FDA Briefing Document

BLA# 125781/00

Drug name: delandistrogene moxeparvovec

Applicant: Sarepta Therapeutics, Inc.

Cellular, Tissue and Gene Therapies Advisory Committee Meeting

05/12/2023

Office of Therapeutic Products (OTP) / CBER

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the biologic delandistrogene moxeparvovec to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation; instead, it is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AAV	adeno-associated virus
AE	adverse event
ALI	acute liver injury
ALT	alanine aminotransferase
BLA	Biologics License Application
BMD	Becker muscular dystrophy
CI	confidence interval
DAPC	dystrophin-associated protein complex
DMD	Duchenne muscular dystrophy
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
IF	immunofluorescence
LS	least square
MMRM	Mixed Model for Repeated Measures
NSAA	North Star Ambulatory Assessment
PDPF	percent Sarepta's micro-dystrophin positive fibers
POC	proof-of-concept
SAE	serious adverse event
SD	standard deviation
SE	standard error
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
VGC	vector genome copy number
WB	western blot

1. Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

Duchenne muscular dystrophy (DMD) is a serious condition with an urgent unmet medical need. DMD results from mutation of the *DMD* (also known as *Dystrophin)* gene, the largest known human gene, which is carried on the X chromosome. DMD affects about 1 in 3,300 boys. 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.

Corticosteroids are the primary pharmacologic treatment for DMD. Deflazacort (Emflaza) is Food and Drug Administration (FDA)-approved for treatment of DMD in patients 5 years of age and older. In addition, four exon-skipping drugs have received FDA approval, via the accelerated approval pathway, for a subset of patients with specific *DMD* mutations; clinical benefit of these drugs remains to be verified.

Sarepta Therapeutics, Inc. (the Applicant) has developed the adeno-associated virus (AAV) vector-based gene therapy product SRP-9001 (delandistrogene moxeparvovec) for treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene. SRP-9001 encodes a novel protein, Sarepta's micro-dystrophin. The Applicant submitted Biologics License Application (BLA) 125781 to seek accelerated approval for SRP-9001 based on the surrogate endpoint of expression of Sarepta's micro-dystrophin at Week 12 following administration of SRP-9001.

The goal of treatment with SRP-9001 is to change the disease trajectory of DMD into a milder, Becker muscular dystrophy (BMD)-like phenotype. To qualify for accelerated approval, the Applicant proposes to utilize a surrogate endpoint—expression of Sarepta's micro-dystrophin protein at Week 12 after administration of SRP-9001—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.

Sarepta's micro-dystrophin is a novel, engineered protein; no epidemiologic or pathophysiologic evidence of its function 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 only provides information about expression of the transgene product in cells transduced by SRP-9001, rather than insight into a pharmacologic effect on a biomarker in the pathway of the disease.

Having reviewed nonclinical data and three clinical studies, including a randomized, double-blinded, placebo-controlled trial demonstrating expression of Sarepta's micro-dystrophin at Week 12 following infusion of SRP-9001, FDA notes that the clinical studies conducted to date do not provide unambiguous evidence that SRP-9001 is likely beneficial for ambulatory patients with DMD. It is challenging to conclude with reasonable certainty from the data provided by the Applicant either that SRP-9001 is likely effective for younger patients, or that it is likely ineffective for older patients or those with somewhat poorer functional status. Additionally, FDA has safety concerns related to the possibility of administering an ineffective gene therapy.

The FDA is therefore convening this Advisory Committee meeting to discuss several issues:

- Whether expression of Sarepta's micro-dystrophin protein at Week 12 after administration of SRP-9001 can serve as a surrogate endpoint that is "reasonably likely to predict clinical benefit" in support of the BLA for accelerated approval;
- The potential clinical implications of findings, including exploratory subgroup analyses, from the only randomized, double-blind, placebo-controlled clinical study;
- The potential benefits, risks, and uncertainties that may be associated with administration of SRP-9001 for the treatment of ambulatory patients with DMD in the context of accelerated approval; and
- The potential impact of granting accelerated approval on the ability to bring to conclusion the ongoing randomized, double-blind, placebo-controlled 52-week Part 1 of Study SRP-9001-301 (Study 301), which is proposed to serve as the required postmarketing confirmatory trial to verify and describe clinical benefit, without missing the collection of critical data.

2. Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

DMD is a serious condition with an urgent unmet medical need. DMD results from mutation of the *DMD* (also known as *Dystrophin)* gene, the largest known human gene, which is carried on the X chromosome. DMD affects about 1 in 3,300 boys. 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.

Weakness is symmetric and progressive, beginning in proximal and then spreading to distal muscles of the limbs. The lower extremities are affected first, followed by the upper extremities. In addition to skeletal muscle, cells in the heart and brain also normally express dystrophin isoforms. DMD also manifests with dilated cardiomyopathy, as well as cardiac conduction abnormalities. About one-third of affected boys have cognitive and behavioral difficulties, including reduced verbal activity and attention.

Boys typically lose the ability to walk by age 12 or 13 years, and in the past would die by late adolescence or early twenties from respiratory insufficiency or cardiomyopathy. Median life expectancy more recently has increased to 29.9 years with some patients living into the fourth decade, primarily through improved respiratory and cardiac management.[1]

There is no known cure for DMD. The main pharmacologic treatment is corticosteroids (usually deflazacort or prednisone), typically initiated in boys ages 4 years or older. In addition, effort is made to control symptoms using physical therapy, surgery to correct progressive scoliosis, medications for cardiac function, assisted ventilation, and tracheostomy, which can delay progression of disease by several years.[2]

[1] Wahlgren, L, AK Kroksmark, M Tulinius, and K Sofou, 2022, One in five patients with Duchenne muscular dystrophy dies from other causes than cardiac or respiratory failure, Eur J Epidemiol, 37(2):147-156.
[2]MedLine Plus, 2022, Duchenne muscular dystrophy, https://medlineplus.gov/ency/article/000705.htm

Deflazacort received FDA approval in 2017 for the treatment of patients with DMD age 2 years and older.[3] Data from a Phase 3 randomized, double-blind, placebo-controlled trial evaluating muscular strength in 196 boys aged 5-15 years showed a significant change compared with placebo in the primary outcome measure, muscle strength at 12 weeks, on par with the efficacy observed with prednisone. Additionally, deflazacort was found to be superior to prednisone with regard to changes in muscle strength after 12 weeks of treatment and led to fewer adverse effects of therapy.[4]

Four exon-skipping drugs have received FDA approval, through the accelerated approval pathway, to treat the small percentage of patients with DMD harboring amenable mutations in the *DMD* gene: eteplirsen (Exondys 51), golodirsen (Vyondys 53), viltolarsen (Viltepso), and casimersen (Amondys 45).[5,6,7,8] Importantly, the clinical benefit of these products remains unknown, as none of the confirmatory clinical studies have been completed.

2.2 Clinical Outcome Measure: North Star Ambulatory Assessment

The North Star Ambulatory Assessment (NSAA) is a 17-item rating scale that is commonly used in clinical studies to measure motor function in ambulatory patients with DMD. The NSAA evaluates abilities including standing, walking, arising from a chair, standing on one leg, climbing onto and descending from a box step, transitioning from supine to sitting position, rising from the floor, jumping, hopping, and running. These tasks are performed by a patient in a clinical setting, according to instructions administered by a health care professional.

Each item is scored as 0 (unable to achieve independently), 1 (modified method, but not requiring assistance), or 2 (normal). The total score ranges from 0 (unable to perform any activities) to 34 (all activities achieved normally).

Performance on the NSAA can be affected both by the consistency of administration (process-dependent) and by the effort of the subject and/or coaching or encouragement by a family member, caregiver, or medical staff (effort-dependent).[9] Therefore, blinding to treatment assignment is important for clear interpretation of results in clinical studies employing the NSAA.

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[3]FDA, 2017, FDA approves drug to treat Duchenne muscular dystrophy, accessed April 4, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-duchenne-muscular-dystrophy#:~:text=The%20U.S.%20Food%20and%20Drug,progressive%20muscle%20deterioration%20and%20weakness.

[4]Griggs, RC, JP Miller, CR Greenberg, DL Fehlings, A Pestronk, JR Mendell, RT Moxley, 3rd, W King, JT Kissel, V Cwik, M Vanasse, JM Florence, S Pandya, JS Dubow, and JM Meyer, 2016, Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy, Neurology, 87(20):2123-2131.

[5]FDA, 2016, FDA grants accelerated approval to first drug for Duchenne muscular dystrophy, accessed April 4, 2023, https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy

[6]FDA, 2019, FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation, accessed April 4, 2023, 2023, https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation.

[7]FDA, 2020, FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation, accessed April 4, 2023, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation.

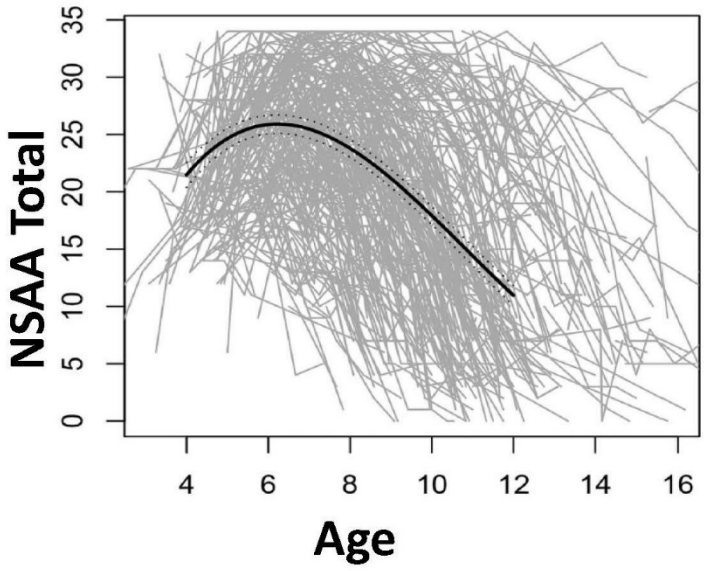
[8]FDA, 2021, FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation, accessed April 4, 2023, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0.

[9]FDA, 2018, *Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*, https://www.fda.gov/media/92233/download

Natural history data of 395 subjects selected from the NorthStar Clinical Network database showed heterogeneous disease progression and identified four general trajectories of ambulatory function (as measured by the NSAA total score) over time. Twenty-five percent of the boys were in cluster 1 (NSAA falling to ≤5 at age ~10 years), 35% were in cluster 2 (NSAA ≤5 at age ~12 years), 21% were in cluster 3 (NSAA ≤5 at age ~14 years), and 19% were in cluster 4 (NSAA >5 up to 15 years). Mean ages at diagnosis of DMD were similar across clusters (4.2, 3.9, 4.3, and 4.8 years, respectively).[10]

In the studied population, it was reported that the overall mean trajectory of NSAA total scores versus age initially increased at a rate of approximately 3 points per year and peaked at age 6.3 years with a mean NSAA score of 26. Following the peak, scores eventually approached a rate of decline of approximately 3 points per year (Figure 1).

FIGURE 1. NSAA TOTAL SCORE TRAJECTORIES FOR INDIVIDUAL PATIENTS BY AGE



Source: Muntoni F, et al. PloS One. 2019
Abbreviation: NSAA, North Star Ambulatory Assessment.

2.3 FDA Approval Pathways and the Role of Surrogate Endpoints

By law, approval of new drugs—small molecule medications as well as biologics, which include gene therapies—must be based on adequate and well-controlled studies demonstrating both substantial evidence of effectiveness, and evidence of safety. FDA has two pathways for approval of new drugs: traditional approval and accelerated approval. These pathways are further discussed below.

Effectiveness is determined by gauging the impact of the drug on endpoints in clinical studies. Clinical endpoints directly measure whether patients in a clinical study feel or function better or live longer. In certain cases, however, such as when obtaining direct measurements would require an impractically long time, clinical studies may instead use surrogate endpoints. A surrogate endpoint is a marker—such as a laboratory measurement, radiographic image, physical sign, or as in this case, a biomarker—that is expected to predict clinical benefit but is not itself a measure of clinical benefit.

[10]Muntoni, F, J Domingos, AY Manzur, A Mayhew, M Guglieri, G Sajeev, J Signorovitch, and SJ Ward, 2019, Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy, PLoS One, 14(9):e0221097.

Before a surrogate endpoint can be accepted in place of a clinical outcome, the surrogate endpoint must be supported by sufficient clinical evidence indicating that it can be relied upon to predict, or to correlate with, clinical benefit. When extensive evidence is available, including results of epidemiologic investigation and clinical studies, such surrogate endpoints are called validated surrogate endpoints. Validated surrogate endpoints may be accepted by FDA in place of clinical endpoints for approval of new drugs via the traditional approval pathway.

Accelerated approval, however, is intended to provide more rapid access to promising therapies for patients with serious diseases and does not rely either on clinical endpoints or on validated surrogate endpoints. Rather, FDA may grant accelerated approval based on surrogate endpoints for which there is less evidentiary support. Such surrogate endpoints instead are expected to meet the threshold of being "reasonably likely to predict clinical benefit." Substantial evidence of effectiveness must still be demonstrated in adequate and well-controlled clinical studies. While FDA may exercise regulatory flexibility, substantial evidence of effectiveness needs to be established for approval. The accelerated approval pathway thus may not be used to compensate for weak or inconsistent clinical findings. Moreover, drugs receiving accelerated approval subsequently are required to undergo postmarketing confirmatory clinical study(ies) to verify the anticipated clinical benefit; approval may be withdrawn if the confirmatory study(ies) fail to verify the clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug.

Determination of whether a surrogate endpoint can be considered "reasonably likely to predict clinical benefit" is a matter of judgment and is made on a case-by-case basis.[11] The key considerations include:

(1) Biological plausibility of the relationship of the disease, the candidate surrogate endpoint, and the desired effect;

(2) Empirical evidence, which "may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data" (although evidence of pharmacologic activity alone is not sufficient)[12,13,14]; and

(3) Clinical data supporting the relationship of an effect on the candidate surrogate endpoint to an effect on the clinical outcome. An effect on the surrogate endpoint is expected to correlate with a clinical outcome measure that directly assesses benefit in clinical studies by evaluating how a patient feels, functions, or survives.

2.4 Special Risks of AAV Vector-Based Gene Therapy Products

For small molecule drugs as well as for biologics, accelerated approval carries the risk that patients will be exposed to a therapy for which subsequent clinical trials ultimately show no clinical benefit.

Accelerated approval of an ineffective gene therapy product poses an additional, unique risk. Patients receiving a systemically administered (e.g., intravenous) AAV vector-based gene therapy mount an immune response against the AAV vector carrying the transgene. That immune response has been found to show cross-reactivity against some other AAV vectors of different serotypes. As a result, patients have only one opportunity to receive a systemically administered AAV vector-based gene therapy.

[11]FDA-NIH Biomarker Working Group, 2016, Reasonably Likely Surrogate Endpoint, Food and Drug Administration, accessed April 13, 2023, https://www.ncbi.nlm.nih.gov/books/NBK453485/.
[12]Under section 506(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
[13]57 FR 58942
[14]FDA, 2014, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, https://www.fda.gov/media/86377/download.

Patients for whom the dose is inadequate are unable to receive additional doses of the same medication; moreover, those patients for whom SRP-9001 is ineffective would be unable to receive subsequent treatment with a different, beneficial AAV vector-based gene therapy product.

2.5 Pertinent Regulatory History

Table 1 below is a brief summary of the main regulatory milestones and interactions between the FDA and the Applicant.

TABLE 1. MAIN REGULATORY HISTORY OF SRP-9001

Date	Milestone	Background Information
October 5, 2017	IND received from Dr. Jerry Mendell (Nationwide Children's Hospital)	—
November 3, 2017	IND may proceed	—
June 27, 2018	IND placed on Clinical Hold – Clinical Hold letter issued July 22, 2018	IND placed on clinical hold because human subjects were or could have been exposed to an unreasonable and significant risk of illness or injury, and the IND did not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies. Specific deficiencies in CMC were communicated.
September 21, 2018	Clinical Hold removed – study may proceed	—
October 11, 2018	IND transferred to Sarepta Therapeutics, Inc.	—
(b) (4)	(b) (4)	—
December 20, 2018	Type B multidisciplinary meeting	FDA stated that expression of Sarepta's micro-dystrophin protein is not currently accepted as a surrogate endpoint considered "reasonably likely to predict clinical benefit" to support accelerated approval. FDA recommended that Sarepta choose an endpoint that assesses clinically meaningful benefit, as manifested by how a patient feels, functions, or survives.
(b) (4)	(b) (4)	—
June 4, 2020	Request for Fast Track designation granted	—

Date	Milestone	Background Information
September 4, 2020	Type C CMC and Clinical Meeting	FDA expressed concern about the lack of correlation between clinically meaningful benefit and the primary efficacy endpoint, expression of Sarepta's micro-dystrophin at Week 12 after SRP-9001 administration. FDA recommended that Sarepta revise the design of Study SRP-9001-103 from a single-arm, open-label study to a randomized, blinded and concurrent-controlled study.
July 27, 2021	Type B End of Phase 2 teleconference	FDA stated that based on the results of Study SRP-9001-101 and Study SRP-9001-102, the Agency is not convinced that there is a clear correlation between expression of Sarepta's micro-dystrophin and clinical benefit.
August 6, 2021	IND placed on Clinical Hold due to SAE – letter issued September 1, 2021	IND placed on Clinical Hold as it did not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies. An unexpected SAE was reported, of asthenia in a 9-year-old subject, requiring hospitalization and respiratory support after he received therapy in Study SRP-9001-103.
October 1, 2021	Clinical Hold removed – study may proceed	—
April 29, 2022	Type C Meeting to discuss possible Accelerated Approval pathway	FDA expressed concerns regarding the predictive relationship of expression of Sarepta's micro-dystrophin to clinical benefit. Sarepta stated that regulatory precedent exists for granting accelerated approval to drugs promoting expression of "shortened forms of dystrophin." FDA replied that "shortened forms of dystrophin" constitute a diverse group, which are not necessarily equivalent with regard to being considered "reasonably likely to predict clinical benefit" for accelerated approval.
September 28, 2022	Original BLA submission	—

Source: FDA
Abbreviations: BLA, Biologics License Application; CFR, Code of Federal Regulations; CI, confidence interval; CMC, chemistry, manufacturing, and controls; IND, Investigational New Drug; NSAA, North Star Ambulatory Assessment; RMAT, Regenerative Medicine Advanced Therapy; SAE, serious adverse event.

3. Investigational Product – SRP-9001

3.1 Drug Product Description

3.1.1 SRP-9001

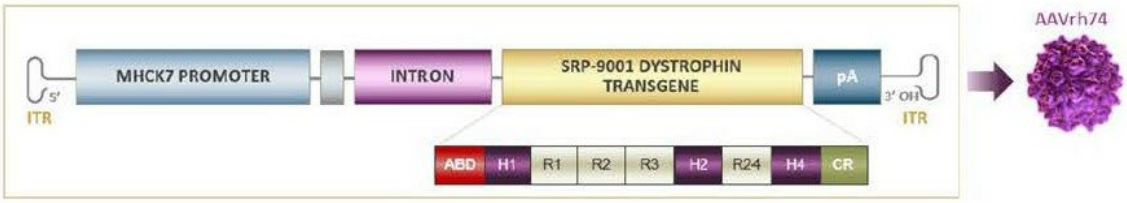
The Applicant has developed the gene therapy product SRP-9001 for the treatment of ambulatory patients with DMD. Because dystrophin is the largest known human gene—with sizes spanning over

2,200 kb in the genome,[15] resulting in a complementary DNA of about 11 kb encoding a protein of about 427 kDa—the wild-type *DMD* gene cannot be delivered via a gene therapy vector based on AAV, which is limited to about 4.7 kb. This constraint led to the design of various much smaller, novel transgenes encoding "micro-dystrophin" proteins containing few critical domains of wild-type dystrophin (Figure 4). The transgene encoding Sarepta's micro-dystrophin, delivered by SRP-9001, is one of these. It is based on a mutant, shortened form of dystrophin identified in a patient with milder disease (BMD; Figure 3). Unlike the shortened forms of dystrophin in that patient or in other patients with BMD, or those generated by treatment with exon-skipping drugs, none of these micro-dystrophin proteins—including Sarepta's micro-dystrophin—are naturally expressed in any patients.

The goal of treatment with SRP-9001 is to change the disease trajectory of DMD into a milder, Becker-like phenotype. The Applicant is seeking accelerated approval of SRP-9001 for treatment of ambulatory patients with DMD. To qualify for accelerated approval, the Applicant proposes to utilize a surrogate endpoint—expression of Sarepta's micro-dystrophin protein at Week 12 after administration of SRP-9001—as primary evidence of effectiveness. This biomarker thus is intended to serve as the required surrogate endpoint considered "reasonably likely to predict clinical benefit" of SRP-9001.

SRP-9001 (rAAVrh74.MHCK7.micro-dystrophin) 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 intended to carry out functions of the full-length dystrophin protein, which is essential for muscle health and function. The vector genome expression cassette contains essential elements to control gene expression, including AAV2 inverted terminal repeats, chimeric (SV40) intron, and a synthetic polyadenylation signal (See Figure 2). Expression of the 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.

FIGURE 2. SRP-9001 VECTOR DESIGN



Source: Sarepta Therapeutics, Inc.
Abbreviations: AAVrh74, adeno-associated virus vector rhesus serotype 74; ABD, actin-binding domain; CR, cysteine-rich region; H, hinge; ITR, inverted terminal repeat; MHCK7, a-myosin heavy-chain creatine kinase 7; pA, polyadenylation signal; R, spectrin-like repeat.

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.

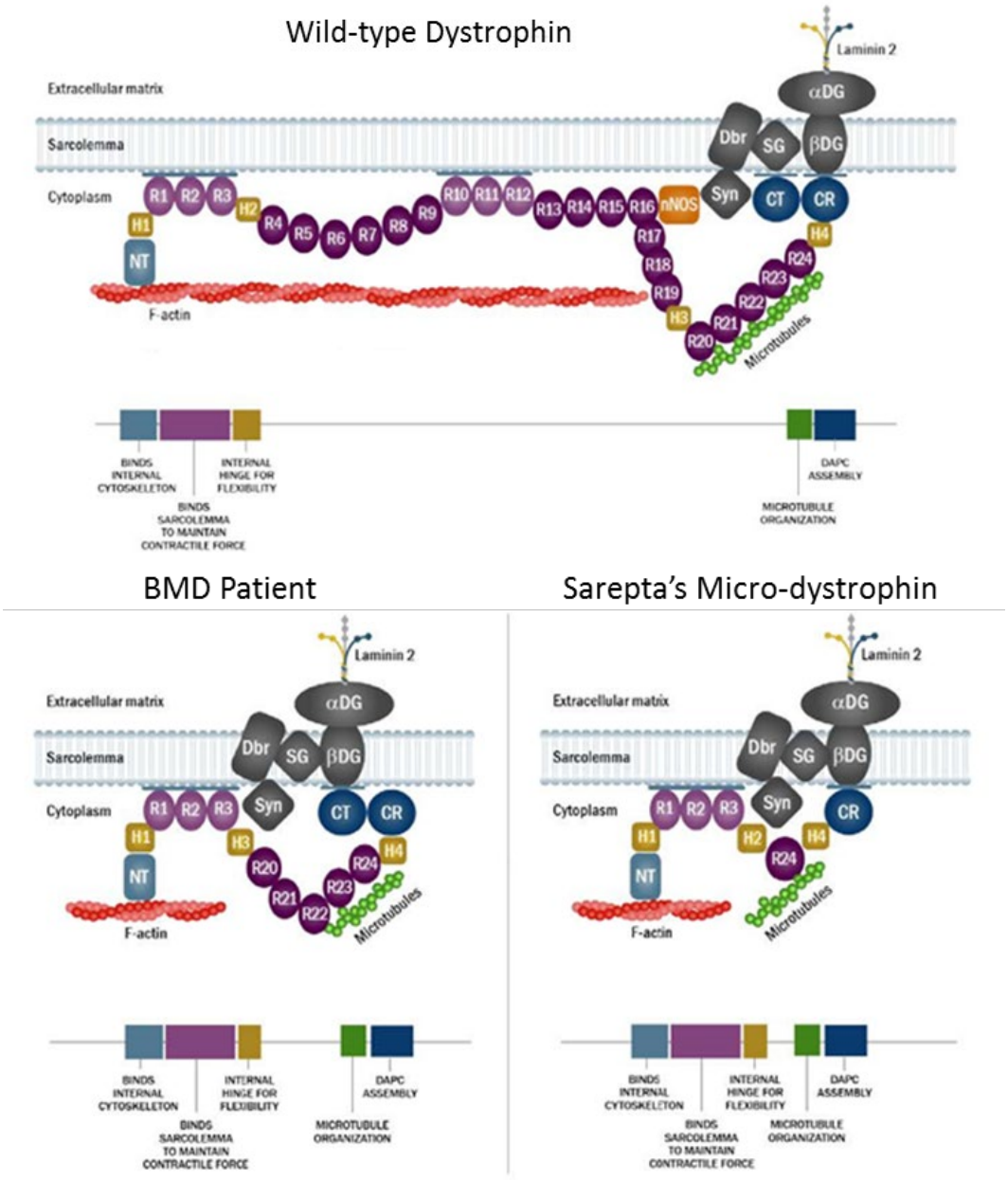
3.2 Mechanism of Action of SRP-9001

The schematic below summarizes the structure and functions of wild-type dystrophin; a mutated but partially functional dystrophin protein from a patient with mild BMD; and Sarepta's micro-dystrophin

[15]Koenig, M, EP Hoffman, CJ Bertelson, AP Monaco, C Feener, and LM Kunkel, 1987, Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals, Cell, 50(3):509-517.

protein (Figure 3). Wild-type dystrophin forms part of the dystrophin-associated protein complex (DAPC), a transmembrane oligomeric complex of proteins that spans the sarcolemma of skeletal and cardiac muscle cells. The DAPC is composed of the sarcoglycan complex, sarcospan, the dystroglycan complex, syntrophins, and dystrobrevins.

FIGURE 3.SUMMARY OF STRUCTURE AND FUNCTIONS OF WILD-TYPE DYSTROPHIN, MUTANT DYSTROPHIN IN A PATIENT WITH BMD, AND SAREPTA'S MICRO-DYSTROPHIN



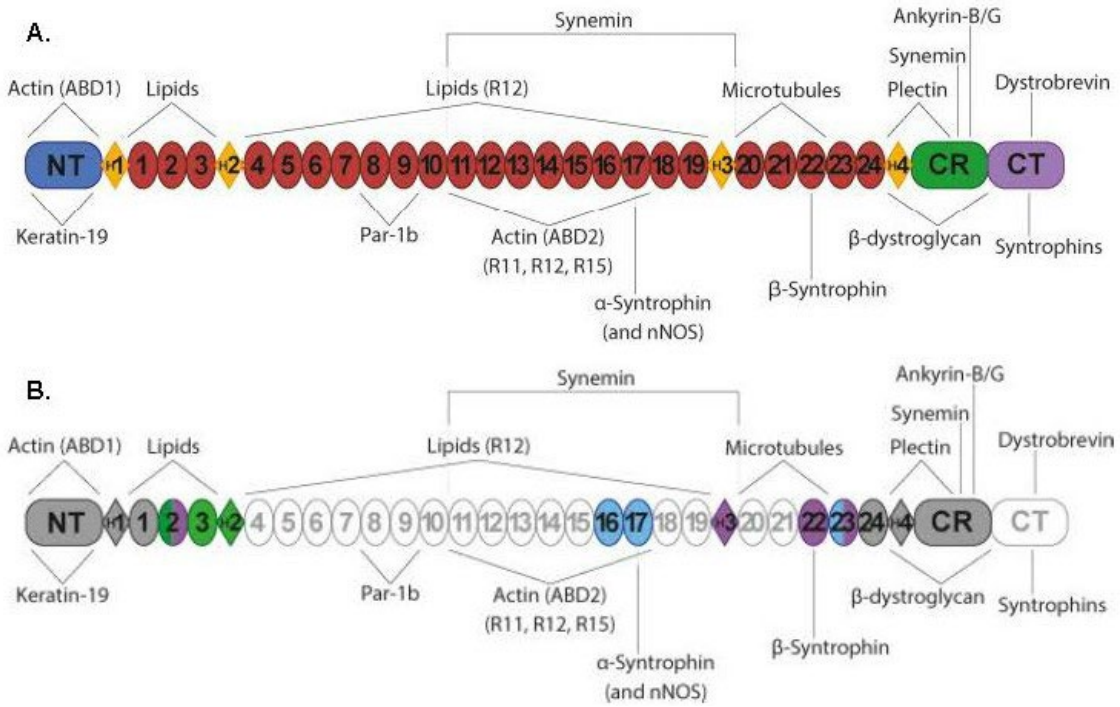
Source: Sarepta Therapeutics, Inc.; Adapted from: Zhao J, et al. Hum Mol Genet. 2016; 25:3647-3653.
Note: Micro-dystrophin and wild-type dystrophin are 138 kDa and 427 kDa, respectively.
Abbreviations: αDG, α-dystroglycan; βDG, β-dystroglycan; BMD, Becker muscular dystrophy; CR, cysteine-rich region; DAPC, dystrophin-associated protein complex; Dbr, dystrobrevin; H, hinge region; nNOS, neuronal nitric oxide synthase; NT, N-terminus; R, rod domain; SG, sarcoglycan; Syn, syntrophin.

The DAPC links the cytoskeleton to the extracellular matrix via laminin and helps to transmit and absorb the shock associated with muscle contraction and to maintain sarcolemmal integrity during muscle use, thereby preventing membrane and muscle damage. In the absence of a functional DAPC, muscle contraction in patients with DMD results in loss of sarcolemmal integrity, leakage of intracellular contents such as creatine kinase, chronic muscle breakdown, and ultimately loss of function.

Recent reports suggest that the role of wild-type dystrophin protein extends beyond serving only as a spring or shock absorber. Evidence strongly suggests that the 24 spectrin-like repeats (Figure 4) play an important scaffolding role, helping to recruit sodium, potassium, and calcium channels; nitric oxide synthase; and multiple signaling proteins, such as kinases.[16] The extreme truncations in Sarepta's micro-dystrophin protein result in absence of important functional domains (Figure 4). For example, Sarepta's micro-dystrophin does not bind either neuronal nitric oxide synthase or α-syntrophin, two proteins known to play a synergistic role to protect muscle cells. Recruitment of neuronal nitric oxide synthase by wild-type dystrophin at the sarcolemma through spectrin-like repeats 16 and 17 (R16/17) helps control local blood flow by antagonizing sympathetic vasoconstriction.[17,18,19] It is therefore unclear to what extent Sarepta's micro-dystrophin can function similarly to wild-type dystrophin or to shortened forms of dystrophin in patients with BMD.

[16]Adams, ME, GL Odom, MJ Kim, JS Chamberlain, and SC Froehner, 2018, Syntrophin binds directly to multiple spectrin-like repeats in dystrophin and mediates binding of nNOS to repeats 16-17, Hum Mol Genet, 27(17):2978-2985.
[17]Cirak, S, L Feng, K Anthony, V Arechavala-Gomeza, S Torelli, C Sewry, JE Morgan, and F Muntoni, 2012, Restoration of the dystrophin-associated glycoprotein complex after exon skipping therapy in Duchenne muscular dystrophy, Mol Ther, 20(2):462-467.
[18]Lai, Y, GD Thomas, Y Yue, HT Yang, D Li, C Long, L Judge, B Bostick, JS Chamberlain, RL Terjung, and D Duan, 2009, Dystrophins carrying spectrin-like repeats 16 and 17 anchor nNOS to the sarcolemma and enhance exercise performance in a mouse model of muscular dystrophy, J Clin Invest, 119(3):624-635.
[19]Nelson, DM and JM Ervasti, 2021, Structural proteins: Dystrophin: A multifaceted protein critical for muscle health, Encyclopedia of Biological Chemistry: Third Edition, 3rd edition: Elsevier, 3: 625-638.

FIGURE 4. DYSTROPHIN DOMAINS



Source: Nelson, DM and JM Ervasti, 2021, Structural proteins: Dystrophin: A multifaceted protein critical for muscle health, Encyclopedia of Biological Chemistry: Third Edition, 3rd edition: Elsevier, 3: 625-638.
Note: Image A represents dystrophin regions and their associated protein and lipid binding partners; image B represents the dystrophin domains present in the three clinical stage micro-dystrophin gene therapy constructs. Gray domains are present in all three micro-dystrophins. Green domains are present only in Sarepta's micro-dystrophin, blue only in Solid Biosciences' micro-dystrophin, and purple only in Pfizer's micro-dystrophin. Two-color dystrophin domains are present in both companies' constructs. Semi-transparent, white domains are missing from all 3 micro-dystrophins. Diamonds represent hinge regions and ovals represent spectrin-like repeats.
Abbreviations: ABD2, actin binding domain 2; CR, cysteine rich domain; CT, C-terminus; nNOS, neuronal nitric oxide synthase; NT, N-terminus.

3.3 Pertinent Drug Development Changes and Regulatory History

Two manufacturing processes were utilized to generate purified Good Manufacturing Practice-grade SRP-9001 drug product to support the clinical program. The products made by the two manufacturing processes were not analytically comparable for the critical quality attribute of full viral particles.

For early clinical studies (Study SRP-9001-101 and Study SRP-9001-102), the drug product was made using manufacturing Process A. Process A used a AAV -based purification process that allows near-complete removal of empty AAV capsids (i.e., capsids lacking the viral genome encoding Sarepta's micro-dystrophin) from the final formulated product. Process A material was manufactured at Nationwide Children's Hospital (Ohio State University, Columbus, OH).

For Study SRP-9001-103 (Study 103) and Study 301, the drug product was made using the to-be-commercial manufacturing process, referred to as Process B. Process B utilizes a scaled-up purification method that incorporates chromatography-based methods for separation of empty capsid residuals from the full capsids. The Process B purification method results in poor separation of empty AAV capsids from full AAV capsids. Process B is manufactured by Catalent Pharma Solutions (Baltimore, MD).

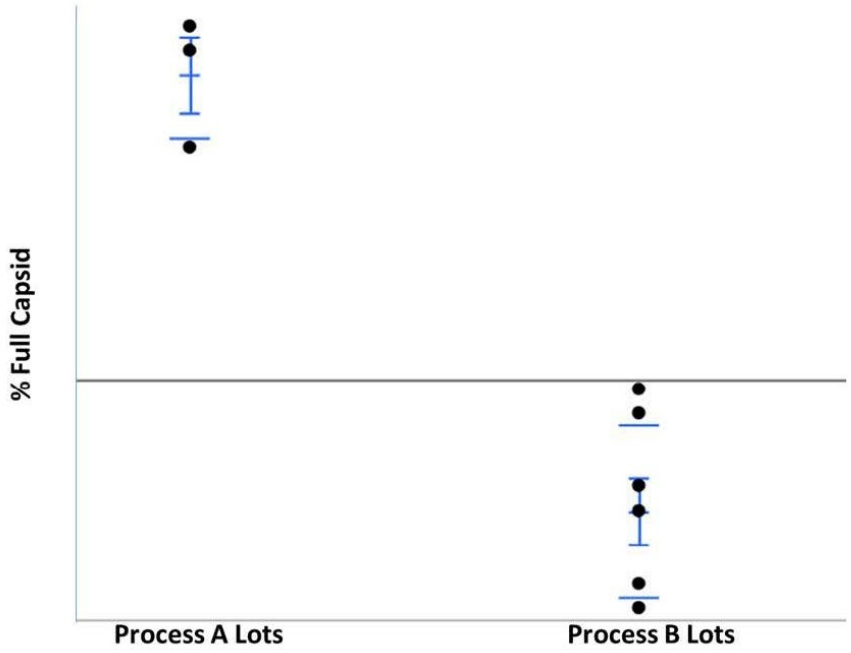
Comparability of Process A and Process B Materials

Based on both the Applicant's and FDA's assessment, it was concluded that the Process A and Process B materials are not analytically comparable with regard to levels of empty capsid residuals. The percent

full capsids of Process A and Process B material were found to be significantly different (t-test, p=0.0002).

The percent full capsid attribute was measured by a commercial test, that assesses the levels of empty and full capsids, for product lot release. As part of the comparability study, the Applicant used the described method to test the level of percent full capsids for Process A and Process B materials. However, the Process A and Process B samples were tested at different times and at different contract testing labs, without method transfer; therefore, no direct side-by-side analysis was conducted. Figure 5 below summarizes the results with significantly lower full capsids for Process B.

FIGURE 5. COMPARABILITY OF PROCESS A AND PROCESS B DRUG PRODUCTS



Source: Sarepta BLA.

3.4 Concerns Regarding Increased Percentage of Empty Capsids

The dose of the drug product is reported as vector genomes per kilogram (vg/kg) and does not take into account the level of empty capsid residual impurities in each lot. Because of the high dose of vector administered (Applicant proposed doses: 10-70 kg: 1.33×10^{14} vg/kg of body weight; ≥70 kg: 9.31×10^{15} vg) and the proposed acceptance criterion for percent full capsids patients who receive Process B material may receive drug product lots containing a substantial number of empty capsids, potentially resulting in more than 100% additional viral particles being administered, compared to patients who received Process A material. For example, a subject weighing 50 kg administered a product with 50% full capsids will receive 6.7×10^{15} capsids containing the vector genome, and 6.7×10^{15} empty capsids with no potential therapeutic benefit. Reports show that immune responses and associated adverse events (AEs; e.g., T-cell mediated liver injury, thrombocytopenic microangiopathy associated with complement activation) are directly linked to vector doses.[20,21] In addition, empty capsids can lead

[20]Kishimoto, TK and RJ Samulski, 2022, Addressing high dose AAV toxicity - 'one and done' or 'slower and lower'?, Expert Opin Biol Ther, 22(9):1067-1071.
[21]Mingozzi, F and KA High, 2013, Immune responses to AAV vectors: overcoming barriers to successful gene therapy, Blood, 122(1):23-36.

to increased antigenic load, with the potential to enhance recognition and clearance of AAV-transduced cells by activated capsid-specific cytotoxic CD8+ T cells.[22,23,24,25] These properties may result in decreased overall safety and efficacy of the treatment. Therefore, the effects on long-term safety and efficacy of such high levels of empty capsid impurities cannot be determined by analytical testing, and instead require clinical data.

4. Nonclinical Data

Proof-of-concept (POC) studies for SRP-9001 were conducted using rodent models of DMD. The *Dmd*^{mdx} mouse (C57BL/10ScSn-DMD^{mdx}/J) exhibits a mild phenotype with minimal clinical signs, compared with the severe muscle dysfunction in patients with DMD. *Dmd*^{mdx} mice undergo an acute phase of skeletal muscle necrosis that peaks around 3-4 weeks of age, followed by robust regeneration and stabilization of the disease phenotype which is not observed in patients with DMD. With the exception of the diaphragm, which displays more severe and progressive pathology, skeletal muscles of the *Dmd*^{mdx} mouse remain at a chronic low level of damage and muscle pathology as they cycle between muscle degeneration and regeneration.[26]

Damaged skeletal muscle fibers in the *Dmd*^{mdx} mouse show a decrease of approximately 20%-30% in specific force; unlike in patients with DMD, myofibers in the *Dmd*^{mdx} mouse hypertrophy without atrophy in later stages. The *Dmd*^{mdx} mouse has a mild cardiac phenotype, and more severe dystrophic phenotypes such as fibrosis become more pronounced around 15 months of age. Finally, the *Dmd*^{mdx} mouse has a lifespan equivalent to 80% that of a healthy mouse, whereas the lifespan of patients with DMD is only about one-third of the normal human lifespan.

Three primary nonclinical POC studies (Study Report Numbers: SR-20-001 [Process A material, Nationwide Children Hospital], SR-19-061 [Process B material, Thermo Fisher], and SR-21-025 [Process B material, Catalent]) were performed with single intravenous administration of SRP-9001 at dose levels between 8×10^{13} vg/kg to 6×10^{14} vg/kg (Process A) and 4.43×10^{13} vg/kg to 4.01×10^{14} vg/kg (Process B) in 4-8 week old *Dmd*^{mdx} mice. Due to use of different methodologies to determine the physical titers, the dose levels between Processes A and B cannot be directly compared. Functional assessment in these studies was limited to isolated muscle force measurements of the diaphragm and tibialis anterior muscles.

Unlike other shortened forms of dystrophin expressed from the endogenous *DMD* gene, Sarepta's micro-dystrophin is expressed from an AAV vector with a *MHCK7* promoter and is thus regulated differently. The biodistribution analysis indicated that the number of vector genomes per nucleus varied widely across tissues, with the highest quantities of vector DNA present in the liver, followed by the heart and skeletal muscles. Additionally, there were distinct differences in the micro-dystrophin expression profile compared to endogenous dystrophin expression, with supraphysiological levels of

[22]Hui, DJ, SC Edmonson, GM Podsakoff, GC Pien, L Ivanciu, RM Camire, H Ertl, F Mingozzi, KA High, and E Basner-Tschakarjan, 2015, AAV capsid CD8+ T-cell epitopes are highly conserved across AAV serotypes, Mol Ther Methods Clin Dev, 2:15029.
[23]Pien, GC, E Basner-Tschakarjan, DJ Hui, AN Mentlik, JD Finn, NC Hasbrouck, S Zhou, SL Murphy, MV Maus, F Mingozzi, JS Orange, and KA High, 2009, Capsid antigen presentation flags human hepatocytes for destruction after transduction by adeno-associated viral vectors, J Clin Invest, 119(6):1688-1695.
[24]Finn, JD, D Hui, HD Downey, D Dunn, GC Pien, F Mingozzi, S Zhou, and KA High, 2010, Proteasome inhibitors decrease AAV2 capsid derived peptide epitope presentation on MHC class I following transduction, Mol Ther, 18(1):135-142.
[25]Mingozzi, F and KA High, 2013, Immune responses to AAV vectors: overcoming barriers to successful gene therapy, Blood, 122(1):23-36.
[26]Egorova, TV, II Galkin, YV Ivanova, and AV Polikarpova, 2022, Duchenne Muscular Dystrophy Animal Models, Preclinical Animal Modeling in Medicine, Purevjav, P., J. F. Pierre and L. Lu: InTech Open.

micro-dystrophin in the heart, and lower levels in skeletal muscles and liver. The functional consequences of these differences in the expression profile are unclear.

Across the three studies, dose-dependent increases in expression of Sarepta's micro-dystrophin were demonstrated by immunofluorescence (IF) and western blot (WB) in target tissues at 12 weeks post-administration of SRP9001. Increased specific force in the tibialis anterior and diaphragm were observed compared with vehicle-injected *Dmd*^{mdx} control mice, although force measurements generally did not normalize to wild-type levels and were inconsistent across studies and between product lots. Co-localization of beta-sarcoglycan and partial correction of muscle pathology (e.g., decreased central nucleation, decreased collagen deposition, and increased muscle fiber diameter) were observed. Assessment of creatine kinase values (evaluated in Study SR-20-001 only) was inconclusive due to the frequency of missing data and high variability in the individual animal data.

The Applicant provided an exploratory post hoc correlation analysis based on the studies in *Dmd*^{mdx} mice and found a correlation between relative specific force and percentage of micro-dystrophin positive fibers by IF, but no correlation with micro-dystrophin expression by WB. Of note, WB is considered more reliable for quantitative assessment of protein expression due to methodological limitations of using IF (e.g., background fluorescence, variability in intensity, etc.). Additionally, it is unclear whether it is appropriate to pool these data given the differences in methods used for measurement of specific force and IF staining at the different testing facilities where the studies were performed.

Additional POC studies for SRP-9001 (Process B material, Catalent) were also performed in *Dmd*^{mdx} rats at 3-4 weeks of age (Study Report Number: SR-20-012) and 3-5 months of age (Study Report Number: SR-20-013). This rodent model of DMD has a more severe phenotype than the *Dmd*^{mdx} mouse, with measurable motor deficits (reduction in muscle strength and spontaneous motor activity) at 3 months of age, along with dystrophic pathology in the skeletal muscles and heart, including necrosis, degeneration, and fibrosis.[27] No wild-type/normal Sprague Dawley rats were included as controls in these studies.

In Study SR 20-012, single intravenous administration of 1.33×10^{14} vg/kg SRP-9001 in 3–4-week-old *Dmd*^{mdx} rats resulted in broad micro-dystrophin protein expression determined by IF and WB in the skeletal muscles and micro-dystrophin levels in the heart reaching supraphysiological levels. Increased spontaneous activity was observed in SRP-9001-administered animals in an open field test compared with vehicle-injected *Dmd*^{mdx} control rats at 12 and 24 weeks post-administration, although spontaneous activity demonstrated a similar decline compared with the control group between the two time points. Assessment of cardiac parameters by echocardiography demonstrated a trend towards improvement in several parameters; however, the only measurements reaching statistical significance were increased heart rate and decreased left ventricular internal diameter in the SRP-9001 group at the 12-week timepoint. Additionally, no SRP-9001-related reduction in Troponin-I or creatine kinase was observed. SRP-9001-related improvement of dystrophic skeletal muscle pathology (e.g., decreased central nucleation, increased muscle fiber diameter, and reduced fibrosis) was observed at 12 and 24 weeks post-administration.

In Study SR 20-013 in the 3-5 months of age group, despite robust levels of micro-dystrophin expression measured by WB following administration of 1.33×10^{14} vg/kg SRP-9001, no statistically significant functional improvement by open field tests, echocardiography, or improvement of the dystrophic muscle pathology was observed in SRP-9001-administered animals at 12 weeks post-administration.

[27]Larcher, T, A Lafoux, L Tesson, S Remy, V Thepenier, V François, C Le Guiner, H Goubin, M Dutilleul, L Guigand, G Toumaniantz, A De Cian, C Boix, JB Renaud, Y Cherel, C Giovannangeli, JP Concordet, I Anegon, and C Huchet, 2014, Characterization of dystrophin deficient rats: a new model for Duchenne muscular dystrophy, PLoS One, 9(10):e110371.

Thus, although broad micro-dystrophin expression was achieved in both studies, it did not result in similar functional outcomes.

The distinct functional outcomes observed in *Dmd*^{mdx} rats in Study SR-20-012 and Study SR-20-013 suggest that micro-dystrophin expression is not a reliable predictor of functional benefit. Expression of the engineered micro-dystrophin and proper localization to the sarcolemma may be readily achieved but does not directly correspond with meaningful biological activity or functional improvement. Even in rodents, the conditions under which the engineered micro-dystrophin can provide functional benefit are complex and these studies indicate that factors such as the stage of disease progression may play an important role.

Species-specific differences in compensatory mechanisms, increased regenerative capacity of muscle fibers in rodents, and physiological differences (e.g., muscle volumes, physiological loads, etc.) in the skeletal and cardiac muscles of rodents and humans make it challenging to extrapolate function of the micro-dystrophin protein from the nonclinical studies to predict clinical benefit. These non-Good Laboratory Practice (GLP) POC studies had significant limitations in their study designs, documentation, and data reporting. These studies were not designed or adequately powered (e.g., studies in *DMD*^{mdx} mice included 3-8 animals/group) to determine correlation of functional outcomes with micro-dystrophin expression and measures to reduce bias such as randomization of animals to study groups, masked assessment of activity endpoints, and standardization of experimental methods (e.g., sampling procedures, WB, IF, muscle force measurements, etc.) were not implemented consistently across studies.

The limited nonclinical data for SRP-9001 underscore the importance of well-controlled clinical trials to determine whether the engineered micro-dystrophin expressed by SRP-9001 has clinically meaningful function in humans and its appropriateness as a surrogate endpoint that is likely to predict clinical benefit.

5. Efficacy and Safety

5.1 Clinical Efficacy Assessment

5.1.1 Source of Clinical Data

Data from three ongoing clinical studies are available and submitted in the BLA. Table 2 summarizes the three studies.

TABLE 2. CLINICAL STUDIES INTENDED TO SUPPORT EFFICACY OF SRP-9001

Study Identifier	Study Population	Study Design	Treatment (SRP-9001 vg/kg)	Primary and Key Secondary Endpoints	Number of Subjects	Number of Centers
9001-101	Ambulatory boys with DMD, age 4-7 years	Open- label, single-arm	1.33 x 10^{14}[a]	Primary: Safety Secondary: • Micro-dystrophin expression at 12 weeks • 100-meter timed walk test	4	Single US site
9001-102	Ambulatory boys with DMD, age 4-7 years	Part 1: Randomized (1:1), double-blind, placebo-controlled (48 weeks) Part 2: cross-over, blinding maintained (48 weeks) Part 3: Open-label follow-up (5 years)	Part 1[a]: intended dose 1.33 × 10^{14} (n=8) 6.29 × 10^{13} (n=6) 8.94 × 10^{13} (n=5) Placebo (n=21) Part 2[a]: intended dose 1.33 × 10^{14} (n=20)	Primary: • Micro-dystrophin expression at 12 weeks • NSAA at 48 weeks Secondary: • Time to rise from floor at 48 weeks • Time to ascend 4 steps at 48 weeks • 100-meter timed walk test at 48 weeks • 10-meter timed walk test at 48 weeks	41	2 US sites
9001-103	Boys with DMD • Cohort 1: 20 ambulatory boys ages 4-7 years old • Cohort 2: 7 ambulatory boys age 8-17 years old • Cohort 3: 6 nonambulatory boys, no age restriction • Cohort 4: ambulatory boys ages 3-4 years old	Open- label, single-arm	1.33 × 10^{14}[b]	• Micro-dystrophin expression at 12 weeks • To support use of micro-dystrophin as surrogate endpoint reasonably likely to predict clinical benefit, NSAA results of Cohort 1 at 52 weeks were compared with controls from external DMD registries.	39 total (cohort 1, 20)	5 US sites

Source: Sarepta BLA

[a]SRP-9001 manufactured using Process A

[b]SRP-9001 manufactured using Process B

Abbreviations: DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; US, United States.

5.1.2 Clinical Efficacy Outcomes

5.1.2.1 Study 101

Study SRP-9001-101 (Study 101) is a first-in-human, open-label, single-arm study. The primary objective was to evaluate safety. The secondary objectives were to evaluate expression of Sarepta's micro-dystrophin and performance of subjects on the 100-meter timed test.

Four ambulatory subjects with DMD had a mean age of 4.8 years (range: 4 to 6 years), mean weight of 18.1 kg (range: 13.7 to 21.4 kg), mean NSAA total score of 20.5 (range: 18.0 to 26.0), and mean time to rise from floor of 3.7 seconds (range: 3.0 to 4.1 s). All subjects were on a stable dose of corticosteroids for at least 12 weeks prior to SRP-9001 infusion and throughout the first year of the study and had a baseline anti-AAVrh74 total binding antibody titers $\leq$1:100 as determined by clinical trial enzyme-linked immunosorbent assay (ELISA).

At Year 1 post-SRP-9001 infusion, a mean decrease from baseline in time to walk 100 meters of 9 seconds (range: 2 to 24 seconds) was observed. In addition, a mean increase from baseline in NSAA total score of 5.5 (range: 2 to 8) was also observed.

At Year 4 post-SRP-9001 infusion, a mean decrease from baseline in time to walk 100 meters of 7 seconds (range: 0 to 14 seconds) was observed. In addition, a mean increase from baseline in NSAA total score of 7 (range: 4 to 11) was also observed.

5.1.2.2 Study 102

Study SRP-9001-102 (Study 102) is an ongoing multi-center study. Data from Part 1 and Part 2 are available.

Part 1

In the 48-week randomized, double-blind, placebo-controlled Part 1, 41 ambulatory subjects with DMD 4-7 years old who either have a confirmed frameshift mutation or premature stop codon mutation between exons 18 to 58 in the *DMD* gene were randomized in a 1:1 ratio to receive either a single intravenous infusion of SRP-9001 (N=20) at the intended dose of 1.33×10^{14} vg/kg or placebo (N=21). However, in the SRP-9001 group it was retrospectively determined, 8 subjects received the intended dose, 6 subjects received approximately two-thirds of the intended dose (8.94×10^{13} vg/kg), and 6 subjects received about half of the intended dose (6.29×10^{13} vg/kg) and this was driven by a change in the analytical method. Randomization was stratified by age (4-5 years old vs 6-7 years old). Key demographic and baseline characteristics are presented in Table 3 below. All subjects were on a stable dose of corticosteroids for at least 12 weeks prior to SRP-9001 infusion and had a baseline anti-AAVrh74 total binding antibody titers $\leq$1:100 as determined by clinical trial ELISA. The day prior to treatment, the subject's background dose of corticosteroid for DMD was increased to at least 1 mg/kg of a corticosteroid (prednisone equivalent) daily and continued at this level for at least 60 days after the infusion, unless earlier tapering was clinically indicated.

TABLE 3. DEMOGRAPHIC AND BASELINE CHARACTERISTICS, STUDY 102 PART 1

Characteristic	SRP-9001 (N=20)	Placebo (N=21)
Race group White (%)	65	81
Mean age [range] (years)	6.3 [4.5 to 7.9]	6.2 [4.3 to 7.98]
Mean weight [range] (kg)	23.3 [18.0 to 34.5]	21.6 [15.0 to 30.0]
Mean NSAA total score [range]	19.8 [13 to 26]	22.6 [15 to 29]
Mean time to rise from floor [range] (seconds)	5.1 [3.2 to 10.4]	3.6 [2.7 to 4.8]

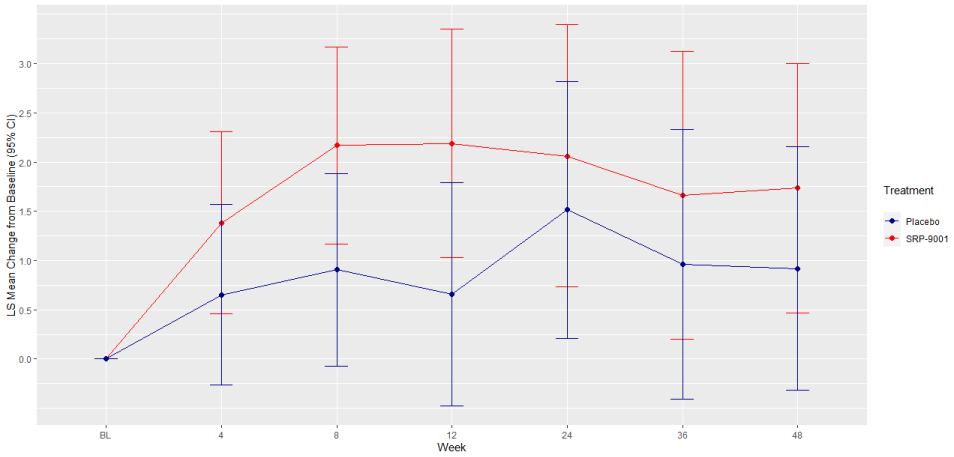
Source: Sarepta BLA

One of the primary objectives was to evaluate the effect of SRP-9001 on NSAA total score.

A Mixed Model for Repeated Measures (MMRM) was used to compare SRP-9001 with placebo. In this model, the response consists of the NSAA total score change from baseline at each postbaseline visit. The model includes the covariates of treatment group, visit, treatment group by visit interaction, age group (4-5 years old and 6-7 years old), baseline NSAA total score, and baseline NSAA total score by visit interaction. A random intercept is incorporated to account for the within-subject correlations and an unstructured covariance matrix is used to model the within-subject variance-covariance structure. Missing data are assumed to be missing at random.

Based on MMRM analysis in the modified-Intent to Treat analysis set (defined as all randomized subjects who receive study treatment with treatment group designated according to randomization), the least square (LS) mean changes (standard error [SE]) in NSAA total score from baseline to Week 48 were 1.7 (0.6) and 0.9 (0.6) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference (0.8 [0.9]) at Week 48 between SRP-9001 and placebo is not statistically significant (95% confidence interval [CI]: -1.0, 2.7; p=0.37). The LS mean change from baseline in NSAA total score over time for SRP-9001 and placebo groups is shown in Figure 6. The Applicant states that the mean change from baseline in NSAA total score was “numerically greater at all time-points” for the SRP-9001 group. FDA’s assessment is that the difference between the SRP-9001 and placebo groups at all time points is well within uncertainty bounds, which is also demonstrated by the lack of even a trend toward statistical significance.

FIGURE 6. NSAA TOTAL SCORE: LS MEAN CHANGE FROM BASELINE OVER TIME



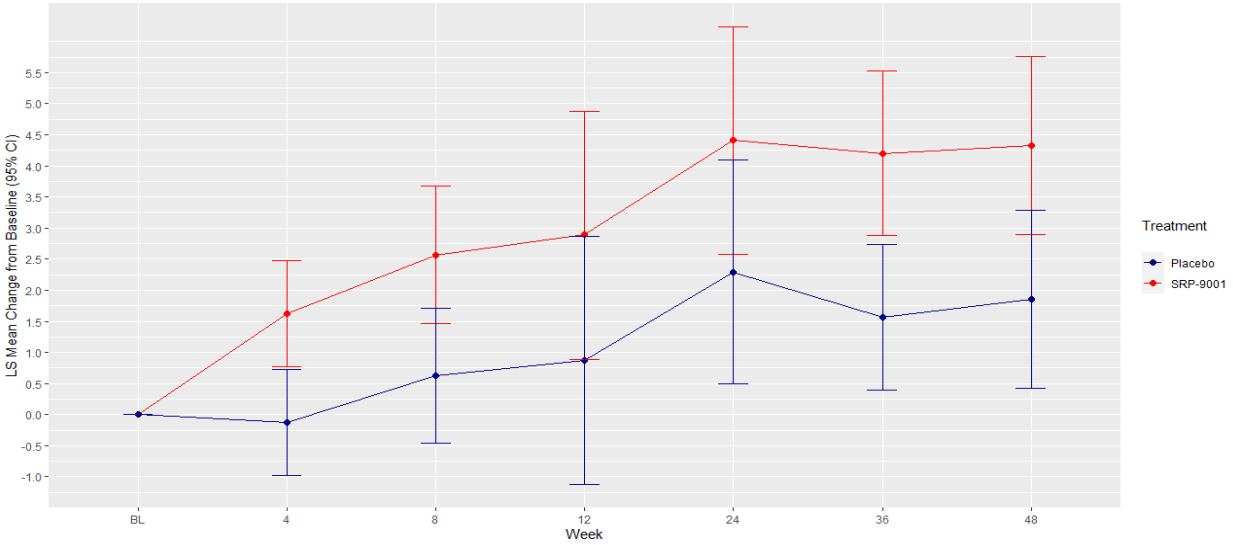
Source: FDA
Abbreviations: LS, least square; NSAA, North Star Ambulatory Assessment; CI, confidence interval.

Age is an important prognostic factor in the progression of DMD and thus the treatment effect on the outcome was further evaluated by stratifying on two age subgroups, 4-5 years old and 6-7 years old. Figure 7 and Figure 8 summarize the LS mean change from baseline in NSAA total score over time for SRP-9001 and placebo in the subgroups 4-5 years old and 6-7 years old, respectively.

For subjects aged 4-5 years old, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were 4.3 (0.7) and 1.9 (0.7) for the SRP-9001 placebo groups, respectively. While the LS mean (SE) treatment difference (2.5 [0.9]) at Week 48 between SRP-9001 and placebo resulted in a p-value of 0.017, it is important to note that this analysis was not prespecified for hypothesis testing and no prespecified multiplicity adjustment strategy was employed. Post hoc subgroup tests following an overall nonsignificant test in the population as a whole can only be considered hypothesis-generating, and this subgroup analysis therefore must be interpreted with caution.

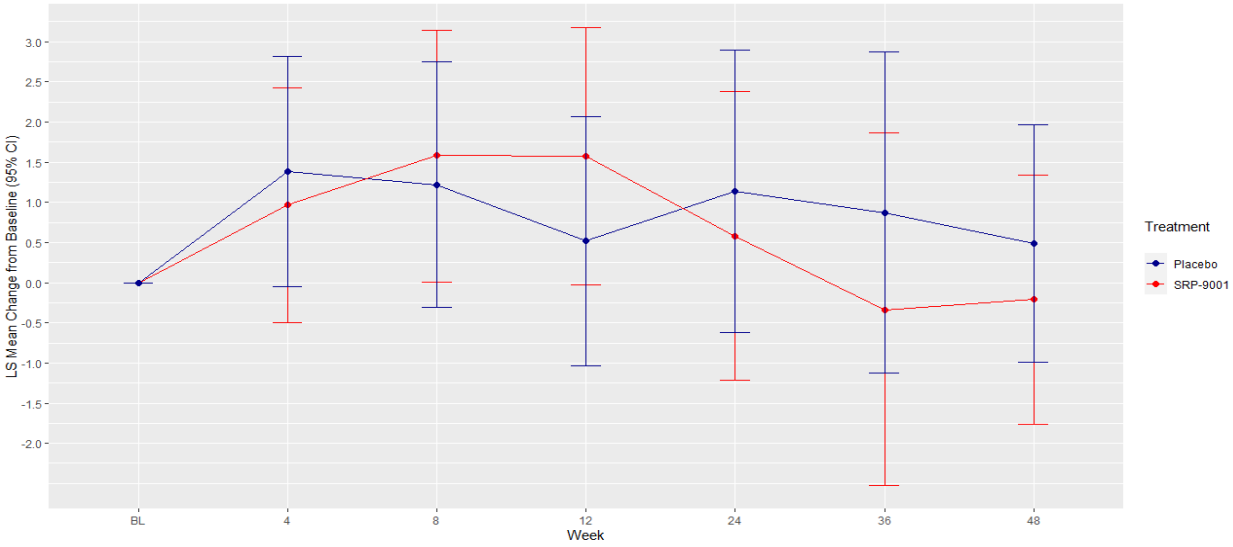
For subjects aged 6-7 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) and 0.5 (0.7) for the SRP-9001 and placebo groups, respectively. The LS mean (SE) treatment difference was -0.7 (1.1) at Week 48 between SRP-9001 and placebo with a 95% CI of [-3.0, 1.6] and a two-sided p-value of 0.54. Similarly, this subgroup analysis is also exploratory, given the inadequate group size and lack of alpha control.

FIGURE 7. NSAA TOTAL SCORE: LS MEAN CHANGE FROM BASELINE OVER TIME (4-5 YEARS OLD)



Source: FDA
Abbreviations: LS, least square; NSAA, North Star Ambulatory Assessment; CI, confidence interval.

FIGURE 8. NSAA TOTAL SCORE: LS MEAN CHANGE FROM BASELINE OVER TIME (6-7 YEARS OLD)



Source: FDA
Abbreviations: LS, least square; NSAA, North Star Ambulatory Assessment; CI, confidence interval.

For all three dose levels of SRP-9001 that were administered during Study 102 Part 1, the 95% CIs of LS mean treatment difference in NSAA total score at Week 48 included zero (Table 4). However, due to the small sample sizes in each dose level, it is not possible to draw any strong conclusions from this analysis, which can only be considered as exploratory.

TABLE 4. NSAA TOTAL SCORE: LS MEAN CHANGE FROM BASELINE BY LOT/DOSE

Lot	Dose (vg/kg)	SRP-9001 (N=19)	Placebo (N=21)	LS Mean Treatment Difference (SE)	95% CI
G02A0918-1	6.29×10^{13} [0.5X]	6	21	0.7 (1.5)	(–2.5, 4.0)
G02A0918-2	8.94×10^{13} [0.67X]	5[a]	21	2.6 (1.3)	(–0.04, 5.3)
Others	1.33×10^{14} [1.0X]	8	21	–1.5 (1.2)	(–4.0, 1.0)

Source: FDA
a. One subject did not have NSAA at Week 48.
Abbreviations: CI, confidence interval; LS, least-square; NA, not applicable; NSAA, North Star Ambulatory Assessment; SE, standard error.

The secondary endpoints in Part 1 include change from baseline to Week 48 in 100-meter timed test, time to ascend 4 steps, time to rise from the floor, and 10-meter timed test. SRP-9001 group did not show improvement in change from baseline to Week 48 for any of the secondary endpoints compared to the placebo (please see 8.1. Exploratory Assessments of Secondary Endpoints of Study 102 Part 1). As the primary functional endpoint, NSAA total score change from baseline to Week 48, failed, the secondary endpoints in this study were not formally tested and the analyses of secondary endpoints can only serve as exploratory.

Part 2

In Part 2, subjects in the Part 1 placebo group received SRP-9001 and had a mean increase from Part 2 baseline to Week 48 in NSAA total score of 1.3 (standard deviation [SD]: 2.7).

For subjects who received SRP-9001 in Part 1, the mean NSAA total score change from Part 2 baseline to Week 48 is 0.1 (SD: 6.6). However, exploratory analysis of the group by age range shows that at Part 2 Week 48, the mean NSAA total score change from Part 2 baseline was 0.4 (SD 2.4) for the 4-5 years old subgroup while the mean NSAA total score declined by 4.3 (SD 5.1) from Part 2 baseline for the 6-7 years old subgroup.

5.1.2.3 Study 103 Cohort 1

The study is an ongoing, open-label study with 4 cohorts of male subjects with DMD. The primary objective of the study was to evaluate Sarepta's micro-dystrophin protein expression as measured by WB. One of the exploratory objectives was to evaluate the effect of SRP-9001 on NSAA total score in ambulatory subjects with DMD.

Cohort 1 enrolled 20 male ambulatory subjects with DMD and a confirmed frameshift mutation or premature stop codon in the *DMD* gene with a mean age of 5.8 years (range: 4.4 to 7.9 years), mean weight of 21.2 kg (range: 15.2 to 33.1 kg), mean NSAA total score of 22.1 (range: 18 to 26). All subjects were on a stable dose of corticosteroids for at least 12 weeks prior to SRP-9001 infusion and throughout the first year of the study and had a baseline anti-AAVrh74 total binding antibody titers $\leq$1:100 as determined by clinical trial ELISA (only patients with baseline anti-AAVrh74 total binding antibody titers <1:400 are eligible for enrollment).

At Week 52 post-SRP-9001 infusion, a mean change from baseline in NSAA total score of 4.0 (SD: 3.5) was observed.

5.1.2.4 External Control Analysis

The comparison with external control subjects with DMD included study-level and integrated-level analyses, based on subjects treated with SRP-9001 at the intended dose of 1.33×10^{14} vg/kg in Studies

101 (N=4), 102 Part 1 (N=8) and Part 2 (N=21), and 103 Cohort 1 (N=20). The propensity score weighting method was applied to select external control subjects with greater similarity to the subjects from the SRP-9001 studies.

The external control data were obtained from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS); the Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) clinical study, which evaluated three protocols for administering corticosteroids to boys with DMD; and Eli Lilly and Company's Study of Tadalafil for Duchenne Muscular Dystrophy (NCT01865084; Lily Dataset), a Phase 3 randomized, double-blind, placebo-controlled parallel 3-arm study assessing the effect of tadalafil on maintenance of ambulation in boys with DMD. Among a total of 765 subjects from these datasets, 131 met all the applied entry criteria to be considered consistent with the characteristics of subjects enrolled in the SRP-9001 studies and were followed for at least 1 year for outcomes.

It is important to note that the external control comparison has the following limitations/weakness:

- The disease course of DMD is highly heterogeneous across this age range, increasing the likelihood of non-comparable patients across data sources.
- The intended treatment effect is unlikely to be more than moderate, and thus the analysis would not be able to provide results persuasive enough to overcome potential biases in the non-concurrent analysis.
- There are significant concerns regarding the comparability of the study population to external controls and it is difficult to determine that the external population is similar to the study population with regard to all key baseline characteristics including unobserved baseline characteristics.
- Outcome measures (e.g., NSAA total score) are process-dependent, so data generated from different studies are not directly comparable.

The validity of the propensity score weighting method depends on critical and unverifiable assumptions, including the incorporation of all important confounding factors (and some important confounding factors may not even be measured) and appropriate specification of the functional form of the relationship between confounding factors and probability of SRP-9001 treatment. For the integrated analysis, the LS mean treatment difference in NSAA total score from baseline to one year between two groups is 2.5 (95% CI: [1.6, 3.5]). Although zero is not included in the 95% CI, due to the critical limitations of external control comparisons, this analysis and other study-level analyses can only serve as exploratory and do not provide confirmatory evidence to support clinical benefit of SRP-9001.

5.1.3 Biomarker Assessment

5.1.3.1 Biomarkers Overview

After one-time intravenous infusion, SRP-9001 is expected to be transduced to the target cells and lead to expression of SRP-9001 transgene, Sarepta's micro-dystrophin. Muscle biopsy samples were collected at baseline and Week 12 post-infusion to evaluate the quantity of expression of the SRP-9001 transgene (micro-dystrophin levels by WB), the level of vector genome copy numbers (VGCs), correct localization of the expressed protein at the sarcolemma membrane (immunofluorescence fiber intensity [IF fiber intensity], and IF percent Sarepta's micro-dystrophin positive fiber (PDPF) [%]).

5.1.3.2 Key Biomarkers Results

5.1.3.2.1 Quantity of Micro-dystrophin Expression in Muscle Tissue Biopsy Measured by Western Blot

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 dystrophin in normal subjects without DMD or BMD) in biopsied muscle tissue 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.

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 9 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 5). 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 9A).

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 9B).

TABLE 5. 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	—

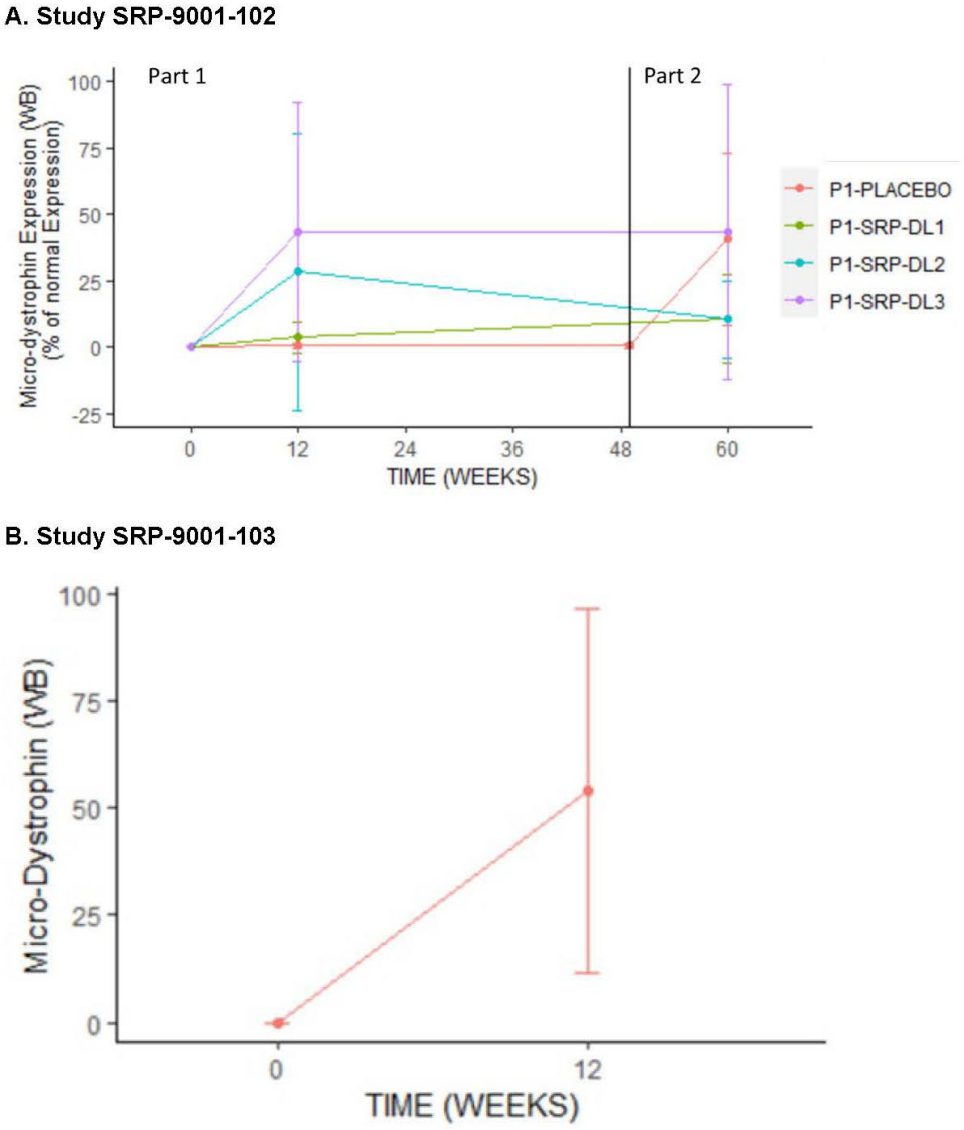
Source: FDA

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.

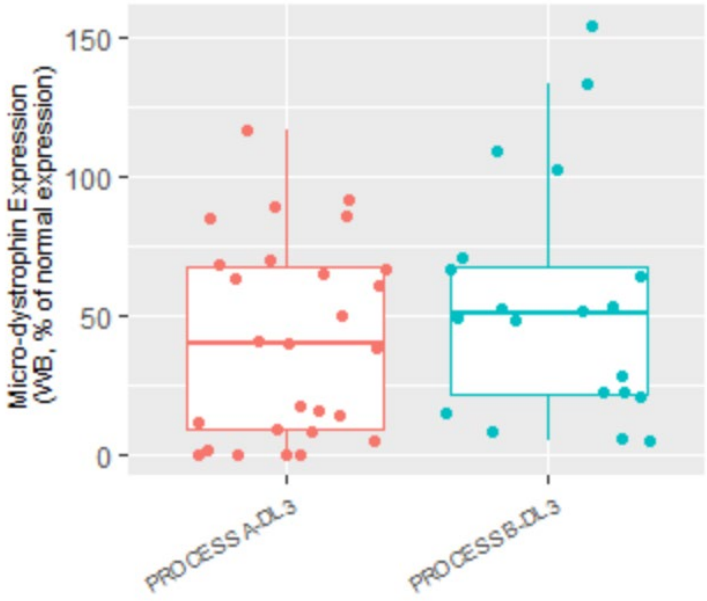
FIGURE 9. SAREPTA'S MICRO-DYSTROPHIN EXPRESSION (WESTERN BLOT ASSAY) OVER TIME



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 10, 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.

FIGURE 10. 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

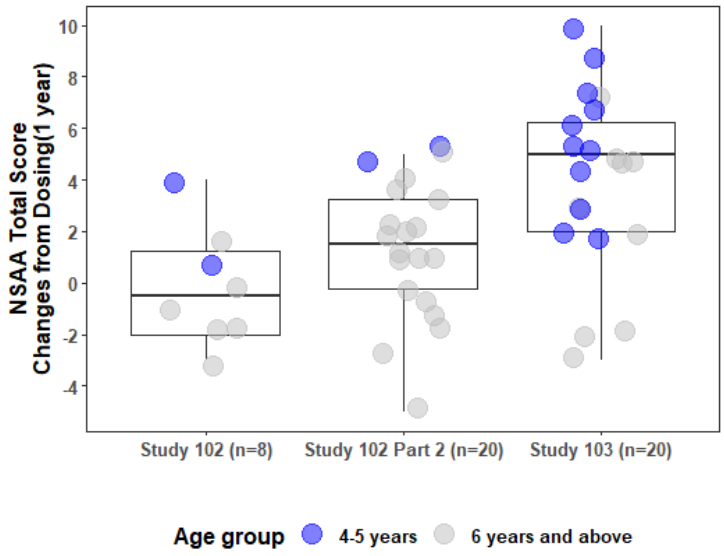


Source: FDA
Note: PROCESS A-DL3: subjects in Study 102 who received placebo in Part 1 (102-P1-PLACEBO) and received SRP-9001 in Part 2 at the dose of 1.33×10^{14} vg/kg.
Abbreviation: WB, Western blot.

5.1.4 Relationship Between Micro-dystrophin Protein Expression and Clinical Efficacy Outcome

The relationship between Sarepta's micro-dystrophin protein expression by WB and the functional outcome was evaluated using both (i) Study 102 Part 1, the only randomized, double-blinded, placebo-controlled study, and (ii) the pooled data from Study 102 Part 1 and Part 2 and Study 103 Cohort 1. The analysis from the pooled data assumes that the difference in study design (open-label, single-arm versus randomized, double-blind, concurrent-controlled) does not affect the effort-driven functional outcome assessment (NSAA) or the relationship between expression of Sarepta's micro-dystrophin and the functional outcome. However, such assumption is likely problematic. As shown in Figure 11 below, the NSAA total score change in subjects of the randomized, double-blind, placebo-controlled Study 102 Part 1 is lower than that in subjects of the functionally open-label Study 102 Part 2 or the open-label Study 103 for the proposed dose of 1.33×10^{14} vg/kg.

FIGURE 11. BOXPLOT OF NSAA TOTAL SCORE CHANGES FROM DOSING AT 1 YEAR ACROSS STUDY 102 PART 1, STUDY 102 PART 2 AND STUDY 103 FOR THE DOSE 1.33 × 10^{14} VG/KG



Source: FDA
Note: Solid circles represents subjects colored by age groups.
Abbreviations: NSAA, North Star Ambulatory Assessment.

For the functional outcome, NSAA total score change from baseline to Year 1 post-infusion (48 weeks for Study 102, and 52 weeks for Study 103) was used. For Sarepta's micro-dystrophin protein expression, micro-dystrophin change from baseline to Week 12 post SRP-9001 infusion measured by WB was used. The preference of using WB data rather than IF data (the number of positive fibers) to quantify Sarepta's micro-dystrophin protein is due to the following reasons:

(1) Sarepta's micro-dystrophin assessed by WB was the primary endpoint in both Studies 102 and 103.

(2) WB assay measures the absolute quantity of Sarepta's micro-dystrophin from each muscle biopsy sample. The quantity of Sarepta's micro-dystrophin was then adjusted by total sample protein amount of the biopsy sample.

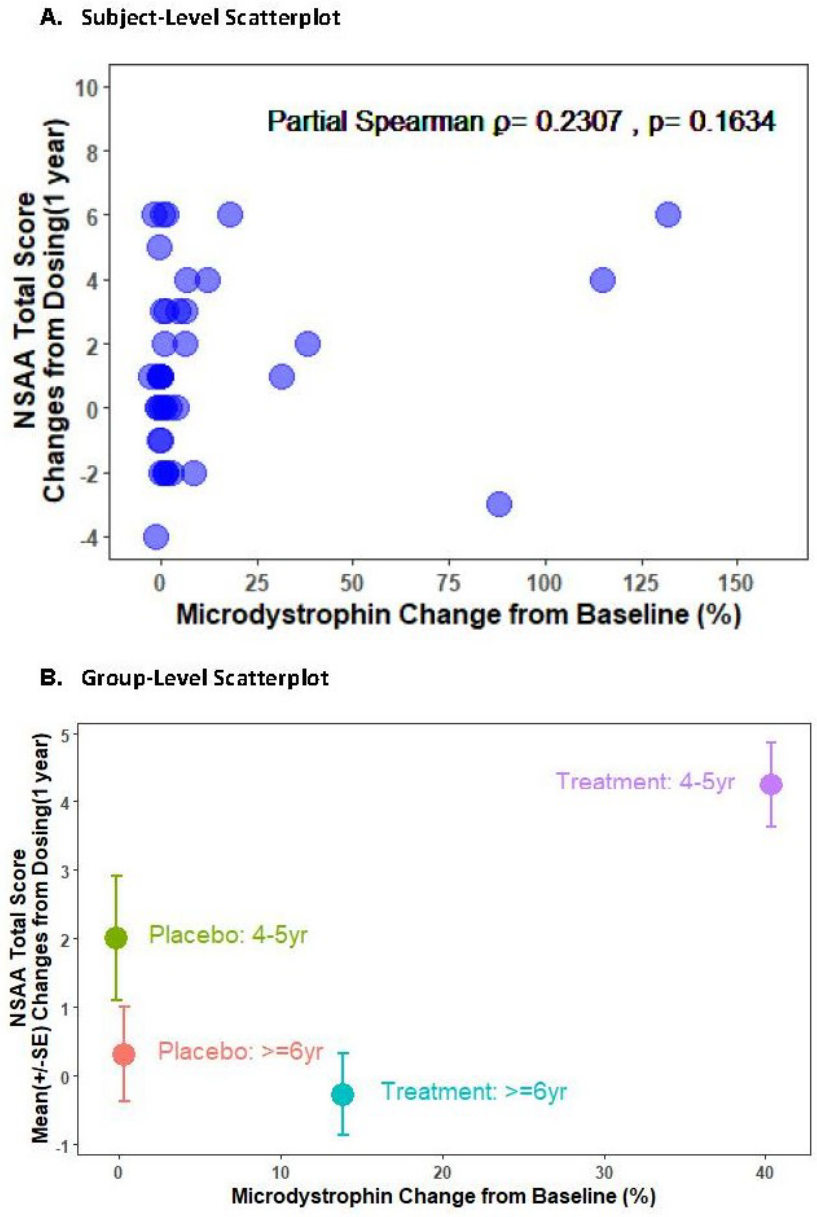
(3) IF staining assay localizes the expressed protein at the sarcolemma membrane. IF staining provides information of IF fiber intensity and the percentage of Sarepta's micro-dystrophin positive fibers within the muscle biopsy samples. The percentage of Sarepta's micro-dystrophin positive fibers information 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.

5.1.4.1 Analysis Based on Study 102 Part 1

The subject-level scatterplot of Week 12 micro-dystrophin and Year 1 (48 weeks) NSAA total score changes along with partial Spearman correlation coefficient is shown in Figure 12A. The partial Spearman correlation was adjusted for NSAA total score and age at baseline. The result does not show clear association between Week 12 Sarepta's micro-dystrophin protein expression and Year 1 NSAA total score changes.

The group-level relationship between Week 12 Sarepta's micro-dystrophin and Year 1 NSAA total score changes by treatment and age group are shown in Figure 12B. The result shows the differences in treatment effect by age group (4-5 years old vs >6 years old).

FIGURE 12. RELATIONSHIP BETWEEN WEEK 12 MICRO-DYSTROPHIN CHANGES FROM BASELINE AND NSAA TOTAL SCORE AT YEAR 1 USING SRP-9001-102 PART-1 DATA ONLY



Source: FDA
Note: Partial spearman correlation coefficient is adjusted for baseline NSAA score and age at dosing
Abbreviations: NSAA, North Star Ambulatory Assessment, SE: Standard Error.

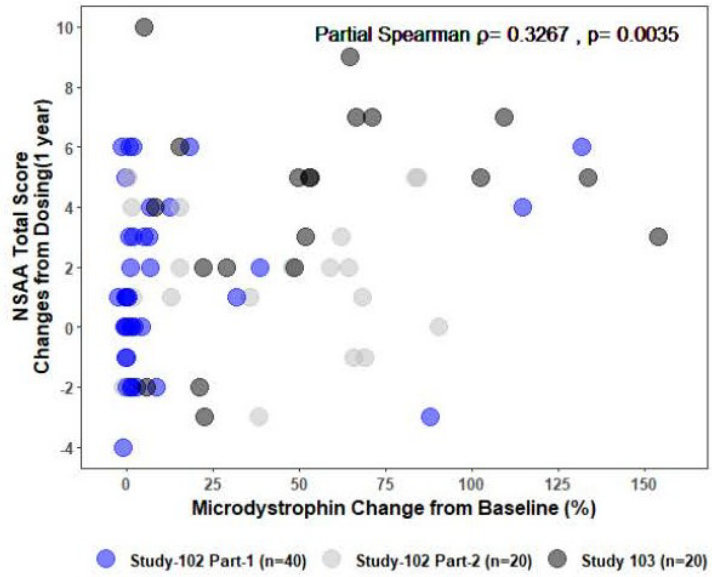
5.1.4.2 Analysis Based on Pooled Data from Study 102 and Study 103

The subject-level scatterplot of Week 12 micro-dystrophin and Year 1 NSAA total score changes along with partial Spearman correlation coefficient is shown in Figure 13. The partial Spearman correlation

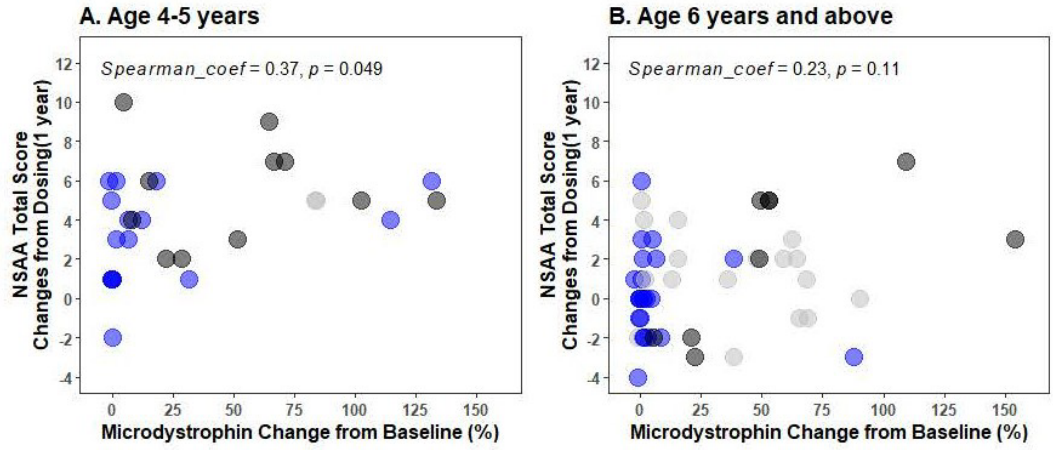
was adjusted for NSAA total score and age at baseline. The result showed that increase in Week 12 Sarepta's micro-dystrophin protein expression is associated with Year 1 NSAA total score changes (Figure 13A). The association observed using the pooled data of all subjects from Study 102 and Study 103 may be primarily driven by subjects 4-5 years old as there is an association for the 4-5 years old subgroup versus no clear association for the ≥6 years old subgroup (Figure 13B).

FIGURE 13. RELATIONSHIP BETWEEN WEEK 12 MICRO-DYSTROPHIN CHANGES FROM BASELINE AND NSAA TOTAL SCORE AT YEAR 1

A. Pooled Data



B. Pooled Data by Age Group

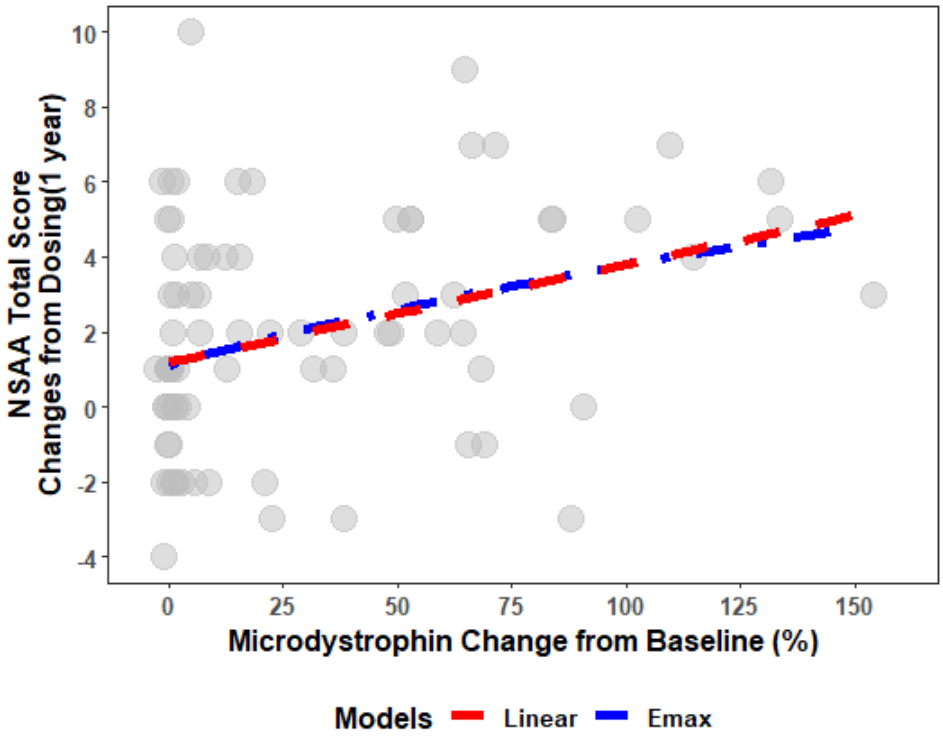


Source: FDA
Note: Partial spearman correlation coefficient is adjusted for baseline NSAA score and age.
Abbreviations: NSAA, North Star Ambulatory Assessment.

The relationship between Week 12 Sarepta's micro-dystrophin and Year 1 NSAA total score change was then evaluated using linear and saturable effect (Emax) model. The findings showed linear model as an adequate model to describe the data among the three structural models evaluated (Figure 14). The

estimate of slope, based on linear model, was 0.026 (p-value 0.0038), i.e., every 10% increase in micro-dystrophin expression is associated with 0.26 units improvement in NSAA total score. Additional analyses were done to evaluate if micro-dystrophin effect is significant even after adjusting for multiple baseline predictors such as baseline age and NSAA total scores. After inclusion of baseline prognostic factors, such as age and NSAA total score in the linear model, the estimate of slope remained nominally significant (p-value <0.05).

FIGURE 14. RELATIONSHIP BETWEEN WEEK 12 MICRO-DYSTROPHIN CHANGES FROM BASELINE AND NSAA TOTAL SCORE AT YEAR 1



Source: FDA
Abbreviations: NSAA, North Star Ambulatory Assessment.

Overall, the analyses of pooled data from Study 102 (Part 1 and Part 2) and Study 103 Cohort 1 suggest that Sarepta's micro-dystrophin at Week 12 is associated with NSAA total score changes at Year 1. However, the persuasiveness of such associations is uncertain, considering that since approximately two-thirds of the subjects were from open-label studies (Study 102 Part 2 and Study 103), their inclusion would be expected to favor an association between treatment with SRP-9001 and subsequent improvement on NSAA. In addition, the observation of no clear association for the ≥6 years old subgroup raises further doubt that expression of Sarepta's micro-dystrophin at Week 12 is reasonably likely to predict clinical benefit for all ambulatory patients with DMD.

5.1.5 Efficacy Issues in Detail

Clinical outcomes are a key factor in concluding that a candidate surrogate endpoint can be considered "reasonably likely to predict clinical benefit." Since Sarepta's micro-dystrophin does not occur in nature, these data can only be obtained from clinical studies.

Because the NSAA is effort-driven, scores are susceptible to bias when evaluated under open-label conditions. Thus, the only reliable data are from Study 102 Part 1, which was randomized, double-blind, and placebo controlled.

- That study demonstrated no statistically significant difference in change in NSAA scores at Week 48 between subjects who received SRP-9001 compared with those who received placebo despite the demonstration of Sarepta's micro-dystrophin expression at Week 12.

- Based on the results of partial Spearman analysis at the individual subject level (correlation coefficient 0.23, p=0.1637), there is no clear association established between Sarepta's micro-dystrophin expression at Week 12 (determine by WB) and NSAA total score change.

- The group-level scatterplots showed no relationship between Week 12 Sarepta's micro-dystrophin and Year 1 NSAA total score changes, as suggested by negative weighted Spearman coefficient, with the intended dose of 1.33×10^{14} vg/kg showing less NSAA total score improvement than the placebo group. The group-level scatterplots also seem to indicate that the subgroup of subjects who received 8.94×10^{13} vg/kg (approximately two-thirds of the intended dose) had better clinical outcomes at Year 1 despite a smaller increase in Sarepta's micro-dystrophin protein expression at Week 12.

5.2 Safety Issues

As outlined below, the key safety concerns of SRP-9001 can be summarized into three main categories:

- Safety of the class of AAV vector-based gene therapy products

- Serious adverse events (SAEs) observed in the clinical studies of SRP-9001

- Concern of cross-reactivity with other AAV vector-based gene therapy products

5.2.1 Toxicities Associated with Class of AAV Vector-Based Gene Therapy Products

In recent years, there have been multiple reports of treatment-emergent serious adverse events (TESAEs; SAEs that occur after treatment has started) in studies with systemic administration of AAV vector-based gene therapy products. These TESAEs include hepatotoxicity [e.g., acute liver injury [ALI] and hepatic failure] and thrombotic microangiopathies, with some TESAEs resulting in the death of study subjects.[28,29]

Oncogenicity due to integration and insertional mutagenesis is also a potential risk of AAV vectors, based on findings of tumors in mice and, more recently, hepatocyte clonal expansion in dogs. Specifically, integration and clonal expansion were noted in the livers of hemophilic dogs many years after administration of an AAV vector, with insertions noted near genes that control cell growth.[30] Although AAV vectors have not been shown to cause tumors in humans or nonrodent species, studies in animals indicate a potential for oncogenicity and suggest a need for long-term monitoring.

[28]FDA, 2021, Briefing Document: Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting #70, Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT), https://www.fda.gov/media/151599/download.
[29]Zolgensma, U.S. Prescribing Information, 2019, Novartis Gene Therapies, Inc., https://www.fda.gov/media/126109/download
[30]Nguyen, GN, JK Everett, S Kafle, AM Roche, HE Raymond, J Leiby, C Wood, CA Assenmacher, EP Merricks, CT Long, HH Kazazian, TC Nichols, FD Bushman, and DE Sabatino, 2021, A long-term study of AAV gene therapy in dogs with hemophilia A identifies clonal expansions of transduced liver cells, Nat Biotechnol, 39(1):47-55.

The emerging information about these risks and toxicities of systemically administered AAV vector-based gene therapy product has to be considered in the benefit-risk assessment of SRP-9001 for its intended pediatric patient population who will receive the product at a young age.

5.2.2 Serious Adverse Events Observed in Clinical Studies of SRP-9001

5.2.2.1 Sources of Data for Safety

Safety was assessed in 85 male DMD subjects with a confirmed mutation in the *DMD* gene in the 3 ongoing clinical studies (101, 102, and 103) (Exposure Analysis Set). All subjects had exposure to a one-time intravenous infusion of SRP-9001 (Table 2). The mean age of subjects was 7.1208 years (range: 3.24 to 20.23 years)

Forty-five subjects in Study 101 and Study 102 received SRP-9001 using manufacturing Process A and 40 subjects in Study 103 received SRP-9001 using manufacturing Process B.

Seventy-three subjects received the proposed dose of 1.33×10^{14} vg/kg (33 received Process A SRP-9001 and 40 received Process B SRP-9001), and 12 received a lower dose.

In Study 103, Cohort 2 enrolled ambulatory subjects ≥8 to <18 years old, and there were no age restrictions for enrollment in Cohort 3. Therefore, subjects treated with Process B SRP-9001 were older (Mean of 7.57 years vs Mean of 6.87 years) and weighed more (Mean of 28.7 kg vs Mean of 24.1 kg) than those treated with Process A SRP-9001 at the proposed dose.

The median duration of follow-up in the combined Studies 101, 102, and 103 was 1.8 (Mean of 2.15) years, with a range of 0.5 to 4.8 years.

5.2.2.2 Safety Summary of SRP-9001 Clinical Studies

For the Exposure Analysis Set, 85 subjects had a total of 1230 treatment-emergent adverse events.

No deaths occurred during any of the studies.

The percentage of subjects with treatment-related treatment-emergent adverse events were similar between subjects who received intended dose of Process A SRP-9001 (91%) and Process B SRP-9001 (83%).

Overall, 11 subjects (12.9%) had 13 SAEs: 8 (17.8%) were treated with Process A SRP-9001 and 5 (10.3%) were treated with Process B SRP-9001.

The most frequent adverse reactions (incidence ≥5%) observed in the three studies include vomiting (61%), nausea (40%), acute liver injury (37%), pyrexia (24%), and thrombocytopenia (12%).

There were no AEs leading to study discontinuation; however, two subjects who received SRP-9001 in Study 102 Part 1 did not receive placebo in Part 2 due to AEs (irritability due to steroids, femoral fracture), but remained in the study for follow-up.

5.2.2.3 Adverse Event of Special Interests

Acute Serious Liver Injury

In ambulatory patients with DMD, high aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase up to ~22 × upper limit of normal [ULN]) originating from degenerating muscle are often observed.[31]

Both ALI and acute serious liver injury have been reported in clinical trials of SRP-9001. ALI is defined as gamma-glutamyl transferase >3 × ULN, glutamate dehydrogenase (GLDH) >2.5 × ULN, alkaline phosphatase >2 × ULN, or ALT >3 × baseline excluding ALT elevation from degenerating muscle in patients with DMD. Acute serious liver injury is defined as an AE satisfying the definition for ALI and the seriousness criteria of death, life-threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, or important medical event.

Fourteen subjects (31%) treated with Process A SRP-9001 (13 [40%] treated at the intended dose) and 17 subjects (44%) treated with Process B SRP-9001 developed ALI. Of these subjects, hospitalization was necessary for 3 subjects treated with Process A SRP-9001 (7%) and 2 subjects treated with Process B SRP-9001 (5%).

Although the percentage of subjects treated with Process B SRP-9001 who had ALI based on elevated GLDH is higher than in subjects treated with Process A material, we note that in earlier studies—Study 101 and Study 102 Part 1, which utilized Process A material—GLDH was not measured. Therefore, there were no GLDH-based events of ALI. GLDH was monitored later in Study 102, Part 2 and Study 103 with corresponding GLDH-based ALI events because GLDH may be a more sensitive indicator.[32] However, when utilizing gamma-glutamyl transferase-based criteria, the number of ALI events for subjects treated with Process B material (18%) is comparable with subjects treated with Process A material (16%) (Table 6).

Overall, hepatotoxicity was observed at a similar frequency for SRP-9001 manufactured using Process A and Process B.

TABLE 6. OCCURRENCE OF ALI IN STUDY 101, 102, AND 103

Criteria	Study 101 N=4 n (%)	Study 102 Part 1 SRP-9001 N=20 n (%)	Study 102 Part 1 Placebo N=21 n (%)	Study 102 Part 2 N=41 n (%)	Study 103 N=40 n (%)
GGT >3 × ULN	3 (75.0)	2 (10.0)	0	3 (7.3)	7 (17.5)

Source: FDA
Abbreviations: ALI, acute liver injury; GGT, Gamma-glutamyl transferase; ULN, upper limit of normal.

All events of ALI resolved without clinical sequelae spontaneously or with additional corticosteroid treatment.

[31]McMillan HJ, Gregas M, Darras BT, et al. Serum transaminase levels in boys with Duchenne and Becker muscular dystrophy. Pediatrics. 2011 Jan;127(1):e132-6.
[32]Harrill, AH, J Roach, I Fier, JS Eaddy, CL Kurtz, DJ Antoine, DM Spencer, TK Kishimoto, DS Pisetsky, BK Park, and PB Watkins, 2012, The effects of heparins on the liver: application of mechanistic serum biomarkers in a randomized study in healthy volunteers, Clin Pharmacol Ther, 92(2):214-220.

Immune-mediated Myositis

One life-threatening, treatment-related immune reaction to Sarepta's micro-dystrophin protein causing immune-mediated myositis, without evidence of cardiac involvement, was observed in a subject in Study 103 with a deletion mutation involving exons 3 through 43 in the *DMD* gene and received SRP-9001 manufactured by Process B. The subject presented with muscle weakness, dysphagia, dysphonia, and difficulty sitting and walking approximately one month after receiving SRP-9001. Muscle biopsy revealed a diagnosis of inflammatory myopathy in background of chronic dystrophinopathy. The symptoms partially resolved with supportive care, plasmapheresis, and corticosteroid treatment. As a result, the Applicant proposes that SRP-9001 be contraindicated in patients with any deletion that fully includes exons 9 through 13 in the *DMD* gene.

Myocarditis and Elevated Troponin-I

(b) (4) (b) (4)

One subject in Study 103 developed chest pain on Day 3 post SRP-9001 infusion. Elevated troponin-I was observed on Day 2 and increased over several days with a peak of >40 ng/mL on Day 6 post SRP-9001 infusion. Myocarditis was subsequently diagnosed, which resolved with residual changes on myocardial MRI scan and required adjustment of his medication for chronic cardiomyopathy (adding aldosterone and carvedilol).

The other subject in the ongoing, double-blind Study 301 Part 1 presented with high fever, vomiting, and seizure-like episode within 24 hours after receiving study treatment (either SRP-9001 or placebo) and his troponin-I increased to 2,724.64 pg/m (reference range: ≤45.00 pg/mL). He was admitted to Pediatric Intensive Care Unit due to hypotension and was treated with corticosteroids, antibiotics, and intravenous fluids. Troponin-I levels reached peak of 6,283.38 pg/mL and total creatine kinase level was 42,567 U/L (reference range: <15 to 87 U/L) on Day 2 post study treatment. Electrocardiogram and echocardiogram did not change from baseline and subject was discharged home on Day 3 post treatment. Myocarditis was diagnosed based on the clinical presentation and resolved without clinical sequelae.

In Study 103, four subjects had elevations in cardiac troponin-I levels that was above ULN (>0.058 μg/L), but no clinical complications were observed.

Although none of these events were associated with acute cardiac imaging changes from baseline, at this time the long-term effects of increased troponin-I and the associated risk of myocarditis on the underlying Duchenne cardiomyopathy in this patient population, especially in older boys, is unknown.

Myocarditis and elevated troponin-I have been observed only in subjects receiving SRP-9001 manufactured with Process B. Testing for troponin-I was not in place for Studies 101 and 102 where Process A material was used.

Immunogenicity

In the clinical studies with SRP-9001, clinical trial ELISA was used to assess preexisting anti-AAVrh74 total binding antibodies and these studies enrolled only subjects with baseline anti-AAVrh74 total binding antibody titer ≤1:100 using the ELISA (only patients with the antibody titer <1:400 were eligible). Based on limited information provided in the submission, we do not have the confidence to conclude that the ELISA is reliable (i.e., consistent results with acceptable precision) or accurate (i.e., ability to give an

expected result). Across the three clinical studies (101, 102 and 103), following SRP-9001 infusion, increases from baseline in anti-AAVrh74 total binding antibody titers occurred in all subjects. Anti-AAVrh74 total binding antibody titers reached at least 1: 409,600 in every patient, and the maximum titers exceeded 1: 26,214,400 in certain patients. Re-administration of SRP-9001 in the presence of high anti-AAVrh74 total binding antibody titer has not been evaluated in patients. The safety of re-administration of SRP-9001 or any other AAVrh74 vector-based gene therapy in the presence of high anti-AAVrh74 total binding antibody titer has not been evaluated in human.

Thrombocytopenia

Decreases from baseline in platelet count were observed in 5 subjects in Study 102 and 5 subjects in Study 103, which occurred between 7-16 days post SRP-9001 infusion. The platelet count fell to as low as 51,000 /mm^3, but clinical complications were not observed.

5.2.3 Concern of Cross-Reactivity with Other AAV-Based Gene Therapy Products

AAV capsids are immunogenic and induce anti-AAV antibodies and T-cell responses. AAV capsids may block transduction and inhibit transgene expression in the target cells. Also, binding of antibodies to Fc receptors of different immune cells, such as macrophages, can potentiate inflammatory response by production of inflammatory cytokines (e.g., interferons) or increasing vector-specific immune responses. These antibodies may also activate the complement cascade and generate inflammatory cytokines (e.g., C3a) and induce thrombotic microangiopathy.

Antibodies against one AAV serotype can cross-react with capsids of other AAV serotypes.[33] Because of the concerns of cross-reactivity with other AAV-based gene therapy products, patients with DMD who have received SRP-9001 will likely not be eligible for participating in other AAV vector-based gene therapy clinical trials or receiving any future approved AAV vector-based gene therapy.

5.3 Risk Mitigation

If SRP-9001 were approved, the identified risks, such as myocarditis ALI, immune-mediated myositis, immunogenicity, hepatoxicity and other adverse reactions, and mitigation plan would be described in appropriate sections of the prescribing information. A Risk Evaluation and Mitigation Strategy (REMS) is not recommended at this time.

5.4 Summary of Efficacy and Safety Issues

The Applicant has developed the gene therapy product SRP-9001 (delandistrogene moxeparvovec), which encodes a novel protein, Sarepta's micro-dystrophin. The product utilizes an AAV vector and is intended for treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene. The Applicant is seeking accelerated approval for SRP-9001 based on the surrogate endpoint of expression of Sarepta's micro-dystrophin in muscle tissue at Week 12 after a single intravenous administration of the product.

To support accelerated approval of a BLA, a candidate surrogate endpoint must be judged "reasonably likely to predict clinical benefit." Considerations underlying that determination are biological plausibility, empirical evidence, and clinical data. An effect on the surrogate endpoint is expected to correlate with a clinical outcome measure that directly assesses benefit in clinical studies, by evaluating how a patient feels, functions, or survives. In this case, the clinical outcome measure used for correlation is the NSAA.

[33]American Society of Gene + Cell Therapy and FDA, 2023, Immune Responses to AAV Vectors, accessed, April 4, 2023, https://asgct.org/asgct-events/january-2023/immune-responses-to-aav-vectors.

5.4.1 Concerns Surrounding Efficacy

(4) Randomized, double-blinded, placebo-controlled Study 102 Part 1, designed as an adequate and well-controlled study, did not meet its primary efficacy endpoint, change in NSAA from baseline to Week 48 after treatment.

(5) Data from Study 102 Part 1 is suggestive of potential benefit of treatment with SRP-9001 in the 4-5 years of age group, but potentially no benefit in the 6-7 year of age group.

(6) Study 101 and Study 103 were single-arm, open-label studies, so assessment of the clinical outcome, NSAA change from baseline to Week 52, is not reliable due to effort-driven assessments of NSAA being subject to expectation bias in this unblinded, single-arm trial setting.

(7) Significant concerns exist regarding methods and covariates used for propensity score matching of the SRP-9001-treated study population with the external controls.

(8) Significant limitations of external controls for comparison with a heterogeneous condition such as DMD, with inter-subject variability in the rate of disease progression.

(9) Limitation of available clinical data to demonstrate an association between Sarepta's micro-dystrophin expression and clinical benefit in ambulatory patients with DMD.

(10) Uncertainty in the selection of the target age group.

5.4.2 Key Safety Concerns of SRP-9001

(1) Safety of AAV vector-based gene therapy products as a treatment class—effects such as hepatotoxicity (e.g., ALI and hepatic failure) and thrombotic microangiopathies, with some resulting in death of patients who received AAV vector-based gene therapy product in studies or as a treatment post-approval;

(2) AEs and SAEs observed in the clinical studies of SRP-9001, including myocarditis, immune-mediated myositis, ALIs, and other adverse reactions; and

(3) Immunogenicity of AAV vector-based products, including potential cross-reactivity to AAV vectors of other serotypes—which would likely preclude future administration of other AAV vector-based gene therapies which prove to be effective

6. Issues for Discussion at the Advisory Committee Meeting

6.1 Sarepta's Micro-Dystrophin as a Possible Surrogate Endpoint "Reasonably Likely to Predict Clinical Benefit"

To assess whether there is sufficient evidence to support the use of expression of Sarepta's micro-dystrophin as a surrogate endpoint that is "reasonably likely to predict clinical benefit" for accelerated approval of SRP-9001, it is critical to consider the following:

6.1.1 Biological Plausibility

Biological plausibility that a surrogate endpoint is "reasonably likely to predict clinical benefit" relies on the strength of available evidence of the relationship of the disease, the candidate surrogate endpoint, and the desired effect. Multiple factors can impact the ability of Sarepta's micro-dystrophin to predict clinical benefit, including: the extent to which Sarepta's micro-dystrophin can carry out the critical

functions of wild-type dystrophin; the expression profile of Sarepta's micro-dystrophin (e.g., which muscles express it, and the magnitude of expression); and the durability of expression and function of Sarepta's micro-dystrophin.

Sarepta's micro-dystrophin, as noted earlier, was engineered such that the transgene complementary DNA could fit within the limited genome capacity of the AAV vector. Consequently, Sarepta's micro-dystrophin does not contain the full functionality of wild-type dystrophin; Sarepta's micro-dystrophin lacks key regions such as those binding neuronal nitric oxide synthase and alpha-syntrophin, and domains recruiting signaling molecules and ion channels (for further details, please see 3.2 Mechanism of Action of SRP-9001).

Sarepta's micro-dystrophin thus 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 only provides information about expression of the transgene product in cells transduced by SRP-9001, rather than insight into a pharmacologic effect on a biomarker in the pathway of the disease.

6.1.2 Mechanism of Action

To ameliorate disease in patients with DMD, the SRP-9001 vector first must transduce the appropriate cells. Sarepta's micro-dystrophin then has to be expressed in sufficient quantity; localize appropriately to the sarcolemma; interact with endogenous components of the DAPC; and function sufficiently similarly to wild-type dystrophin or to various naturally occurring mutant or shortened dystrophin proteins, such as those present in patients with BMD.

In contrast to shortened forms of dystrophin generated by exon-skipping drugs, which aim to restore the reading frame of an out-of-frame mutation in the endogenous *DMD* gene, Sarepta's micro-dystrophin is expressed from the AAV vector genome under the control of the *MHCK7* promoter, so is not regulated by the endogenous regulatory elements of the *DMD* gene. The number of vector genomes per nucleus and resulting micro-dystrophin expression level can vary widely across muscles and occurs independently of the endogenous dystrophin expression pathways. For example, in nonclinical Study SR21-025 in *Dmd*^{mdx} mice, administration of SRP-9001 at the clinical dose level resulted in expression of Sarepta's micro-dystrophin at supraphysiological levels relative to wild-type dystrophin in the heart (251.02 ± 51.8% of normal dystrophin), and lower levels in the diaphragm (54.18 ± 30.83% of normal) and tibialis anterior (39.83 ± 26.11% of normal) and the long-term consequences of these differences are unknown.

WB, IF, and VGC data from biopsies of the gastrocnemius muscle in study subjects demonstrate transduction (although inconsistent) of skeletal muscle; expression of Sarepta's micro-dystrophin protein; localization to the sarcolemmal membrane; and co-localization with alpha-, beta-, gamma-, and delta-sarcoglycans. However, no further data regarding interactions of Sarepta's micro-dystrophin with other members of the DAPC are available. WB and IF can detect vector-driven expression of Sarepta's micro-dystrophin, but do not provide insight into the downstream effects on muscle function, or the relationship between expression of Sarepta's micro-dystrophin and the clinical endpoint. Additionally, quantitation of WB and IF results was highly variable, precluding further determinations such as of a minimum level of expression that can be associated with clinical benefit.

6.1.3 Empirical Evidence

Because Sarepta's micro-dystrophin is a novel, engineered protein, no epidemiologic or pathophysiologic evidence of its function is available. This situation differs from that with shortened

forms of dystrophin generated by treatment with exon-skipping drugs, such as eteplirsen, which are intended to mimic specific mutated forms of dystrophin found in patients with BMD.

Moreover, no therapeutic data regarding SRP-9001 outside of clinical studies are available, unlike a situation, for example, in which "off-label" use of a medication may provide information regarding its utility for a different condition.

While the full function of wild-type dystrophin remains unclear, a primary role appears to be structural, maintaining the integrity of the sarcolemma membrane. This situation is in contrast, for example, to that of an enzyme for which substrate and products may be measured chemically. The Applicant has measured serum creatine kinase levels as an indicator of muscle breakdown, but creatine kinase is a nonspecific and imprecise indicator. Therefore, satisfactory pharmacologic evidence is also lacking. The only clear potential demonstration of benefit of Sarepta's micro-dystrophin is clinical function, which can be assessed solely from clinical studies.

6.1.4 Nonclinical Studies

POC studies (Study Report Numbers SR-20-001, SR-19-061, and SR-21-025) were conducted in *Dmd*^{mdx} mice, which show a milder clinical phenotype compared to patients with DMD. Assessment of function of Sarepta's micro-dystrophin in these studies was limited to isolated muscle force measurements for the tibialis anterior and diaphragm muscles, which showed variable increases in specific force, with partial correction of the deficit. The Applicant provided post hoc correlation analyses of data across these studies and concluded that the functional outcome measured by relative specific force did not correlate with expression of Sarepta's micro-dystrophin protein as measured by WB, but did correlate with percentage of micro-dystrophin-positive fibers determined by IF.

In nonclinical studies (Study Report Numbers SR-20-012 and SR-20-013) in *Dmd*^{mdx} rats, administration of SRP-9001 led to different responses despite broad expression of Sarepta's micro-dystrophin in the two studies. In Study SR-20-012, conducted in 3-4 week old rats, administration of SRP-9001 led to increased spontaneous activity and decreased dystrophic pathology in muscles, compared to control animals. However, in Study SR-20-013, conducted in 3-5 month old rats, no improvement in any of these parameters was observed following administration of SRP-9001, despite robust expression of Sarepta's micro-dystrophin in muscle.

Thus, although SRP-9001 micro-dystrophin expression was readily achieved in the mouse and rat studies, expression did not accurately reflect functional benefit or therapeutic response in these rodent models of DMD.

The Applicant also cites the functional improvement observed in the nonclinical studies as supportive evidence that expression of Sarepta's micro-dystrophin can be considered "reasonably likely to predict

clinical benefit" in patients. There are significant limitations, however, in trying to extrapolate clinical benefit from these nonclinical studies, including the following:

(1) Study design limitations (e.g., lack of robustness, missing data, potential for bias, non-compliance with GLP, etc.) since these were POC studies and were not designed or powered to assess correlation between micro-dystrophin expression and functional outcomes;

(2) Differences between the *Dmd*^{mdx} rodent models and patients with DMD, since these models show a milder phenotype, with less motor impairment and cardiac dysfunction compared to patients with DMD;

(3) Species-specific differences in disease pathophysiology in these models compared to humans, including differences in compensatory mechanisms and increased regenerative capacity of muscle fibers in these rodent models;

(4) Physiological differences between rodents and humans, such as relative differences in muscle volumes and physiological loads sustained; and

(5) Unknown clinical significance of the functional endpoints assessed (e.g., muscle specific force) and the magnitude of change observed.

6.1.5 Clinical Studies

To support use of expression of Sarepta's micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit," the Applicant has submitted data from three clinical studies: Study 101, Study 102 Part 1 and Part 2, and Study 103. As noted above, in order to support accelerated approval, an effect on the candidate surrogate endpoint is expected to correlate with an effect on a clinical outcome measure that evaluates how a patient feels, functions, or survives. The clinical outcome measure in this case is the NSAA.

Study 101 and Study 103 are open label. Study 102 is a randomized, double-blind, placebo-controlled crossover study: subjects who received SRP-9001 in Part 1 were then administered placebo in Part 2, and vice-versa. Although the blind was maintained in Part 2, by that point the subjects, caregivers, and evaluators were aware that all subjects had now received SRP-9001, rendering Part 2 effectively an open-label study. Thus, the only data available from a randomized, double-blind, placebo-controlled study are that from Study 102 Part 1.

This distinction is important because of the nature of the NSAA clinical outcome measure. Performance on the NSAA is effort-dependent (the effort by subjects in a clinical treatment study is likely to be greater than that of patients in settings such as a natural history study or a registry), so scores are susceptible to increased bias when evaluated under open-label conditions. In addition, administration of the NSAA is process-dependent: without uniform training and standards of evaluation, scores from different sources may vary to an extent that can affect overall outcomes. NSAA results from any of the Applicant's clinical studies therefore cannot be reliably compared to NSAA results from external data sources, including natural history studies, registries, or clinical studies of other investigational drugs. Particularly in situations such as with Sarepta's micro-dystrophin, where any effect is expected to be moderate, comparison to an appropriate control group (e.g., a concurrent control) incorporating randomization and blinding is vital in order for the effect to be determined accurately.

Taking into account the limitations of the available clinical study data, FDA evaluated 4 different analyses to assess for a persuasive association between expression of Sarepta's micro-dystrophin at

12 weeks, and benefit on the NSAA after 1 year. The analyses were (1) NSAA change for subjects in Study 102 Part 1 who received SRP-9001 versus those who received placebo; (2) NSAA change for pooled subjects from all three clinical studies who received the intended dose of SRP-9001, versus external controls; as well as NSAA change for subjects from each study who received the intended dose of SRP-9001, versus external controls; (3) NSAA change for subjects in Study 102 Part 1, relative to level of expression of Sarepta's micro-dystrophin; and (4) NSAA change for pooled subjects from the clinical studies, relative to level of expression of Sarepta's micro-dystrophin. The results of all four analyses raised major concerns for which FDA seeks input from the Advisory Committee, regarding whether expression of Sarepta's micro-dystrophin can be considered a surrogate endpoint "reasonably likely to predict clinical benefit" to support accelerated approval of SRP-9001.

First, no statistically significant difference in NSAA scores was observed between subjects in Study 102 Part 1 who received SRP-9001 compared with subjects who received placebo.

Second, the Applicant pooled all subjects from Study 101, Study 102, and Study 103 who received the intended dose of SRP-9001 and compared their NSAA changes with NSAA changes of patients drawn from external databases as controls. The Applicant also compared NSAA changes of subjects from each study who received the intended dose of SRP-9001 with NSAA changes of patients drawn from external databases as controls. While a benefit was observed for the subjects receiving SRP-9001, FDA has major concerns regarding the validity of such a comparison to external controls. Although the Applicant used propensity scores to enhance matching of the SRP-9001 study populations with the external control subjects, such comparisons still can only be considered exploratory: in a situation such as this one where the treatment effect is expected to be moderate, propensity scores cannot suitably account for the influence of known factors such as the heterogeneity of DMD or the effort- and process-driven nature of the NSAA, or of unknown factors.

Third, FDA examined subject-level data to investigate if a persuasive association can be identified between change in NSAA score from baseline to Week 48, and expression of Sarepta's micro-dystrophin (measured by WB) at Week 12 after SRP-9001 infusion. Here, FDA used data from Study 102 Part 1, since that is the only reliable source of NSAA results. No clear association was present.

Finally, FDA considered subject-level data on NSAA scores and expression of Sarepta's micro-dystrophin from the Applicant's studies, regardless of study design. (Data from Study 101 were not included, since a different WB method was used to measure expression, and the reliability of that assay was uncertain.) Even though the pooled Study 102 and Study 103 Cohort 1 results, incorporating flawed NSAA measurements, suggested an association, FDA has concerns regarding meaningfulness of that association since: 69% (45 of 65) of the subjects were from open-label settings and their inclusion would be expected to favor an association between treatment with SRP-9001 and subsequent improvement on NSAA. In addition, the result appears largely driven by the 4-5 year old subgroup, as no clear association was suggested in the ≥6 year old subgroup.

6.2 Potential Clinical Implications of Study 102 Part 1 Results

In general, the most interpretable and rigorous evidence to support correlation of a candidate surrogate endpoint and a clinical outcome, such that the surrogate endpoint can be considered "reasonably likely to predict clinical benefit," comes from data obtained from randomized, double-blind, placebo-controlled clinical studies. Under the following conditions, however, data from single-arm, open-label clinical studies and external controls may be sufficient: when the disease course is well-documented, highly predictable, and can be objectively measured and verified (such as high and temporally predictable mortality); the expected treatment effect is large, self-evident, and closely associated

temporally with the intervention; and the study population and the external controls are suitably comparable. Even under these circumstances, however, external controls still may be inadequate, such as if important prognostic covariates either are unknown or were not recorded in the historical record.

As detailed below, use of external controls is not satisfactory to properly assess the effect of SRP-9001 in patients with DMD. Rather, randomized, double-blind, placebo-controlled studies are critical.

Patients with DMD as a group follow a clear trajectory on standard of care treatment, but for individual patients the disease course is heterogeneous and not readily predictable. SRP-9001 is expected to alter the disease course from the DMD phenotype to instead resemble that of patients with the milder condition, BMD. While that result would constitute an important advance in treatment, such a relatively moderate change is difficult to detect in the brief duration of a clinical study unless the study design includes randomization, blinding, and a concurrent control to permit clear comparison. In addition, as discussed previously, results on the NSAA are both effort-dependent and process-dependent.

As noted earlier, Study 102 Part 1 is the Applicant's only randomized, double-blind, placebo-controlled study for which data are available. The study involved 41 ambulatory patients with DMD, age 4 to 7 years at enrollment. Subjects were randomized 1:1 to receive either a single intravenous infusion of SRP-9001 (N=20) or placebo (N=21). The primary clinical outcome measure was change in NSAA score from baseline to Week 48 after treatment. The study demonstrated no statistically significant difference between the SRP-9001 group compared to the placebo group.

A major flaw in Study 102 Part 1 resulted from shortcomings in dose determination, discovered after subsequent analysis revealed that three different doses of SRP-9001 were administered to the 20 subjects in the active treatment group: 6 subjects received one-half the intended dose, 6 subjects received two-thirds the intended dose, and 8 subjects received the full intended dose. For all three dose groups, however, CIs for change from baseline in NSAA score included zero, indicating no effect. Moreover, subjects who received the full intended dose appear to have had the poorest outcome.

The Applicant performed subgroup analyses based on age, examining change in NSAA from baseline to Week 48 for subjects 4 to 5 years old, and for subjects 6 to 7 years old. Importantly, these analyses can only be considered exploratory: although planned in advance, they were not prespecified for statistical hypothesis testing, and no prespecified multiplicity adjustment strategy was employed. The analyses suggested that subjects 4-5 years old receiving SRP-9001 did better than those receiving placebo; however, subjects 6 to 7 years old who received SRP-9001 had no improvement in NSAA, and did worse than those receiving placebo. The Applicant attributed this outcome in the 6 to 7 year old subgroup to imbalance in the baseline NSAA scores of subjects receiving SRP-9001, versus those receiving placebo—an interpretation which then raises the questions of whether SRP-9001, if effective, may only benefit ambulatory patients below a certain age or above some threshold functional status.

Therefore, despite demonstrating expression of Sarepta's micro-dystrophin at Week 12 following infusion of SRP-9001, Study 102 Part 1 does not provide clear evidence that SRP-9001 is likely beneficial for ambulatory patients with DMD. It is challenging to conclude from these data either that SRP-9001 is likely effective for younger patients, or that it is likely ineffective for older patients or those with somewhat poorer functional status.

6.3 Study 301 Part 1

The Applicant proposes that Study 301 Part 1 serve as the confirmatory study if SRP-9001 receives accelerated approval. Topline results from Study 301 Part 1 are expected later this year (Q4 2023).

Study 301 includes a 52-week randomized, double-blind, placebo-controlled Part 1 and a 52-week crossover Part 2 (all subjects who received placebo during Part 1 administered SRP-9001, and all subjects who received SRP-9001 during Part 1 administered placebo). The study is fully enrolled, with approximately 120 male ambulatory DMD subjects ≥4 to <8 years old being randomized in a 1:1 ratio to receive either SRP-9001 or placebo. The primary efficacy outcome measure in Study 301 Part 1 is change in NSAA total score from baseline to Week 52.

There are approximately US 80 subjects in Study 301. The Applicant estimates that approximately 29 US subjects will cross over to Part 2 of the study by June 1, 2023. In other words, about 50 subjects will still be in Part 1 follow-up period, and about half of the 50 subjects have not received SRP-9001 by June 1, 2023.

DRAFT QUESTIONS

1. Discussion:

   Please discuss the strengths and limitations of the available evidence supporting the use of measurement of Sarepta's micro-dystrophin expressed through the administration of SRP-9001 as a surrogate endpoint that is reasonably likely to predict clinical benefit in ambulatory patients with DMD.

2. Discussion:

   Part 1 of Study 102 was the only randomized, double-blind, placebo-controlled clinical study for which data currently are available. The study failed to demonstrate a statistically significant effect of treatment with SRP-9001 versus placebo on the primary clinical outcome measure, the NSAA at Week 48.

   Exploratory subgroup analyses suggest that the SRP-9001 group may have had a better NSAA outcome compared to the placebo group among ambulatory patients between 4 to 5 years of age; however, for among ambulatory patients between 6 to 7 years of age, there appeared to be no difference between the SRP-9001 group and the placebo group, and the SRP-9001 group showed no improvement from baseline.

   Please discuss the clinical significance of these findings.

3. Discussion:

   Please discuss the potential benefits, risks, and uncertainties that may be associated with administration of SRP-9001 for treatment of ambulatory patients with DMD.

4. Discussion, then Vote:

   Do the overall considerations of benefit and risk, taking into account the existing uncertainties, support accelerated approval of SRP-9001, using as a surrogate endpoint expression of Sarepta's micro-dystrophin at Week 12 after administration, for the treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene?
   a. Yes
   b. No

5. Discussion:

   If the investigational product were to be approved under Accelerated Approval provisions, Sarepta proposes that Part 1 of Study 301, the Phase 3 randomized, double-blind, placebo-controlled 52-week, may serve as the required postmarketing confirmatory trial to verify and describe clinical benefit. Note that the 52-week analysis timepoint is expected to be completed by the end of September 2023.

   Please discuss the impact of marketing approval on completion of Part 1 of the study.

7. References

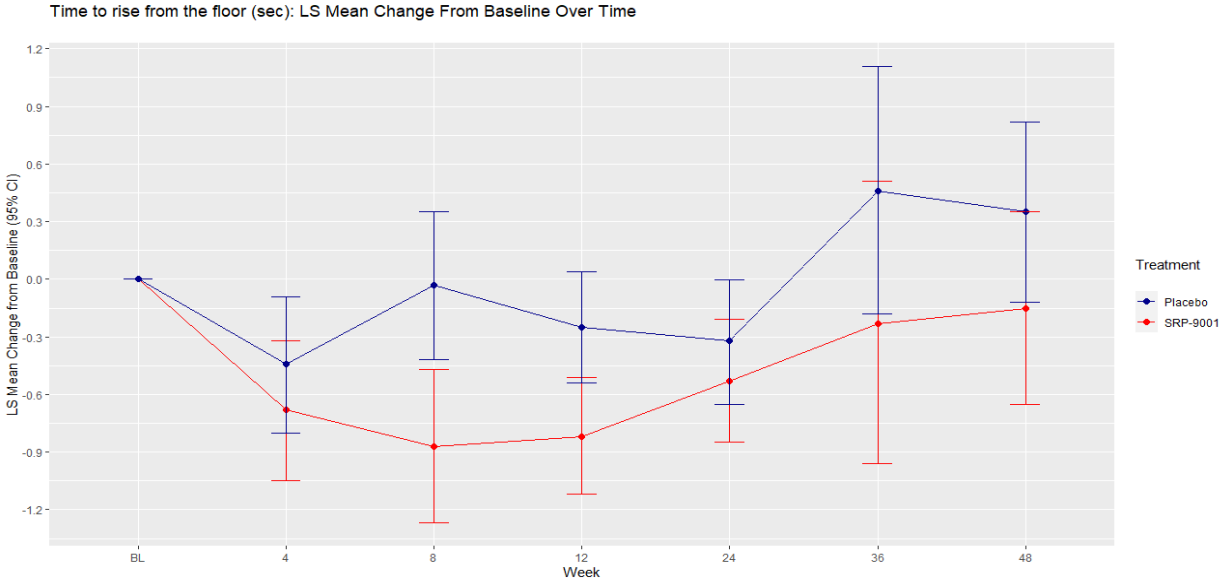
Please refer to footnotes throughout the document.

8. Appendix

8.1. Exploratory Assessments of Secondary Endpoints of Study 102 Part 1

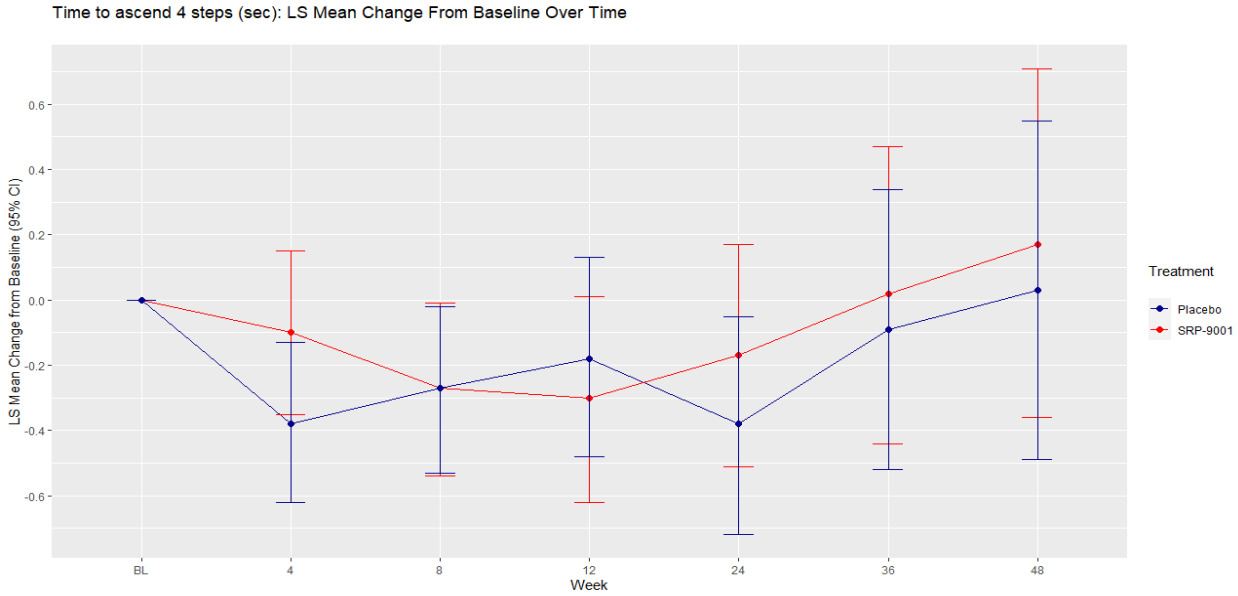
Please note that for each secondary endpoint, a negative change from baseline means less time to complete the task.

8.1.1 Change in Time to Rise from the Floor from Baseline to Week 48



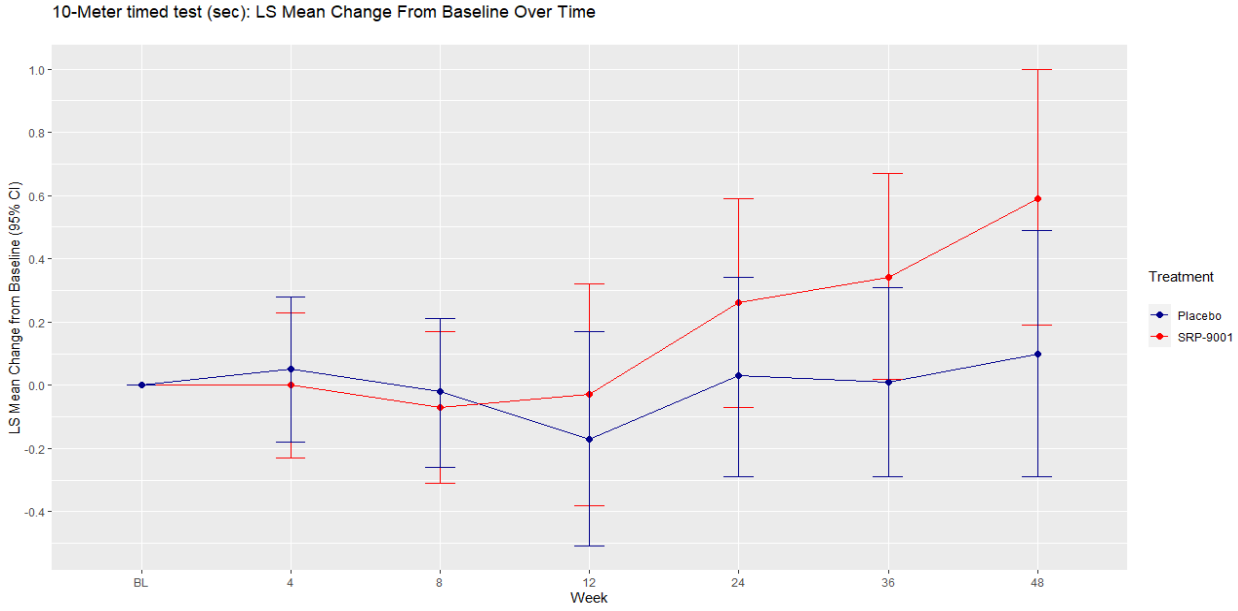
Source: FDA
Abbreviations: LS, least square; CI, confidence interval.

8.1.2 Change in Time to Ascend 4 Steps From Baseline to Week 48



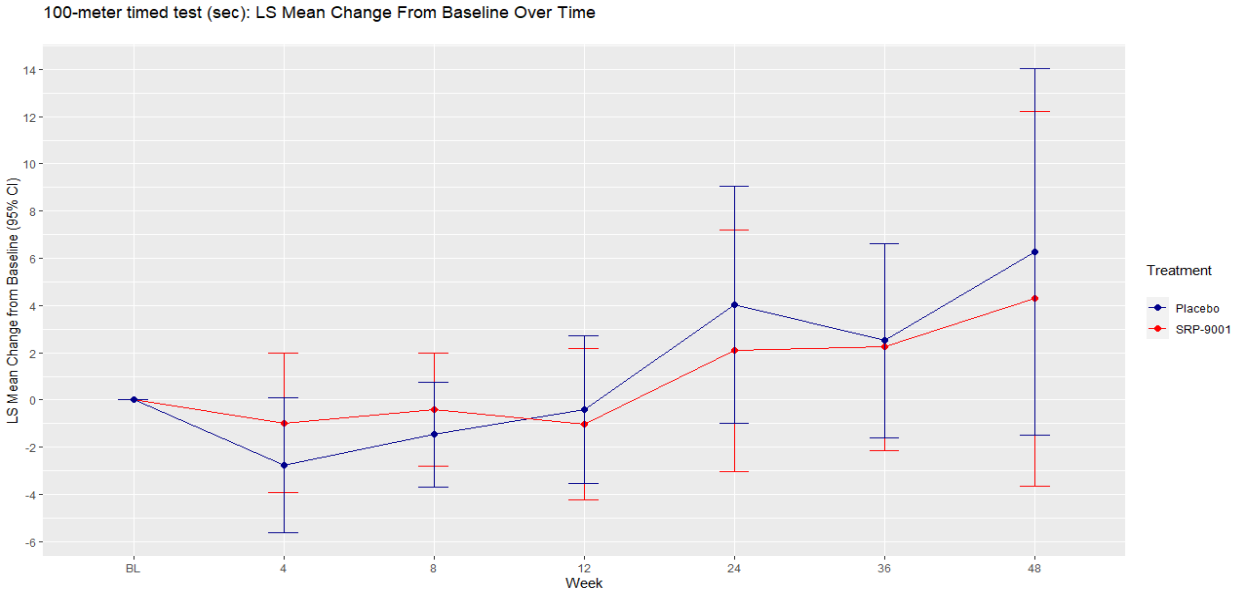
Source: FDA
Abbreviations: LS, least square; CI, confidence interval.

8.1.3 Change in Time of 10-Meter Timed Test From Baseline to Week 48



Source: FDA
Abbreviations: LS, least square; CI, confidence interval.

8.1.4 Change in Time of 100-Meter Timed Test From Baseline to Week 48



Source: FDA
Abbreviations: LS, least square; CI, confidence interval.

8.2 Vector Genome Copies in Muscle Tissue Biopsy

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 digital droplet 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 below Table 7 and Figure 15. 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 7. 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

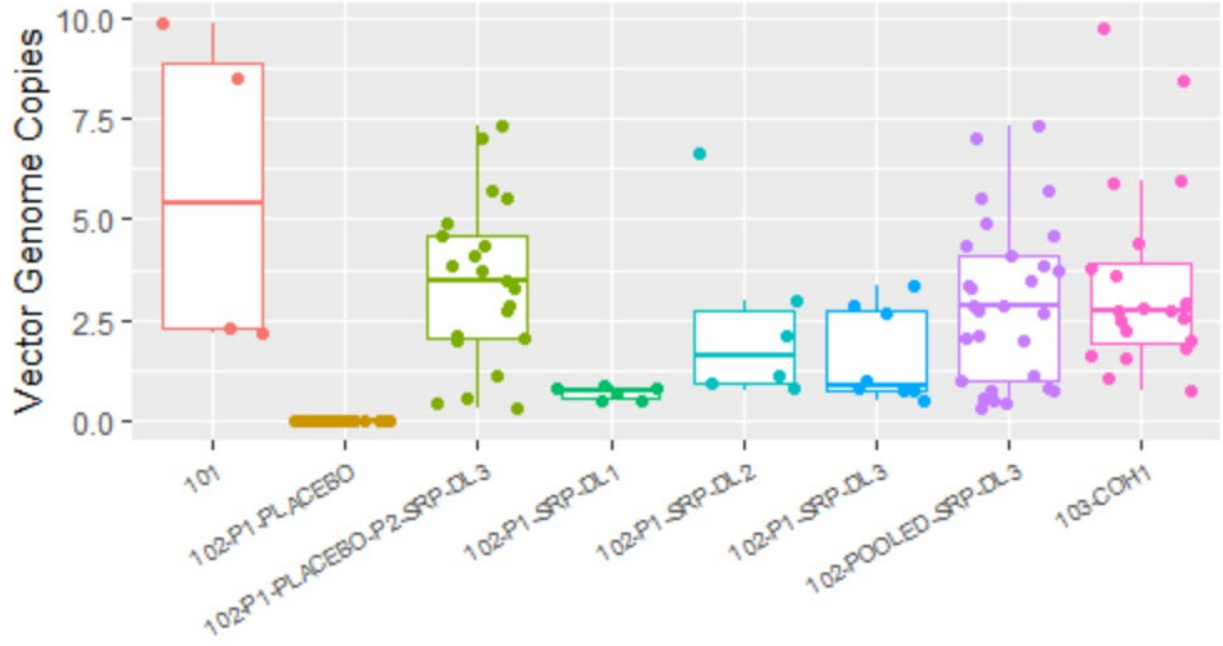
Source: FDA

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-SRP-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 quantile; Q3, third quantile; SD, standard deviation.

FIGURE 15. BOXPLOT OF VECTOR GENOME COPIES PER NUCLEUS AS MEASURED BY DDPCR IN MUSCLE TISSUE BIOPSY POST-INFUSION



Source: FDA

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-SRP-DL3).

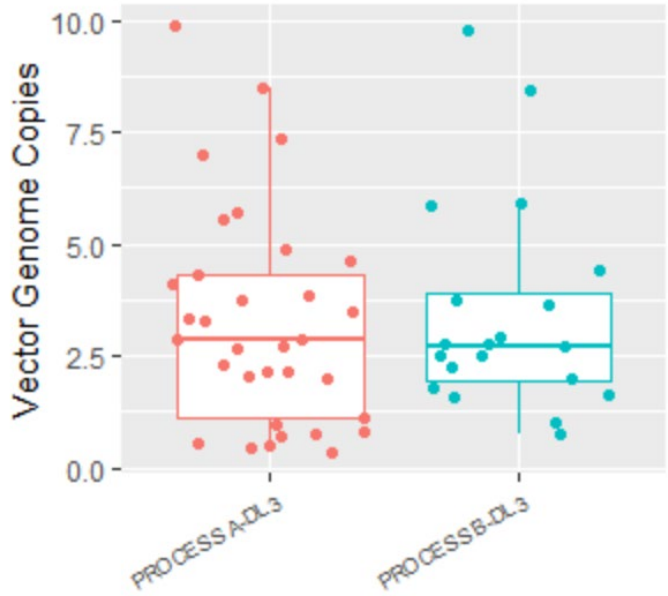
102-POOLED-SRP-DL3 includes two subgroups of subjects who received SRP-9001 at the dose of 1.33×10^{14} vg/kg in Part 1 (102-P1-SRP-DL3) and Part 2 (102-P1-PLACEBO-P2-SRP-DL3).

Abbreviation: ddPCR, droplet digital polymerase chain reaction

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

The mean (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 16).

FIGURE 16. BOXPLOT OF VECTOR GENOME COPIES 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 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

8.3 Micro-dystrophin Expression in Muscle Tissue Biopsy Measured by Immunohistochemistry (IF Fiber Intensity and PDPF)

Localization of Sarepta's micro-dystrophin measured by immunohistochemistry assay (IF Fiber Intensity (% of control), and percent Sarepta's micro-dystrophin positive fiber (PDPF, %) 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).

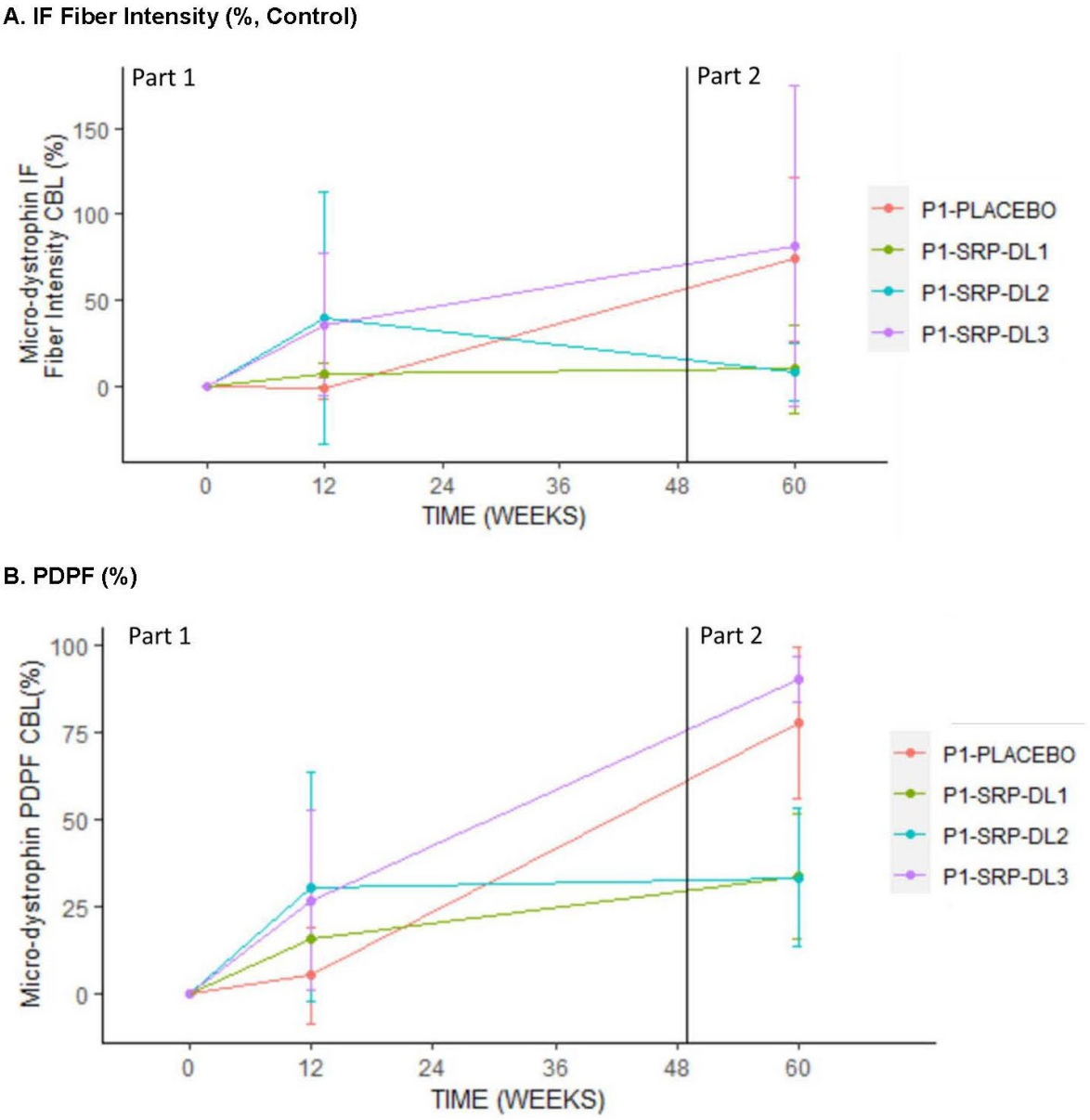
As discussed earlier, two subjects in Study 102 Part 1 targeted dose level (1.33×10^{14} vg/kg) showed high baseline levels of micro-dystrophin protein, the two subjects were excluded from analysis of immunohistochemistry results.

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 PDPF (%) were 93.6 (43.9) and 81.2 (10.2), respectively.

In Study 102 Part 1, both IF Fiber Intensity (% of control) and PDPF (%) 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 PDPF (%) 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 17).

FIGURE 17. SAREPTA'S MICRO-DYSTROPHIN EXPRESSION (IMMUNOFLUORESCENCE) OVER TIME (STUDY SRP-9001-102)



Source: FDA
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; PDPF, percent Sarepta's micro-dystrophin positive fiber.

Both IF Fiber Intensity (% of control) and PDPF (%) 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 PDPF (%) 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 PDPF (%), 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 PDPF (%), respectively.

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

8.4 Sarepta's Micro-dystrophin Expression Quantity and NSAA Total Score Change in Study 102

In Study 102, subjects who received SRP-9001 in Part 1 had completed clinical functional tests at Part 2 Week 48. 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 2Expression of 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 below 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 in 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 reduced 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

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.