IF fiber intensity], and IF percent Sarepta’s micro-dystrophin positive fiber (PMDPF) [%]).

6.3.1 Micro-dystrophin Expression in Muscle Tissue Biopsy Measured by Western Blot Assay

Sarepta's micro-dystrophin at 12 weeks post SRP-9001 infusion as measured by WB (adjusted by muscle content) and expressed as a percent of control (levels of wild-type dystrophin in normal subjects without DMD or Becker muscular dystrophy) in biopsied muscle tissue (gastrocnemius) was listed as one of the primary endpoints in Study 102 Part 1, and the primary endpoint in Study 103. It should be noted the difference between Sarepta's micro-dystrophin and dystrophin. Sarepta's micro-dystrophin is a novel shortened form of dystrophin (approximately one-third in size).

Results for Study 101 are not included because a different method was used to quantify Sarepta's micro-dystrophin and reliability of the method was uncertain. In addition, two subjects in Study 102 Part 1 had substantially high baseline values, which, according to the Applicant, may be due to baseline expression of a nonfunctional truncated form of dystrophin resulting from subjects' specific mutations. The two subjects' micro-dystrophin expression results were excluded from analysis.

Figure 4 shows mean Sarepta's micro-dystrophin expression from SRP-9001 at 12 weeks post-infusion (WB assay) for Study 102 and Study 103. High inter-subject variability was observed in Sarepta's micro-dystrophin expression results.

As described earlier, subjects in Study 102 Part 1 received three different dose levels of SRP-9001: half of intended dose (6.29×10^{13} vg/kg, SRP-9001-DL1), two-thirds of intended dose (8.94×10^{13} vg/kg, SRP-9001-DL2), and intended dose (1.33×10^{14} vg/kg, SRP-9001-DL3). The level of Sarepta's micro-dystrophin at 12 weeks post-infusion increased with increasing dose of SRP-9001. At Week 12 of Study 102 Part 1, the mean (SD) change from baseline levels of Sarepta's micro-dystrophin (% of control) were 3.6 (5.7), 28.2 (52.2), and 43.4 (48.6) for subjects receiving SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. At Week 12 of Study 102 Part 2, the mean (SD) change from baseline levels of Sarepta's micro-dystrophin (% of control) were 10.6 (17.0), 10.4 (14.7), and 43.5 (55.6) for subjects receiving SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively (Table 7). In Study 101 Part 2, subjects who were in the Part 1 Placebo group received SRP-9001 at the intended dose. At 12 weeks post-dosing of SRP-9001 in Part 2, the mean (SD) level of Sarepta's micro-dystrophin (% of control) was 40.8 (32.5) (Figure 4A).

Among the 20 ambulatory subjects with DMD who were 4-7 years old and received the intended dose of SRP-9001 (Process B) in Study 103 Cohort 1, the mean (SD) level of Sarepta's micro-dystrophin was 54.2 (42.6) at Week 12 (Figure 4B).

Table 7. Summary of Sarepta’s Micro-dystrophin Expression (Change from Baseline by Western Blot Assay) in Muscle Tissue Biopsy Post-infusion

Sarepta’s Micro-dystrophin Expression (% of Control)	102-P1-PLACEBO (n=21)	102-P1-SRP-DL1 (n=6)	102-P1-SRP-DL2 (n=6)	102-P1-SRP-DL3 (n=6)	102-POOLED-SRP-DL3^a (n=27)	103-COH1 (n=20)
Part 1 (Study 102) (First year post-dosing for Study 103)						
Mean (SD)	0.1 (1.7)	3.6 (5.7)	28.2 (52.2)	43.4 (48.6)	—	54.2 (42.6)
Median (Q1, Q3)	0.0 (0.0, 1.2)	0.0 (0.0, 6.2)	5.8 (3.7, 17.1)	24.3 (6.0, 76.6)	—	50.6 (21.8, 67.5)
Min, Max	-4.8, 3.7	0.0, 13.1	0.0, 133.8	1.6, 116.3	—	4.8, 153.9
Part 2 (Study 102)						
Mean (SD)	40.8 (32.5)	10.6 (17.0)	10.4 (14.7)	43.5 (55.6)	41.4 (35.6)	—
Median (Q1, Q3)	40.8 (11.8, 66.7)	0.0 (0.0, 14.0)	1.0 (0.0, 18.1)	22.0 (10.7, 51.1)	39.7 (8.8, 67.5)	—
Min, Max	0.00, 92.0	0.0, 38.9	0.0, 32.7	0.0, 149.0	0.0, 116.3	—

Source: FDA clinical pharmacology reviewer’s analysis.

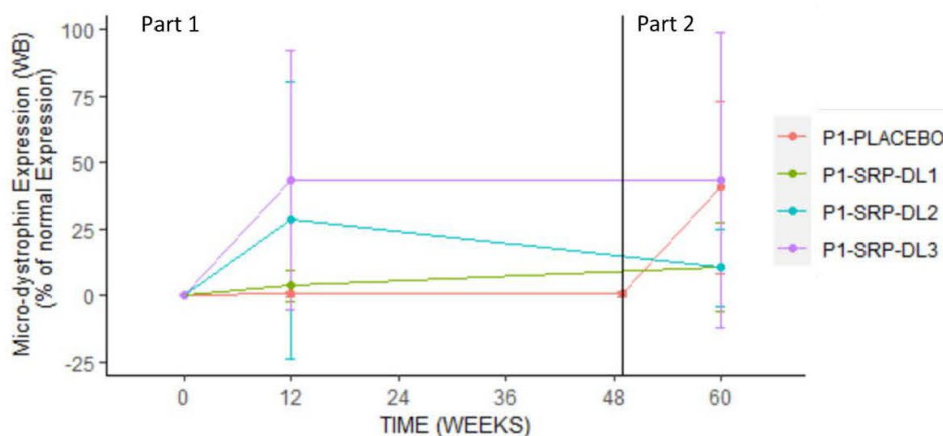
Note: Sarepta’s micro-dystrophin is a novel shorten form of dystrophin. Sarepta’s micro-dystrophin expression was described as a percentage of expression of dystrophin levels in normal subjects. The expression of dystrophin levels in normal subjects without DMD or BMD serves as control for Sarepta’s micro-dystrophin levels measured by western blot assay.

a. 102-POOLED-SRP-DL3: Pooled Sarepta’s micro-dystrophin expression (change from baseline) after 12 weeks post-infusion at dose level 3 (1.33×10^{14} vg/kg) data of SRP-DL3 group in Part 1 and SRP-PLACEBO group in Part 2 (received SRP-9001 in Part 2).

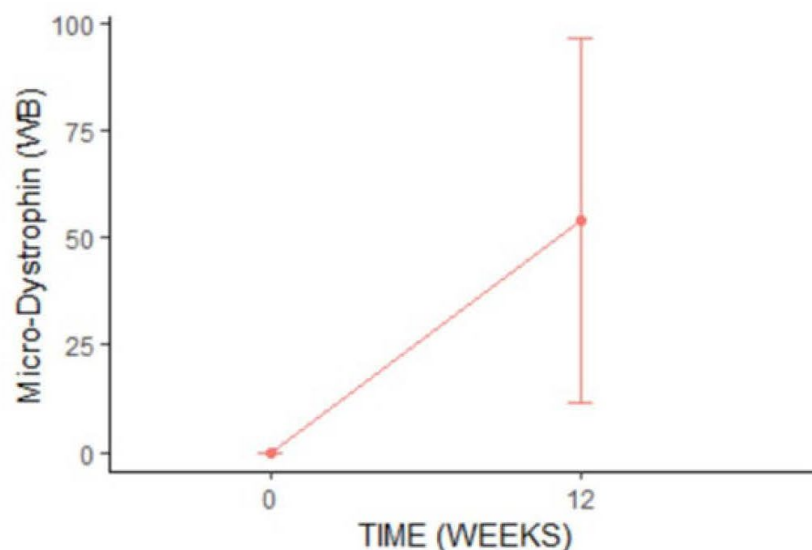
Abbreviations: SD, standard deviation; WB, western blot.

Figure 4. Sarepta's Micro-dystrophin Expression (Western Blot Assay) Over Time

A. Study SRP-9001-102



B. Study SRP-9001-103



Source: FDA

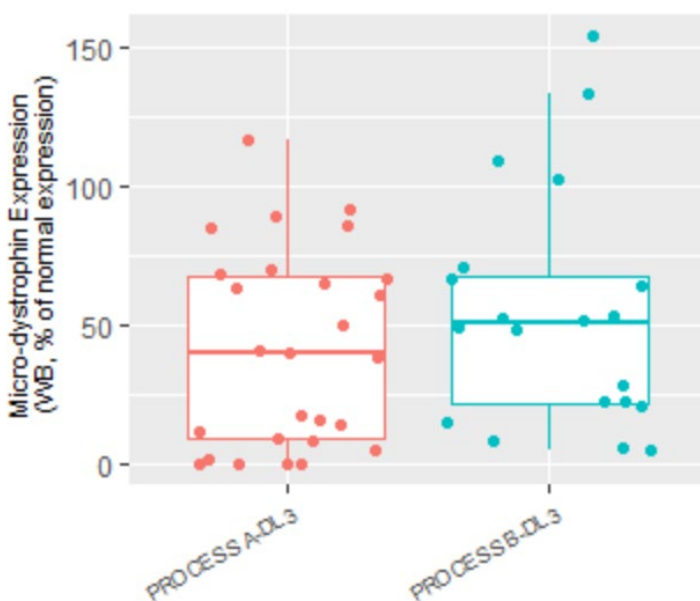
Note: SRP-9001 was administered at three different dose levels: 6.29×10^{13} vg/kg (SRP-9001-DL1), 8.94×10^{13} vg/kg (SRP-9001-DL2), and 1.33×10^{14} vg/kg (SRP-9001-DL3).

Abbreviation: SD, standard deviation; WB, western blot.

As shown in Figure 5, the quantity of SRP-9001 transgene expression (Sarepta's micro-dystrophin measured by WB assay) from manufacturing Process B was slightly higher than SRP-9001 from manufacturing Process A. The mean (SD) and median (min, max) of Sarepta's micro-dystrophin levels (% of control) in muscle tissue biopsy samples from SRP-9001 Process A (n=27) product were 41.3 (35.4) and 39.7 (0.0, 116.3), respectively. The mean (SD) and median (min, max) of Sarepta's micro-dystrophin levels (% of control) in muscle tissue biopsy samples from SRP-9001 Process B (n=20) product were 54.2 (42.6) and 50.6 (4.8, 153.9), respectively.

For subjects aged 4 to 5 years of age who received 1.33×10^{14} vg/kg of SRP-9001, the mean (SD) Sarepta's micro-dystrophin expression levels (change from baseline) at Week 12 post-infusion were 95.7% (N=3, SD: 17.9%) in Study 2 Parts 1 and 2 (Process A Product) and 51.7% (N=11, SD: 41.0%) in Study 3 Cohort 1 (Process B Product).

Figure 5. Boxplot of Sarepta's Micro-dystrophin Expression (Western Blot) in Muscle Tissue Biopsy of Process A SRP-9001 and Process B SRP-9001 Post-Infusion



Source: FDA

Note: PROCESS A-DL3: subjects in Study 102 who received placebo in Part 1 (102-P1-PLACEBO) and received SRP-9001 in Part 2 at the dose of 1.33×10^{14} vg/kg.

Abbreviation: WB, Western blot.

6.3.2 Micro-dystrophin Expression in Muscle Tissue Biopsy Measured by Immunohistochemistry Assay (IF Fiber Intensity and PMDPF)

Localization of Sarepta's micro-dystrophin measured by immunohistochemistry assay (IF Fiber Intensity (% of control), and percent Sarepta's micro-dystrophin positive fiber (PMDPF, %)) is one of the secondary endpoints in Study 101 and Study 103, and one of the exploratory endpoints in Study 102 (Part 1 and 2).

As discussed earlier, two subjects in Study 102 Part 1 targeted dose level (1.33×10^{14} vg/kg) showed high baseline levels of micro-dystrophin protein, the two subjects were excluded from analysis of immunohistochemistry results.

In Study 101, at Week 12 post-dosing, Sarepta's micro-dystrophin was detected in all 4 subjects with immunohistochemistry assays. The mean (SD) change from baseline of IF Fiber Intensity (% of control) and PMDPF (%) were 93.6 (43.9) and 81.2 (10.2), respectively.

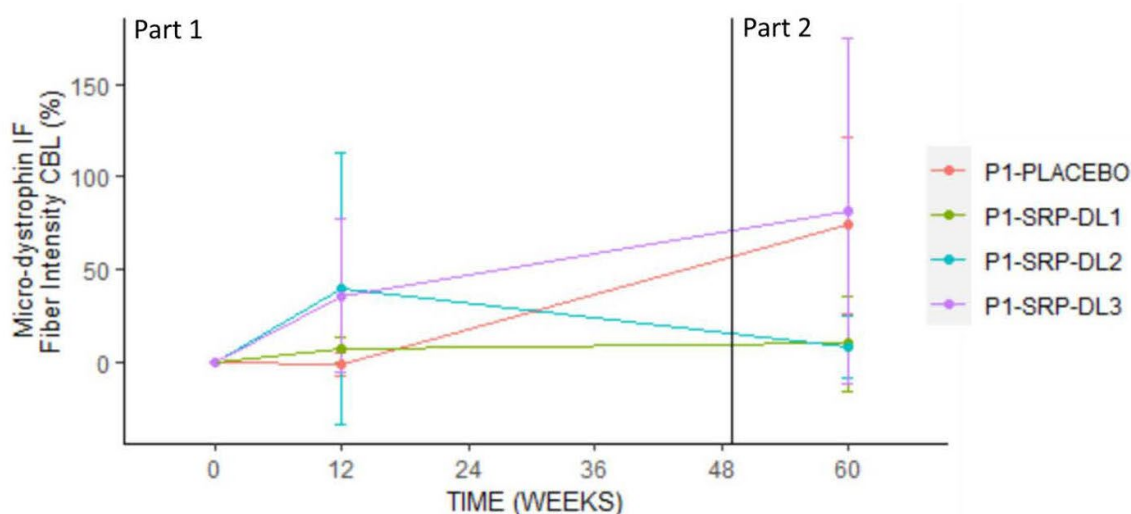
In Study 102 Part 1, both IF Fiber Intensity (% of control) and PMDPF (%) increased with increasing dose of SRP-9001. At Week 12, the mean change from baseline of IF Fiber Intensity (% of control) were 7.3 (SD: 7.0), 40.1 (SD: 73.3), and 36.2 (SD: 41.3) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3 dose levels, respectively. The mean (SD) increases of PMDPF (%) from baseline were 15.6 (14.8), 30.3 (32.9), and 26.7 (26.0) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3 dose levels, respectively (Figure 6).

Reviewer Comment:

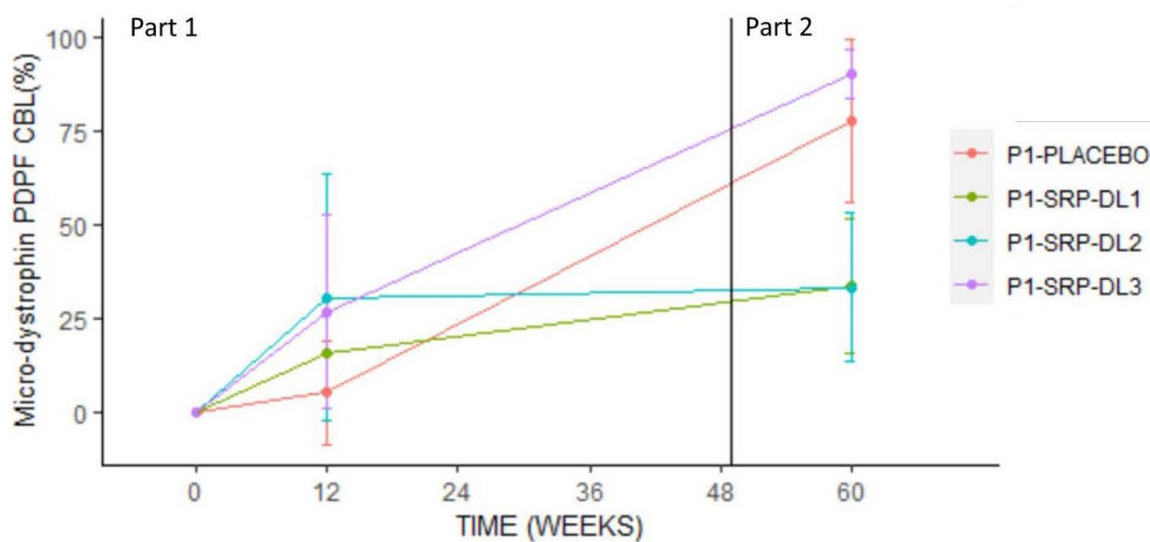
IF staining assay localizes the expressed protein at the sarcolemma membrane. IF staining provides information of IF fiber intensity and the percentage of Sarepta's micro-dystrophin positive fibers within the muscle biopsy samples. The percentage of Sarepta's micro-dystrophin positive fibers information obtained from IF staining assay does not clearly inform the quantity of expressed Sarepta's micro-dystrophin protein. The level of expressed micro-dystrophin among muscle fibers of a subject can vary substantially and may have different functional impact on each of those muscle fibers. Therefore, measurement of the percentage of positive Sarepta's micro-dystrophin fibers by IF is not considered as fully quantitative.

Figure 6. Sarepta's Micro-dystrophin Expression (Immunofluorescence) Over Time (Study SRP-9001-102)

A. IF Fiber Intensity (% Control)



B. PDPF (%)



Source: Reviewer.

Note: SRP-9001 were dosed at three different dose levels: 6.29×10^{13} vg/kg (SRP-9001-DL1), 8.94×10^{13} vg/kg (SRP-9001-DL2), and 1.33×10^{14} vg/kg (SRP-9001-DL3).

Abbreviation: CBL, change from baseline; IF, immunofluorescence; PMDPF, percent Sarepta's micro-dystrophin positive fiber.

Both IF Fiber Intensity (% of control) and PMDPF (%) continued to increase for all three dose levels except dose level 2 (SRP-9001-DL2: 8.94×10^{13} vg/kg). At Week 12 in Study 102 Part 2, the mean (SD) levels of IF Fiber Intensity (% of control), adjusted from baseline, were 10.2 (25.2), 8.6 (17.1), and 81.9 (93.0) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3 dose levels, respectively. The mean increase of PMDPF (%) were 33.6 (17.9), 33.1 (19.9), and 89.9 (6.5) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3 dose levels, respectively. Subjects in Part 1 Placebo group received SRP-9001 (1.33×10^{14} vg/kg). At 12 weeks post-dosing (Study 102 Part 2 Week 12), the mean (SD) change of Sarepta's micro-dystrophin were 74.1 (47.7) and 77.6 (21.9) for IF fiber intensity (% of control) and PMDPF (%), respectively.

The mean (SD) change of Sarepta's micro-dystrophin at Week 12 in Study 103 Cohort 1 were 66.5(64.1) and 48.3 (25.4) for IF fiber intensity (% of control) and PMDPF (%), respectively.

High inter-subject variability was observed for the IF fiber intensity (% of control) and PMDPF (%) results.

6.4 Correlation Analysis of Biomarkers and Clinical Outcome Endpoint(s)

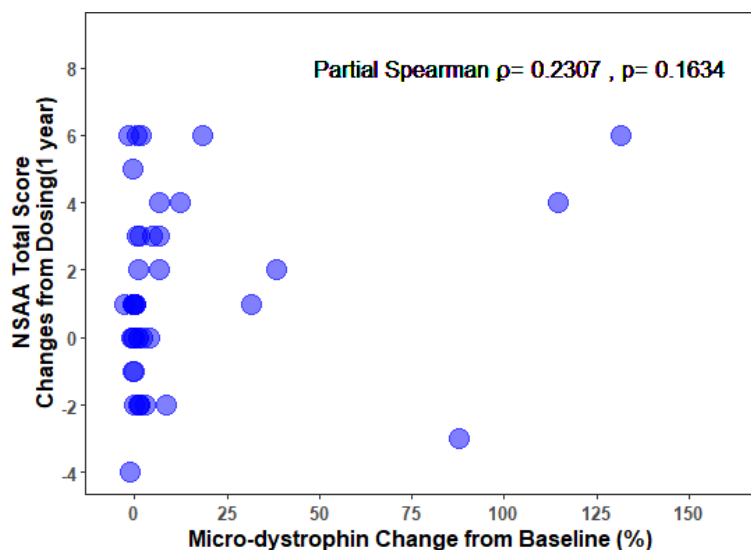
6.4.1 Pharmacodynamic Biomarker and Clinical Efficacy Outcome Endpoint

In this application, the Applicant proposed to use the transgene expression of SRP-9001, Sarepta's micro-dystrophin as the surrogate endpoint to support its accelerated approval approach. Correlation analysis was conducted to explore the relationship between Sarepta's micro-dystrophin protein expression and clinical function endpoint, North Star Ambulatory Assessment (NSAA) total score change.

Sarepta's Micro-dystrophin Protein Expression and NSAA Total Score Change in Study 102 Part 1

Correlation analysis was performed to evaluate the relationship between Sarepta's micro-dystrophin expression at Week 12 and NSAA total score change at YEAR 1 (which was evaluated at Week 48) using Study 102 Part 1 data. Figure 7 shows partial spearman analysis adjusted for baseline age and NSAA total score. There was a wide range of NSAA total score change. The range of NSAA total score change in SRP-9001 treated patients was similar to the placebo group. Based on the limited data available for the evaluation, there is no clear association b/w Sarepta's micro-dystrophin expression and NSAA total score change.

Figure 7. Relationship between Week 12 Sarepta's Micro-dystrophin Changes from Baseline and NSAA Total Score at Year 1 (Week 48) Using SRP-9001-102 Part-1 Data Only



Partial spearman correlation coefficient is adjusted for baseline NSAA score and age at dosing;

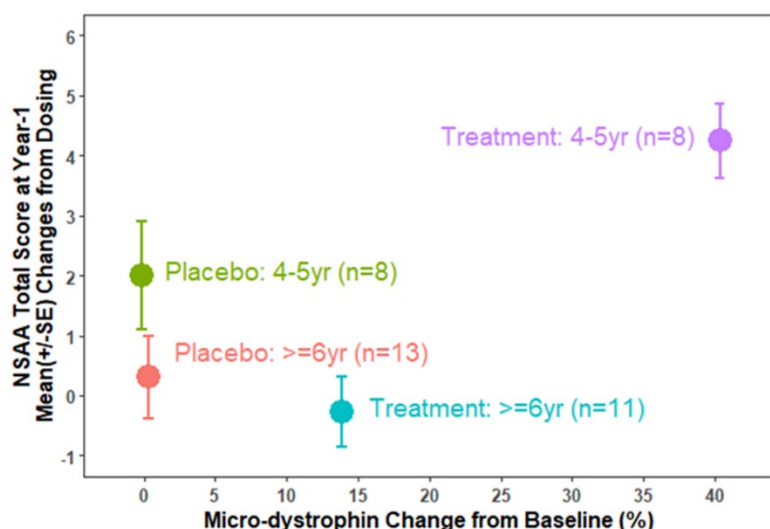
Source: Pharmacometric Consult Review.

Additional analysis was conducted to evaluate the relationship between Sarepta's micro-dystrophin expression and NSAA total score change (Δ NSAA total score) at age group level.

Figure 8 shows the group-level relationship between Sarepta’s micro-dystrophin at Week-12 and Δ NSAA total score at Year-1 with spearman analysis. In general, at age group level, there is no clear association between micro-dystrophin expression and NSAA total score change based on the limited data.

In the 4-5 years of age subjects receiving SRP-9001 treatment, we observed improved NSAA total score with increased micro-dystrophin expression. However, because of the very limited data from small number of subjects in this age group, these results need to be interpreted with caution.

Figure 8. Relationship between Week 12 Sarepta’s Micro-dystrophin Changes from Baseline and NSAA Total Score at Year 1 by Age Group Using SRP-9001-102 Part-1 Data Only



Source: FDA Pharmacometric Consult Review.

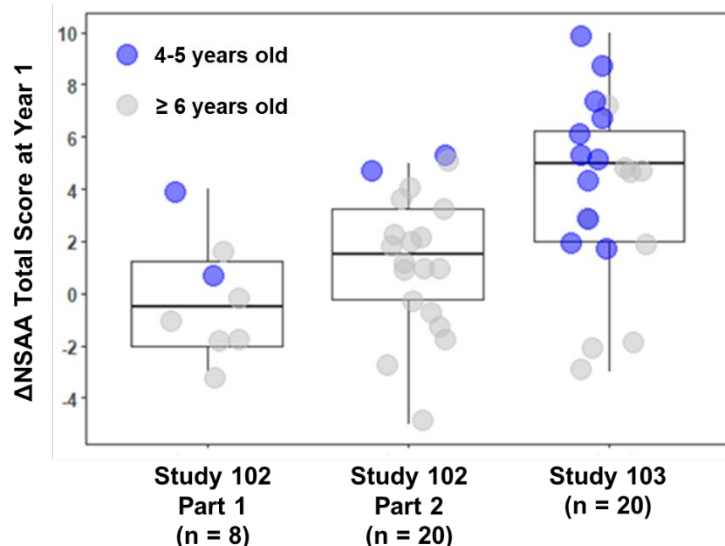
Sarepta’s Micro-dystrophin Protein Expression and NSAA Total Score Change in Study 102 and 103 (Pooled Data Analysis)

Correlation analysis was performed to evaluate the relationship between Sarepta’s micro-dystrophin expression at Week 12 and NSAA total score change at YEAR 1 (Week 48 for Study 102) using pooled datasets from Study 102 (Part1 & Part 2) and Study 103 Cohort 1.

There are two major concerns for the approach of exploring correlation using pooled dataset. The first concern is that the open-label Design will likely affect Δ NSAA total scores. The SRP-9001 clinical program has used different study designs: Study 102 Part 1 was a randomized, double-blind, placebo-controlled study, while Study 102 Part 2 and Study 103 were open-label studies. NSAA is an effort-and process-dependent clinical endpoint. Blinding is critical for NSAA

assessment. Figure 9 shows the comparison of the NSAA total score change at Year-1 between different study designs. Compared to the NSAA total score change in Study 102 Part 1, which was a double-blind, placebo-controlled study, the NSAA total scores in open-label studies (Study 102 Part 2 and Study 103) were higher. Therefore, this open-label design may confound the association between Sarepta’s micro-dystrophin Expression and NSAA total score change.

Figure 9. Comparison

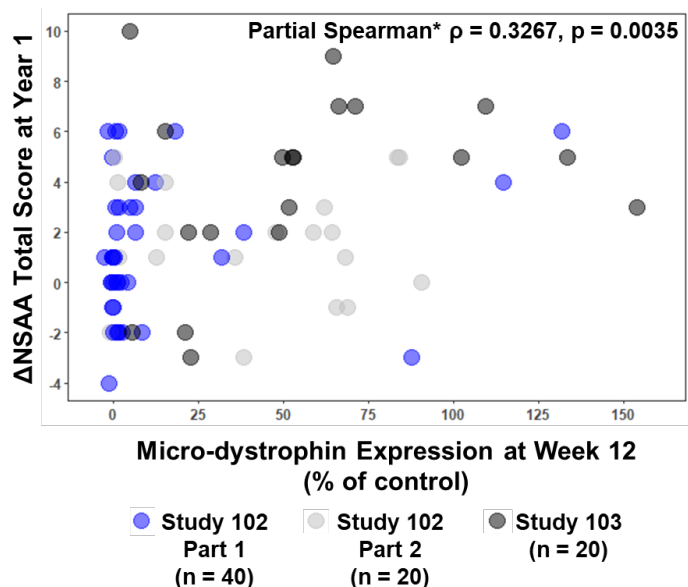


Source: Pharmacometric Consult Review.

The second concern is that open-label design without concurrent control may confound association between Sarepta’s micro-dystrophin and NSAA total score change. Study 102 Part 2 and Study 103 do not have concurrent control. It is unclear whether the improvement in NSAA total score was due to SRP-9001, the open-label design, baseline characteristics, or some combination. It is very challenging to interpret the correlation analysis results from pooled data.

Figure 10 shows the correlation between Sarepta’s micro-dystrophin at Week 12 and NSAA total score change at YEAR 1. The analysis indicated that Sarepta’s micro-dystrophin accounts for 11% of variation in ΔNSAA Total Score after adjustment for baseline age and NSAA Total Score: R^2 , the square of rho is 0.11. The correlation using pooled datasets, which includes open-label data, was not sufficiently persuasive to consider expression of Sarepta’s micro-dystrophin “reasonably likely to predict clinical benefit.”

Figure 10. Relationship between Week 12 Sarepta’s Micro-dystrophin Changes from Baseline and NSAA Total Score at Year 1 (Week 48) Using Pooled Data from Study 102 and 103



Source: FDA Pharmacometric Consult Review.

6.4.2 Sarepta’s Micro-dystrophin Expression and NSAA Total Score Change in Study 102 (2-year follow-up)

In Study 102, subjects who received SRP-9001 in Part 1 had completed clinical functional tests at Week 48 in Part 2. The expression of Sarepta’s micro-dystrophin (WB) was assessed at Week 12 in Part 1 as well as Week 12 in Part 2. NSAA total score change was assessed at Week 48 in Part 1 and Week 48 in Part 2. Expression of Sarepta’s micro-dystrophin and NSAA total score change were compared between two different age groups: 4 to 5 years old and 6 to 7 years old. As shown in Table 8, the baseline NSAA total score of the two age groups were similar. There was no statistically significant difference in the expression of Sarepta’s micro-dystrophin between the two age groups for both Part 1 and Part 2. At Part 2 Week 48, the NSAA total score improved by 5.29 (mean) from baseline for the 4-5 years age group; while the NSAA total score worsened by 3.7 (mean) from baseline for the 6-7 years age group.

Table 8. Comparison of Sarepta’s Micro-dystrophin Expression and NSAA Total Score Change between Different Age Groups (Study 102 Part 1 and 2)

Age Groups (years)	NSAA Total Score Part 1 Baseline	Micro-dystrophin Part 1 Week 12 (% of Control) (WB)	NSAA Total Score Change at Part 1 Week 48	NSAA Total Score Part 2 Baseline	Micro-dystrophin Part 2 Week 12 (% of Control) (WB)	NSAA Total Score Change from Part 1 Baseline to Part 2 Week 48	NSAA Total Score Change from Part 2 Baseline to Part 2 Week 48
4-5 years (N)	7	7	7	7	7	7	7
Mean (SD)	20.0 (2.0)	42.2 (57.2)	4.7 (1.3)	24.9 (3.3)	19.3 (15.4)	5.3 (3.0)	0.4 (2.4)
Median (Q1, Q3)	20.0 (19.0, 21.0)	13.1 (5.9, 68.3)	4.0 (4.0, 6.0)	24.0 (23.0, 27.5)	18.1 (7.5, 31.6)	7.0 (3.0, 7.0)	0.0 (-0.5, 1.0)
Min, Max	17.0, 23.0	0.0, 133.8	3.0, 6.0	20.0, 29.0	0.0, 38.9	1.0, 9.0	-3.0, 5.0
6-7 years (N) ^a	11	11	10	10	9	10	9
Mean (SD)	19.1 (3.9)	14.2 (27.3)	-0.2 (2.0)	18.7 (5.54)	25.6 (49.9)	-3.7(6.5)	-4.3 (5.1)
Median (Q1, Q3)	20.0 (17.0, 20.5)	3.9 (0.0, 8.3)	0.0 (-2.0, 1.5)	18.0 (16.0, 21.8)	0.0 (0.0, 13.5)	-4.0 (-7.0, 1.8)	-4.0 (-4.0, 0.0)
Min, Max	13.0, 26.0	0.0, 88.9	-3.0, 3.0	10.0, 29.0	0.0, 149.0	-17.0, 4.0	-15.0, 1.0

Source: FDA Clinical Pharmacology Reviewer’s analysis

a. Two subjects at the dose levels 3 (1.33×10^{14} vg/kg) were excluded from analysis.

Note: Sarepta’s micro-dystrophin measured by western blot assay is expressed as % of Control. The control refers to the dystrophin levels expressed in normal subjects without DMD or BMD.

Abbreviations: NSAA, North Star Ambulatory Assessment; SD, standard deviation.

6.4.3 Exposure-response Analysis of SRP-9001 Clinical Safety Biomarkers

The Applicant also explored the relationship between SRP-9001 drug exposure and serum-based clinical safety biomarkers that are representative of the presence and/or severity of an adverse event in the liver, heart, and immune-related response. The serum-based clinical safety biomarkers of interest include biomarkers of liver injury (Glutamate Dehydrogenase [GLDH] and Gamma Glutamyl Transferase [GGT]), cardiac tissue injury (troponin [TPN]), and immune complement system (complement components C3, C4, CH50) and platelet counts. The Applicant’s analyses suggested that increasing SRP-9001 drug exposure following the weight-based dosing paradigm (vg/kg) does not affect the levels of serum-based clinical safety biomarkers. Please refer to Clinical Review for safety aspect of SRP-9001.

6.5 Immunogenicity

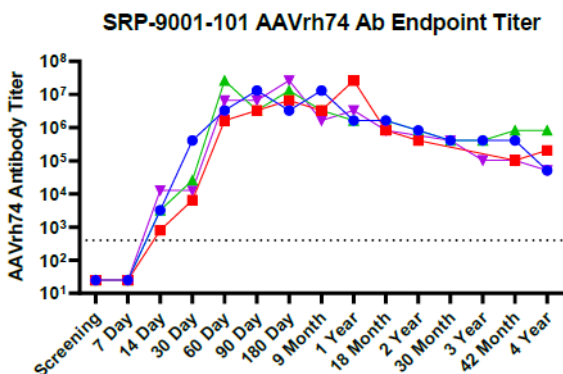
Immunogenicity assessment of SRP-9001 included humoral and cellular immunogenicity against 1) vector AAVrh74 capsid and 2) transgene product, SRP-9001-micro-dystrophin.

6.5.1 Anti-AAVrh74 Antibodies

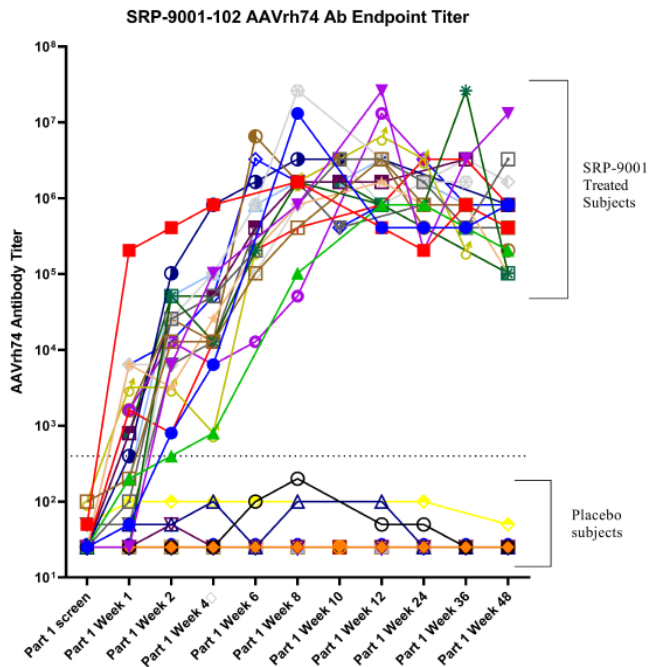
As shown in Figure 11, all subjects had anti-AAVrh74 antibodies $\leq 1:400$ based on an investigational assay at screening in all three clinical studies. Following administration of SRP-9001, elevated anti-AAVrh74 antibody titers were observed in all subjects. The levels of anti-AAVrh74 antibodies exceeded threshold (1:400) by Week 2 post dosing in majority subjects. Anti-AAVrh74 antibody titers continued to increase over time, reaching the peak levels within Week 8 to 24, and remained positive during the observation period in all three studies (up to Year 4, YEAR 2 (part 2 Week 48), and 52 weeks for Study 101, 102 and 103, respectively). Anti-AAVrh74 total binding antibody titers reached at least 1:409,600 in every subject, and the maximum titers exceeded 1:26,214,400 in certain subjects.

Figure 11. Anti-AAVrh74 Antibody Responses Over Time after Administration of SRP-9001

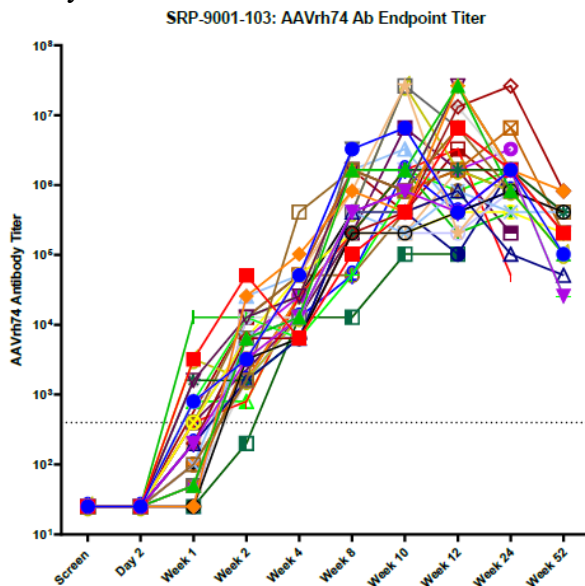
a. Study 101



b. Study 102



c. Study 103



Source: Applicant. Module 5, section 5.3.5.3. Integrated Summary of Immunogenicity.

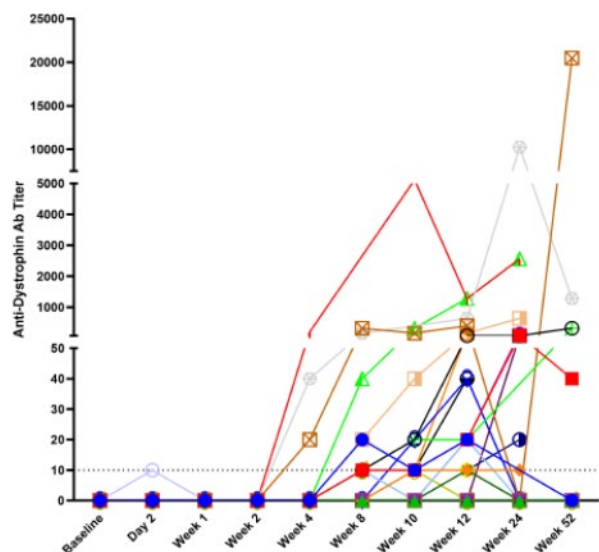
There was no dose-dependent relationship between SRP-9001 dose and anti-AAVrh74 antibody response established.

There was no evident impact of anti-AAVrh74 antibodies on muscle transduction or Sarepta's micro-dystrophin protein expression (western blot assay) observed.

6.5.2 Anti-Micro-dystrophin Antibodies

Anti-micro-dystrophin antibodies were assessed in Study 103. All enrolled subjects were below assay threshold for positivity (< 10) for anti-micro-dystrophin antibodies prior to treatment of SRP-9001. As shown in Figure 12, twenty-one of the 39 subjects developed elevated (positive) anti-micro-dystrophin antibodies throughout the 52 weeks post-dosing. No consistent pattern of anti-micro-dystrophin antibody development was observed.

Figure 12. Anti-Micro-dystrophin Antibodies Responses (Study 103)



Note: Each line represents an individual subject.

Figure Legend: Dotted line represents 1:10 cutoff. Antibodies $\geq 1:10$ marks the threshold for assay positivity.

Source: Applicant. Module 5, section 5.3.5.3. Integrated Summary of Immunogenicity.

No association was observed between levels of anti-micro-dystrophin antibodies at Week 4 and Sarepta's micro-dystrophin protein expression in muscle biopsies at Week 12.

6.5.3 T-Cell Mediated Cellular Immune Responses against AAVrh74

Cellular immune responses were inconsistently observed across all subjects treated with SRP-9001. In Study 101, all 4 subjects displayed a positive IFN γ cytokine release (threshold of ≥ 50 spot forming units [SFU] per million) in at least 1 of the AAVrh74 antigen pools after administration of SRP-9001. At Week 4 post-dosing of SRP-9001, 4 out of 41 subjects (9.8%) and 23 out of 39 (59.0%) subjects displayed a positive cellular immune response against AAVrh74 for Study 102 and 103, respectively.

There was no evident impact of T-cell mediated cellular response against AAVrh74 capsids on Sarepta's micro-dystrophin protein expression in muscle biopsy samples (Week 12) observed.

6.5.4 T-Cell Mediated Cellular Immune Responses against Sarepta's Micro-dystrophin

A total of 8 subjects (1 subject in Study 102 and 7 subjects in Study 103) had an elevated cellular immune response greater than threshold at 4 Weeks post administration of SRP-9001.

There was no evident impact of T-cell mediated cellular response against micro-dystrophin on Sarepta's micro-dystrophin protein expression in muscle biopsy samples (Week 12) observed.

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study SRP-9001-101 (Study 101)

Data cutoff: June 15, 2021

Title: Systemic Gene Delivery Phase I/IIa Clinical Trial for Duchenne Muscular Dystrophy using rAAVrh74.MHCK.micro-dystrophin (microDys-IV-001)
Objectives: Primary: To evaluate the safety of SRP-9001. Secondary: To evaluate micro- dystrophin expression from SRP-9001 at 90 days post dosing as quantified by Western blot and immunofluorescence (IF) assays. To evaluate the effect of SRP-9001 on physical functional assessment over 5 years
Methodology: Study SRP-9001-101 is an ongoing Phase I/IIa, open-label, non-randomized, single-dose study sponsored and conducted by Sarepta where subjects with Duchenne Muscular Dystrophy (DMD) received a gene transfer of rAAV carrying micro-dystrophin. The primary objective of this study is to evaluate the safety of IV administration of rAAVrh74.MHCK7 micro-dystrophin.
Number of Subjects: Enrolled: 4 Completed: 4
Diagnosis and Criteria for Inclusion: Subjects with DMD were enrolled in Study SRP-9001-101. Key inclusion criteria for Cohort B subjects included: 1. Age of enrollment: between 4 to 7 years of age, inclusive, 2. Molecular characterization of the DMD gene with frameshift (deletion or duplication), or premature stop codon mutation between exons 18 to 58 3. Indication of symptomatic muscular dystrophy: CK elevation > 1000 u/L and below average on the 100 m defined as $\leq 80\%$ predicted 4. Stable dose equivalent of oral corticosteroids for at least 12 weeks prior to screening and the dose is expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the first year of the study.
Study Treatments Investigational medicinal product(s): All subjects in this study received IV infusions of rAAV carrying micro-dystrophin vector (2×10^{14} vg/kg measured by supercoiled standard, in 10 mL/kg, which is equivalent to 1.33×10^{14} vg/kg as measured with linear standard) from batch number G02A0317.
Pharmacokinetic and Pharmacodynamic Sampling Times Muscle biopsy samples were collected at baseline and Day 90 post-dosing to evaluate levels of SRP-9001 vector genome copy and Sarepta's micro-dystrophin protein expression.
Clinical Pharmacology Results: The change from Baseline in micro-dystrophin level (% control) by Western blot at the Day 90 visit were 38.76, 13.50, 47.18, and 182.63 in each of the 4 subjects. For all 4 subjects, no micro-dystrophin levels were detected by Western blot at Baseline and at the Day 90 visit, the mean \pm SD change from Baseline was 70.52 ± 76.10 (median change from Baseline was 42.97). The change from Baseline in micro-dystrophin expression as measured by IF fiber intensity (percent fluorescent expression) at the Day 90 visit were 79.84, 58.77, 77.96, and 157.82 in each of the 4 subjects. For all 4 subjects, the mean \pm SD expression at Baseline was 2.31 ± 2.19 and at the Day 90 visit, the mean \pm SD change from Baseline was 93.59 ± 43.86 (median change from Baseline was 78.90). The change from Baseline in micro-dystrophin expression by IF PDPF at the Day 90 visit were 78.03, 73.45, 77.07, and 96.19 in each of the 4 subjects. For all 4 subjects, no micro-dystrophin levels were detected by PDPF at Baseline and at the Day 90 visit, the mean \pm SD change from Baseline was 81.18 ± 10.19 (median

change from Baseline was 77.55).

Conclusions:

- The (b) (4) and ddPCR results show efficient transduction of the viral genome (i.e., the micro-dystrophin transgene) into the skeletal muscle cells.
- Improvements were observed in the 3 years following gene transfer for the 4 subjects for the following efficacy endpoints, as demonstrated by the change from Baseline: time to walk 100-meters, the NSAA total score, percent predicted time to walk 100 meters, the time to ascend 4 steps, the time to rise from the floor, and the time to run 10 meters.
- The delivery of transgene to the nuclei and the robust expression and proper localization of micro-dystrophin coincided with reductions in CK levels.
- Together with the benefit prospect of SRP-9001, the safety findings in terms of vomiting, transient platelet count decrease, and manageable acute liver injury from the 4 participants of this study are considered to be in line with an acceptable safety profile.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.2 Study SRP-9001-102 (Study 102)

Data cutoff: December 14, 2021:

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial for Duchenne Muscular Dystrophy Using SRP-9001

Objectives:

Safety: To evaluate the safety of SRP-9001 (Part 1 & 2)

Primary:

- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks post dosing (Part 1) as measured by western blot of biopsied muscle tissue (Part 1)
- To evaluate the effect of SRP-9001 on physical functional assessments as assessed by the North Star Ambulatory Assessment (NSAA) over 48 weeks (Part 1)

Secondary:

- To evaluate the effect of SRP-9001 on physical functional assessments over 48 weeks (Part 1)
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 1) as measured by immunofluorescence (IF) fiber intensity of biopsied muscle tissue (Part 1)
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 1) as measured by IF percent dystrophin positive fibers (PDPF) of biopsied muscle tissue (Part 1)

Exploratory

- To assess rAAVrh74 genome exposure levels in target skeletal muscle tissues (Part 1 & 2)
- To evaluate the effect of SRP-9001 on creatine kinase (CK) levels over 48 weeks (Part 1 & 2)
- To evaluate the effect of SRP-9001 on physical functioning and mobility over 48 weeks (Part 1 & 2)
- To evaluate effect of SRP-9001 on social functioning over 48 weeks (Part 1)
- To evaluate the effect of SRP-9001 on overall wellbeing of the parent/caregiver over 48 weeks (Part 1)
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 2) as measured by Western blot of biopsied muscle tissue (Part 2)
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 2) as measured by IF fiber intensity of biopsied muscle tissue (Part 2)
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 2) as measured by IF PDPF of biopsied muscle tissue (Part 2)
- To evaluate cardiac structure and function over time as part of a cardiac magnetic resonance imaging (MRI) sub-study (Part 2)
- To evaluate the structure and physiology of skeletal muscles, as well as lean body mass, over time as part of a skeletal muscle MRI imaging sub-study.

Methodology:

This is an ongoing, randomized, double-blind, placebo-controlled, 3-part clinical study of systemic gene delivery of SRP-9001. This study planned to randomize up to 44 Duchenne muscular dystrophy (DMD) subjects (22 subjects per treatment group) 4 to 7 years of age (inclusive) who either had a confirmed frameshift (deletion or duplication) between exons 18 to 58, or premature stop codon mutation between exons 18 to 58. Subjects were randomized in a 1:1 ratio to SRP-9001 or placebo by the interactive voice/web response system. The Sponsor chose to stratify randomization by age group at Baseline (4 to 5 vs. 6 to 7 years) since age is an important prognostic factor in the progression of DMD. All subjects will have the opportunity to receive intravenous (IV) SRP-9001 (1.33×10^{14} vg/kg as measured by the Sponsor's qPCR method using a linear standard) in this study. Subjects randomized to SRP-9001 in Part 1 of the study will receive placebo in Part 2. Subjects randomized to placebo in Part 1 of the study will crossover to receive SRP-9001 in Part 2. Subjects randomized to placebo in Part 1 of the study will crossover to receive SRP-9001 in Part 2. Part 3 of the study will be an open-label follow-up period.

Part 1:

Part 1 was a 48-week randomized, double-blind, placebo-controlled period. Subjects may have been admitted to the hospital the day before the study drug was infused at the discretion of the Investigator.

On Day -1, the subject received a physical examination, had vital signs collected, and provided blood and urine samples.

The day prior to the study drug infusion (SRP-9001 or placebo), subject's background dose of steroid for DMD was increased to at least 1 mg/kg of a glucocorticoid (prednisone equivalent) daily and continued at this level for at least 60 days after the infusion unless earlier tapering was judged by the Investigator to be in the best interest of the subject.

SRP-9001 or placebo was administered IV on Day 1 over 1 to 2 hours. Vital signs were monitored during and after the infusion. On the day after the infusion (Day 2), subjects received a physical examination, had vital signs collected, and provided blood and urine samples before being discharged or in-clinic, as applicable.

Subjects were followed for 48 weeks in Part 1. All subjects had a muscle biopsy performed pretreatment and at Week 12 in Part 1. The biopsy involved the gastrocnemius muscle, or an alternative muscle selected by the Investigator if the gastrocnemius muscle was not feasible.

Part 2:

In Part 2, subjects who were randomized to placebo during Part 1 received IV SRP-9001 (1.33×10^{14} vg/kg) in Part 2. To maintain blinding for patients and investigators throughout the study, subjects who were previously randomized and treated with SRP-9001 in Part 1 received up to 10 mL/kg placebo (lactated Ringer's solution). Infusions were given in the same manner as in Part 1. On the day prior to the infusion in Part 2, selected patients underwent cardiac and musculoskeletal imaging assessments; note that the first magnetic resonance imaging (MRI) collection occurred after the Part 1 Week 48 visit, but no later than the Part 2- Day -1 visit. Subjects were followed for 48 weeks in Part 2.

All subjects had a muscle biopsy performed pretreatment and at Week 12 in Part 1 and at Week 12 in Part 2. The biopsy involved the gastrocnemius muscle, or an alternative muscle selected by the Investigator if the gastrocnemius muscle was not feasible.

Number of Subjects:

Up to 44 subjects were planned. Forty-three subjects were randomized; 2 subjects withdrew consent before dosing.

Part 1:

Forty-one subjects were treated: 20 subjects in the SRP-9001 group and 21 subjects in the placebo group

Part 2:

Forty-one subjects completed Part 2 and 39 subjects were treated in Part 2: 21 subjects who had received placebo in Part 1 were treated with SRP-9001 in Part 2 and 18 subjects who had received SRP-9001 in Part 1 were treated with placebo in Part 2. Two subjects who had received SRP-9001 in Part 1 completed Part 1 but were not treated in Part 2.

Diagnosis and Criteria for Inclusion:

This study included male DMD subjects aged 4 to 7 years, inclusive, with either frameshift (deletion or duplication) between exons 18 and 58, or premature stop codon mutation between exons 18 to 58. At Screening, subjects should have had a CK elevation > 1000 U/L and been below the 95th percentile predicted time on the 100-meter walk test. All subjects were required to be on a stable dose equivalent of oral corticosteroids for at least 12

weeks before Screening and the dose was to remain constant (except for potential modifications to accommodate changes in weight) throughout Parts 1 and 2 of the study. Detailed inclusion and exclusion criteria are provided in the study protocol.

Study Treatments

Part 1:

Test / Investigational Product:

SRP-9001 was administered as a single IV infusion through a peripheral limb vein.

Lots G02A0918-1 and G02A0918-2 were titrated and dosed at 2.0×10^{14} vg/kg according to the dose measured by NCH's qPCR method using a supercoiled standard.

Later in the study, the Sponsor's qPCR method using a linear standard was validated. A linearized plasmid DNA standard is used to generate the calibration curve utilized for quantification of the genome titer in comparison to supercoiled plasmid DNA for vector genome titer determination. Therefore, the qPCR method using a linear plasmid method is more accurate at determining the viral titer (vg/mL).

Following development of the Sponsor's validated qPCR method using a linear standard, Lots G18A0119, G18A0319, and G18A0819R were titrated and dosed at 1.33×10^{14} vg/kg according to the dose measured by the Sponsor's qPCR method using a linear standard.

Retrospectively, Lot G02A0918-1 and G02A0918-2 were retested based on the Sponsor's qPCR method using a linear standard. The administered doses with the linear standard for Lot G02A0918-1 and G02A0918-2 were 6.29×10^{13} vg/kg and 8.94×10^{13} vg/kg, respectively.

Therefore, 3 doses were administered in Part 1 of the study (1.33×10^{14} vg/kg, 6.29×10^{13} vg/kg, and 8.94×10^{13} vg/kg) with 12/20 (60%) subjects receiving a dose lower than the target dose. In Part 2 of the study, subjects receiving SRP-9001 will receive the target dose of 1.33×10^{14} vg/kg.

Reference /Placebo Product:

Matching volume of placebo (lactated Ringer's solution)

Part 2:

Test / Investigational Product:

SRP-9001 was administered as a single IV infusion through a peripheral limb vein.

In Part 2 of the study, subjects who received SRP-9001, received a dose of 1.33×10^{14} vg/kg.

Clinical Pharmacology Results:

Part 1:

- The primary biological endpoint of change in quantity of micro-dystrophin expression from Baseline to Week 12 (Part 1) as measured by western blot adjusted by muscle content was met. Treatment with SRP-9001 resulted in a statistically significantly greater increase in micro-dystrophin expression by western blot adjusted by muscle content from Baseline to Week 12 compared to placebo ($p < 0.0001$). Further, for the SRP-9001 group, the mean increase in micro-dystrophin expression from Baseline to Week 12 (23.82%) was statistically significant ($p = 0.0002$).
- In total, 9 (22.0%) subjects had rAAVrh74 antibody titers $\geq 1:25$ at baseline: 6 (30.0%) subjects in the SRP-9001 group and 3 (14.3%) subjects in the placebo group. No associated safety findings were observed for these subjects. None of the subjects in the placebo group had AAVrh74 antibody titer levels that exceeded the level required for inclusion in the study (ie, $\leq 1:400$) for the duration of Part 1. The highest titer in the placebo group was a titer of 1:200 measured at Week 8. No subjects had a positive ELISpot at Baseline.

Part 2:

- The efficacy endpoints defined for Part 2 of the study were all exploratory. For the subjects who received SRP-9001 in Part 2, the mean increase in micro-dystrophin level (% control) measured by western blot adjusted by muscle content, by IF fiber intensity (% control), and by IF PDPF were statistically significant; the mean increase in vector genome copies per nucleus from Baseline to Week 12 of Part 2 was also statistically significant.

Conclusions:**Part 1:**

The primary biological endpoint of change in quantity of micro-dystrophin expression from Baseline to Week 12 as measured by western blot was met. Treatment with SRP-9001 resulted in a statistically significantly greater increase in micro-dystrophin expression by western blot from Baseline to Week 12 compared to placebo ($p < 0.0001$). As muscle content in DMD subjects is highly variable, to normalize the variability, dystrophin levels were adjusted. In the ad-hoc analysis of the primary biological endpoint of change in quantity of micro-dystrophin expression from Baseline to Week 12 as measured by western blot adjusted by muscle content, results were consistent with the pre-specified analysis (ie, treatment with SRP-9001 resulted in a statistically significantly greater increase in micro-dystrophin expression from Baseline to Week 12 compared to placebo [$p < 0.0001$]).

The primary functional endpoint of change in NSAA total score from Baseline to Week 48 (Part 1) was not met in the ITT population. The LS mean (SE) treatment difference (0.8 [0.9]) between SRP-9001 and placebo was not statistically significant (95% CI: [-1.0, 2.7]; $p = 0.3730$). A pre-specified analysis showed nominally statistically significant difference in functional improvement between treatment groups in the 4 to 5 year old age group.

Key secondary and exploratory endpoints confirmed transduction of the transgene and localization of expressed protein while functional tests did not demonstrate consistent improvement relative to placebo. Results from Part 1 of this study showed that treatment with SRP-9001 was generally safe and well tolerated. The study established 2 potential risks as identified risks: acute liver injury and nausea and vomiting. Acute liver injury was adequately monitored with GGT levels and managed with corticosteroids. Nausea and vomiting were monitored and managed with standard care. No important risks of SRP-9001 other than acute liver injury were observed.

In the 6 subjects who had rAAVrh74 antibody titers $\geq 1:25$ at baseline; no associated safety findings were observed for these subjects. No subjects had a positive ELISpot at baseline. No apparent association with positive ELISpot results and efficacy findings were noted. A post-hoc exploratory analysis showed an association between a positive ELISpot and an elevation of GGT in the first 12 weeks after infusion. This supports the hypothesis that the acute liver injury risk involves T-cell reactivity to viral capsid. All GGT elevations resolved.

Part 2:

Key efficacy endpoints for Part 2 of the study confirmed transduction of the transgene and localized expression of protein in subjects who received SRP-9001 in Part 2 of the study. In Part 2, in which all 21 crossover subjects received the dose of 1.33×10^{14} vg/kg, an improvement in mean NSAA, time to rise from floor, time to ascend four steps, the 10-meter timed test, and the 100-meter timed test at Part 2 Week 48 relative to Part 2 Baseline was seen.

Almost all subjects had at least 1 TEAE during Part 2 of the study, the majority of which were mild or moderate in severity. The most common TEAEs the subjects who received SRP-9001 in

Part 2 were vomiting, decreased appetite, nausea, and procedural pain. No deaths or discontinuations from the study due to AEs were observed. Three subjects had at least 1 treatment-emergent SAE: 1 subject who received SRP-9001 in Part 2 (appendicitis) and 2 subjects who received SRP-9001 in Part 1 (both with femur fracture). None of the SAEs were considered by the Investigators to be related to study treatment.

The safety results from Part 2 of this study were similar to the safety results from Part 1 of the study. Treatment with SRP-9001 demonstrated an acceptable safety profile.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.3 Study SRP-9001-103 (Study 103)

Data cutoff: June 06, 2022

Title: An Open-label, Systemic Gene Delivery Study Using Commercial Process Material to Evaluate the Safety of and Expression from SRP-9001 in Subjects with Duchenne Muscular Dystrophy (ENDEAVOR)

<p>Objectives:</p> <p>Primary: To evaluate microdystrophin expression from SRP-9001 at 12 weeks (Part 1) post-infusion as measured by Western blot of biopsied muscle tissue</p> <p>Secondary:</p> <ul style="list-style-type: none"> To assess vector shedding following SRP-9001 administration To evaluate the immunogenicity of SRP-9001 as assessed by detection of antibodies to rAAVrh74 To evaluate the safety of SRP-9001 To evaluate microdystrophin expression from SRP-9001 at 12 weeks (Part 1) as measured by: Immunofluorescence (IF) fiber intensity of biopsied muscle tissue; IF percent dystrophin positive fibers (PDPF) of biopsied muscle tissue
<p>Methodology:</p> <p>This is an ongoing Phase Ib, open-label systemic gene delivery study to evaluate the safety of and expression from SRP-9001 in patients with Duchenne Muscular Dystrophy (DMD), across 4 cohorts.</p> <p>Cohort 1 patients consists of male DMD ambulatory patients who were ≥ 4 to < 8 years of age.</p> <p>Cohort 2 consists of male DMD ambulatory patients who were ≥ 8 to < 18 years of age.</p> <p>Cohort 3 consists of male DMD non-ambulatory patients, with no age restriction.</p> <p>Cohort 4 consists of male DMD ambulatory patients who were ≥ 3 to < 4 years of age.</p> <p>The first 2 enrolled subjects in each cohort were sentinel subjects, dosed at least 1 week apart. In Cohorts 2 and 3 combined, at least 3 subjects who weighed < 50 kg were enrolled, and at least 3 subjects who weighed ≤ 50 kg were enrolled.</p>
<p>Number of Subjects:</p> <p>Planned: Cohort 1: 20 patients; Cohort 2: 6 patients; Cohort 3: 6 patients; Cohort 4: 6 patients</p> <p>Actual: Cohort 1: 20 patients; Cohort 2: 7 patients; Cohort 3: 6 patients; Cohort 4: 6 patients</p> <p>Data from subjects enrolled in the study were analyzed for safety and efficacy.</p>
<p>Diagnosis and Criteria for Inclusion:</p> <ol style="list-style-type: none"> Cohort 1 only (ambulatory < 8 years): Is male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of Screening and has a North Star Ambulatory Assessment (NSAA) score > 17 and ≤ 26 at the Screening visit. Cohort 2 only (ambulatory ≥ 8 years): Is male at birth, ambulatory, and ≥ 8 to < 18 years of age at the time of Screening and has an NSAA score ≥ 15 and ≤ 26 at the Screening visit. Cohort 3 only (non-ambulatory): Is male at birth and has been non-ambulatory for a minimum of 9 months, with an NSAA walk score of "0" and inability to perform the 10-meter walk/run (MWR) at Screening visit, and with a Performance Upper Limb (PUL) entry item score ≥ 2. Onset of loss of ambulation is defined as participant- or caregiver reported age at continuous wheelchair use, approximated to the nearest month. Cohort 4 only (ambulatory < 4 years): Is male at birth, ambulatory, and ≥ 3 to < 4 years of age at the time of Screening. Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the DMD gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein: Mutations between or including exons 1-17 are not eligible (implemented after protocol version 5) Has an indication of symptomatic muscular dystrophy: Creatine Kinase (CK) elevation > 1000 U/L and Cohorts 1 and 2 only (ambulatory): Below 95 percent predicted time on 100MWR For Cohort 1, 2, and 3 only: Stable weekly dose equivalent of oral corticosteroids for at least 12 weeks before Screening and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the first year of the study. For Cohort 4: subjects who do not yet require use of chronic steroids for treatment of their DMD in the opinion of the Investigator and are not receiving steroids at the time of Screening. Has rAAVrh74 antibody titers $\leq 1:400$ (i.e., not elevated) as determined by an ELISA.
<p>Study Treatments</p> <p>All subjects received SRP-9001 by single intravenous (IV) infusion, through a peripheral limb vein. Dosing was stratified by weight: subjects weighing < 70 kg on Day 1 were dosed with 1.33×10^{14} vg/kg, and subjects</p>

weighing ≥ 70 kg on Day 1 were dosed with 9.31×10^{15} vg total fixed dose, which is equivalent to the dose of 1.33×10^{14} vg/kg for a 70 kg subject.

Clinical Pharmacology Results:

Pharmacokinetic:

- For all patients, at Week 12, the mean (SD) vector genome copies per nucleus as measured by ddPCR was 3.44 (2.38) for Cohort 1, 1.61 (0.53) for Cohort 2 and 2.76 (1.08) for Cohort 3. The mean increase in vector genome copies per nucleus from baseline to Week 12 was statistically significant for Cohort 1 ($p < 0.0001$), Cohort 2 ($p = 0.0313$) and Cohort 3 ($p = 0.0313$).
- The mean peak vector DNA concentration in saliva and urine was 56,354,000.0 vgc/ml and 476,158.8 vgc/ml, respectively. The concentration peaked at Day 1. The mean concentration in saliva and urine declined significantly by Week 4 to 14,440.8 vgc/ml and 1731.1 vgc/ml respectively. In feces, the mean peak vector DNA concentration was 133,000,000 vgc/ug at Week 1 and declined at Week 4 to 10,622.7 vgc/ml. The percentage decrease from peak to Week 4 was greater than 99% for saliva, urine, and feces. The above preliminary data show that vector DNA is shed for a transient period and is cleared as early as the first two weeks in all matrices.

Pharmacodynamic

- The mean (SD) increase in micro-dystrophin expression from baseline to Week 12 as measured by Western blot, was 54.21% (42.57) for Cohort 1, 11.92% (4.21) for Cohort 2, and 45.53% (40.59) for Cohort 3. The mean change in micro-dystrophin expression from baseline to Week 12 was statistically significant for Cohort 1 ($p < 0.0001$), Cohort 2 ($p = 0.0313$) and Cohort 3 ($p = 0.0313$).
- The mean (SD) increase in micro-dystrophin expression by IF fiber intensity from baseline to Week 12 was 66.52% (64.06) for Cohort 1, 13.23% (8.74) for Cohort 2, and 34.86% (18.21) for Cohort 3. The mean change in micro-dystrophin expression by IF fiber intensity from baseline to Week 12 was statistically significant in Cohort 1 ($p < 0.0001$), Cohort 2 ($p = 0.0313$) and Cohort 3 ($p = 0.0313$).
- The mean (SD) increase in micro-dystrophin expression by IF PDPF from baseline to Week 12 was 48.27 (25.37) for Cohort 1, 15.85 (8.95) for Cohort 2, and 28.29 (15.17) for Cohort 3, with the changes statistically significant for Cohort 1 ($p < 0.0001$), Cohort 2 ($p = 0.0313$), and Cohort 3 ($p = 0.0313$).

Immunogenicity

- Monitoring of immune responses against AAVrh74 capsid revealed antibody (AB) titers in all patients during the first weeks after SRP-9001 infusion with only minimal decline by Week 52 (Cohort 1), and positive responses from the ELISpot-IFN directed against AAVrh74 in most patients. The relationship of AB titers and ELISpot responses to AEs remains unclear
- Monitoring of immune responses against SRP-9001 conveyed micro-dystrophin revealed high antibody titers and strong positive responses in the ELISpot-IFN assay particularly in the SUSAR patient with immune-mediated myositis. The immune responses in the remaining 8 patients with mutations in exons 1-17, without complaints of asthenia / muscle weakness were generally similar as observed in patients with mutation beyond exon 17. The SUSAR patient with immune-mediated myositis repeated extraordinarily high sport forming units (SFUs) contributing to the hypothesis of the underlying pathophysiology.

Conclusions:

- Results show efficient transduction of SRP-9001 in muscle tissue.
- The delivery of the transgene to the nuclei and the robust expression and proper localization of micro-dystrophin protein coincided with reductions in CK levels
- Functional improvements were observed in the 52 weeks following gene transfer for patients in Cohort 1
- Safety data for all 39 patients in the study (Cohorts 1 to 4) showed an acceptable profile for the treatment with SRP-9001. The safety profile appears consistent with the safety profile seen in previous SRP-9001 trials.
- Two new safety signals emerged:
SUSAR of immune-mediated myositis probably related to certain Duchenne mutation in the exon 1-17 area preventing auto-tolerance development to the N-terminal portion of the SRP-9001 conveyed micro-dystrophin.

SUSAR of myocarditis whose pathophysiology remains unclear. Troponin I monitoring should be maintained in clinical trials with SRP-9001.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.