SAREPTA THERAPEUTICS

SRP-9001 (DELANDISTROGENE MOXEPARVOVEC) FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY (DMD)

SPONSOR BRIEFING DOCUMENT

CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
AAV	Adeno-associated virus
AE	Adverse event
ALI	Acute liver injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLA	Biologics License Application
BMD	Becker muscular dystrophy
BMI	Body mass index
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CK	Creatine kinase
DAPC	Dystrophin-associated protein complex
ddPCR	Droplet digital polymerase chain reaction
DILI	Drug-induced liver injury
DMD	Duchenne muscular dystrophy
EC	External natural history control
E_{max}	Maximum effect
ER	Exposure-response
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
ICC	intraclass correlation
IF	Immunofluorescence
INR	international normalized ratio
ITT	Intent-to-treat
IV	Intravenous
LSM	Least squares mean
LVEF	Left ventricular ejection fraction
MAR	Maximum acceptable risk of mortality
NSAA	North Star Ambulatory Assessment
PD	Pharmacodynamics
PDPF	Percent dystrophin positive fibers
PK	Pharmacokinetics

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
TEAE	Treatment-emergent adverse events
TMA	Thrombotic microangiopathy
ULN	Upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

1.1 Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a well-characterized, rare, progressive and fatal, X-linked, neuromuscular monogenetic disease with a significant unmet medical need. The incidence of DMD in the United States (US) is approximately 1 in 5,000 live male births (Mendell 2012).

DMD is caused by mutations in the *DMD* gene that prevent the production of functional dystrophin protein. As a result of the mutation, individuals with DMD produce little or no functional dystrophin in their muscle. This lack of functional dystrophin is the sole cause of DMD.

Dystrophin is expressed in multiple tissue types including skeletal muscle, smooth muscle, and cardiac muscle. Dystrophin prevents sarcolemma membrane damage during eccentric contraction. The clinical effect of the lack of functional dystrophin is progressive muscle wasting and weakness.

Irreversible muscle damage is present at birth (Mackenzie 2021) and the first clinical symptoms of DMD are delay in motor developmental milestones, such as walking, seen around 2 years of age (Ciafaloni 2009, van Ruiten 2014). Motor function peaks on average at 6.3 years of age (Muntoni 2019), below the level of normal boys of that age, and begins to decline after that. By 8 years of age, most patients lose the ability to rise from the floor or climb stairs. On average, by 10 to 14 years of age, patients lose ambulation and become wheelchair dependent.

DMD is a multisystem disease impacting all muscle types, with decline in the cardiac and respiratory systems during the first to second decades of life. The most common causes of death for patients with DMD are respiratory failure, respiratory infection, cardiomyopathy, and cardiac arrhythmias (Brooke 1983, Eagle 2002, Ballard 2012) with median life expectancy of 28.1 years (Broomfield 2021).

There are limited treatment options for patients suffering from DMD. Current management of DMD has been focused on supportive care using a multidisciplinary team.

Muscle degeneration in DMD is relentless, with continuous accumulation of irreversible damage and progressive loss of critical functional milestones. The Sponsor estimates that Accelerated Approval will hasten broad access to this therapy by approximately 1-1.5 years. In the US, over the course of just 1 year, approximately 400 boys will lose the ability to walk, while approximately another 400 at more advanced stages will die due to the disease.[1] The community's desire for further treatments is highlighted by independent patient preference work showing a remarkably high tolerance of mortality

[1] derived from McDonald 2018, Passamano 2012, Broomfield 2021, Crisafulli 2020, US Census Bureau Projections for the United States: 2017 to 2060, and Klimchak 2021.

in return for a gene therapy that slowed the progression of disease (Sections 1.10 and 8; Peay 2021). This highlights the urgency to implement treatments that can slow or stabilize the progression of DMD.

1.2 SRP-9001

SRP-9001 (delandistrogene moxeparvovec) is an adeno-associated virus (AAV) vector-based gene therapy designed to treat the proximate cause of DMD by replacing dysfunctional or missing dystrophin protein with a functional shortened dystrophin, called SRP-9001 dystrophin, in cardiac, respiratory, and skeletal muscle, the key tissues affected in this lethal degenerative disease.

1.3 Product Indication and Dose

1.3.1 Proposed Indication

The proposed indication for SRP-9001 is for the treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.

1.3.2 Administration and Dose

SRP-9001 is administered as a one-time intravenous (IV) infusion, over 1 to 2 hours, through a venous catheter inserted into a peripheral vein at a dose equivalent of 1.33×10^{14} vg/kg for patients weighing 10 to 70 kg. All patients weighing 70 kg or above receive a dose of 9.31×10^{15} vg (equivalent of 1.33×10^{14} vg/kg for a 70 kg patient).

1.4 Accelerated Approval

Sarepta submitted the Biologics License Application (BLA) on 28 September 2022 requesting accelerated approval of SRP-9001 (delandistrogene moxeparvovec). The Food and Drug Administration (FDA) Accelerated Approval Program allows for earlier approval of drugs that treat serious conditions and fill an unmet medical need based on a surrogate endpoint reasonably likely to predict clinical benefit (FDA 2014). The accelerated approval provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) in section 506(c) of the Federal Food, Drug, and Cosmetic Act provide that FDA may grant accelerated approval to:

. . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

In the accelerated approval process, the FDA has the authority to consider pharmacologic or other evidence developed using biomarkers or other scientific

methods or tools, in conjunction with other data, in determining whether an endpoint is reasonably likely to predict clinical benefit. In addition, when considering whether to grant accelerated approval, the FDASIA reinforces the commitment to regulatory flexibility by indicating that the FDA should take into account, *". . . the severity, rarity, or prevalence of the condition…."* when considering whether to grant accelerated approval for the treatment of serious or life-threatening diseases with limited therapeutic options, such as DMD.

A "reasonably likely" surrogate endpoint for support of an accelerated approval does not yet have sufficient evidence to be a validated endpoint which may support traditional approval. Instead, reasonably likely surrogate endpoints are supported by strong mechanistic and/or epidemiologic rationale, but the amount of clinical data available is not sufficient to show that they are a validated surrogate endpoint. Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, the desired effect, and the empirical evidence to support that relationship.

Of note, the FDA Human Gene Therapy for Neurodegenerative Diseases guidance (FDA 2022) encourages sponsors to incorporate biomarkers in development and states that '*Use of a surrogate endpoint may be appropriate under certain circumstances such as when a [gene therapy] GT product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder'* as is the case in DMD and '*when a suitable surrogate endpoint is identified, it may be used to support a marketing application under the accelerated approval pathway.*'

SRP-9001 meets all 3 of the FDA's accelerated approval criteria:

1. **Treats a serious condition**

   DMD is a serious, devastating, and fatal condition with high unmet need. Progression is inevitable and irreversible and leads to early morbidity and mortality.

2. **Provides a meaningful advantage over available therapies**

   Current treatment options that increase dystrophin are limited to specific DMD mutations. Standard of care has recognized limitations and does not address the underlying cause of the disease.

3. **Demonstrates effect on an endpoint reasonably likely to predict clinical benefit**

   The SRP-9001 dystrophin produced by the SRP-9001 construct is a suitable surrogate endpoint reasonably likely to predict the clinical benefit of SRP-9001, as supported by (Sections 1.5 and 3):

- The biological plausibility that a shortened functional dystrophin could be therapeutic
- The empirical evidence supporting the expression, localization and function of SRP-9001, and the relationship between its expression and North Star Ambulatory Assessment (NSAA) changes at 1 year

As noted in Section 1.8, the confirmatory study is fully enrolled. If the confirmatory trial verifies that the drug provides a clinical benefit, the FDA may then grant a traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit, the FDA has regulatory procedures in place that could lead to removing the drug from the market.

The totality of data generated to date for SRP-9001 meets all the FDA's qualification criteria for the Accelerated Approval Pathway and exceeds that of the anti-sense oligonucleotide therapies for DMD already approved by this Accelerated Approval Pathway.

Accelerated Approval of DMD Therapies

FDA's Center for Drug Evaluation and Research Neuroscience Division has established a precedent for the approval of DMD therapies under the Accelerated Approval Pathway. Accelerated approval has been granted to 4 anti-sense oligonucleotides (EXONDY 51, VYONDY 53, AMONDY 45, VILTEPSO™) based on the judgment that production of small amounts of shortened dystrophin is reasonably likely to predict clinical benefit in patients with DMD with amenable mutations. SRP-9001 meets and exceeds the standards of evidence established with those approvals. The key positive distinguishing features of the evidence set for SRP-9001 compared to the approved anti-sense oligonucleotides are:

- The quantity of shortened dystrophin produced by SRP-9001 is consistently and substantially greater and is demonstrated to be present 12 weeks post-treatment.
- The nonclinical and biological mechanism of action data for SRP-9001 are more extensive and robust.
- The clinical effect data and safety database supporting SRP-9001 are derived from a significantly larger pool of treated patients and the 1-year time to treatment effect allows for more robust comparison to natural history data and external natural history control (ECs).

In the face of the totality of the biological and empirical evidence, the functional protein made by SRP-9001 should also be deemed reasonably likely to predict a clinical benefit in DMD and an accelerated approval is similarly justified.

1.5 Surrogacy of SRP-9001 Dystrophin

This briefing document outlines the Sponsor's position that an increase in SRP-9001 dystrophin protein is a suitable surrogate endpoint for the purposes of accelerated approval of SRP-9001. In this regulatory context, a surrogate endpoint is a marker that is reasonably likely to predict clinical benefit but is not itself a measure of clinical benefit. As described in FDA guidance, "determining whether a marker is reasonably likely to predict clinical benefit is ultimately a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship."

FDA has clear statutory authority to consider different types of empirical evidence in determining whether an endpoint meets the bar of a reasonably likely surrogate, which may include:

"…epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

FDA guidance further specifies the following:

"Clinical data should be provided to support a conclusion that a relationship of an effect on the surrogate endpoint or intermediate clinical endpoint to an effect on the clinical outcome is reasonably likely."

Importantly, in this context, SRP-9001 dystrophin expression is the surrogate endpoint, but the dystrophin expressed is also the therapeutic agent. Therefore, given that it is well established that low level expression of functional dystrophin is sufficient to improve outcomes in DMD, the foundational question for accelerated approval is whether the evidence supports that SRP-9001 dystrophin is adequately expressed and exhibits the biological functions of endogenous dystrophin such that it is reasonably likely to predict clinical benefit.

The support for SRP-9001 dystrophin protein as a surrogate endpoint reasonably likely to predict a clinical benefit in DMD is based on the totality of biological plausibility, empirical evidence, and clinical data as follows:

Biological Plausibility

1. The correction of the sole cause of DMD, restoration of a functional dystrophin protein, will confer benefit.
2. Functional, shortened dystrophins that conserve key structural domains are observed in nature and are known to modify the clinical course of dystrophinopathies (England 1990, Koenig 1989, Morandi 1993, Passos-Bueno 1994).
3. SRP-9001 dystrophin, a rationally designed shortened dystrophin based on these observations in nature and reflecting the convergence of over 15 years of global research, would therefore plausibly confer benefit when expressed in myocytes.

Empirical Evidence

1. ***Transduction***: SRP-9001 successfully and consistently enters myocyte nuclei at levels sufficient to generate therapeutic protein expression.
2. ***Expression:*** Treatment with SRP-9001 drives expression of SRP-9001 dystrophin in muscle at levels well in excess of those associated with clinical benefit in observational studies of patients with DMD.
3. ***Localization***: The SRP-9001 protein successfully localizes to its expected location on the muscle cell membrane where dystrophin acts to protect cells from contraction induced damage.
4. ***Biological Function***: SRP-9001 impacts the muscle microenvironment in a way analogous to endogenous dystrophin, including expression of dystrophin-associated proteins and sarcolemma membrane stabilization.
5. ***Relationship with Motor Function***: Clinical data support the conclusion that SRP-9001 dystrophin is reasonably likely to have an effect on clinical outcomes (NSAA). Consistent with evidence on endogenous dystrophin, in both nonclinical and clinical studies, a positive and statistically significant correlation was observed between SRP-9001 dystrophin and function with a saturable response, where low levels of functional dystrophin expression are sufficient to modify the course of disease. This supports that the functionality of SRP-9001 dystrophin and its relationship with functional improvement mirrors that of endogenous dystrophin. After controlling for key prognostic factors of baseline age and motor function, the magnitude of NSAA gain at 1-year predicted by SRP-9001 dystrophin is clinically meaningful. Initial data on patients followed for 2-4 years after SRP-9001 administration indicates a high potential for larger magnitudes of benefit to accrue over longer follow-up times.

1.6 SRP-9001 Development

Four studies are ongoing including the currently blinded Phase 3 confirmatory trial. The 3 studies that contribute data to this application are:

- Study SRP-9001-101 (Study 101): an ongoing, open-label, first-in-human, single-arm, single-dose proof-of-concept study in 4 patients with DMD ≥ 4 to < 8 years of age at time of SRP-9001 administration. The primary objective of this study is to evaluate safety. Key secondary objectives are to evaluate SRP-9001 dystrophin expression, as measured by western blot of biopsied muscle tissue, at Day 90 following SRP-9001 administration and to evaluate the effect of SRP-9001 on physical functional assessments as assessed by

the NSAA and timed function tests. Patients in this study are now in their sixth year of follow-up post-dosing.

- Study SRP-9001-102 (Study 102): an ongoing, randomized, double-blind, placebo-controlled, multicenter, 3-part clinical study in 41 patients with DMD ≥ 4 and < 8 years of age at time of infusion in Part 1. The primary objectives of this 3-part study are to evaluate SRP-9001 dystrophin expression from SRP-9001 at 12 weeks post-dosing (Part 1) as measured by western blot of biopsied muscle tissue and to evaluate the effect of SRP-9001 on physical function as assessed by the NSAA over 48 weeks (Part 1). In Part 2, also blinded, patients who received placebo in Part 1 received SRP-9001 and those that received SRP-9001 received a placebo infusion. All patients in this study have been dosed with SRP-9001 and are now in the open-label follow-up period (Part 3).
- Study SRP-9001-103 (Study 103/Endeavor) is an open-label, single-arm, single-dose, multicenter study with 4 cohorts and a 2-part follow-up period. The primary objective of the study is to evaluate SRP-9001 dystrophin expression from SRP-9001 as measured by western blot of biopsied muscle tissue at 12 weeks post-infusion. For ambulant patients (ie, Cohorts 1, 2, and 4), NSAA and other timed function tests were exploratory endpoints.

The NSAA is a well validated and accepted primary endpoint by regulators and is performed by trained evaluators (see Section 2.5.3).

To provide additional context for the open-label SRP-9001 studies, and for comparison after the placebo-controlled period in Study 102 ended, a prospective comparison to propensity score weighted ECs was performed according to a pre-specified analysis plan. The EC analysis was designed to meet the requirements of evidentiary standards and scientific validity specified in the FDA Draft Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological products* (FDA 2019).

1.7 Effects of SRP-9001

The evidence for the effect of SRP-9001 supporting SRP-9001 dystrophin expression as a biomarker reasonably likely to predict benefit is organized to reflect the key components of the Sponsor's position as laid out in Section 1.5.

1.7.1 Transduction Efficiency

Nonclinical

Transduction efficiency has been an important component of studies performed with SRP-9001 in well-established DMD mouse models, DMD rat models, wildtype mouse models, and non-human primate models (Potter 2021). Transduction efficiency demonstrates preferential SRP-9001 biodistribution to the skeletal muscle and heart,

with consistent levels of transduction across all animal models evaluated. Transduction efficiency of SRP-9001 has been well characterized in the nonclinical setting and confirmed in patients with DMD.

Clinical

Mean transduction across Studies 101, 102, and 103 ranges from 2.91 to 5.71 vg/nucleus (Table 2). Given the novelty of the gene therapy field, it is challenging to supply a benchmark for this measure; however, vg/nuclei values of 0.16-1.5 in skeletal muscle have reported benefit in other skeletal muscle disease programs (Flanigan 2022, Martin 2021). In hemophilia A, ~3 vg/nuclei were seen in 50% of hepatocytes that were transduced (Fong 2022).

1.7.2 SRP-9001 Dystrophin Expression

Nonclinical

SRP-9001 dystrophin expression relies on the SRP-9001 promoter, which was optimized to solely lead to production of protein in skeletal and cardiac muscle. In well-established DMD animal models, there is consistent evidence of robust SRP-9001 dystrophin expression in skeletal, cardiac, and diaphragm tissues with mean expression ranges from 33.92 to 86.65% normal dystrophin levels in muscle by western blot.

Clinical

Mean expression across Studies 101, 102 and 103 ranges from 42.08% to 70.52% of normal by western blot. Given epidemiological evidence that low levels of dystrophin may confer benefit (de Feraudy 2021), and the approval under the accelerated approval pathway of medicines expressing ~1% of normal, the level of expression observed with SRP-9001 is clearly consistent with providing functional benefit.

1.7.3 Appropriate Localization

Nonclinical

Nonclinical studies demonstrated correct anatomic localization to the sarcolemma membrane of the cell, which points to the functionality of SRP-9001 to anchor to the sarcolemma. Localization of SRP-9001 dystrophin to the sarcolemma membrane was measured using immunofluorescence (IF) and was consistently demonstrated across all DMD animal models tested.

Clinical

Localization of SRP-9001 dystrophin to the sarcolemma membrane was seen consistently across patients in Studies 101, 102, and 103 (Cohort 1). The mean percent dystrophin positive fibers (PDPF) across the studies ranged from 56.68% to 81.18%.

1.7.4 Biological Activity

Nonclinical

The nonclinical totality of evidence demonstrates a predictable and consistent improvement in muscle micro-environment in DMD animal models, which includes restoration of the dystrophin-associated protein complex (DAPC), decreased central nucleation (central nucleation is a muscle phenotype associated with myofiber degeneration in the DMD^{MDX} model), decreased level of fibrosis in cardiac and muscle tissue, and a sharp reduction in creatine kinase (CK) (which further demonstrates evidence of improved muscle health), further supporting the functionality of SRP-9001 dystrophin.

Clinical

In the setting of a functional dystrophin protein, the DAPC is reconstituted, which is evidenced by increased DAPC proteins at the sarcolemma membrane. In Study 103 (Cohort 1), the sarcoglycan proteins were measured by IF and show an increase compared to Baseline after SRP-9001 administration, consistent with what is observed in the nonclinical setting. These results indicate that SRP-9001 dystrophin expression leads to restoration and reconstitution of the DAPC (Mendell 2020) supporting the biological activity of SRP-9001 dystrophin at the muscle fiber level.

Although CK values are variable and are not predicative of disease severity, they can be used to demonstrate impact to sarcolemma membrane stability and early biologic activity of SRP-9001. For this reason, CK was measured in the SRP-9001 clinical studies and found to be dramatically lowered post-treatment compared to Baseline and, in Study 102, statistically significantly lower when compared to placebo (p=0.0040 at Week 12). The reduction seen post-SRP-9001 administration is supportive of stabilization of the sarcolemma membrane consistent with the mechanism of action and biological effect of SRP-9001. The magnitude of change in CK is unprecedented based on standard of care and not expected in this age group based on the natural history of the disease (Burch 2015).

Histology was reported across studies but quantification was limited to Study 101, where muscle histology was evaluated pre-and post-treatment and demonstrated a mean reduction of 26.7% in collagen deposition.

1.7.5 Relationship to Functional Benefit

Nonclinical

In the DMD^{MDX} mouse model, the treatment response of SRP-9001 was evaluated through quantification of SRP-9001 dystrophin protein expression (a surrogate biomarker) measured as IF PDPF (week 12 change from baseline), as well as functional outcome measured as relative specific force. Across an approximately 10-fold dose range studied (0.0443 to 4.01×10^{14} vg/kg), a positive association was observed

between increasing SRP-9001 dystrophin and functional outcome, with a moderate but highly statistically significant correlation observed (Pearson r=0.42, $p < 0.00001$).

Exploratory analysis of relative specific force versus SRP-9001 dystrophin indicated that functional effect showed a trend for saturation with increasing SRP-9001 dystrophin. Further evaluation demonstrated that the saturable profile was well characterized by a maximum effect (E_{max}) model, indicating an initial linear phase where relative specific force increases with low levels of SRP-9001 dystrophin expression and additional benefit plateaus at higher levels of expression. Both the magnitude of the correlation coefficient and the saturable relationship are consistent with literature evidence on endogenous dystrophin and the observations in nature where very low levels of dystrophin are seen to confer benefit (de Feraudy 2021, van Putten 2014). Together, these findings substantiate the functionality of SRP-9001 and its relationship with functional improvement mirrors that of endogenous dystrophin.

Clinical

The clinical biomarker-to-functional efficacy relationship was evaluated in ambulant patients with DMD (4 to 7 years old at the time of dosing) using available data across 3 clinical studies (Studies 101, 102, and 103 Cohort 1). SRP-9001 dystrophin protein expression in patients were measured by western blot (total protein expression), IF (membrane-localized dystrophin, PDPF and fiber intensity), all evaluated as Week 12 change from Baseline.

Consistent with the nonclinical findings, a positive association was observed between SRP-9001 dystrophin (protein expression change from baseline) and NSAA total score (1 year change from baseline). For all 3 SRP-9001 dystrophin expression endpoints, statistically significant correlation was determined with Spearman correlation coefficients of 0.38 (western blot) and 0.33 (IF PDPF and fiber intensity) and p-values < 0.005. A high linear correlation coefficient over the entire range of SRP-9001 dystrophin protein expression is not expected based on the magnitude of correlation reported between endogenous dystrophin and function, as well as evidence of the saturable relationship observed for both endogenous dystrophin and in SRP-9001 nonclinical studies, where a plateau in functional improvement (as opposed to a monotonic increase) is expected at higher protein expression. Importantly, clinical trial data to date (as described in detail in Section 3.2.3.4) showed a similar profile as the E_{max} relationship identified in the nonclinical studies and indicate the presence of SRP-9001 dystrophin across the range of expression achieved after SRP-9001 administration predicts clinically meaningful gains in 1-year NSAA after controlling for key prognostic factors such as age and baseline motor function. The totality of this evidence provides confidence that expression of SRP-9001 dystrophin is reasonably likely to predict clinical benefit throughout the treated population of patients with DMD.

1.8 Confirmatory Trial

Study 301 (Embark) is a global Phase 3, randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 (1.33×10^{14} vg/kg) in approximately 120 male patients with DMD who are ≥ 4 to < 8 years of age. Data from Studies 101, 102, and 103 informed the design of the confirmatory Phase 3 study, including inclusion/exclusion criteria, study population, endpoints, and sample size to ensure that this study will generate definitive results with high probability of success.

Eligible patients were randomized 1:1 to receive either SRP-9001 or placebo in Part 1 and will be followed for 52 weeks. In Part 2, patients who received placebo in Part 1 receive SRP-9001, and those who received SRP-9001 in Part 1 receive placebo, with a follow-up duration of 52 weeks.

In keeping with FDA's requirement for the confirmatory study to verify and describe the anticipated clinical benefit and “ensure that any remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved” the primary objective of Study 301 Part 1 is to evaluate the effect of SRP-9001 on physical function as assessed by change in NSAA total score from Baseline to Week 52. Patients remain blinded during both Part I and Part 2 of the study.

The primary assessment of Study 301 is based on Part 1 data. Consistent with FDA’s guidance recommendations, and most recently Congress’ recognition in the Food and Drug Omnibus Reform Act of the importance of having confirmatory trials underway prior to approval where possible, Part 1 of the study is not only underway but fully enrolled (125 patients randomized and dosed). This mitigates a known and often cited major impediment to timely completion of confirmatory trials – trying to enroll a placebo-controlled study post-approval. By the end of May 2023, just under half of the US patients will have completed their Week 52 visits. Given that all patients in this study will have guaranteed access to SRP-9001 by the end of September (the majority significantly earlier), and all patients are blinded to their current treatment allocation, the Sponsor sees any residual risk of US patients dropping out to access commercial therapy with associated uncertainties on eligibility, access, and timing to be extremely low. Any remaining risk to this study is further mitigated by having 45 patients recruited ex-US and conservative estimations on dropouts within the power calculations.

1.9 Clinical Safety

AAV is the most commonly utilized vector for gene therapies across various disease states (metabolic, cardiovascular, hematological, neurological, and ophthalmological). AAV-mediated gene therapies are associated with recognized risks. These risks arise from the capsid or transgene of the respective therapy. Adverse events (AEs) commonly observed with AAV-mediated gene therapy are hepatotoxicity exhibited by increased liver enzymes (acute liver injury [ALI]), liver failure, immune-mediated myositis with cardiac involvement, elevated troponin-I, myocarditis, and complement-

mediated thrombotic microangiopathy/hemolytic uremic syndrome. Carcinogenicity and hypersensitivity to pre-existing AAV antibodies are theoretical risks often discussed with AAV-mediated gene therapy.

Across the 3 SRP-9001 clinical studies in 85 patients, ages 3–20 years old, with a mean follow-up time of 2.15 years (43.5% of patients have over 2 years of follow-up) and 182.75 patient-years of exposure, there were no deaths or discontinuations due to an AE. The observed AEs were consistent in type and frequency with recognized AEs associated across AAV-mediated gene-based therapies. Identified serious (death, life-threatening, hospitalization, disability, or permanent damage) safety concerns with SRP-9001 are ALI, myocarditis, and immune-mediated myositis.

ALI, defined as gamma-glutamyl transferase (GGT) > 3 × upper limit of normal (ULN) or glutamate dehydrogenase (GLDH) > 2.5 × ULN or ALT > 3 × Baseline, or ALB > 2 × ULN, was seen in 36.5% of patients. All events resolved either spontaneously or with corticosteroid treatment. Four (3 in 120-Day Safety Update and 1 in ongoing, blinded Study 301) events met Hy's Law biochemical criteria without any progression to liver dysfunction or failure. No sequalae or chronic effect have been observed. The onset (4–8 weeks after SRP-9001 infusion) and clinical course (median resolution of 35 days, improves with corticosteroids, and resolution without dysfunction) has been consistently observed which supports the Sponsor's proposed pre-infusion and post-infusion monitoring and immunosuppression.

Myocarditis has been reported in 2 patients. One of the events occurred in the ongoing, blinded Study 301 and therefore is not included in the 120-Day Safety Update; however, the event is included in the benefit-risk evaluation. Both of these events were diagnosed incidentally during hospitalization for other events (vomiting) when elevated Troponin-I was found seen on routine testing. Neither case was associated with signs or symptoms of cardiac compromise. No acute electrocardiogram changes or abnormal cardiac function on echocardiography were observed. Both events resolved, 1 with sequalae (residual changes on cMRI and change in pre-existing cardiac modifying medications for pre-existing cardiomyopathy). The timing of the events, immediately following SRP-9001 therapy, is suggestive of a response to the capsid. Sporadic troponin-I elevations throughout DMD disease progression may also occur unrelated to gene therapy. Consistent with other approved gene therapies, the Sponsor is proposing troponin-I monitoring pre-infusion to establish a baseline and post-infusion to guide any necessary additional cardiac evaluation or management.

Immune-mediated myositis has been observed in a single patient, with an exon 3-43 deletion mutation, 4 weeks after infusion. The patient presented with muscle weakness, dysphagia, dysphonia, and difficulty sitting and walking. He was treated with additional immunomodulatory treatment (steroids), plasmapheresis and discharged home on tacrolimus. The event recovered with sequalae (residual weakness). Based upon positive ELISpot (to epitope to exons 8 and 9) and antibodies to the transgene an

immune reaction to transgene was suspected. The Sponsor has proposed a contraindication in patients with any deletion that fully includes exons 9–13 in the *DMD* gene which, by definition, excludes larger deletions such as 8–17 and 3–43. Further the Sponsor is proposing a warning and precaution that patients with deletions in the DMD gene between exons 1 to 17 and exons 59 to 71 may be at risk for severe immune-mediated myositis reaction.

In addition to the above-mentioned serious safety concerns, thrombocytopenia and vomiting were seen following SRP-9001 administration. Decreases in platelets were mild to moderate (none below 50,000/µL) and none were associated with clinical symptoms. Thrombocytopenia occurred within the first week following SRP-9001 infusion and spontaneously resolved within the second week. Platelet monitoring is proposed for the corresponding time period. Vomiting was the most commonly observed AE (61% of patients). Two of the vomiting events were serious due to hospitalization for IV administration of study related medications (corticosteroids). All of these events resolved with standard of care.

These AEs should be considered in light of the specific disease state being treated. Even with current standards of care, DMD remains inexorably progressive, leading to irreversible muscle injury, loss of ambulation, and death. While important risks of SRP-9001 have been identified, they are monitorable during clinical use and have been treatable with corticosteroids and other standard medical interventions. To date, severe complications that have been observed during clinical use of other AAV gene therapies (eg, liver failure, thrombotic microangiopathy) have not been observed in the clinical development of SRP-9001.

1.10 Benefit-Risk Profile

SRP-9001 has demonstrated a favorable benefit-risk profile throughout the clinical study program that supports an accelerated approval in the context of DMD. Factors supporting a positive benefit-risk include:

- Disease state – DMD is a serious, progressive, and fatal disease. In the absence of functional dystrophin, myocytes of patients with DMD continue to die and are replaced by fat and fibrosis leading to irreversible muscle loss with loss of motor, respiratory and cardiac function and premature death. Therefore, the urgency of treatment is high and any delay in availability of therapy that provides functional dystrophin to patients with DMD will result in irreversible progression of disease.
- High unmet medical need – Treatment options for patients with DMD are limited, and there is an urgent need for treatments that offer disease modification across the spectrum of possible DMD genotypes. Corticosteroids are recognized as the current standard of care with Emflaza™ (deflazacort) approved in 2017 for patients with DMD > 2 years of age. Evidence suggests that corticosteroid treatment may prolong ambulation, reduce the need for spinal surgery, and

increase both survival and quality of life (Mendell 2012). However, most importantly, corticosteroids are not disease modifying and do not treat the underlying cause of DMD and are associated with significant side effects and morbidity (Biggar 2006a, Manzur 2004, Moxley 2010).

- Patient-caregiver perspective – A published assessment of the maximum acceptable risk of mortality (MAR) in the first week after gene therapy showed mean acceptability of 2.1% if dosed as a newborn, up to 6.3% if given in the last year of being able to lift hand to mouth. Looking specifically at those caregivers willing to accept the highest risk of mortality in the first week after dosing (≥ 200/2,000), 13% would accept this risk to dose as a newborn rising to 36% if dosing was in the last year of the patient being able to lift their hand to their mouth (Peay 2021).
- Risk profile – Safety data from the clinical studies with SRP-9001 have shown that treatment with SRP-9001 was generally safe and well tolerated. The observed AEs and identified risks are monitorable, manageable, and reversible. The observed AEs have been mild to moderate in severity without any deaths. Associated risks are consistent in type with other AAV-mediated gene therapy. In recognition of theoretical risks, specifically carcinogenicity and hypersensitivity to pre-existing AAV antibodies, the Sponsor is proposing 2 long-term studies to better understand any potential risks.
- Risk management –To ensure a favorable benefit-risk profile in the post-marketing setting, the Sponsor has proposed a risk management program to provide targeted education and outreach to relevant stakeholders involved in the treatment of a DMD patient with a specific focus on communicating the associated risks of ALI, immune-mediated myositis, myocarditis, thrombocytopenia, and thrombotic microangiopathy (TMA). A variety of targeted educational materials and tools for the patient/caregiver, prescriber, and sites of care team will be deployed. The strategic approach is aimed at providing stakeholders with the necessary information to fully understand the associated risks with the product and recommended testing.
- Efficacy – As described in this briefing document, treatment with SRP-9001 results in robust expression of SRP-9001 dystrophin which demonstrates the expected anatomic localization and functional effects of endogenous dystrophin, including expression of other dystrophin-associated proteins and stabilization of the myocyte cell membrane evidenced by robust reductions in serum CK. Furthermore, the presence of SRP-9001 dystrophin is a predictor of clinically meaningful gain in NSAA at 1-year independent of age and pre-treatment motor function. The totality of these data in the setting of a monogenic disorder of known etiology meets the standard of a biomarker reasonably likely to predict clinical benefit.

- Reversal of muscle damage or recovery of lost functions is not an anticipated effect of dystrophin restoration, highlighting the importance of early intervention. The fully enrolled ongoing Phase 3 trial greatly mitigates the period of residual uncertainty in benefit associated with accelerated approval based on SRP-9001 dystrophin as a surrogate endpoint. However, given the urgency, ongoing accrual of irreversible disability in patients with DMD, and overwhelming need for disease modifying therapies in DMD, availability of treatment should not be delayed pending completion of this trial, and the Accelerated Approval Pathway was established to provide early access to therapies in this context. With a total of 182.75 patient-years of follow-up and nearly 5 years of follow-up for individual patients, SRP-9001 has demonstrated efficacy and an acceptable and manageable safety profile. The benefit-risk assessment is positive for the proposed indication in the context of accelerated approval.

2 BACKGROUND

2.1 Overview of Duchenne Muscular Dystrophy

DMD is a well-characterized, rare, progressive and fatal, X-linked, neuromuscular monogenetic disease with a significant unmet medical need. The incidence of DMD in the US is approximately 1 in 5,000 live male births (Mendell 2012).

DMD is caused by mutations in the *DMD* gene that prevent the production of functional dystrophin protein. As a result of this mutation, individuals with DMD produce little or no functional dystrophin in their muscles. This lack of functional dystrophin is the sole cause of DMD.

Dystrophin is a critical structural protein that protects muscle fibers from damage during muscle contraction. Therefore, without some form of functional dystrophin, normal activity in these patients causes excessive damage to muscle fiber cells, and over time the muscle cells are replaced with fat and fibrotic tissue.

Irreversible muscle damage is present at birth in DMD, with increasing histological evidence of inflammation and fibrosis in the first years of life (Mackenzie 2021). Despite achieving developmental gains, infants with DMD show diminished performance on motor, language, and cognitive Bayley-III tasks relative to typically developing, age-matched peers (Connolly 2014, Connolly 2019). Natural history studies of DMD have shown that symptom onset, including delayed walking, abnormal gait, frequent falls, and developmental delays, occur in the first few years of life (< 5 years of age) (Mackenzie 2021). Functional decline occurs after 6.3 years of age (Muntoni 2019), and patients are typically wheelchair dependent by 12 years of age (Darras 2000). Patients die of cardiorespiratory complications and have a median life expectancy of 28.1 years (Broomfield 2021).

There is no known cure for DMD. Studies on the heterogeneity of disease have demonstrated that very low levels of a dystrophin protein, when the product of endogenous exon skipping from alternative splicing, can exert profound effects on the rate of progression (Aartsma-Rus 2006). Approved treatments, some based upon the concept of exon skipping or stop codon read-through have been found to slow progression and extend survival (Iff 2022). However, these treatments require repeat administration and are indicated for a minority (~30%) of patients with specific amenable mutations.

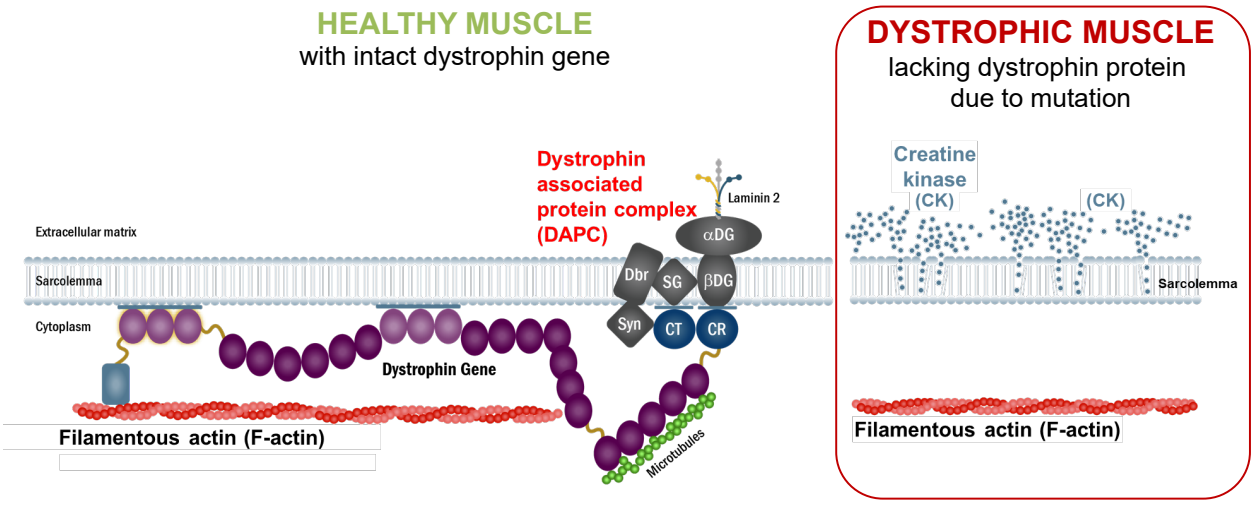
2.1.1 Role of Dystrophin in Duchenne Muscular Dystrophy

DMD is the largest human gene, totaling 2.3 megabases in size, composed of 79 exons with numerous different isoforms in muscle and non-muscle tissues under the control of 7 different promoters via alternative splicing (Chamberlain 2017).

In a normal muscle cell, dystrophin serves as a flexible structural protein linking the intracellular space with actin to the with the sarcolemma (muscle cell membrane) in a

complex called the DAPC, which then links to the extracellular matrix via laminin (Figure 1). This link, like a shock absorber, helps transmit force related to muscle contraction and to maintain sarcolemma membrane integrity during muscle use. Without this structural link, normal muscle contraction in patients with DMD results in tears to the sarcolemma membrane leading to chronic muscle breakdown with loss of function and translates to a loss of sarcolemma membrane integrity, leakage (including that of CK), and undesired permeability (Fairclough 2013).

Figure 1: Dystrophin Protein in Healthy and Dystrophic Muscle



αDG: alpha dystroglycan; βDG: beta dystroglycan; CR: cysteine-rich domain; CT: C-terminal domain; DBR: dytrobrevin; SG: sarcoglycan; Syn: syntrophin

2.1.2 Diagnosis and Disease Characteristics

In the absence of newborn screening (CK testing), the first clinical symptoms of DMD are typically seen around 2 years of age, but often there is a delay in diagnosis until the age of 3 to 5 years. As muscle weakness progresses, children frequently develop a waddling gait, toe-walking, calf hypertrophy, and increasing difficulty climbing stairs, falling behind normal peers in terms of motor function, and never achieving the peaks of function seen in normal boys.

Although DMD is often first diagnosed via skeletal muscle weakness and difficulty with walking, it is a multisystem disease impacting all muscle types, and there is decline in the cardiac and respiratory systems during the first to second decades of life. Cardiac manifestations of DMD include dilated cardiomyopathy, which is caused by progressive fibrosis within the cardiac muscle. The prevalence of cardiomyopathy in patients with DMD increases with age and disease progression, with the majority of patients affected by age 18 (Gulati 2005, Spurney 2014). Due to reduced ambulation, the majority of patients are asymptomatic of cardiac failure until very late stage. Cardiac arrhythmias are more prevalent and can be life-threatening in DMD. Arrhythmias such as a fast resting heart rate (sinus tachycardia) have been associated with increased risk of

developing cardiomyopathy earlier (Thomas 2012). Subclinical impairment of respiratory muscle function occurs in ambulatory patients but decline of respiratory function accelerates after loss of ambulation (Khirani 2014, Mayer 2015). The most common cause of death for patients with DMD are respiratory failure, respiratory infection, cardiomyopathy, and cardiac arrhythmias (Brooke 1983, Eagle 2002, Ballard 2012).

In addition to the clinical manifestations, patients with DMD have grossly elevated CK values due to leakage of the enzyme from degenerating muscle fibers (Zatz 1991). At birth, these levels are over six times normal and peak between 2-5 years of age at levels that are usually 50 to 300 times the ULN. After age 5, the levels decrease over time as muscle is lost and replaced by fibrotic tissue and fat. High transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] up to approximately 22 × ULN) and lactate dehydrogenase levels, originating from degenerating muscle, are also generally observed in these patients (McMillan 2011).

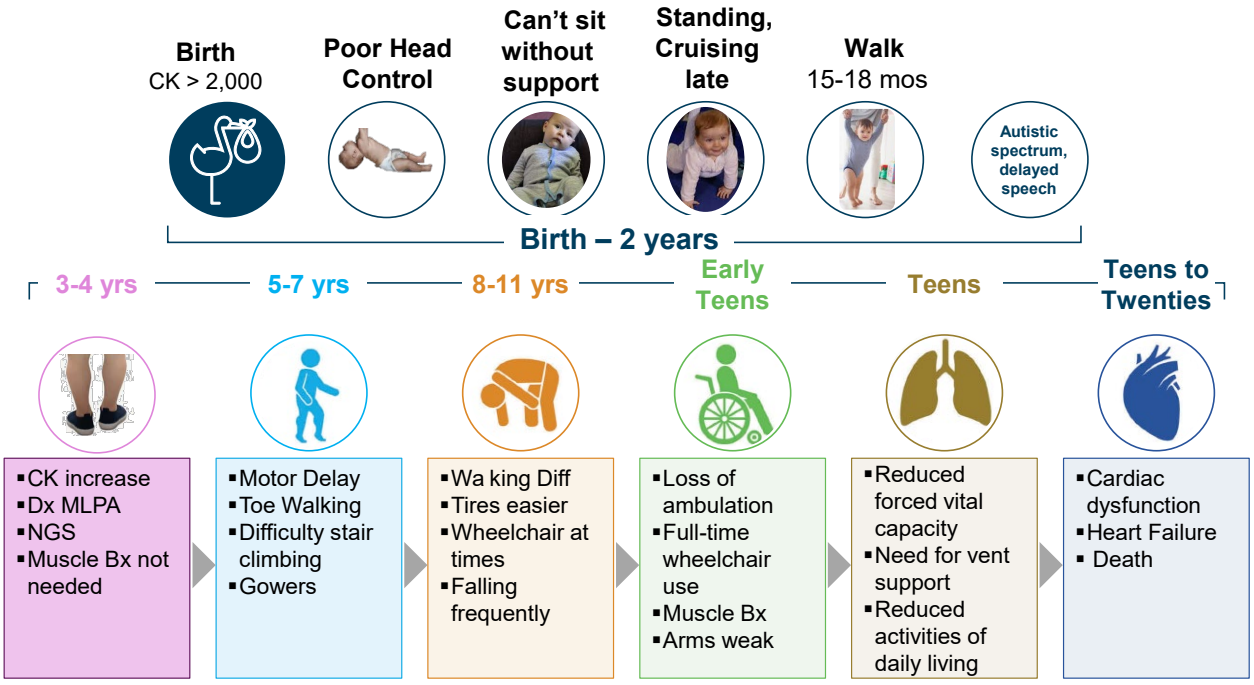
2.1.3 Natural History of DMD and Disease Progression

The natural history of DMD is well characterized and follows a predictable course. It has been extensively characterized by groups such as The North Star Clinical Network, The Association Française contre les Myopathies, The DMD Italian Group, The Collaborative Trajectory Analysis Project, Treat-NMD (global), Cooperative International Neuromuscular Research Group (CINRG; global), and others with collectively over 30 years of observation in thousands of patients. DMD is a chronically progressive and predictable disease that begins in utero.

Age is an important prognostic factor in the progression of DMD. Peak gains in NSAA (see Figure 4) are achieved by 6.3 years of age and begin to decline after that (Muntoni 2019). Over a period of years, ambulation becomes increasingly difficult due to both progressive weakness and the development of contractures.

The natural history of DMD is that by 8 years of age, most patients lose the ability to rise from the floor or climb stairs (Figure 2). Patients often fall while walking, which leads to the increased need for use of mobility devices. Between 10–14 years of age patients lose ambulation and are wheelchair dependent. In their teens, patients progressively lose the ability to independently perform activities of daily living. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. Patients with DMD typically succumb to the disease in their 20’s or 30’s. The median life expectancy is 28.1 years (Broomfield 2021).

Figure 2: Progression of Duchene Muscular Dystrophy



CK: creatine kinase; Bx: biopsy; Dx MLPA: diagnosis by multiplex ligation probe amplification

2.2 Current Treatment Options for Duchenne Muscular Dystrophy

There are limited treatment options for patients suffering from DMD.

2.2.1 Supportive Care

The aim of supportive care is to reduce the effect of the disease on different systems. As outlined in consensus documents, supportive care includes management of respiratory, cardiac, endocrinological, orthopedic, gastroenterological, and psychological issues (AAN 2016, Birnkrant 2018, Passamano 2012). Although these measures provide symptomatic relief and may prolong ambulation and life span, the disease still causes an irreversible progressive decline in function and quality of life.

2.2.2 Corticosteroids

Corticosteroids, such as prednisolone and EMFLAZA™ (deflazacort), are used in treatment of DMD, and approved for use in children > 2 years of age. The mechanism of corticosteroids in DMD is unknown but likely includes immunomodulatory actions which decrease muscle inflammation, caused by repeated cycles of damage and repair, leading to some membrane stabilization. Although chronic corticosteroid use in DMD leads to increased time to loss of ambulation (average age with corticosteroids is 13 years), reduction in rates of scoliosis, and delay of respiratory failure (McDonald 2018, Mendell 2012, Miller 2020), corticosteroids do not sufficiently ameliorate symptoms or

directly address the underlying cause of DMD, namely the lack of functional dystrophin due to *DMD* gene mutations.

Corticosteroids are associated with multiple significant side effects, most notably: weight gain, behavioral and mood effects, elevation in blood pressure, reduced growth, delay in puberty, cataracts, and osteoporosis (Biggar 2006a, Manzur 2004, Moxley 2010). These side effects are a reason why treatment with corticosteroids is delayed and discontinued.

2.2.3 Exon-Skipping Anti-sense Oligonucleotide Therapy

Four anti-sense oligonucleotide treatments that partially correct the underlying pathophysiology of DMD have been approved using the Accelerated Approval Pathway. These 4 anti-sense oligonucleotides promote production of an internally shortened dystrophin protein for exon 45, 51 and 53 skip amenable mutations. Anti-sense oligonucleotides such as EXONDYS 51 (eteplirsen), VYONDYS 53 (golodirsen), VILTEPSO™ (viltolarsen), and AMONDYS 45 (casimersen) are applicable for a small proportion of the DMD population (approximately 30% combined) who have skip amenable mutations (EXONDYS Package Insert; VYONDYS Package Insert, VILTEPSO Package Insert, AMONDYS 45 Package Insert).

Eteplirsen, golodirsen, casimersen, and viltolarsen require weekly infusions, which may require invasive indwelling venous catheter insertion and create both risk and burden for patients with DMD and their families. Exon-skipping therapies have shown that a modest increase in dystrophin (> 0–1%) has a functional benefit, delaying time to loss of ambulation and death, supporting the observation from untreated patients that even low levels of dystrophin can confer a milder phenotype (de Feraudy 2021).

2.3 Patient Unmet Medical Need

The treatment goal of DMD therapies and SRP-9001 is to beneficially modify disease trajectory compared to the expected course of DMD, slowing disease progression and, over the long-term, extending preservation of critical functions, such as ambulation, upper limb mobility, pulmonary capacity, and myocardial health, and improve quality of life. The optimal outcome is stabilization of disease, meaning preservation of level of function present at time of treatment. Reversal of muscle damage that has occurred prior to treatment or recovery of lost functions is not an anticipated effect of dystrophin restoration, highlighting the importance of early treatment. Current therapies are associated with significant side effects (steroids) and, in the case of anti-sense oligonucleotides, limited to patients with specific *DMD* mutations and require weekly infusions. Thus, there is a significant unmet medical need for patients with DMD, their caregivers, and their families.

2.4 Mechanism of Action

The biological activity of SRP-9001 dystrophin has been assessed in nonclinical and clinical studies. These show that SRP-9001 administration leads to transduction of the target cells (vg/nucleus), expression of the SRP-9001 dystrophin transgene (SRP-9001 dystrophin expression, western blot), correct localization of the expressed protein at the sarcolemma membrane (IF), % and PDPF, %) and an increase of beta-sarcoglycan, indicative of reconstitution of the DAPC. Biological measures demonstrated normalization of muscle micro-environment (decrease in serum CK, reduced fibrosis) induced by the biological effect of SRP-9001. Collectively, these data confirm the mechanism of action of SRP-9001 and support that the critical functional regions of the dystrophin gene selected allow the transduction of target cells and the expression of SRP-9001 dystrophin protein which associates with the various elements of the sarcolemma membrane and the cytoskeleton and exerts stabilization of muscle function.

2.5 Clinical Development Plan for SRP-9001

The data submitted with the BLA includes a total of 85 patients in 3 studies who have been dosed with SRP-9001 (Table 1), 56 of whom are beyond 52 weeks since dosing. Among the 85 patients dosed, 73 received a dose of 1.33×10^{14} vg/kg.

These 3 studies include:

- Study 101: an ongoing, open-label, first-in-human, single-arm, single-dose, proof-of-concept study in 4 patients with DMD, ≥ 4 to < 8 years of age at time of dosing, with frameshift (deletion or duplication) or premature stop codon mutation between exons 18 to 58 in the *DMD* gene; patients in this study are now in their sixth year of follow-up post-dosing.
- Study 102: an ongoing, randomized, double-blind, placebo-controlled, multicenter, 3-part clinical study in 41 patients with DMD, ≥ 4 and < 8 years of age at time of dosing in Part 1, and either have a confirmed frameshift (deletion or duplication) between exons 18 to 58, or a premature stop codon mutation between exons 18 to 58. Patients in this study are now in the open-label follow-up period (Part 3).
- Study 103: an open-label, single-arm, single-dose, multicenter study with 4 cohorts and a 2-part follow-up period.

Study 301/Embark, the confirmatory study, is a global Phase 3, randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 (1.33×10^{14} vg/kg). Study 301 is fully enrolled with 125 male patients with DMD, ≥ 4 to < 8 years of age at time of dosing in Part 1.

Additional planned studies include:

- Study 302: a multinational, open-label, single-arm, systemic gene delivery study in ambulatory patients with DMD aged ≥ 6 months to < 4 years.
- Study 303: a multinational, randomized, double-blind, placebo-controlled study in non-ambulatory (Cohort 1, no age restriction) and ambulatory (Cohort 2, ages ≥ 8 to < 18) patients with DMD.
- Study 305: an open-label, multinational, long-term extension study in patients who have previously participated in SRP-9001 studies to confirm the longer-term safety of SRP-9001.
- Study 401: a US multicenter, prospective, observational Phase 4, real world evidence study of comparative effectiveness and safety will be conducted post-approval to collect up to 10-year follow-up safety data for all enrolled patients, including a comparator of untreated patients.

All patients in the clinical program will be followed for at least 5 years following SRP-9001 infusion. This follow-up period is in line with the Guidance for Industry “Long Term Follow-up After Administration of Human Gene Therapy Products” for AAV (FDA 2020).

Table 1: Clinical Studies Supporting the Efficacy and Safety of SRP-9001

	Study 101	Study 102	Study 103
Purpose	First-in-human and proof-of-concept	Efficacy and safety	Expression, safety, and vector shedding of intended commercial process SRP-9001
Primary endpoint	Safety	12-wk SRP-9001 dystrophin expression by WB (Part 1), 48-wk NSAA (Part 1), and safety	12-wk SRP-9001 dystrophin expression by WB
Key secondary/exploratory endpoints	Day 90 (~12 weeks) SRP-9001 dystrophin expression by WB, NSAA, TFTs, safety	12-wk (Part 2, crossover) SRP-9001 dystrophin expression by WB, IF, vector genome copies, NSAA (Part 2), TFTs, CK	Vector shedding, immunogenicity, IF, vector genome copies, NSAA, TFTs, CK, safety
Design	Open-label	DBRPC 1:1 randomization with blinded crossover in Part 2	Open-label
Status	Ongoing; fully enrolled	Ongoing; fully enrolled	Ongoing, fully enrolled
Number of patients enrolled and dosed	4	41	40 (Cohort 1, n=20; Cohort 2, n=7; Cohort 3, n=6; Cohort 4, n=7)
Population	Ambulatory	Ambulatory	Ambulatory (Cohorts 1, 2 and 4) and non-ambulatory (Cohort 3)
Ages	≥ 4 and < 8 years	≥ 4 and < 8 years	Cohort 1: ≥ 4 to < 8 years of age Cohort 2: ≥ 8 to < 18 years of age Cohort 3: no age restriction Cohort 4: ≥ 3 to < 4 years of age
Excluded mutations	1–17 and 59–79	1–17 and 59–79	Cohort 1 and 3: none Cohorts 2 and 4: 1–17 [a]
Study duration	5 years	Up to 260 weeks	260 weeks

CK: creatine kinase; DBRPC: double-blind, randomized, placebo-controlled; IF: immunofluorescence; NSAA: North Star Ambulatory Assessment; PDPF: percent dystrophin positive fibers; TFT: timed function test; WB: western blot; wk: week

As of Amendment 4, Version 5 of the Study 103 protocol, no additional patients with mutations between or including exons 1–17 will be included in this study. This applied to the last patient enrolled and dosed in Cohort 2 and all patients in Cohort 4.

2.5.1 SRP-9001 Program Goals

SRP-9001 was rationally designed to produce a functional shortened dystrophin that addresses the absence or lack of native functional dystrophin. The treatment goal is to beneficially modify disease trajectory compared to the expected course of DMD, slowing disease progression and, over the long-term, extending preservation of critical functions such as ambulation, upper limb mobility, pulmonary capacity, and myocardial health and improve quality of life. The optimal outcome was disease stabilization, meaning preservation of level of function present at time of treatment. Given the underlying pathophysiology of DMD and the SRP-9001 mechanism of action, the SRP-9001 development program was designed to evaluate both biological and functional outcomes of treatment with SRP-9001. Total SRP-9001 dystrophin protein was assessed by western blot and additional biological measures were included to assess the downstream effect of SRP-9001 dystrophin expression on the biological cascade of events such as PDPF, DAPC reconstitution, CK reduction, and functional improvement.

Together the biological and functional results support that the SRP-9001 development program met its goal to alter the trajectory of DMD.

2.5.2 Biological Endpoints

Biological endpoints, derived from skeletal muscle biopsies, include:

- Vector genome copies per nucleus as measured by droplet digital polymerase chain reaction (ddPCR) from Baseline to Week 12 post-SRP-9001 infusion (assessment of transduction of the target cells)
- Change in quantity of SRP-9001 dystrophin protein expression as measured by western blot from Baseline to Week 12 post-SRP-9001 infusion (assessment of expression of SRP-9001 dystrophin transgene)
- Change in SRP-9001 dystrophin expression as measured by IF PDPF from Baseline to Week 12 post-SRP-9001 infusion (assessment of correct localization of the expressed protein at the sarcolemma membrane and percent of muscle fibers recruited)
- Change in SRP-9001 dystrophin expression as measured by IF fiber intensity from Baseline to Week 12 post-SRP-9001 infusion (assessment of correct localization and intensity of the expressed protein at the sarcolemma membrane)
- Change in sarcoglycan (α, β, γ, and δ) expressions from Baseline as measured by IF (positive percent fibers and mean stain intensity which corresponds to DAPC expression) to Week 12

Biological endpoints based on blood evaluation included:

- Change in CK levels from Baseline over time post-SRP-9001 infusion (assessment of sarcolemma membrane integrity)

2.5.3 Functional Endpoints

Functional efficacy was evaluated through the NSAA and timed function tests. The functional endpoints included:

- Change from Baseline in NSAA total score
- Change from Baseline in time of 100-meter timed walk
- Change from Baseline in time to ascend 4 steps
- Change from Baseline in time to rise from the floor
- Change from Baseline in time of 10-meter timed walk

2.5.3.1 North Star Ambulatory Assessment

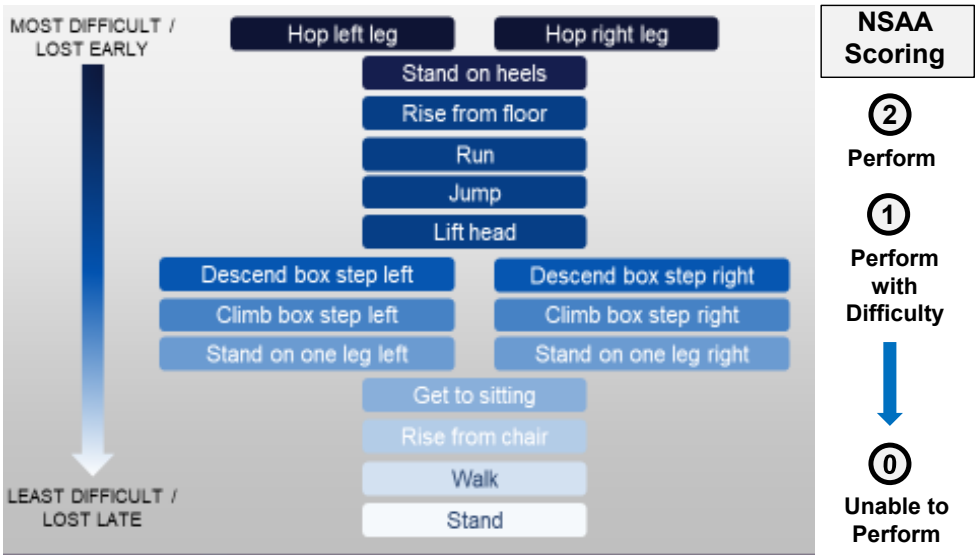
The NSAA is a clinical outcome assessment designed specifically to measure the ambulatory function of patients with DMD using items that mark the distinct features of disease progression important to patients and caregivers (Muntoni 2019; FDA 2018; Scott 2012). It is accepted as a primary endpoint for DMD studies by regulatory agencies including the FDA. The NSAA has undergone a validation process including focus groups and workshops with experienced pediatric neuromuscular physiotherapists to determine the scale content (Scott 2012). A global study of 196 boys with DMD showed that boys 4 – 7 years old demonstrate excellent repeatability of the NSAA with test-retest reliability at 30 days (intraclass correlation [ICC]: 0.91, 95% confidence interval [CI]: 0.87) (Mayhew 2022). The reproducibility of scoring the NSAA has been demonstrated with inter-rater reliability (ICC: 0.995) and with intra-rater reliability (ICC: 0.95) (Mazzone 2009). The scale has also been found to be reliable and valid in a Rasch analysis (Mayhew 2011) and is able to detect change over time in the context of an intervention (Mayhew 2013).

The NSAA is used by DMD experts to monitor disease progression up until loss of ambulation and in clinical studies of ambulatory patients with DMD to test the responsiveness and clinical meaningfulness of treatment effect. The NSAA is validated for use in patients 4 years of age and older (Coratti 2019, Coratti 2022, De Sanctis 2015, Mayhew 2022, Mazzone 2010, Miller 2020, Muntoni 2019). The NSAA has been adopted and widely used as a primary or secondary endpoint in both natural history studies and clinical trials in DMD (Muntoni 2022) with 61 studies on clinicaltrials.gov (as of April 2023) listing NSAA as an endpoint.

The NSAA is assessed by trained clinical evaluators who perform rigorous and standardized face-to-face and remote training including reliability testing on boys with DMD. To optimize standardization and consistency of testing, the NSAA is performed in the same assessment area, in the same order, and at approximately the same time of day for each patient (Duong 2021). Quality control of the data is confirmed by the data management team (Duong 2021, Mayhew 2022, McDonald 2013, Muntoni 2022).

The NSAA consists of 17 items testing 13 motor skills and is scored evaluators on a 0-, 1- or 2-point scale with score of 2 = 'normal' – no obvious modification of activity, score of 1 = modified method but achieves goal with no physical assistance, and score of 0 = unable to achieve goal independently. The items include motor function ranging from those easier to perform and lost late during disease progression (eg, standing) and more difficult tasks (eg, hopping) that are never achieved by a boy with DMD which allows for the assessment of a broad spectrum of ambulatory individuals with DMD (Figure 3).

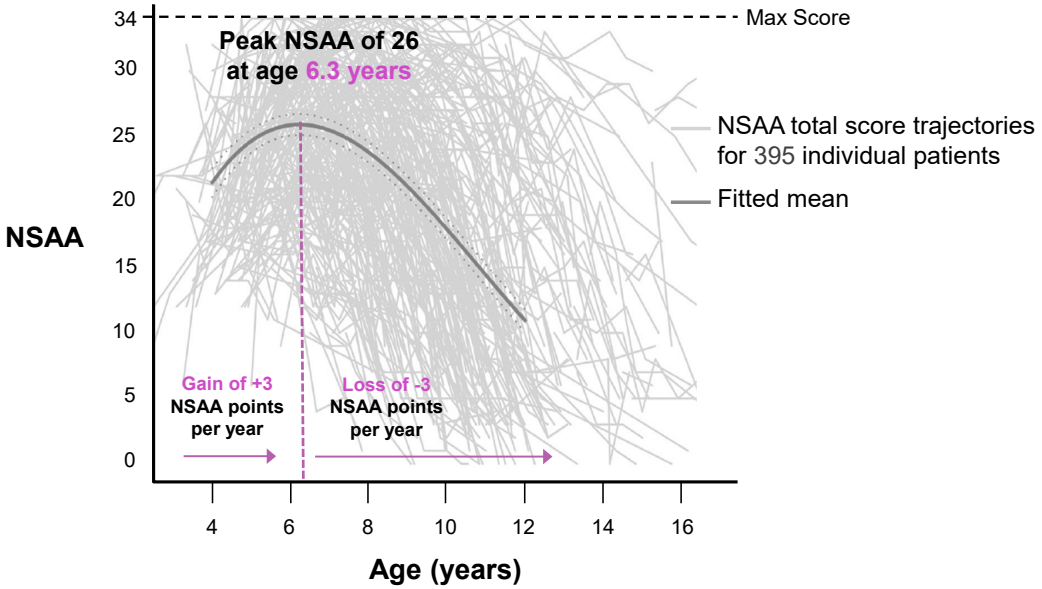
Figure 3: Schematic Depiction of the NSAA Tests and Scoring Method



DMD: Duchenne muscular dystrophy; NSAA: North Star Ambulatory Assessment
Source: Straub 2018

Natural history data demonstrate the trajectory of NSAA score initially increases at a rate of 3 units/year, peaks at age 6.3 years at a score of 26 and then declines at a rate of 3 units/year (Figure 4; Muntoni 2019, Ricotti 2016). Compared to typically developing boys who are able to perform all tasks completely and receive a full score of 34 by age 4, boys with DMD are both delayed in time to achieve maximum score and have a reduced maximum score, with the majority never able to perform all tasks fully (Coratti 2019, Coratti 2022, De Sanctis 2015, Mayhew 2022, Mercuri 2016; Miller 2020, Muntoni 2019).

Figure 4: Progression of DMD in a Natural History Cohort Measured with NSAA



DMD: Duchene muscular dystrophy; NSAA: North Star Ambulatory Assessment
Figure adapted from Muntoni 2019

The NSAA total score captures longitudinal disease progression and correlates with key disease milestones such as losing the ability to rise independently from the floor, loss of ability to stand still, and loss of ambulation (Mayhew 2013, Ricotti 2016). Individual item scores have a predictive value for the ambulatory function decline (Muntoni 2019). For example, a score of 2 on the walking item represents a patient who can walk with no obvious modification, a score of 1 means the patient has some degree of ambulation via a modified method (ie, toe-walking), and a score of 0 means the individual is unable to walk independently. These levels are qualitatively distinct and meaningfully impact daily function. Therefore, achieving the same score over time on an activity in the context of a declining disease is meaningful to the patient's everyday life, in that, it represents a change in trajectory relative to the known natural history of DMD (Muntoni 2019, Ricotti 2016).

Additional information on the clinical relevance of the timed function tests is provided in Appendix Table 31.

2.5.4 Comparison to Natural History

To provide additional context for the open-label SRP-9001 studies (Study 101 and Study 103), for comparison to Part 2 of Study 102, and to understand an imbalanced subgroup in Part 1 of Study 102, a prospective comparison to propensity score weighted ECs was performed according to a pre-specified analysis plan. The EC analysis was designed to meet the requirements of evidentiary standards and scientific

validity specified in the FDA's Draft Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological products* (FDA 2019).

The EC databases contain 3 functional assessments (NSAA, time to rise from floor, and 10-meter walk/run), assessed by trained and reliable clinical evaluators, that overlap with the variables collected and analyzed in the SRP-9001 clinical studies, and these were used for the external comparison analyses.

3 DEMONSTRATION OF SURROGACY OF SRP-9001 DYSTROPHIN

As discussed, determining whether a marker is reasonably likely to predict clinical benefit is based on the biological plausibility of the relationship between the disease, the endpoint, the desired effect, and the empirical evidence to support that relationship. To that end, the discussion of the surrogacy of SRP-9001 dystrophin is outlined as follows:

Biological Plausibility

1. The correction of the sole cause of DMD, restoration of a functional dystrophin protein, will confer benefit.
2. Functional, shortened dystrophins that conserve key structural domains are observed in nature and are known to modify the clinical course of dystrophinopathies (England 1990, Koenig 1989, Morandi 1993, Passos-Bueno 1994).
3. SRP-9001 dystrophin, a rationally designed shortened dystrophin based on these observations in nature and reflecting the convergence of over 15 years of global research, would therefore plausibly confer benefit when expressed in myocytes.

Empirical Evidence

1. ***Transduction:*** SRP-9001 successfully and consistently enters myocyte nuclei at levels sufficient to generate therapeutic protein expression.
2. ***Expression:*** Treatment with SRP-9001 drives expression of SRP-9001 dystrophin in muscle at levels well in excess of those associated with clinical benefit in observational studies of patients with DMD.
3. ***Localization***: The SRP-9001 protein successfully localizes to its expected location on the sarcolemma membrane where dystrophin acts to protect cells from contraction induced damage.
4. ***Biological Function***: SRP-9001 impacts the muscle micro-environment in a way analogous to endogenous dystrophin, including expression of dystrophin-associated proteins and sarcolemma membrane stabilization.
5. ***Relationship with Motor Function***: Clinical data support the conclusion that SRP-9001 dystrophin is reasonably likely to have an effect on clinical outcomes (NSAA). Consistent with evidence on endogenous dystrophin, in both nonclinical and clinical studies, a positive and statistically significant correlation was observed between SRP-9001 dystrophin and function with a saturable response, where low levels of functional dystrophin expression are sufficient to modify the course of disease. This supports that the functionality of SRP-9001 dystrophin and its relationship with functional improvement mirrors that of endogenous dystrophin. After controlling for key prognostic factors of baseline age and motor function, the magnitude of NSAA gain at 1-year predicted by SRP-9001

dystrophin is clinically meaningful. Initial data on patients followed for 2-4 years after SRP-9001 administration indicates a high potential for larger magnitudes of benefit to accrue over longer follow-up times.

3.1 Biological Plausibility

3.1.1 The Correction of the Sole Cause of DMD, Restoration of a Functional Dystrophin Protein, will Confer Benefit

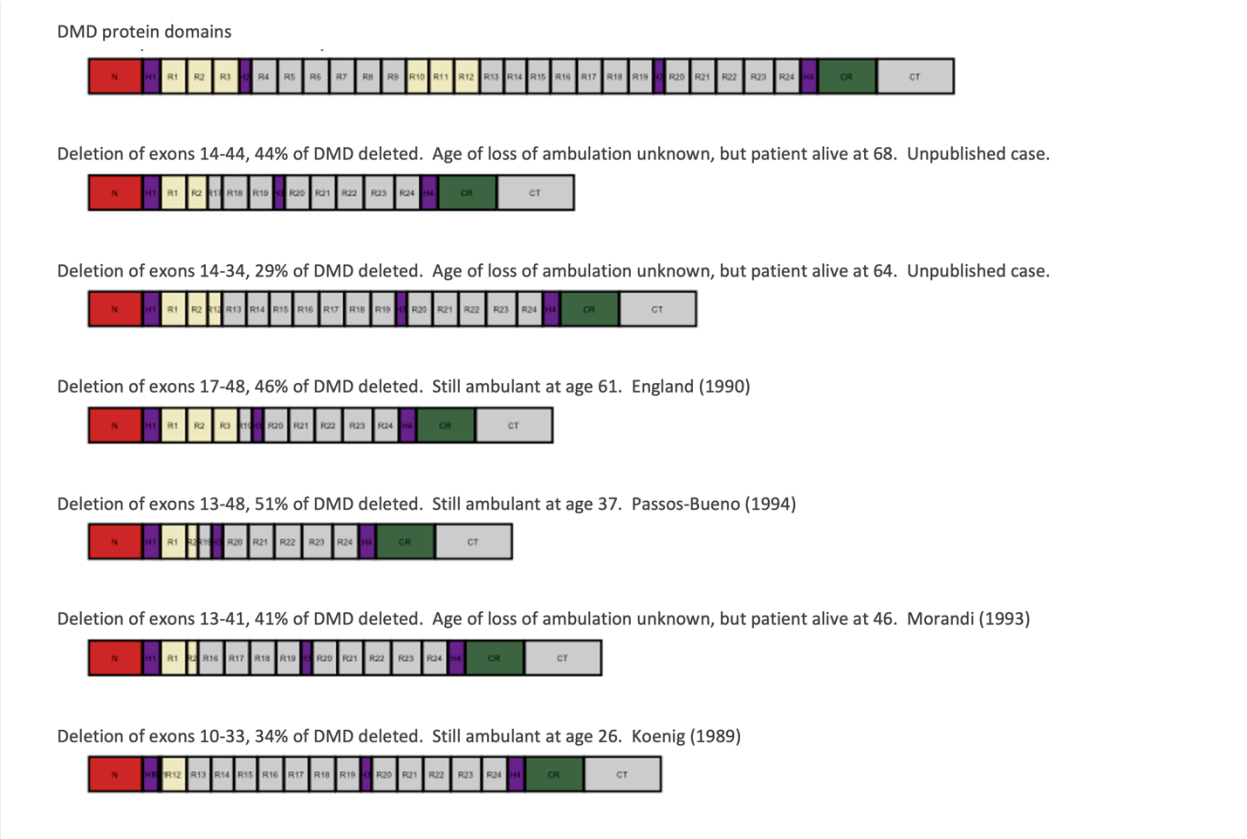
The sole cause of DMD is the absence of functional dystrophin protein caused by loss of function mutations in the *DMD* gene. It is highly plausible that replacement of this protein with a functional equivalent will confer benefit.

Observations from natural history studies indicate that low dystrophin levels confer clinical benefit and slow disease progression (Waldrop 2018, de Feraudy 2021). Additionally, studies of patients with Becker muscular dystrophy (BMD) with higher levels of dystrophin expression (> 15%) did not demonstrate a linear relationship between dystrophin and function (NSAA, loss of ambulation, timed function tests, 6-minute walk test; Bello 2016, Koeks 2021, van den Bergen 2014). Van Putten et al (2014) demonstrated in mdx-Xist$^{\Delta hs}$ mice expressing varying levels of endogenous dystrophin protein, improvement in heart function (measured as left ventricular ejection fraction [LVEF]) was observed at low dystrophin levels and the relationship exhibits a saturable profile in cardiac improvement at higher level of dystrophin expression. Taken together these observations suggest that the relationship between dystrophin and function may follow a non-linear and saturable profile, where small amounts of endogenous dystrophin confer significant benefit (Bello 2016, Koeks 2021, van den Bergen 2014).

3.1.2 Functional, Shortened Dystrophins that Conserve Key Structural Domains are Observed in Nature and are Known to Modify the Clinical Course of Dystrophinopathies

Observations from BMD, a related dystrophinopathy also caused by mutations in the *DMD* gene, have identified individuals and families with large deletions of the gene leading to natural production of shortened dystrophin proteins that exhibit a mild phenotype of the disease. While DMD typically arises from frameshift mutations that lead to lack of production of the dystrophin protein, BMD typically arises from in-frame mutations that lead to a shortened dystrophin being produced. Patients with BMD exhibit great variance in their clinical course, but patients expressing even dramatically shortened dystrophins have been shown to remain ambulatory well into their 60's (Figure 5). This suggests that shortened dystrophin proteins with the correct composition and pattern of expression can confer high degrees of functional benefit.

Figure 5: Shortened Dystrophins Leading to Sustained Ambulation and/or Increased Survival



Key binding regions represented in red (actin binding domain), yellow (sarcolemma membrane binding domain), and green (DAPC binding domain); hinges represented in purple

The literature also contains examples of both large and small in-frame deletions, including single exon deletions (Gualandi 2003, Toh 2016) and single nucleotide variants (Aartsma-Rus 2006, Prior 1995) resulting in production of large dystrophin proteins that still lead to extremely severe phenotypes since critical domains such as the actin binding or cysteine-rich domains are affected (see Section 3.1.3). Overall, these epidemiological findings support the hypothesis, later refined in extensive preclinical work, that there are crucial structural domains within the dystrophin protein, and that the preservation of these domains, and not size of the resulting dystrophin, confers the majority of the functionality of the dystrophin protein.

3.1.3 Rational Design of SRP-9001 Dystrophin

Restoring functional dystrophin to patients with DMD has long been considered a critical and widely accepted therapeutic goal in the treatment of DMD, and the rational design of AAV transferred dystrophin isoforms is fundamentally based on epidemiological findings and extensive preclinical testing (Asher 2020).

Vector/Promoter

SRP-9001 is a non-replicating, recombinant AAV containing a shortened dystrophin gene (Rodino-Klapac 2013) under the control of the alpha-myosin heavy-chain creatine kinase 7 (α-MHCK7) promotor/enhancer which has been optimized for driving expression in cardiac and skeletal muscle (Salva 2007). The recombinant AAV serotype rhesus type 74 (rAAVrh74) vector, being of nonhuman primate origin, was selected to decrease the likelihood of patients having pre-existing immunity to the vector. Seroprevalence studies have suggested that antibodies against AAVrh74 are present in approximately 13.9-15% of the target population (Griffin 2019, Goedeker 2023).

The vector genome contains the key functional elements from the full-length wildtype human dystrophin gene required for gene expression, including AAV2 inverted terminal repeats, the codon optimized human SRP-9001 dystrophin complementary DNA, chimeric simian virus 40 intron, and synthetic polyadenylation signal, all under the control of the MHCK7 promoter to restrict expression to skeletal and cardiac muscle. All DNA from the wildtype AAVrh74 has been removed.

Transgene

The dystrophin gene is 2.3 megabases in size with a resulting 11 kb cDNA (Mendell 2012), and as such, it cannot be delivered in its entirety by AAV-based gene therapy since AAV capsids typically have a gene packaging size limit of 5 kilobases (Naso 2017). This size limitation led to the need to design shorter dystrophin gene constructs, which encode key elements for function and could be packaged into an AAV viral capsid. In addition to the previously described epidemiological evidence (see Section 3.1.2), extensive nonclinical research over 2 decades supports that multiple regions of the full dystrophin protein can be deleted in various combinations to generate functional mini- and micro-dystrophins (Harper 2002b, Nelson 2018).

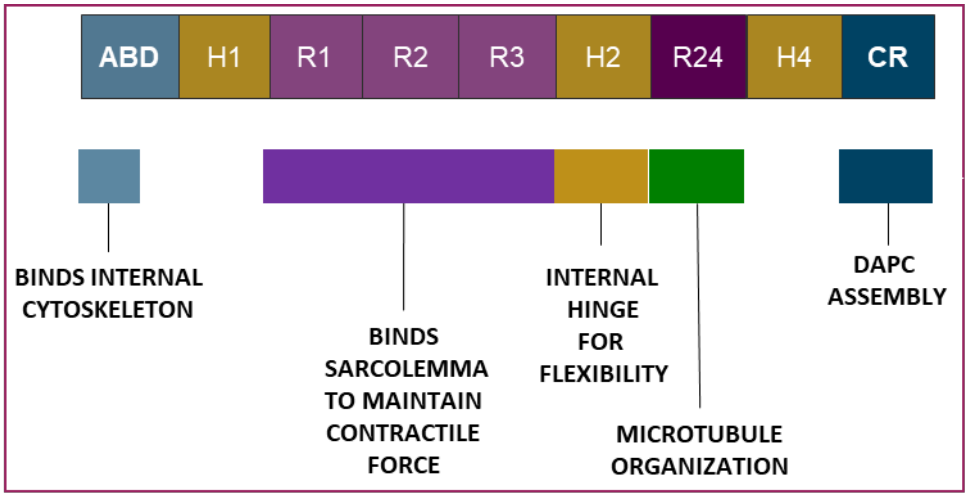
Preclinical evidence utilizing multiple transgenic mouse models have helped to determine the functional effects of shortened dystrophins. Transgenic mice express shortened isoforms of dystrophin in utero, so the functional impacts and phenotype are determined by the dystrophin isoform present. In general, these studies demonstrated that restoration of shortened dystrophins that retained key functional domains led to improved function in well-established DMD mouse models. Importantly, the specific key domains that make up the shortened dystrophin – referred to as the quality of the protein – drove the functional benefits as some smaller proteins had no change or worsened disease severity in well-established DMD mouse models, and longer dystrophin proteins were not necessarily more functional than shorter ones (Belanto 2014, Boehler 2023, Corrado 1996, Cox 1994, Crawford 2000, Ferrer 2004, Greenberg 1994, Harper 2002a, Harper 2002b, Phelps 1995, Rafael 1994, Rafael 1996, Wasala 2018, Wells 1995). These studies demonstrated that deletions of non-essential coding

regions, namely spectrin repeats and the C-terminus allow dystrophin to retain significant function if the reading frame is intact (Rodino-Klapac 2013).

SRP-9001 dystrophin was designed to retain key functional domains, as identified from epidemiological evidence and nonclinical experimentation. Importantly, a myriad of shortened dystrophin constructs have been tested over decades and the key functional elements have been retained as a part of the rational design of SRP-9001. Specifically, as shown in Figure 6, SRP-9001 dystrophin includes:

- Four spectrin-like repeats to provide the essential structural, shock-absorbing functionality of dystrophin (Harper 2002, Nelson 2018).
- The key anchor domains:
  - Actin binding domain region (internal cytoskeletal linkage) (Harper 2002b).
  - Complete sarcolemma membrane binding region R1-R3 (muscle sarcolemma linkage) (Cooper-Olson 2021; Potter 2021).
  - Cysteine-rich region (DAPC recruitment and subsequent linkage to extracellular matrix) (Harper 2002b).
  - Hinges 1, 2, and 4 for intramolecular flexibility. Hinge 2 was included to minimize novel junctions, as these could lead to immunogenicity or misfolding. Reports of abnormal fiber architecture using hinge 2 have not been observed (Potter 2021).
- A single novel junction to minimize synthetic linkages that could disrupt protein function or create immunogenic epitopes and to mimic naturally existing functional shortened dystrophins found in nature (England 1990).

Figure 6: Schematic of the Key Domains in the SRP-9001 Construct



ABD: actin binding domain; CR: cysteine rich; DAPC: dystrophin-associated protein complex; H: hinge; R: region

SRP-9001 dystrophin thus retains crucial domains that confer functionality of the protein in both the nonclinical and clinical setting and follows the principles for dystrophin functionality exemplified by the dramatically shortened dystrophin possessed by some patients with BMD with a notably mild clinical course (England 1990, Koenig 1989, Morandi 1993, Passos-Bueno 1994). Such mild BMD cases establish that substantial portions of the dystrophin protein are not essential to maintain a high degree of functionality, as long as crucial structural domains are retained.

The SRP-9001 construct differs from others being evaluated in clinical studies since it contains the third spectrin-like repeat and second hinge region, which have been shown to play a critical role in force production and protection from muscle damage (Cooper-Olson 2021, Nelson 2018, Potter 2021).

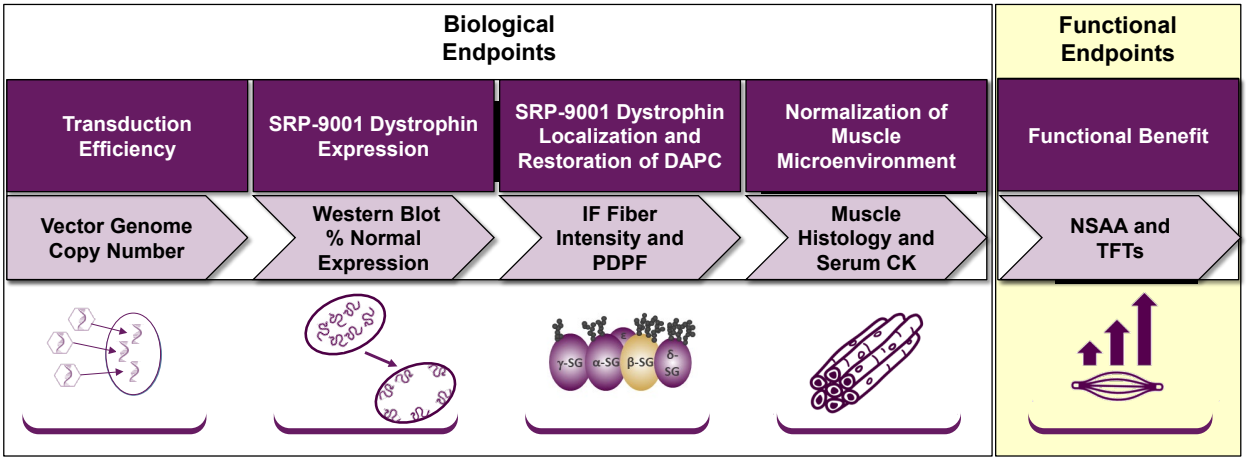
As described in Section 3.2.1, nonclinical studies with SRP-9001 validate that the inclusion of these key functional domains in a shortened dystrophin protein leads to functional benefit by demonstration of the following:

- SRP-9001 protein localization at the sarcolemma membrane
- Restoration of DAPC proteins
- Histological improvement of muscle (decreased fibrosis and inflammation; decreased myofiber degeneration)
- Reduction of serum CK
- Improvement of specific force in skeletal muscle and protection from contraction induced muscle damage

3.2 Empirical Evidence

Empirical evidence from SRP-9001 nonclinical and clinical datasets is presented below. This evidence follows the cascade of biological events consistent with the pathophysiology of DMD and demonstrates both nonclinically and clinically that SRP-9001 dystrophin is expressed at high levels within myocytes, localizes to the sarcolemma membrane and impacts the cellular biology in a manner analogous to full-length dystrophin (Figure 7).

Figure 7: SRP-9001 Biological Cascade



CK: creatine kinase; DAPC: dystrophin-associated protein complex; IF: immunofluorescence; NSAA: North Star Ambulatory Assessment; PDPF: percent dystrophin positive fibers; SG: sarcoglycan

3.2.1 Nonclinical

Fifteen years of cumulative preclinical data with SRP-9001 utilizing both the DMD^{MDX} mouse model, the most widely used animal model for DMD research (Bulfield 1984, McGreevy 2015, Ryder-Cook 1988, Sicinski 1989) as well as a DMD rat model (Larcher 2014), provide consistent evidence of the biological mechanism of action of SRP-9001.

The DMD^{MDX} mouse model mimics the human disease and has been widely used in the DMD field since its discovery to understand muscle degeneration and regeneration in DMD (Bulfield 1984, Ryder-Cook 1988, Shin 2011, Sicinski 1989). The dystrophic mouse model has a spontaneous and naturally occurring point mutation in the dystrophin gene which results in a premature stop codon in exon 23 (Bulfield 1984, Ryder-Cook 1988, Shin 2011, Sicinski 1989). As a result, no functional dystrophin protein is present other than very low levels of revertant fibers (sporadic dystrophin positive muscle fibers), which are prevalent in some patients with DMD as well. This mimics the progressive muscle degeneration seen in DMD. The DMD^{MDX} mouse model undergoes an extensive round of necrosis around 3 weeks of age and subsequent rounds of degeneration and regeneration which results in deficits in diaphragm and skeletal muscle function and increased histological changes (Anderson 1998). Dystrophic DMD^{MDX} mice show significant muscle pathology and are the most widely utilized models for DMD therapeutic approaches. Thus, DMD^{MDX} mice were used to evaluate the biological events after SRP-9001 administration and SRP-9001 dystrophin protein expression. The effects of SRP-9001 treatment were evaluated across 5 doses over a log range (4.43×10^{13} vg/kg to 4.01×10^{14} vg/kg) in the DMD^{MDX} mouse model. As an additional step to further demonstrate the biologic cascade and totality of evidence, the DMD rat model was also utilized and results were recapitulated across both models. Importantly, there was consistent expression of SRP-9001 dystrophin,

correct cellular localization, and significant functional improvement in ambulation in the DMD rat model.

3.2.1.1 SRP-9001 Results in Robust Expression of SRP-9001 Dystrophin, Correct Cellular Localization, and Biological Effect in Well-established DMD Animal Models

The preliminary biological activity of SRP-9001 was assessed in nonclinical studies which show that SRP-9001 administration leads to:

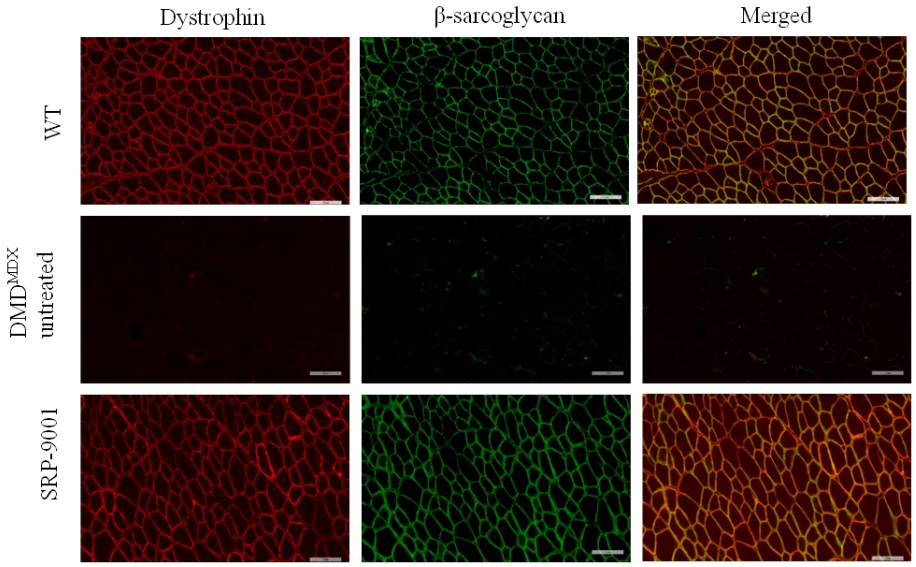
1. ***Transduction*** of the target cells (vg/nucleus), which are myocytes and cardiomyocytes
2. ***Expression*** of the SRP-9001 dystrophin transgene (SRP-9001 dystrophin expression as measured by western blot)
3. ***Correct localization*** of the expressed protein at the sarcolemma membrane (IF, fiber intensity, and PDPF)
4. ***Biological Function***
    a. Restoration of the DAPC complex, as demonstrated by increased DAPC associated proteins at the sarcolemma membrane
    b. Improvements in muscle histology including decreased central nucleation (central nucleation is a muscle phenotype associated with muscle degeneration DMD^{MDX} model) and decreased fibrosis
    c. Reduction in serum CK
5. Improved **muscle function** in the well-established DMD^{MDX} mouse and rat models

Expression of SRP-9001 dystrophin protein and its appropriate localization to the sarcolemma membrane is illustrated in Figure 8. Localization of SRP-9001 dystrophin to the sarcolemma membrane is associated with restoration of the DAPC, significant decreases in serum CK levels, and decreased levels of fibrosis which all demonstrate an improvement of the muscle micro-environment due to SRP-9001 dystrophin functionality (Figure 9).

The functional efficacy of SRP-9001 was established in the DMD^{MDX} mouse model by demonstration of increasing specific force output in the tibialis anterior (Figure 10) and diaphragm muscle.

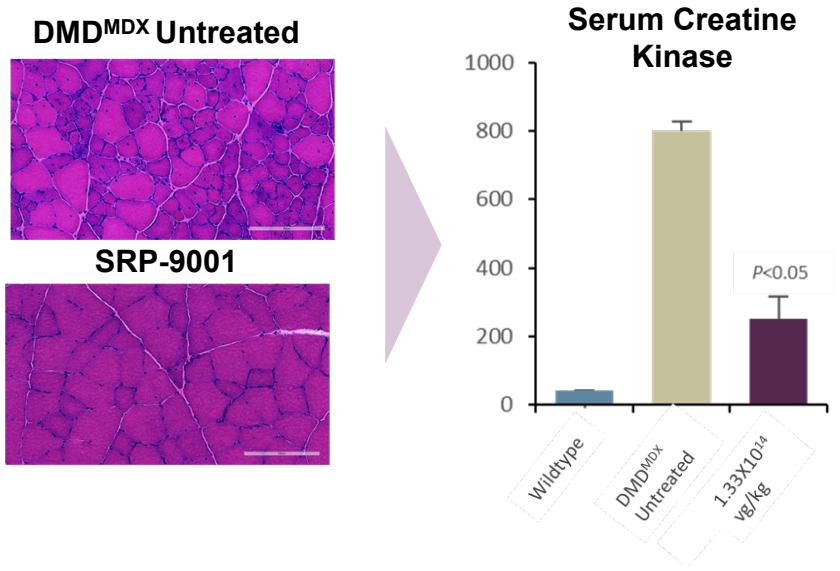
These effects have been observed consistently at the dose of 1.33×10^{14} vg/kg. Importantly, there was no functional difference in outcomes between 1.33×10^{14} vg/kg and 4.01×10^{14} vg/kg. Improvement in functional outcomes was further evidenced in the DMD^{MDX} rat model, which demonstrated an improvement in ambulation similar to wildtype levels.

Figure 8: Representative Immunohistochemistry Images of SRP9001-Treated Mice Demonstrating Restoration of the DAPC



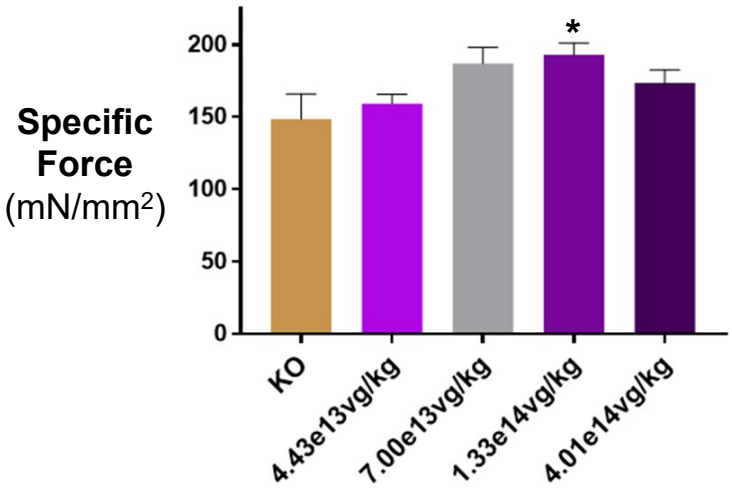
DAPC: dystrophin-associated protein complex; WT: wildtype
Data on file

Figure 9: Improvement in Muscle Micro-environment with SRP-9001 Treatment



Histological improvements in muscle micro-environment demonstrated by decreased central nucleation and increased fiber diameters, as shown qualitatively by hematoxylin & eosin staining. Improvement in muscle micro-environment translates to stabilized sarcolemma membranes and decreased serum creatine kinase release with SRP-9001 treatment.
Source: Potter 2021

Figure 10: Significant Improvement in Muscle Function with SRP-9001 Treatment



*** Clinical dose of 1.33e14vg/kg p<0.05**

KO: knockout; refers to the well-established DMDMDX mouse model; asterisk refers to statistical significance from the KO cohort; $p < 0.05$. The highest dose tested represents a plateau in functional improvement.
Muscle function was evaluated in the tibialis anterior muscle as depicted in the graph
Source: Data on file

3.2.1.2 Nonclinical Empirical Evidence Conclusions

Based on the totality of evidence in nonclinical studies in animal models of DMD, the biologic mechanism of SRP-9001 is further demonstrated as the SRP-9001 dystrophin:

1. Localizes to the sarcolemma membrane
2. Enables an increase in localization of β-sarcoglycan to the sarcolemma membrane, which is evidence of an increase in the reconstitution of the DAPC complex
3. Is associated with a sharp and significant reduction in circulating CK (a marker of muscle fiber damage), supporting the hypothesis that SRP-9001 dystrophin stabilizes the sarcolemma membrane and reduces muscle fiber damage
4. Is associated with an increase in specific force and improvement in contraction induced muscle damage in skeletal muscle with the dose of 1.33×10^{14} vg/kg Further, the dose of 1.33×10^{14} vg/kg is approaching a plateau in functional improvement

These data provide compelling nonclinical evidence that SRP-9001 dystrophin, expressed following treatment with SRP-9001, is both functional and meaningful with similar performance to that of full-length dystrophin.

Importantly, the correctly localized protein expression observed nonclinically consistently translated clinically across multiple studies, fully described in Section 5.

3.2.2 Clinical

The clinical data supporting that SRP-9001 dystrophin is biologically active and functions in patients with DMD in a manner comparable to that of wildtype dystrophin is as follows:

1. ***Transduction*** of the target cells (vg/nucleus)
2. ***Expression*** of the SRP-9001 dystrophin transgene (SRP-9001 dystrophin expression as measured by western blot)
3. ***Correct localization*** of the expressed protein at the sarcolemma membrane (IF, fiber intensity and PDPF)
4. ***Biological Function***
    a. Restoration of the DAPC complex, as demonstrated by increased DAPC associated proteins at the sarcolemma membrane
    b. Improvements in muscle histology
    c. Reduction in serum CK

3.2.2.1 Transduction and Expression

As summarized in Table 2, data from biopsies of the gastrocnemius muscle from across the development program demonstrate consistent SRP-9001 dystrophin transduction, expression, and localization of the expressed protein to the sarcolemma membrane.

Table 2: Studies 101, 102, 103 (Cohort 1) SRP-9001 Dystrophin Expression, Transduction, and Localization Across Clinical Studies at Dose of 1.33×10^{14} vg/kg

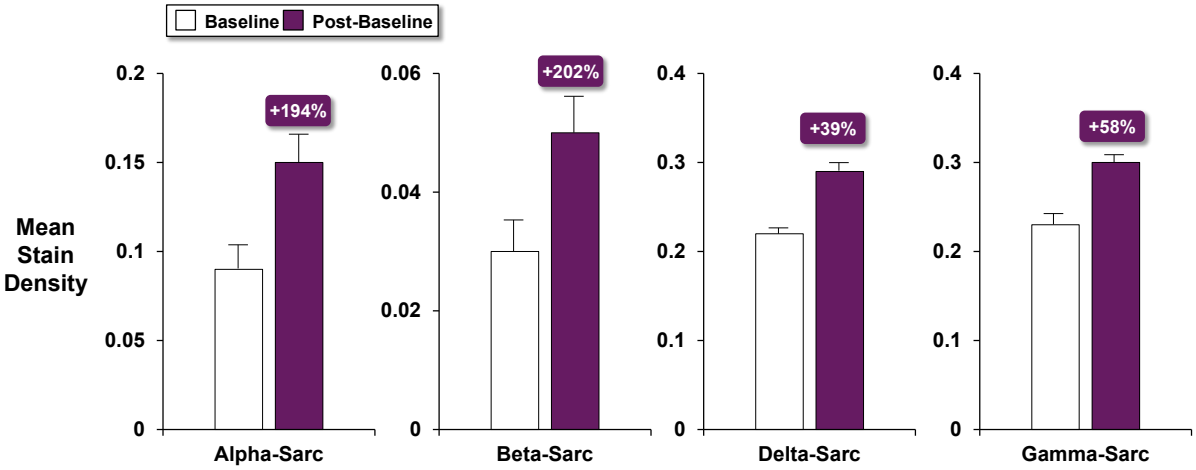
Measure	Timepoint	Study 101 (n=4)	Study 102 Part 1 & 2 1.33×10^{14} [a] (n=29)	Study 103 (Cohort 1) (n=20)
Mean age (years)at time of biopsy	W12	5.43	7.41	6.11
Vector Genome Copy Number	W12 mean (range)	5.71	2.91	3.44
		(2.15-9.88)	(0.33-7.34)	(0.74-9.77)
	Mean change from Baseline to W12 (range)	5.71	2.91	3.44
		(2.15-9.88)	(0.33-7.34)	(0.74-9.77)
SRP-9001 Dystrophin Expression (western blot, % of normal expression)	W12 mean (range)	70.52	42.08	54.21
		(13.50-182.63)	(0.57-116.28)	(4.79-153.92)
	Mean change from Baseline to W12 (range)	70.52	38.58	54.21
		(13.50-182.63)	(-1.13-114.70)	(4.79-153.92)
IF Fiber Intensity (% control)	W12 mean (range)	95.91 [b]	100.17	98.43
		(58.95-159.81)	(26.59-191.21)	(7.83-266.05)
	Mean change from Baseline to W12 (range)	93.59 [b]	61.63	66.52
		(58.77-157.82)	(-7.67-138.09)	(-9.58-263.55)
PDPF, %	W12 mean (range)	81.18 [b]	74.62	56.68
		(73.45-96.19)	(0.75-99.88)	(3.20-92.61)
	Mean change from Baseline to W12	81.18 [b]	64.13	48.27
		(73.45-96.19)	(-7.29-96.10)	(1.13-84.37)

IF: immunofluorescent; PDPF: percent dystrophin positive fibers; W: week
a 1.33×10^{14} vg/kg by droplet digital polymerase chain reaction (PCR).
b IF and PDPF values in Study 101 were calculated using different methods than those used in Studies 102 and 103.

3.2.2.2 Biologic Function: DAPC Restoration and Membrane Stabilization

In the setting of a functional dystrophin protein, the DAPC complex is reconstituted, which is demonstrable through the increased expression of associated DAPC proteins, such as the sarcoglycans. In Study 103, the sarcoglycan proteins were measured by IF and show an increase compared to Baseline after SRP-9001 administration (Figure 11), similar to what is observed in the nonclinical setting. These results indicate that SRP-9001 dystrophin expression promotes restoration and reconstitution of the DAPC (Mendell 2020) supporting the biological activity of SRP-9001 dystrophin at the sarcolemma membrane.

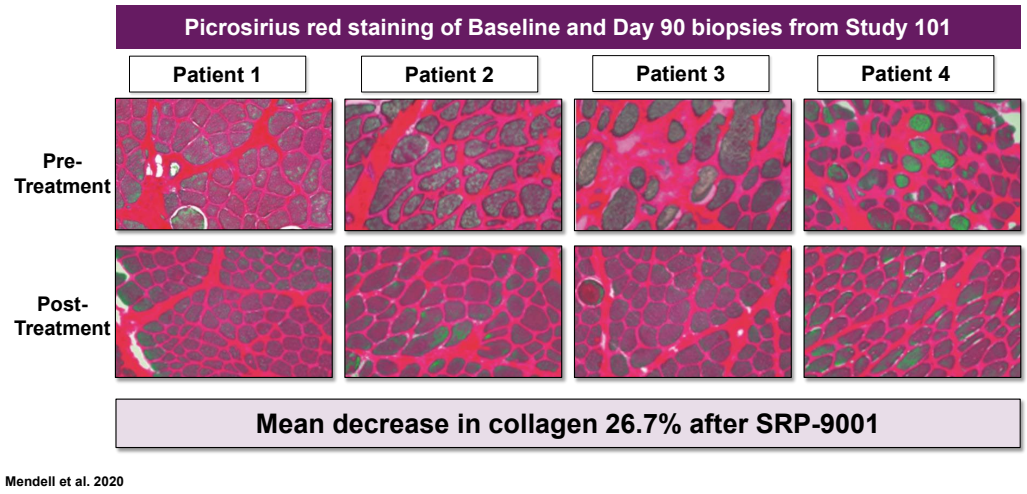
Figure 11: Study 103 Percent Change from Baseline in Sarcoglycan Protein Expression (Cohort 1)



Sarc: sarcoglycan

DAPC reconstitution and stabilization of the sarcolemma membrane result in reductions in collagen deposition, a measure of muscle fibrosis. In Study 101, muscle histology was evaluated pre-and post-treatment, and a mean reduction of 26.7% in collagen deposition was observed post-treatment (Figure 12; Mendell 2020).

Figure 12: Study 101 Muscle Histology Changes From Baseline to Day 90



Mendell et al. 2020

Although serum CK values are variable and are not predicative of disease severity, they can be used to demonstrate impact to sarcolemma membrane stability and early biologic activity of SRP-9001. CK is not a reliable long-term indicator of disease progression, as it can increase with activity and decrease over time if muscle is lost. Serum CK levels in the SRP-9001 clinical studies decreased post-treatment when compared to Baseline across all studies (Table 3). In Study 102, serum CK levels were statistically significantly lower when compared to placebo (p=0.0040 at Week 12), in the

setting of identical peri-infusion steroid regimens. The reduction seen post-SRP-9001 administration is supportive of stabilization of the sarcolemma membrane consistent with the mechanism of action and biological effect of SRP-9001. The magnitude of change in CK is unprecedented based on standard of care and not expected in this age group based on the natural history of the disease (Burch 2015).

Table 3: Studies 101, 102, 103 Change in Serum Creatine Kinase (U/L) from Baseline to Week 12

		Study 102 Part 1		Study 102 Part 2		
Measure	**Study 101 (N=4)**	**Placebo (N=21)**	**SRP-9001 (N=20)**	**SRP-9001 in Part 2 (N=21)**	**SRP-9001 in Part 1 (N=20)**	**Study 103 (N=20)**
Mean age at time of Screening	4.8	6.29	6.24	6.29	6.24	5.81
Creatine Kinase						
Baseline mean (SD)	23167.8 (7924.4)	24888.3 (11884.5)	18845.0 (10421.0)	24888.3 (11884.5)	18845.0 (10421.0)	15431.4 (4247.2)
Week 12 mean (SD)	12073.0 (19905.0)[a]	18602.6 (8968.8)	9200.7 (5556.3)	5264.7 (3678.0)	11291.3 (5905.4)	7795.2 (3804.5)
Mean change (SD) from Baseline	-11094.8(25607.9) [a]	-6285.7 (12038.2)	-9926.6 (9129.5)	-19623.6 (11337.6)	-7423.7 (7215.3)	-7636.2 (4998.5)
P-value*			0.0040			
Mean percent change (SD) from Baseline	-27.58 (126.44)	-9.91 (59.50)	-45.41 (35.44)	-77.03 (14.12)	-34.80 (26.44)	-46.87 (26.60)

SD: standard deviation.
Data extraction date: 9001-101: 15 June 2021; 9001-102: 31 January 2022; 9001-103: 30 April 2021
a. Timepoint is Day 90 for Study 101.
* Modeling change from Baseline with fixed effects of age group, treatment group, visit, treatment group by visit interaction, and model covariates of Baseline value and Baseline value by visit interaction. Estimates wereobtained using unstructured covariance matrix. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

3.2.3 Relationship to Motor Function

3.2.3.1 Treatment of SRP-9001 Leads to Significant Increase in SRP-9001 Dystrophin and Functional Improvement

In the DMD^{MDX} mouse model and across an approximately 10-fold dose range studied (0.0443 to 4.01×10^{14} vg/kg), a pharmacokinetic/pharmacodynamic (PK/PD) relationship with a saturable response was observed, where SRP-9001 dystrophin (measured as IF PDPF, change from baseline) and motor function (measured as specific force of muscle contraction in individual animals and expressed as relative specific force after normalizing to the effect observed at the highest studied dose,

4.01×10^{14} vg/kg) approached the plateau at the high range of tissue drug exposure (vector copies per nucleus). Further, a dose-increase from 1.33×10^{14} vg/kg to 4.01×10^{14} vg/kg did not result in significant increase in protein expression or functional improvement. These foundational studies demonstrate that treatment with SRP-9001 at the proposed dose of 1.33×10^{14} vg/kg drives significant expression of SRP-9001 dystrophin, and the observed motor function improvements are approaching a plateau in response.

The nonclinical findings translated well into patients with DMD. A population exposure-response (ER) relationship was identified for each of the 3 SRP-9001 dystrophin protein expression endpoints (western blot, IF PDPF, and IF fiber intensity, change from baseline) relative to tissue vector genome exposure. Consistent with observations in the DMD^{MDX} mouse model, SRP-9001 dystrophin quantified via IF PDPF (membrane-localized dystrophin) appeared to approach a plateau at the high range of tissue drug exposure. The population ER model on NSAA total score (1-year change from baseline) characterized function improvement across the ambulant patients (≥ 4 – < 8 years old at the time of dosing) studied in the placebo and SRP-9001-treated population. Using the final model, patients treated with SRP-9001 at the clinically proposed dose of 1.33×10^{14} vg/kg are projected to achieve approximately 2 points higher NSAA, on top of steroid therapy (1 year change from baseline) compared to their non-treated counterparts, also on steroid therapy. A 2-point gain is the equivalent of keeping a skill without modification compared to being unable to perform that skill; or keeping 2 skills with modification that would be otherwise lost. These clinical results continue to support that SRP-9001 at the proposed dose of 1.33×10^{14} vg/kg is approaching the maximization of membrane-localized SRP-9001 dystrophin expression, which translated into clinically meaningful benefit in the treated DMD population.

3.2.3.2 Relationship Between SRP-9001 Dystrophin and Functional Improvement in DMD^{MDX} Mouse

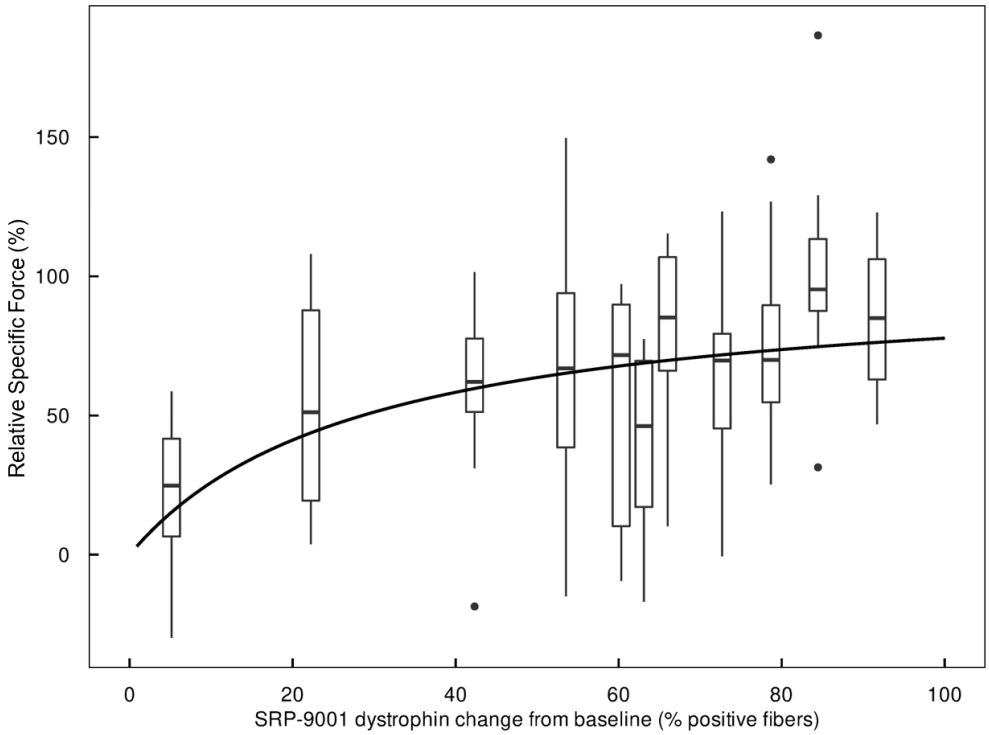
In the DMD^{MDX} mouse model, the treatment response of SRP-9001 was evaluated through quantification of SRP-9001 dystrophin expression (IF PDPF, week 12 change from baseline), as well as functional outcome measured as specific force of muscle contraction in individual animals and expressed as relative specific force after normalizing to the effect observed at the highest studied dose, 4.01×10^{14} vg/kg. Across an approximately 10-fold dose range studied (0.0443 to 4.01×10^{14} vg/kg), a positive association was observed between increasing SRP-9001 dystrophin (IF PDPF change from baseline) and functional outcome. A moderate and statistically significant correlation was determined with a Pearson correlation coefficient of 0.42 and p-value < 0.00001.

Exploratory analysis of relative specific force versus SRP-9001 dystrophin indicated that functional effect showed a trend for saturation with increasing SRP-9001 dystrophin protein given the significant overlap in functional effect observed across the higher dose

range studied (1.33 to 4.01 × 10^{14} vg/kg), achieving the maximum relative specific force across muscle tissues. Further data evaluation was performed using linear and nonlinear models, and the final model selection was guided by exploratory plots, standard model metrics including Bayesian information criterion, objective function value, assessment of model parameter estimates as well as agreement in trends between model predictions and observed data. These results demonstrated that the saturable profile was well characterized by an E_{max} model, indicating an initial phase where relative specific force increases with low levels of SRP-9001 dystrophin expression and additional benefit plateaus at higher levels of expression (Figure 13). The final model estimated that 50% of the maximum functional effect was achieved at 28.6% (estimated with good precision, 17.5% relative standard error [SE]) for SRP-9001 dystrophin expression (IF PDPF, change from baseline), which was well exceeded by the protein expression (median of 62.6% change from baseline) observed at the proposed dose of 1.33 × 10^{14} vg/kg. At this high level of SRP-9001 dystrophin, the functional outcome appears to be approaching a plateau, where the relationship between protein expression and functional efficacy becomes non-monotonic and therefore cannot be adequately described or quantified using a linear relationship. This saturable effect is achieved when SRP-9001 dystrophin is driving significant motor function improvement and maximizing benefit at higher protein expression levels, thus confirming an association between SRP-9001 dystrophin (biomarker) and functional effect. Importantly, the range of SRP-9001 dystrophin expression (> 28.6% IF PDPF, change from baseline) that produced significant functional improvement in the nonclinical studies was also achieved in patients with a median protein expression of 57.3% (IF PDPF change from baseline) at the proposed dose of 1.33 × 10^{14} vg/kg.

Literature evidence on endogenous dystrophin provides important insights on the magnitude of correlation and the profile of the quantitative relationship to be expected for SRP-9001 dystrophin. Like SRP-9001 dystrophin, similar magnitude of correlation between endogenous dystrophin and heart function measured as LVEF (correlation coefficient of 0.464, p=0.019) was reported by van Putten (2014) in mdx-Xist$^{\Delta hs}$ mice expressing varying levels of endogenous dystrophin protein. Importantly, improvement in heart function was observed at low dystrophin levels, and the relationship exhibits a saturable profile in cardiac improvement at higher level of dystrophin expression. As reported by de Feraudy (2021) low expression levels of endogenous dystrophin conferred clinical benefit in DMD observation studies. Together, these provide compelling evidence that the functionality of SRP-9001 and its relationship with functional improvement mirrors that of endogenous dystrophin. Furthermore, a saturable relationship is not unique with SRP-9001 dystrophin, but also evident with additional biological endpoints in the biological cascade of DMD (Figure 7) including tissue transduction (vector copies per nucleus) and DAPC reconstitution. These data suggest that at high levels of biological response, functional improvement in NSAA total scores (1 year change from Baseline) appears to approach a plateau.

Figure 13: Relationship Between Relative Specific Force vs SRP-9001 Dystrophin Expression (IF PDPF, Week 12 Change from Baseline) Demonstrates SRP-9001 Dystrophin is Driving Significant Motor Function Improvement and Maximizing Benefit



% positive fibers: Immunofluorescence Percent Dystrophin Positive F ber; Relative Specific Force: specific force (muscle contractile force from upper muscle [diaphragm] and lower muscle group [t bialis anterior]) normalized to the specific force associated with each tissue group at the highest studied dose. Box and whiskers plot shows the median, interquartile and range of observed data from DMD^{MDX} mouse across a dose range of 0.0443 to 4.01×10^{14} vg/kg. The continuous black line shows the expected mean value of relative specific force predicted by an E_{max} model developed using all observed data.

3.2.3.3 Relationship Between SRP-9001 Dystrophin and Clinical Outcome in Patients with DMD

The clinical biomarker-to-functional efficacy relationship was evaluated in ambulant patients with DMD (≥ 4 – < 8 years old at the time of dosing) using data across 3 clinical studies (Studies 101, 102, and 103 Cohort 1) and a clinical dose range inclusive of 6.29×10^{13}, 8.94×10^{13} vg/kg and 1.33×10^{14} vg/kg. SRP-9001 dystrophin protein expression in patients were measured by western blot (total protein expression), IF (membrane-localized dystrophin, PDPF and fiber intensity), all evaluated as Week 12 change from Baseline. Clinical efficacy was evaluated as NSAA total score 1-year change from Baseline and clinical timed function tests.

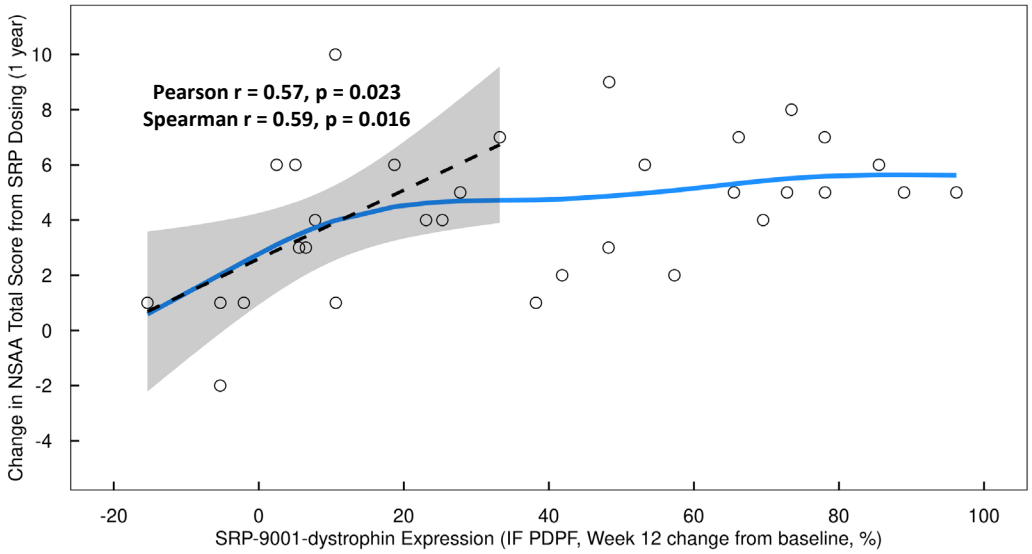
Consistent with the nonclinical findings described in Section 3.2.3.2, a positive association was observed between SRP-9001 dystrophin (protein expression change from baseline) and NSAA total score (1 year change from baseline). For all 3 SRP-9001 dystrophin protein expression endpoints, statistically significant correlation was

determined with Spearman correlation coefficients of 0.38 (western blot) and 0.33 (IF PDPF and fiber intensity) and p-values < 0.005. The magnitude of correlation and statistical significance observed with SRP-9001 are generally consistent with precedent established in other disease indications including Alzheimer's Disease and Amyotrophic Lateral Sclerosis, where clinical biomarkers (amyloid beta peptide, tau proteins, neurofilament) were determined as reasonably likely to predict clinical outcomes with correlation coefficients ≤ 0.4 but statistically significant (FDA 2023, Halbgebauer 2022, Rajagovindan 2021). In the case of SRP-9001, a high linear correlation coefficient over the entire range of SRP-9001 dystrophin expression is not expected based on evidence of a saturable relationship observed for both endogenous dystrophin and in SRP-9001 nonclinical studies, where the plateau in functional improvement becomes non-monotonic at high protein expression (Section 3.2.3.2).

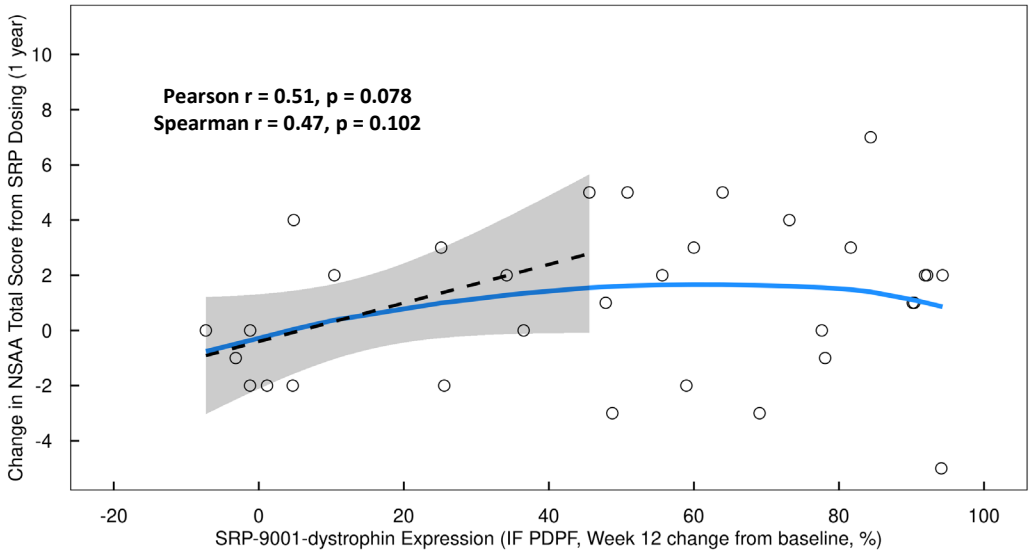
Importantly, clinical trial data to date showed a similar profile as the E_{max} relationship identified in the nonclinical studies, with an initial linear phase where NSAA total score (1 year change from baseline) increases with increasing SRP-9001 dystrophin expression (change from baseline) followed by an apparent plateau at high levels of expression (Figure 14). The magnitudes of 1-year change in NSAA total score were different between 4–5-year-old and 6–7-year-old patients, consistent with the fact that 6 years of age is a pivot point in the overall DMD disease trajectory where NSAA total score begins to decline, eventually reaching -3 points per year, as described in Sections 2.1.3 and 2.5.3.1. As such, the biomarker-to-functional quantitative relationship would be different between the 2 age groups (4–5 vs 6–7 years old), however a saturable profile is apparent in both. Similar to the foundational studies in the animal disease model, this saturable effect is achieved when SRP-9001 dystrophin produced significant functional effect, thus confirming that SRP-9001 dystrophin is predictive of functional outcome. Because the relationship appears non-monotonic at the higher protein expression levels, when the correlation analysis was focused on the earlier phase prior to the plateau, higher correlation coefficients were demonstrated in both 4–5 years old (Pearson r=0.57, Spearman r=0.59) and 6–7 years old (Pearson r=0.51, Spearman r=0.47), as shown in Figure 14.

Figure 14: NSAA (1-Year Change from Baseline) vs SRP-9001 Dystrophin Expression Quantified via IF PDPF (Week 12 Change from Baseline) in Patients (4–7 Years Old at the Time of Dosing) From Studies 101, 102 (Parts 1 and 2), and 103 Cohort 1

A) Age 4–5 Years Old



B) Age 6–7 Years Old



NSAA: North Star Ambulatory Assessment; PDPF: Percent Dystrophin Positive Fiber. Black open circles represent observed data from patients with DMD 4-7 years old at the time of dosing) from Studies 101, 102, and 103 Cohort 1 across a dose range of 6.29×10^{13} to 1.33×10^{14} vg/kg. Blue line shows the non-parametric regression smoothing spline across the observed data. Dashed black line and gray ribbon show the linear regression line and associated 95% confidence interval, and correlation statistics (Pearson and Spearman) corresponding to the area of the curve prior to an apparent plateau. A) Age 4–5-years-old included all SRP-9001-treated and placebo patients well matched to the treated population (n=32). B) Age 6–7-years-old included only SRP-9001-treated patients (n=32) because of the baseline imbalance in Study 102 that resulted in placebo patients not well matched (healthier disease status and higher NSAA total score at baseline) to the treated patients.

In the analyses described above, SRP-9001 dystrophin measured as IF PDPF (change from baseline) was evaluated because it was obtained across nonclinical and clinical studies, and therefore represents a common protein expression endpoint to assess the relationship of protein expression relative to functional improvement in the dystrophic animal model and in patients with DMD. A statistically significant correlation was observed for SRP-9001 dystrophin measured via western blot and IF methods (Pearson correlation coefficient of 0.73 with p-value < 0.0001 between western blot and IF PDPF, and 0.87 with p-value < 0.0001 between western blot and IF fiber intensity). Therefore, it stands to reason that the relationship between SRP-9001 dystrophin (western blot) and clinical efficacy would follow a similar trend.

Furthermore, consistent with the findings for NSAA total score (1 year change from Baseline), trends of improvement in timed function assessments including 10-meter timed test, time to rise from floor, time to ascend 4 steps, and 100-meter timed test were observed with increased SRP-9001 dystrophin expression measured via both western blot and IF methods.

The totality of evidence in the nonclinical program demonstrates a clear association between SRP-9001 dystrophin and specific force output in the DMD animal model. The range of protein expression in the nonclinical studies that demonstrated a clear association to functional benefit is consistent with the protein expression range achieved in the clinical studies. Thus, the positive association between biomarker-to-functional effect observed both in the nonclinical and clinical studies demonstrates that SRP-9001 dystrophin protein expression is predictive of functional improvement and consistent with the observations made in the clinical setting. These findings support the proposed mechanism of action for SRP-9001, and the appropriateness of using SRP-9001 dystrophin expression as a biomarker that is reasonably likely to predict clinical benefit in patients with DMD.

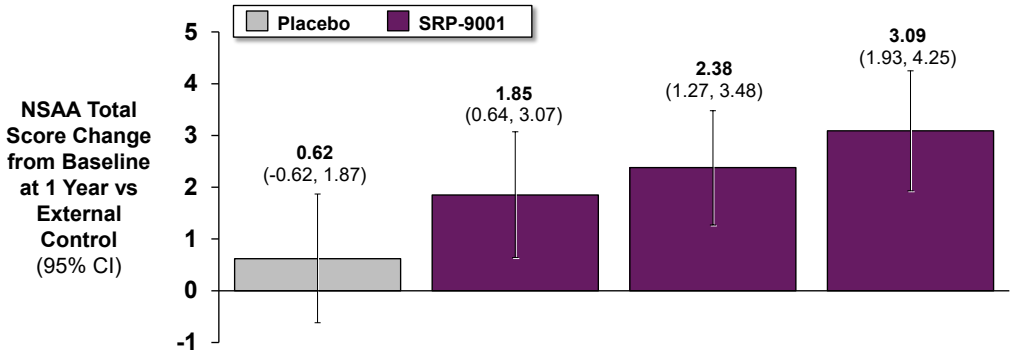
3.2.3.4 SRP-9001 Dystrophin Expression as a Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit

The nonclinical and clinical data on biological activity show that treatment induces a level of SRP-9001 dystrophin protein that produces significant improvements on a variety of biological measures comparable to wildtype dystrophin. This improvement occurs even at low levels of dystrophin, with the level of improvement plateauing at higher levels of protein expression, consistent with an E_{max} relationship. This phenomenon is replicated in the clinical data on functional improvement.

Figure 15 identifies a clear relationship between SRP-9001 dystrophin expression and slowing of disease progression (as assessed by NSAA total score at 1 year) compared to what would be expected based on natural history (as represented by propensity score weighted EC cohorts). When all SRP-9001-treated patients from Studies 102 and 103 are grouped into tertiles based on their level of SRP-9001 dystrophin expression, all

3 tertiles are observed to have improvement in NSAA score compared to their propensity score weighted EC cohorts.

Figure 15: Relationship Between SRP-9001 Dystrophin Expression by Tertile and NSAA Total Score Change from Baseline at 1 Year vs External Control



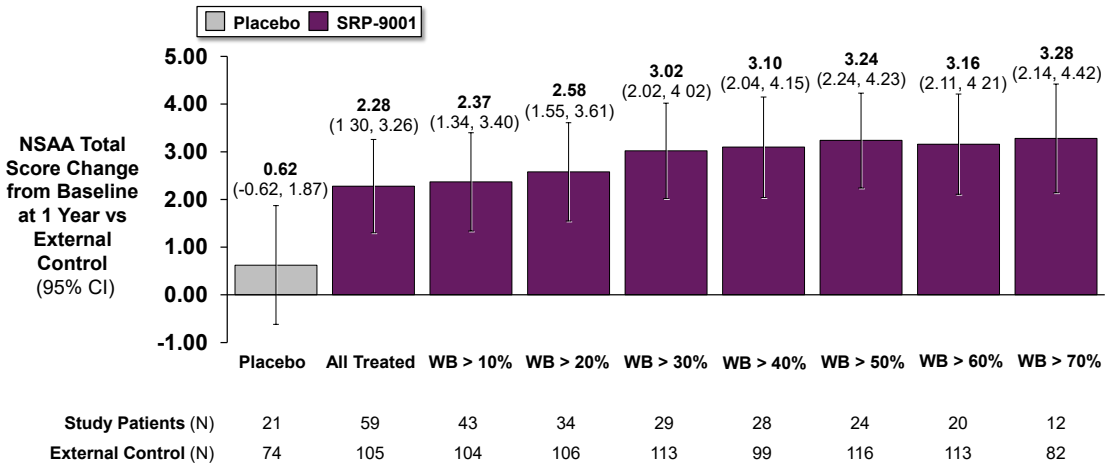
	Placebo	Lowest Expression	Intermediate Expression	Highest Expression
Mean Expression	2.05%	5.77%	34.09%	89.77%
Study Patients (N)	21	20	20	19
External Control (N)	74	97	101	87

CI: confidence interval; NSAA: North Star Ambulatory Assessment; WB: western blot
Study patients from Studies 102 and 103 (Cohort 1)

The lowest expression group of treated patients had a mean expression of 5.77%, which is several fold higher than the expression expected from currently available therapies. When compared to propensity score weighted EC, these patients demonstrated a 1.85 points difference in NSAA total score, favoring the treated patients. This is consistent with what is described in the literature: that even low levels of dystrophin confer clinical benefit.

In order to provide more granularity in the relationship beteween SRP-9001 dystrophin expression and clinical outcomes, Figure 16 shows how NSAA change from Baseline at 1 year varies when SRP-9001 dystrophin expression is above successive thresholds. The figure again demonstrates the evidence of benefit across the range of expression, but also demonstrates a potential plateau in effect, analogous to the nonclinical data, where higher levels of expression do not correspond to linear increases in functional benefit.

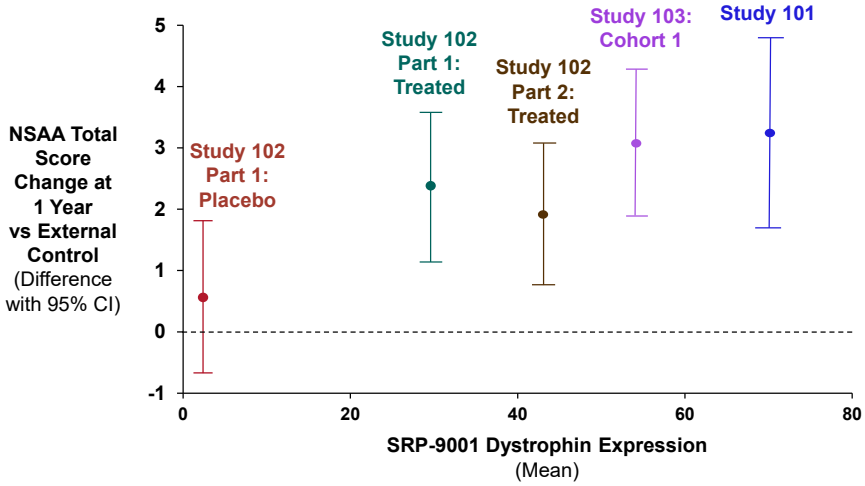
Figure 16: Relationship Between SRP-9001 Dystrophin Expression Above Different Thresholds and NSAA Total Score Change from Baseline at 1 Year vs External Controls



CI: confidence interval; NSAA: North Star Ambulatory Assessment; WB: western blot
Study patients from Studies 102 and 103 (Cohort 1)

A consistent association between expression and functional benefit is further evident at the study level. In Figure 17, the mean expression for each study cohort is plotted against the mean NSAA total score difference between the study and their propensity score weighted EC cohort. In each study, treatment with SRP-9001 resulted in SRP-9001 dystrophin protein expression at 12 weeks, followed by a change in NSAA total score that differs from what natural history, as represented by propensity score weighted ECs, would suggest for those patients.

Figure 17: Relationship Between NSAA Total Score Change at 1 Year vs External Control (Difference) and SRP-9001 Dystrophin Expression (Mean) Across Different Studies in the Program



CI: confidence interval
Note: SRP-9001 dystrophin expression in Study 101 was measured by western blot without normalization for muscle content.

In addition to analyses involving ECs, an analysis of SRP-9001 expression and clinical outcomes without the use of ECs is possible within the well-balanced 4–5-year-old stratum of the randomized, double-blind, placebo-controlled Study 102. For this analysis, treated patients with quantifiable levels of SRP-9001 expression (n=7) were compared to those with no SRP-9001 dystrophin expression (placebo patients, n=8) or treated patients with detectable, but not quantifiable, levels of SRP-9001 dystrophin (n=1). The result was a 2.2 point greater NSAA score in patients with quantifiable SRP-9001 dystrophin present on biopsy (p=0.0467). The magnitude of NSAA benefit associated with the presence of quantifiable SRP-9001 dystrophin in this analysis was similar to the treatment effect estimated in patients 6–8-years-old using ECs (2.1 points, Section 5.5.8.2) and the treatment effect estimated by the integrated 1.33×10^{14} vg/kg analysis using ECs (2.4 points, Section 5.5.7).

The consistency of these findings supports that the benefits predicted by SRP-9001 dystrophin in the EC analyses are not likely to be due to biases related to effort or treatment expectation in those cohorts. This finding, along with the sensitivity analyses (described in Section 5.5) that evaluated the treatment effect using distinct EC databases and different analytic methods supports the reliability of the EC analyses results and underscores the comparability of the propensity score weighted EC cohorts as appropriate comparator populations to support a reasonable likelihood of benefit.

3.2.3.5 *SRP-9001 Dystrophin – Clinical Outcome* Analysis Summary

In summary, a significant Spearman correlation of 0.38 is observed in simple correlation analysis of the amount of SRP-9001 dystrophin expression on western blot at the week 12 biopsy and change from baseline in NSAA at 1-year across all patients in the development program (both placebo and SRP-9001-treated patients). The relationship shows a saturable pattern (rather than a monotonic increase) across the range of SRP-9001 dystrophin expression, consistent with preclinical data and observational studies of patients with DMD, and therefore a modest linear correlation coefficient is expected in this type of analysis. A pre-specified EC analysis was developed to provide quantitative estimates of the magnitude of NSAA gain predicted by SRP-9001 dystrophin. This analysis showed consistent findings of clinically meaningful gains in NSAA at 1-year across the range of SRP-9001 dystrophin expression achieved after SRP-9001 treatment. These results confirm the findings of the biological endpoints measured in the development program demonstrating expression of SRP-9001 dystrophin, correct cellular localization, and expected biological effects within myocytes. The totality of the above evidence provides confidence that the SRP-9001 dystrophin expression observed after SRP-9001 treatment is reasonably likely to predict clinical benefit in patients with DMD.

4 DOSE SELECTION

The totality of SRP-9001 clinical efficacy, safety, and population PK and PD analyses from nonclinical and clinical studies supports the proposed clinical dose of SRP-9001 at 1.33×10^{14} vg/kg. This conclusion is supported by the following evidence:

- The drug target and mechanism of action of SRP-9001 are the same in all patients with DMD regardless of disease severity and ambulatory status. The systemic (serum) PK of SRP-9001 are consistent across the studied DMD population (age 4 – 20 years old) inclusive of patients with ambulatory and non-ambulatory status, which translated into comparable levels of tissue drug biodistribution and transduction across the studied DMD population to justify the proposed dose of 1.33×10^{14} vg/kg.
- Based on the wide dose-ranging evaluation (4.43×10^{13} vg/kg to 4.01×10^{14} vg/kg) in the dystrophic animal model (DMD^{MDX} mouse model), a dose-dependent increase in tissue vector exposure was observed (Potter et al 2021). A robust PK/PD relationship with a saturable response is demonstrated between tissue vector exposure and treatment response (SRP-9001 protein expression and functional improvement) in the DMD^{MDX} mice. The increased vector exposure at the maximum feasible dose (4.01×10^{14} vg/kg) produced marginal increase (less than 17%) in SRP-9001 dystrophin protein expression relative to the clinically proposed dose of 1.33×10^{14} vg/kg, which did not translate into functional improvement in the dystrophic animal model.
- Patients with DMD who were treated with the clinically proposed dose of 1.33×10^{14} vg/kg achieved tissue transduction and SRP-9001 dystrophin expression that translated into clinically meaningful benefit in motor functional outcome as measured by NSAA total score at 1 year post-dose. Importantly, similar to the evidence demonstrated in the foundational nonclinical studies, the dose of 1.33×10^{14} vg/kg was also shown to approach the plateau of biological efficacy (SRP-9001 dystrophin protein expression measured as IF PDPF) in patients with DMD. These findings support that SRP-9001 at 1.33×10^{14} vg/kg is approaching the maximization of membrane-localized and functional SRP-9001 dystrophin protein expression, and a higher dose (above 1.33×10^{14} vg/kg) is not expected to produce significant increase in biological efficacy. The population ER analysis performed on clinical functional efficacy further supports that relative to placebo patients, patients treated with SRP-9001 at the clinically proposed dose of 1.33×10^{14} vg/kg have greater motor functional improvement or stabilization (1-year change in NSAA from baseline).
- Existing clinical experience in patients with DMD treated with SRP-9001 at 1.33×10^{14} vg/kg confirmed that body weight-based dosing up to 70 kg is safe and well tolerated. A dose cap at a maximum body weight cut-off of 70 kg (9.31×10^{15} vg total dose) is recommended for patients with body weight above

70 kg. Based on the growth trajectory in patients with DMD, a weight-cap of 70 kg is expected to cover the majority of the target DMD population up to 18 years of age. To date, patients with body weight of 14 kg to 80 kg (at a maximum total dose of 9.31×10^{15} vg) have been treated with SRP-9001, and no apparent relationship was observed between SRP-9001 drug administration (total administered capsid load or serum vector genome PK) and safety biomarkers associated with liver (GLDH, GGT), cardiac (troponin), complement (C3, C4 and CH50), and platelet counts.

- The progression of DMD follows a predictable course and is fatal. Currently approved therapies are limited, and more treatment options are needed. Taking into consideration the currently recommended NOAEL (no-observed-adverse-effect-level) for SRP-9001 is 1.33×10^{14} vg/kg and the serious safety events seen in other AAV gene therapies, the benefit-risk assessment of SRP-9001 strongly supports the clinically proposed dose of 1.33×10^{14} vg/kg.

5 CLINICAL EFFICACY

5.1 Introduction to SRP-9001 Functional Efficacy

Clinical efficacy comprises biological and functional endpoints. The biological endpoints of the clinical development program are summarized in Section 2.5.2 and many of the results are described in Section 3.2.2. The functional endpoints used throughout the clinical program are described in Section 2.5.3. Here, each study will be described in more detail, with an emphasis on the primary and functional endpoints.

Consistent with FDA advice, the primary evidence of effectiveness comes from Studies 103 Cohort 1, with data from Studies 102, 101, and the integrated analysis across the 3 SRP-9001 studies providing further supportive data and evidence of treatment effect.

Study 103 Cohort 1 provides substantial evidence of effectiveness:

- A mean increase (improved) in NSAA total score of 4.0 from Baseline to Week 52 post-SRP-9001 infusion was observed in Cohort 1 patients (Section 5.4.7.1.1).
- The increase in NSAA total score from Baseline to 1-year post-SRP-9001 infusion was statistically significant when compared to the propensity score weighted EC cohort (least square mean [LSM] change difference 3.2 (0.6) $p < 0.0001$), favoring SRP-9001 (Section 5.5.8.3).
- The mean decreases (improved) from Baseline to Week 52 of the following timed functional tests for Cohort 1 patients were: -12.02 seconds (100-meter timed test), -0.79 seconds (time to ascend 4 steps), -0.48 seconds (time to rise from the floor), and -0.77 seconds (10-meter timed test) (Section 5.4.7.1.2).

Additional evidence from Studies 101, 102, and the integrated analysis of all 3 studies demonstrates:

- In Study 101, a mean (standard deviation [SD]) increase in NSAA at 52 weeks of 5.5 (2.65) points was observed. Improvements were maintained over 4 years, with a mean change from baseline of 7.0 (2.94) points at 4 years (Section 5.2.3).
- While Study 102 did not achieve statistical significance on its primary endpoint, the results are challenging to interpret due to a substantial imbalance in key prognostic factors in the 6–7-year-old age stratum that resulted in patients with more favorable prognosis assigned to placebo treatment. In the 4–5-year-old age stratum, where baseline characteristics were well balanced, there was a nominally significant benefit of SRP-9001 treatment over placebo (2.5 points, $p=0.0172$), Section 5.3.8.3).
- When compared to a propensity score weighted EC cohort, the 6–8-year-old SRP-9001-treated patients in Study 102 demonstrate a LSM change difference

of 1.9 (0.6) points in total NSAA score, favoring SRP-9001 (p=0.004, Section 5.5.8.2).

The treatment effect and overall pattern of NSAA Total Score from the 3 trials is consistent, durable, and attributable to SRP-9001. In the subsequent sections, data from Studies 101, 102, and 103 are first presented individually and then collectively at the 1.33×10^{14} vg/kg dose to demonstrate the consistency of effect throughout the SRP-9001 program. Comparison to EC based on a pre-specified statistical analysis plan (SAP) is provided in Section 5.5 to contextualize the open-label findings.

5.2 Study 101

5.2.1 Study Design Overview

Study 101 is an ongoing, open-label, first-in-human, proof-of-concept, single-arm, single-dose, Phase 1/2a study conducted at a single site in the US (Figure 18). Eligible patients were ≥ 4 to < 8 years of age at Screening, with frameshift (deletion or duplication) or premature stop codon mutation between exons 18 to 58 in the *DMD* gene.

Figure 18: Study 101 Design Schematic

The primary objective of the study was to evaluate the safety of SRP-9001 in patients with DMD. Secondary objectives were to evaluate the biological efficacy and functional efficacy:

- Biological endpoints included change in quantity of SRP-9001 dystrophin expression by western blot, IF fiber intensity, IF PDPF and transduction with vector genome copies per nucleus by ddPCR from Baseline to Day 90; and change in CK levels from Baseline over time.
- Key functional endpoints included change from Baseline in NSAA total score, the time to walk 100 meters, percent predicted time to walk 100 meters, time to ascend 4 steps; time to rise from the floor, and time to run 10 meters.

All patients received a single IV dose of SRP-9001 and were discharged from the hospital the day after study drug administration. Follow-up assessments were or will be performed on Days 7, 14, 30, 60, and Month 3, then every 3 months until Month 12, then every 6 months onwards until Year 5. Physical therapy assessments were

performed during Screening and at all visits from Day 30 onward. Muscle biopsies of the gastrocnemius muscle were performed during Screening and on Day 90.

Patients were on a stable dose of oral corticosteroids for at least 12 weeks prior to Screening and the dose was to remain constant (except for potential modifications to accommodate changes in weight) throughout the first year of the study. Beginning the day prior to SRP-9001 infusion, patients received a daily dose of 1 mg/kg of glucocorticoid for approximately 30 days in addition to their chronic corticosteroid regimen. The dose may have been increased for a short time if GGT was elevated > 150 U/L or there were other clinically significant liver function abnormalities.

5.2.2 Patient Population

Four patients with DMD were screened and enrolled in Study 101. Each patient was treated with a single IV dose of SRP-9001 and completed over 4 years of follow-up.

The enrolled patients had a mean age of 4.8 years (range: 4–6 years) and mean weight of 18.10 kg (range: 13.7–21.4 kg). The DMD mutations of the enrolled patients were deletion of exons 46 to 50, deletion of exons 46 to 49, premature stop codon exon 27, and partial deletion of exon 44. All patients were taking oral prednisolone prior to enrollment.

5.2.3 Results

Results for biological endpoints are summarized in Section 3.2.2.

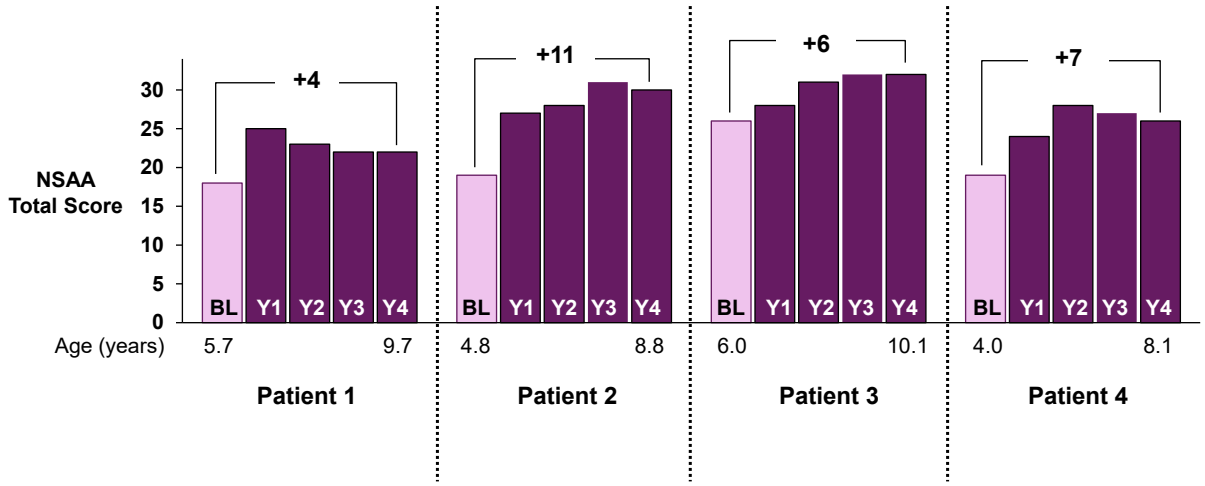
Baseline and Week 52 NSAA scores and timed function test results are summarized in Table 4. At 52 weeks, the mean (SD) total NSAA score was 26 (1.83), representing a mean (SD) 5.5 (2.65) point increase from Baseline. Similarly, there was improvement in all timed function tests, demonstrated by shorter times to complete each skill. These gains were maintained at 4 years of follow-up, with a mean (SD) NSAA score of 27.5 (4.43) at 4 years, which is a mean (SD) 7.0 (2.94) point increase from Baseline (Figure 19).

Table 4: Study 101 Change from Baseline to Week 52 in the NSAA Total Score and Timed Functional Assessments

Assessment, Mean (SD), seconds	**SRP-9001 (N=4)**
NSAA total score	
Baseline	20.5 (3.70)
Week 52	26.0 (1.83)
Change from Baseline	5.5 (2.65)
Time to walk 100 meters	
Baseline	56.40 (8.54)
Week 52	47.35 (5.78)
Change from Baseline	-9.05 (9.84)
Percent predicted time to walk 100 meters	
Baseline	58.38 (9.77)
Week 52	67.75 (8.78)
Change from Baseline	9.38 (13.32)
Time to ascend 4 steps	
Baseline	3.47 (1.20)
Week 52	2.20 (0.37)
Change from Baseline	-1.27 (1.12)
Time to rise from the floor	
Baseline	3.68 (0.48)
Week 52	3.33 (0.54)
Change from Baseline	-0.35 (0.82)
Time to run 10 meters	
Baseline	4.89 (0.48)
Week 52	4.21 (0.43)
Change from Baseline	-0.68 (0.69)

NSAA: North Star Ambulatory Assessment; SD: standard deviation

Figure 19: Study 101 NSAA Total Score Baseline to Year 4



BL: baseline; NSAA: North Star Ambulatory Assessment; Y: year

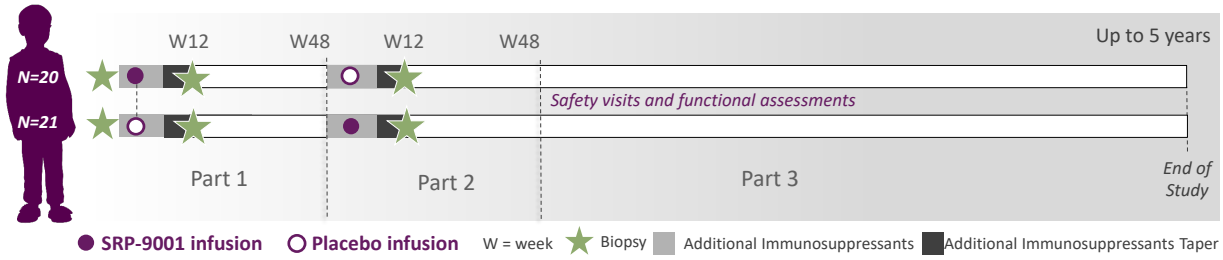
5.3 Study 102

5.3.1 Study Design Overview

Study 102 is an ongoing, randomized, double-blind, placebo-controlled, 3-part study of systemic gene delivery of SRP-9001 in patients with DMD. Study 102 was conducted at 2 sites in the US. The main objectives of the study were to assess the biologic and clinical efficacy as well as safety of SRP-9001.

In Part 1, patients were randomized in a 1:1 ratio to SRP-9001 or placebo (Figure 20). Randomization was stratified by age group at Baseline (4 to 5 vs 6 to 7 years) based on natural history data (Ricotti 2016, Muntoni 2019) indicating the 2 age groups exhibit different trajectories with respect to NSAA (Section 2.5.3.1).

Figure 20: Study 102 Schematic



Part 1 was a 48-week randomized, double-blind, placebo-controlled period.

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

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

Patients were followed for 48 weeks in Part 1. All patients had a muscle biopsy of the gastrocnemius performed pre-treatment and at Week 12 in Part 1.

Part 2 of the study was a crossover design and began after the patient completed Part 1. Patients randomized to SRP-9001 in Part 1 of the study received placebo in Part 2. Patients randomized to placebo in Part 1 of the study crossed over to receive SRP-9001 in Part 2. Infusion and steroid administration were given in the same manner as in Part 1. The physical function assessor, site staff, and Investigators were also blinded to patient assignment in Part 2.

Part 2 of the study was 48 weeks in duration with study visits weekly for the first 2 weeks, then every 2 weeks until Week 12 followed by every 12 weeks until Week 48. Biopsies were collected at least 12 weeks after treatment in Part 2, as described for Part 1. Part 2 of the study is now complete.

Part 3 of the study is an open-label follow-up period (efficacy data not presented).

5.3.2 Study Treatment

IV SRP-9001 (1.33×10^{14} vg/kg) or placebo (lactated Ringer's solution) was administered IV on Day 1 over 1 to 2 hours.

Two methods were used to determine product dose: a qPCR method using a supercoiled standard and a qPCR method using a linear standard. All patients received 1.33×10^{14} vg/kg by supercoiled standard qPCR; however retrospectively, based on linear standard qPCR, 3 dose amounts were administered in Part 1 :

- 6.29×10^{13} vg/kg (6 patients)
- 8.94×10^{13} vg/kg (6 patients)
- 1.33×10^{14} vg/kg (8 patients)

In Part 2, all patients receiving SRP-9001 received a dose of 1.33×10^{14} vg/kg.

5.3.3 Enrollment Criteria

Eligible patients were male patients with DMD, 4 to 7 years old, inclusive, with either frameshift (deletion or duplication) mutations between exons 18 and 58, or premature stop codon mutation between exons 18 to 58. At Screening, patients had to have a CK elevation > 1,000 U/L and performance below the 95th percentile predicted time on the 100-meter walk test. All patients were required to be on a stable dose equivalent of oral corticosteroids for at least 12 weeks before Screening and the dose was to remain constant (except for potential modifications to accommodate changes in weight) throughout Parts 1 and 2 of the study.

5.3.4 Efficacy Endpoints

The primary efficacy objectives with corresponding endpoints for Study 102 are presented in Table 5.

Table 5: Study 102 Primary Efficacy Objectives With Corresponding Endpoints

Efficacy Objective	Efficacy Endpoint
Primary (Part 1)	
Evaluate SRP-9001 dystrophin expression from SRP-9001 at 12 weeks post-dosing as measured by western blot of biopsied muscle tissue	Change in quantity of SRP-9001 dystrophin protein expression from Baseline to Week 12 as measured by western blot
Evaluate the effect of SRP-9001 on physical functional assessments as assessed by the NSAA over 48 weeks	Change in NSAA total score from Baseline to Week 48

NSAA: North Star Ambulatory Assessment

Additional key biological endpoints included IF fiber intensity, IF PDPF and transduction with vector genome copies per nucleus by ddPCR from Baseline Week 12; and change in CK levels from Baseline over time.

Additional key functional endpoints for Cohort 1 included change from Baseline in NSAA total score, the time to walk 100 meters, percent predicted time to walk 100 meters, time to ascend 4 steps, time to rise from the floor, and time to run 10 meters.

5.3.5 Blinding

All patients and study staff were blinded to treatment assignments, with the exception of the pharmacist, during Part 1 of the study and remained blinded until the last patient completed Part 2 Week 48 visit.

Separate study personnel were designated to conduct functional assessments and to treat patients in order to protect against possible unblinding of treatment assignment during regular clinical care of patients.

The Examining Team (physiotherapists) were responsible for conducting the physical functional assessments (NSAA, 10-meter timed test, 100-meter timed test, time to rise from floor, and time to ascend 4 steps) and did not have access to any patient data.

Treating Team members were responsible for the clinical care of the patient. They managed the study drug infusion, steroid dosing changes, review of all laboratory data, assessment of AEs and serious AEs (SAEs) and performed all assessments except for the physical functional assessments. The Treating Team did not have access to the data collected by the Examining Team.

5.3.6 Statistical Methods

5.3.6.1 Sample Size

A treatment difference was expected for the primary (biological) efficacy endpoint of change from Baseline to Week 12 in quantity of SRP-9001 dystrophin expression as measured by western blot. Therefore, the sample size of this study was based on the power for the primary (functional) efficacy endpoint of change in NSAA total score from Baseline to Week 48 (Part 1) with Type 1 error of 0.05 (2-sided), assuming the alpha allocated for the primary (biological) endpoint was recycled (ie, fallback procedure). Assuming the SD was 5 for this endpoint for the Baseline age of 4 to 7, with a Type 1 error of 0.05 (2-sided), a sample size of 22 patients per treatment group would have provided approximately 90% power to detect a mean treatment difference of 5 in change in NSAA total score from Baseline to Week 48 between SRP-9001 and placebo. No dropout was assumed for the sample size calculation.

5.3.6.2 Analysis Populations

Two populations were defined for efficacy analyses:

- ITT population: All randomized patients who received study drug (any dose of SRP-9001 or placebo) during Part 1, with treatment group designated according to randomization.
    - The ITT population was the main analysis population for endpoints for Part 1.
- SRP-9001 treated population: All patients who were treated with SRP-9001 in Part 1 or Part 2.

5.3.6.3 Endpoint Analyses

For the primary biological endpoint of change in quantity of SRP-9001 dystrophin protein expression from Baseline to Week 12 as measured by western blot, the null hypothesis was treatment assignment has no effect on the endpoint, and the alternative hypothesis was treatment assignment affects the endpoint. SRP-9001 dystrophin level (% control) determined by western blot was summarized descriptively by treatment group and visit. In addition, summary of change from Baseline to Week 12 was presented by treatment group. The primary analysis was a re-randomization test using a 2-sample Welch t-test statistic to compare the 2 treatment groups for change from Baseline to Week 12. Within each treatment group, a permutation test based on 1-sample t-test statistic was conducted to compare Week 12 with the Baseline. Subgroup analyses for the primary biological endpoint were conducted with respect to age group, body mass index (BMI) group, and lot group. As muscle content in patients with DMD is highly variable, dystrophin levels were adjusted to normalize the variability. Therefore, the analyses for SRP-9001 dystrophin focus on western blot adjusted by muscle content.

For the primary functional efficacy endpoint of change from Baseline to Week 48 in NSAA total score, the null hypothesis was that the population means for the 2 treatments were equal and the alternative hypothesis was that the population means for the 2 treatments were not equal. The primary analysis of the change in NSAA total score from Baseline to Week 48 was based on data from in-clinic NSAA assessments. If in-clinic NSAA assessment at Week 48 was missed or out of protocol-defined visit window, interpolated NSAA total score using neighboring in-clinic assessments were used. Descriptive statistics were provided for Baseline, post-Baseline, and change from Baseline by treatment and visit.

For the primary analysis, a restricted maximum likelihood -based mixed model for repeated measures was used to compare SRP-9001 with placebo. In this model, the response vector consisted of the change from baseline in NSAA total score at each post-baseline visit in Part 1. The model included the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group (categorical), baseline NSAA total score, and baseline NSAA total score by visit interaction. All covariates were fixed effects in this model. An unstructured covariance matrix was used to model the within-patient variance-covariance. Subgroup analyses for change from Baseline in NSAA total score were conducted by age group, race, BMI group, steroid type, steroid use frequency, lot group, and NSAA group.

Note that because this study had 2 primary endpoints, each primary endpoint was tested for statistical significance based on a multiplicity-adjusted testing procedure that controlled the overall Type 1 error rate at a 2-sided level of 0.05. The 2-sided alpha of 0.05 was first split with 0.01 allocated to the primary biological endpoint and 0.04 allocated to the primary functional endpoint. If any of the primary endpoints were significant, the alpha was recycled to test for the other primary endpoint.

5.3.7 Patient Population

5.3.7.1 Patient Disposition

A total of 41 patients with DMD received treatment in Part 1 and were included in the ITT population (SRP-9001 N=20; placebo N=21). No patient discontinued from the study. All 41 patients completed Part 1 of the study.

A total of 39 patients were treated in Part 2 of the study. All 21 patients who received placebo in Part 1 were treated with SRP-9001 in Part 2; of the 20 patients who received SRP-9001 in Part 1, 18 were treated with placebo in Part 2. Two patients were not treated in Part 2. One patient due to steroid-related AE (irritability), and the second due to femur fracture. Both patients continue to be followed in Part 2 for efficacy and safety.

5.3.7.2 Patient Demographics

Patients included in the ITT population were mostly white and included more 6–7-year-olds than 4–5-year-olds (Table 6).

Table 6: Study 102 Summary of Demographics and Baseline Characteristics – ITT Population (Part 1)

Category	SRP-9001 (N=20)	Placebo (N=21)
Age (years)		
Mean (SD)	6.29 (1.19)	6.24 (1.13)
Min, Max	4.47, 7.85	4.34, 7.98
Age Category, n (%)		
4–5 years	8 (40.0)	8 (38.1)
6–7 years	12 (60.0)	13 (61.9)
Sex, n (%)		
Male	20 (100.0)	21 (100.0)
Race, n (%)		
Asian	4 (20.0)	1 (4.8)
White	13 (65.0)	17 (81.0)
Other	3 (15.0)	3 (14.3)
Ethnicity, n (%)		
Hispanic or Latino	1 (5.0)	4 (19.0)
Not Hispanic or Latino	19 (95.0)	16 (76.2)
Unknown	0	1 (4.8)
Height (cm)		
Mean (SD)	113.34 (7.74)	111.60 (6.24)
Min, Max	102.4, 124.6	97.0, 125.5
Dosing Weight (kg)		
Mean (SD)	23.28 (4.37)	21.60 (3.49)
Min, Max	18.0, 34.5	15.0, 30.0
BMI (kg/m^2)		
Mean (SD)	17.94 (1.67)	17.22 (2.03)
Min, Max	16.08, 22.73	12.93, 21.22
BMI Category (kg/m^2) – n (%)		
< 20	17 (85.0)	19 (90.5)
≥ 20	3 (15.0)	2 (9.5)

BMI: body mass index; ITT: intent-to-treat; SD: standard deviation

5.3.7.3 Patient Baseline Characteristics and Medications

All patients were on steroids prior to enrollment with approximately half of patients on a daily steroid regime, mostly oral prednisolone. Steroid types and frequency of use were balanced between the treatment groups at Baseline in Part 1 (Table 7).

The DMD mutations of the ITT population were mostly whole-exon deletion mutations (75.6%).

Table 7: Study 102 Summary of Baseline Characteristics – ITT Population (Part 1)

Category	SRP-9001 (N=20)	Placebo (N=21)
Steroid Type, n (%)		
Any use of deflazacort at Baseline	7 (35.0)	7 (33.3)
Other	13 (65.0)	14 (66.7)
Steroid use frequency group, n (%)		
Daily	9 (45.0)	11 (52.4)
Other	11 (55.0)	10 (47.6)
Years since diagnosis of DMD		
Mean (SD)	2.54 (1.34)	2.69 (1.30)
Min, Max	0.36, 5.10	0.66, 5.39
Years since corticosteroid treatment started		
Mean (SD)	0.99 (1.07)	1.26 (1.22)
Min, Max	0.22, 3.80	0.23, 5.07
Genetic mutation type, n (%)		
Exon 45 Deletion Only	1 (5.0)	3 (14.3)
Other	19 (95.0)	18 (85.7)

DMD: Duchenne muscular dystrophy; ITT: intent-to-treat; SD: standard deviation

Patients in the SRP-9001 group had a numerically lower mean NSAA score at Baseline (19.8) than patients in the placebo group (22.6). For all other functional assessments, patients in the placebo group completed each timed assessment in numerically less time than patients in the SRP-9001 group at Baseline (Table 8). These findings indicated that patients with a milder DMD trajectory were randomized to placebo compared to those patients randomized to SRP-9001.

Table 8: Study 102 Baseline NSAA Functional Assessments – ITT Population (Part 1)

Functional Assessment Statistic	SRP-9001 (N=20)	Placebo (N=21)
NSAA Total Score		
Mean (SD)	19.8 (3.3)	22.6 (3.3)
Median	20.0	22.0
Min, Max	13, 26	15, 29
NSAA Group, n (%)		
NSAA Baseline total score ≥ median score [a]	8 (40.0)	15 (71.4)
NSAA Baseline total score < median score [a]	12 (60.0)	6 (28.6)
100-Meter Timed Test (sec)		
Mean (SD)	61.04 (12.71)	53.86 (8.30)
Median	57.10	55.60
Min, Max	42.3, 99.3	40.6, 69.1
Time to Ascend 4 Steps (sec)		
Mean (SD)	3.69 (1.46)	3.10 (0.98)
Median	3.30	3.00
Min, Max	2.1, 6.5	1.9, 5.8
Time to Rise from the Floor (sec)		
Mean (SD)	5.10 (2.17)	3.56 (0.65)
Median	4.30	3.40
Min, Max	3.2, 10.4	2.7, 4.8
10-Meter Timed Test (sec)		
Mean (SD)	5.35 (1.14)	4.83 (0.72)
Median	5.00	4.70
Min, Max	4.1, 8.9	4.0, 7.2

ITT: intent-to-treat; NSAA: North Star Ambulatory Assessment; SD: standard deviation
a. Median score = 21.

Given that age is a stratification factor in this study, a summary of NSAA total score and functional assessments at Baseline by age group is provided in Table 9. These data show that the imbalance in functional characteristics was driven by the 6–7-year-old subgroup.

Table 9: Study 102 Summary of Functional Assessments at Baseline by Age Group – ITT Population

Functional Assessment Statistic	Age Group 4–5 Years		Age Group 6–7 Years	
	SRP-9001 (N=8)	Placebo (N=8)	SRP-9001 (N=12)	Placebo (N=13)
NSAA Total Score				
Mean (SD)	20.1 (1.9)	20.4 (2.7)	19.6 (4.1)*	24.0 (2.9)
Median	20.5	20.5	20.0	24.0
Min, Max	17, 23	15, 24	13, 26	19, 29
100-Meter Timed Test (sec)				
Mean (SD)	58.76 (7.09)	59.79 (8.16)	62.56 (15.52)*	50.21 (6.17)
Median	57.90	59.70	57.10	50.40
Min, Max	49.6, 70.1	46.9, 69.1	42.3, 99.3	40.6, 58.3
Time to Ascend 4 Steps (sec)				
Mean (SD)	3.46 (0.88)	3.48 (1.28)	3.83 (1.76)	2.86 (0.71)
Median	3.50	3.00	3.20	3.00
Min, Max	2.3, 4.8	2.0, 5.8	2.1, 6.5	1.9, 4.3
Time to Rise from the Floor (sec)				
Mean (SD)	3.89 (0.70)	3.76 (0.79)	5.91 (2.46)*	3.44 (0.55)
Median	3.70	3.75	5.05	3.40
Min, Max	3.2, 5.2	2.8, 4.8	3.2, 10.4	2.7, 4.7
10-Meter Timed Test (sec)				
Mean (SD)	5.01 (0.61)	5.24 (0.96)	5.58 (1.37)*	4.58 (0.39)
Median	5.05	5.10	5.00	4.60
Min, Max	4.3, 5.8	4.2, 7.2	4.1, 8.9	4.0, 5.2

ITT: intent-to-treat; NSAA: North Star Ambulatory Assessment; SD: standard deviation
*statistically different from placebo ($p < 0.05$)

5.3.8 Part 1 Efficacy Results

5.3.8.1 Biologic Primary Endpoint: Change in Quantity of SRP-9001 dystrophin Protein Expression from Baseline to Week 12 (Western Blot)

The primary biological endpoint of change in quantity of SRP-9001 dystrophin expression from Baseline to Week 12 as measured by western blot was met in Study 102. Treatment with SRP-9001 resulted in a statistically significantly greater mean increase (improvement) from Baseline to Week 12 in SRP-9001 dystrophin expression by western blot than placebo (23.82% vs 0.14%, $p < 0.0001$; Table 10).

Table 10: Study 102 Summary of SRP-9001 Dystrophin Level (% Control) by Western Blot – ITT Population (Part 1)

	SRP-9001 (N=20)		Placebo (N=21)	
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline				
Mean (SD)	4.23 (6.83)		1.91 (1.28)	
Median	2.09		1.89	
Min, Max	0.39, 30.18		0.15, 5.75	
Week 12				
Mean (SD)	28.05 (40.12)	23.82 (39.76)	2.05 (1.34)	0.14 (1.24)
Median	9.59	6.49	1.78	0.02
Min, Max	2.04, 133.77	-0.64, 131.67	0.17, 5.18	-2.76, 2.68
Re-randomization test				
p-value, 2-sided between group		< 0.0001		
Permutation test				
p-value, 2-sided within-group		0.0002		0.6038
Wilcoxon rank sum test				
Hodges-Lehmann est. of treatment difference		6.11		
95% CI		(2.08, 12.58)		
p-value, 2-sided between group		< 0.0001		

CI: confidence interval; SD: standard deviation.
Note: adjusted by muscle content

5.3.8.2 Other Key Biologic Endpoints

Transduction and localization results for Part 1 are summarized below. Serum CK results are described in Table 3 in Section 3.2.2. Section 3.2.2 also includes transduction, expression, and localization results for the subset of patients who received the 1.33×10^{14} dose (Table 2).

Transduction Efficiency

Treatment with SRP-9001 resulted in a nominally statistically significantly greater mean increase (improvement) from Baseline to Week 12 in vector genome copies per nucleus as measured by ddPCR than placebo (1.56 vs 0.00, $p < 0.0001$; Table 11).

Table 11: Study 102 Summary of Vector Genome Copies per Nucleus as Measured by ddPCR – ITT Population (Part 1)

	SRP-9001 (N=20)		Placebo (N=21)	
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline				
Mean (SD)	0.00 (0.00)		0.00 (0.00)	
Median	0.00		0.00	
Min, Max	0.00, 0.00		0.00, 0.00	
Week 12				
Mean (SD)	1.56 (1.51)	1.56 (1.51)	0.00 (0.00)	0.00 (0.00)
Median	0.85	0.85	0.00	0.00
Min, Max	0.48, 6.61	0.48, 6.61	0.00, 0.00	0.00, 0.00
Re-randomization test				
p-value, 2-sided between group		< 0.0001		
Permutation test				
p-value, 2-sided within-group		< 0.0001		N/A

ddPCR: droplet digital polymerase chain reaction; ITT: intent-to-treat; N/A: not applicable; SD: standard deviation

Protein Localization

Compared to placebo, treatment with SRP-9001 resulted in a nominally statistically significantly greater mean increase (improvement) from Baseline to Week 12 SRP-9001 dystrophin expression by IF fiber intensity (25.81% vs -0.48%, p=0.0002) and IF PDPF (23.88% vs 5.09%, p=0.0056; Table 12).

Table 12: Study 102 Summary of SRP-9001 Dystrophin Expression by IF PDPF – ITT Population (Part 1)

	SRP-9001 (N=20)		Placebo (N=21)	
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline				
Mean (SD)	9.07 (6.88)		9.81 (7.31)	
Min, Max	0.35, 22.85		1.75, 29.35	
Week 12				
Mean (SD)	32.94 (28.12)	23.88 (25.58)	14.89 (17.41)	5.09 (12.96)
Min, Max	0.75, 96.05	-7.29, 85.51	0.31, 63.51	-15.36, 34.15
Re-randomization test				
p-value, 2-sided between group		0.0056		
Permutation test				
p-value, 2-sided within-group		0.0004		0.0868

IF: immunofluorescence; ITT: intent-to-treat; PDPF: percent dystrophin positive fibers; SD: standard deviation.

5.3.8.3 Functional Primary Endpoint: Change in NSAA Total Score from Baseline to Week 48

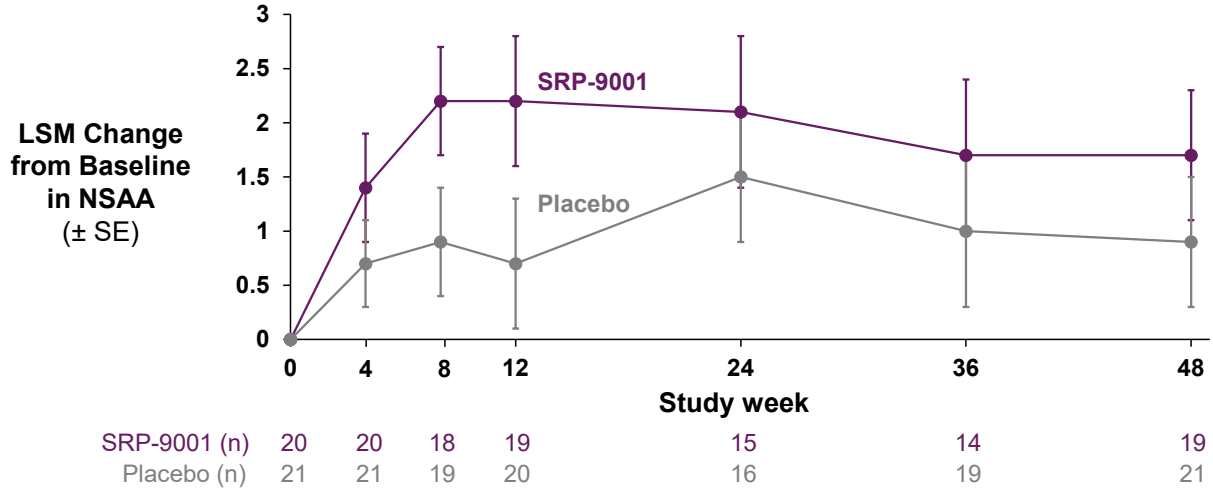
Mean change from Baseline in NSAA total score was numerically greater at all timepoints for the SRP-9001 group than the placebo group, showing a LSM (SE) increase over 48 weeks of 1.7 (0.6) points in SRP-9001-treated patients compared to 0.9 (0.6) points in placebo-treated patients (Table 13 and Figure 21). However, the treatment difference in NSAA total score between SRP-9001 and placebo was not statistically significant at 48 weeks post-SRP-9001 infusion (p=0.3730).

Table 13: Study 102 MMRM Analysis of Change in NSAA Total Score From Baseline to Week 48 Based on In-Clinic Assessments and Interpolated Week 48 Assessments – ITT Population (Part 1)

Timepoint	Treatment	N1	LSM Change (SE)	95% CI	Within-group P-value	Versus Placebo LSM Change Diff (SE)	95% CI	P-value
Week 4	SRP-9001	20	1.4 (0.5)	(0.5, 2.3)	0.0047	0.7 (0.7)	(-0.6, 2.1)	0.2825
	Placebo	21	0.7 (0.4)	(-0.3, 1.6)	0.1539			
Week 8	SRP-9001	18	2.2 (0.5)	(1.2, 3.2)	< 0.0001	1.3 (0.7)	(-0.2, 2.7)	0.0877
	Placebo	19	0.9 (0.5)	(-0.1, 1.9)	0.0685			
Week 12	SRP-9001	19	2.2 (0.6)	(1.0, 3.4)	0.0005	1.5 (0.8)	(-0.2, 3.2)	0.0740
	Placebo	20	0.7 (0.6)	(-0.5, 1.8)	0.2483			
Week 24	SRP-9001	15	2.1 (0.7)	(0.7, 3.4)	0.0038	0.5 (1.0)	(-1.4, 2.5)	0.5690
	Placebo	16	1.5 (0.6)	(0.2, 2.8)	0.0246			
Week 36	SRP-9001	14	1.7 (0.7)	(0.2, 3.1)	0.0272	0.7 (1.0)	(-1.4, 2.8)	0.4971
	Placebo	19	1.0 (0.7)	(-0.4, 2.3)	0.1619			
Week 48	SRP-9001	19	1.7 (0.6)	(0.5, 3.0)	0.0090	0.8 (0.9)	(-1.0, 2.7)	0.3730
	Placebo	21	0.9 (0.6)	(-0.3, 2.2)	0.1411			

CI: confidence interval; ITT: intent-to-treat; LSM: least squares mean; MMRM: mixed model for Repeated Measures; N1: number of patients with non-missing change from Baseline data at a specific timepoint; NSAA: North Star Ambulatory Assessment; SE: standard error

Figure 21: Study 102 NSAA Total Score: LS Mean Change From Baseline Over Time Based on In-Clinic Assessments and Interpolated Week 48 Assessments – ITT Population Part 1



ITT: intent-to-treat; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

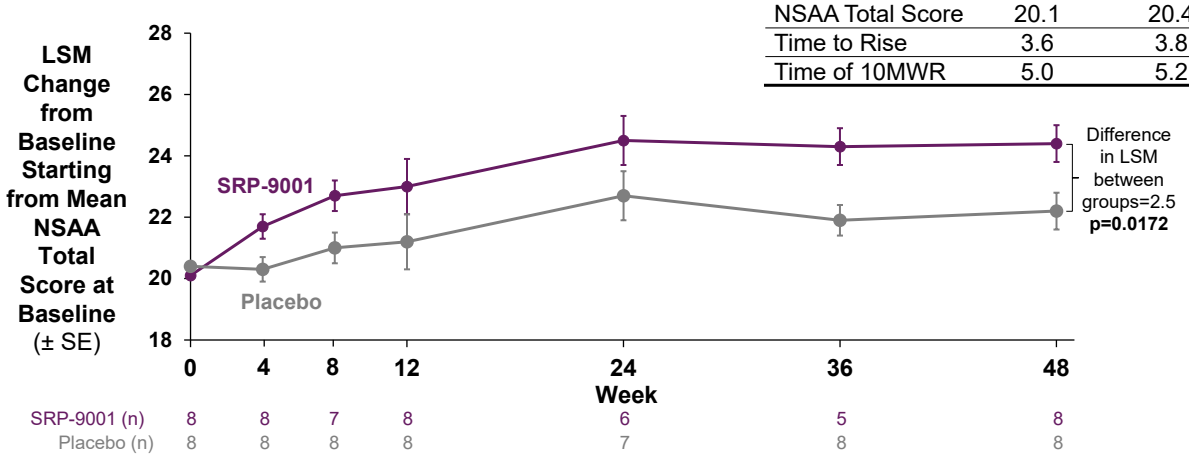
As described in Section 5.3.7.2, because the randomization was stratified by baseline age group, the functional efficacy results in the Study 102 were also analyzed by age group.

For patients 4 to 5 years old, mean change in NSAA total score was greater at all timepoints for the SRP-9001 group for patients aged 4 to 5 years compared to the placebo group; the LS mean treatment difference between groups was statistically significant at all timepoints except Weeks 12 and 24. At Week 48, the LS mean (SE) treatment difference was 2.5 (0.9) points, favoring the treated patients (p=0.0172) (Figure 22).

For patients 6 to 7 years old, the LS mean (SE) treatment difference (-0.7 [1.1]) between SRP-9001 and placebo was not statistically significant (95% CI: -3.0, 1.6; p=0.5384; Figure 23). The within-group difference was not statistically significant for either treatment group. Since there was such a substantial imbalance in baseline functional status within this age stratum, it was uncertain whether the lack of apparent treatment effect was due to residual confounding by both measured and unmeasured functional covariates or potential effect modification by age. To explore this issue further, a pre-specified plan was developed to compare treated patients across the development program, including the prospective Study 102 Part 2 crossover data and Study 103 Cohort 1 data, with propensity score weighted ECs where baseline age and functional status could be more closely matched in a larger sample (see Section 5.5).

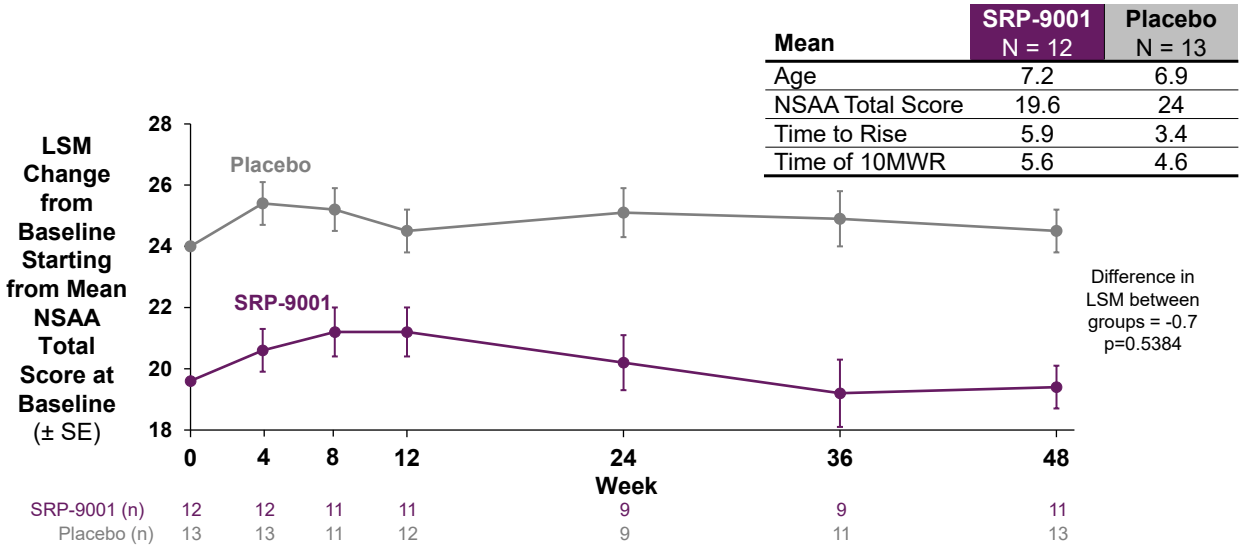
Figure 22: Study 102 Change from Baseline Starting from Mean NSAA Total Score at Baseline Part 1 Patients 4 – 5 Years Old

Mean	SRP-9001 N = 8	Placebo N = 8
Age	5.0	5.2
NSAA Total Score	20.1	20.4
Time to Rise	3.6	3.8
Time of 10MWR	5.0	5.2



10MWR: 10-meter walk/run; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

Figure 23: Study 102 Change from Baseline Starting from Mean NSAA Total Score at Baseline Part 1 Patients 6 – 7 Years Old



10MWR: 10-meter walk/run; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

5.3.8.4 Other key Functional Efficacy Results

5.3.8.4.1 Timed Function Tests (100-Meter Timed Test, Time to Ascend 4 Steps, Time to Rise from Floor, 10-Meter Timed Test)

There was no statistically significant difference between the SRP-9001 and placebo groups in timed functional assessments change from Baseline to Week 48 (see Appendix Table 32). Similar to total NSAA score, the interpretability of these results is complicated by the imbalance in Baseline timed functional assessments between the treatment groups, driven by the 6–7-year-old age group.

5.3.9 Part 2 Efficacy Results

5.3.9.1 Change From Baseline to Week 48 in Part 2 for Biologic Efficacy Endpoints

Patients who received SRP-9001 in Part 1 underwent 2 post-SRP-9001 infusion muscle biopsies: at 12 weeks post-infusion (Part 1) and approximately 60 weeks post-infusion (Week 12 of Part 2). These results demonstrate that the amount of correctly localized SRP-9001 dystrophin increases over time and supports an expectation of functional efficacy at 1 year and beyond (Table 14).

Table 14: Summary of Change from Baseline to Week 12 of Part 2 for Biologic Endpoints

	Patients Who Received SRP-9001 in Part 1	
Mean Change from Baseline (SD)	**Week 12 n=20**	**Week 60 n=18**
Vector genome copy number	1.6 (1.5)	0.9 (1.3)
SRP-9001 dystrophin expression* (western blot, % of normal)	23.8 (39.7)	19.1 (36.4)
IF fiber intensity (% of control)	25.8 (25.6)	38.3 (30.6)
PDPF (%)	23.9 (25.6)	57.1 (30.6)

IF: immunofluorescence; PDPF: percent dystrophin positive fiber; SD: standard deviation

5.3.9.2 Change From Baseline to Week 48 in Part 2 in North Star Ambulatory Assessment Total Score

The mean (SD) NSAA total score improved from Part 2 Baseline to Part 2 Week 48 (Table 15). The mean change in NSAA total score from Part 2 Baseline to Week 48 in Part 2 was 1.3 (2.7).

For the patients who received SRP-9001 in Part 1, the mean (SD) change in NSAA total score from Baseline of Part 1 to Week 48 in Part 2 was 0.1 (6.6). An outlying data point for NSAA was observed (a 17-point decrease) which skewed the mean estimate.

Table 15: Summary of Change from Baseline in NSAA Total Score to Week 48 – ITT Population (Parts 1 and 2)

	SRP-9001 in Part 1 (N=20)		SRP-9001 in Part 2 (N=21)		
Visit / Statistics	**Value**	**Change from Baseline [a]**	**Value**	**Change from Baseline [a]**	**Change from Part 2 Baseline**
Baseline					
n	20		21		
Mean (SD)	19.8 (3.3)		22.6 (3.3)		
Median	20.0		22.0		
Min, Max	13, 26		15, 29		
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	21.4 (5.0)	1.6 (2.9)	23.6 (3.7)	1.0 (2.5)	
Median	22.0	2.0	24.0	1.0	
Min, Max	10, 29	-3, 6	13, 30	-4, 6	
Part 2 Baseline					
n	19		21		
Mean (SD)	21.4 (5.3)		23.6 (3.7)		
Median	22.0		24.0		
Min, Max	10, 29		13, 30		
Part 2 Week 48					
n	19	19	20 [b]	20	20
Mean (SD)	20.0 (8.3)	0.1 (6.6)	25.1 (4.9)	2.4 (4.4)	1.3 (2.7)
Median	22.0	2.0	25.0	2.0	1.5
Min, Max	4, 30	-17, 9	14, 31	-5, 11	-5, 5

ITT: intent-to-treat; NSAA: North Star Ambulatory Assessment; SD: standard deviation
a Part 2 Baseline was defined as the last available assessment before Part 2 dosing (if no dosing in Part 2, then Part 1 Week 48 was used as the Baseline). Part 1 Baseline was used to calculate the change from Baseline, unless otherwise noted.
b. One patient treated with SRP-9001 in Part 2 did not have a Part 2 Week 48 assessment.

5.3.9.3 Timed Functional Test Results

In Part 2, in which all 21 crossover patients received SRP-9001 at a dose of 1.33×10^{14} vg/kg, a numerical improvement in time to rise from floor, time to ascend 4 steps, the 10-meter timed test, and the 100-meter timed test at Part 2 Week 48 relative to Part 2 Baseline was seen (see Appendix Table 32).

5.3.10 Study 102 Summary

The primary biological endpoint of change in quantity of SRP-9001 dystrophin expression from Baseline to Week 12 as measured by western blot was met. Treatment with SRP-9001 resulted in a statistically significantly greater increase in SRP-9001

dystrophin expression by western blot from Baseline to Week 12 compared to placebo ($p < 0.0001$).

The primary clinical functional endpoint of change in NSAA total score from Baseline to Week 48 (Part 1) was not met in the ITT population. In the 4–5-year-old stratum, where randomization resulted in balanced groups with respect to baseline functional characteristics, a pre-specified analysis showed statistically significant difference in functional improvement in SRP-9001-treated patients compared to placebo. In the 6–7-year-old stratum, the randomization resulted in patients with a more aggressive trajectory in the SRP-9001 treated group compared to the placebo group. This imbalance makes interpretation of treatment effect challenging. Therefore, in order to more fully characterize the efficacy of SRP-9001 in this age group and across the open-label studies, and to better inform the design of the Phase 3 confirmatory trial, a pre-specified analysis plan was developed to compare treated patients to propensity score weighted ECs (see Section 5.5).

5.4 Study 103

5.4.1 Design Overview

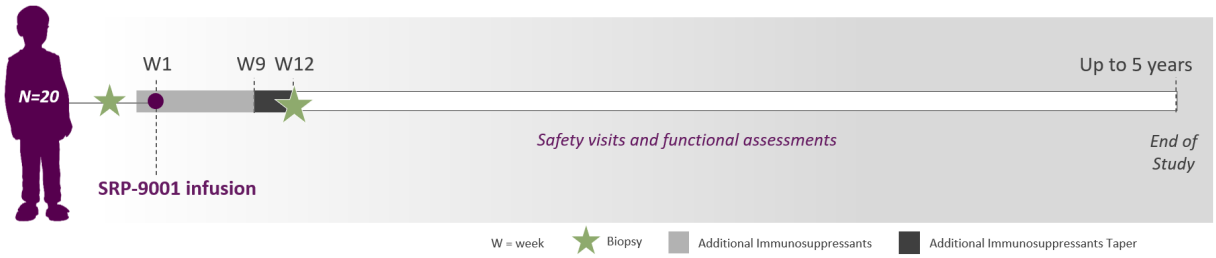
Study 103 is an ongoing, open-label, single-arm, single-dose, Phase 1b study with 4 cohorts and a 2-part follow-up period conducted at 5 sites in the US. The purpose of Study 103 is to collect data on gene expression, safety, and vector shedding of intended commercial process SRP-9001. Eligible patients were enrolled into 4 cohorts:

- Cohort 1: male DMD ambulatory patients ≥ 4 to < 8 years of age at Screening
- Cohort 2: male DMD ambulatory patients ≥ 8 to < 18 years of age at Screening
- Cohort 3: male DMD non-ambulatory patients with no age restriction at Screening
- Cohort 4: male DMD ambulatory patients ≥ 3 to < 4 years of age at Screening.

Study 103 consisted of 4 periods: an up to approximately 3-week Screening Period, an approximately 1 week Baseline Period, a 1 day infusion, and a 260-week Follow-Up Period (Figure 24).

During the Follow-Up Period, patients were expected to attend both remote and in-person visits to complete required procedures/assessments. Part 1 of the Follow-Up Period began post-infusion (Day 1) through Week 12. Part 2 of the Follow-Up Period began post-Week 12 through Week 260.

Figure 24: Study 103 Design Schematic



5.4.2 Treatments

A single IV infusion of open-label SRP-9001 was administered. Dosing was stratified by weight: patients weighing < 70 kg on Day 1 were dosed with 1.33×10^{14} vg/kg, and patients weighing ≥ 70 kg on Day 1 were dosed with 9.31×10^{15} vg total fixed dose, which is equivalent to the dose of 1.33×10^{14} vg/kg for a 70 kg patient.

Patients in Cohorts 1, 2, and 3 received at least 1 mg/kg of a glucocorticoid (prednisone equivalent) daily in addition to their Baseline stable oral corticosteroid dose beginning 1 day prior to infusion and for at least 60 days after the infusion; up to a maximum total daily dose of 60 mg/day. Steroids could be further increased by another 1 mg/kg in the event of relevant GGT increases and/or other clinically significant liver function abnormalities up to a maximum total daily dose of 120 mg/day. Patients in Cohort 4, who were not on oral corticosteroids for their DMD at Screening, started prednisone/prednisolone at 1.5 mg/kg/day 1 week prior to the infusion, which continued for at least 60 days after the infusion.

5.4.3 Enrollment Criteria

Key inclusion criteria in the study included:

1. Cohort Specific:
    a) Cohort 1 : male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of Screening and has an NSAA score > 17 and ≤ 26 at the Screening visit.
    b) Cohort 2 : male at birth, ambulatory, and ≥ 8 to < 18 years of age at the time of Screening and has an NSAA score ≥ 15 and ≤ 26 at the Screening visit.
    c) Cohort 3 : male at birth and non-ambulatory for a minimum of 9 months, with an NSAA walk score of “0” and inability to perform the 10-meter walk/run at Screening visit, and with a Performance Upper Limb entry item score ≥ 2. Onset of loss of ambulation is defined as participant- or caregiver-reported age at continuous wheelchair use, approximated to the nearest month. There were no age restrictions for this cohort.

d) Cohort 4 : male at birth, ambulatory, and ≥ 3 to < 4 years of age at the time of Screening.

2. Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the *DMD* gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.
3. Has an indication of symptomatic muscular dystrophy:
   - CK elevation > 1000 units/liter (U/L) and
   - Cohorts 1 and 2 only (ambulatory): Below 95% predicted time on 100-meter walk/run.
4. For Cohorts 1, 2, and 3 only: Stable weekly dose equivalent of oral corticosteroids for at least 12 weeks before Screening and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the first year of the study. For Cohort 4: patients who do not yet require use of chronic steroids for treatment of their DMD in the opinion of the Investigator and are not receiving steroids at the time of Screening.
5. Has rAAVrh74 antibody titers ≤ 1:400 (ie, not elevated) as determined by an ELISA.

5.4.4 Efficacy Endpoints

The primary endpoint was change in quantity of SRP-9001 dystrophin protein expression from Baseline to Week 12 (Part 1) as measured by western blot.

Key secondary and exploratory biological endpoints included IF fiber intensity, IF PDPF and transduction with vector genome copies per nucleus by ddPCR from Baseline Week 12; and change in CK levels from Baseline over time.

Key functional endpoints for Cohort 1 included change from Baseline in NSAA total score, the time to walk 100 meters, percent predicted time to walk 100 meters, time to ascend 4 steps; time to rise from the floor, and time to run 10 meters.

5.4.5 Statistical Methods

5.4.5.1 Analysis Populations

All patients who received study treatment (SRP-9001) were included in the safety analysis population for Study 103.

Patients in Cohort 1 have completed 52 weeks of follow-up and their efficacy results are presented.

5.4.5.2 Endpoint Analyses

For the primary endpoint, a permutation test based on 1-sample t-test statistic was conducted for each cohort, comparing post-treatment assessment at Week 12 with the Baseline assessment.

5.4.6 Patient Population

5.4.6.1 Patient Disposition

A total of 40 patients were enrolled, dosed, and included in the safety analyses (Cohort 1 N=20; Cohort 2 N=7; Cohort 3 N=6; and Cohort 4 N=7). All patients were treated with the proposed dose of SRP-9001 1.33×10^{14} vg/kg and completed Part 1 of the study as of September 19, 2022.

No patient was discontinued from the study.

5.4.6.2 Patient Demographics

Patients in Cohorts 1–4 were mostly white with mean ages of 5.81 (range: 4.38–7.94 years), 10.11 (range: 8.00–12.05 years), 15.26 (range: 9.86–20.23 years), and 3.47 (range: 3.24–3.95 years, respectively) (Table 16). The increasing age across Cohorts 1–3 reflects the natural history and progressive nature of DMD.

Table 16: Study 103 Demographics and Baseline Characteristics

	Cohort 1 (N=20)	Cohort 2 (N=7) [a]	Cohort 3 (N=6)	Cohort 4 (N=7)
Age (years)				
Mean (SD)	5.81 (1.14)	10.11 (1.51)	15.26 (4.22)	3.48 (0.24)
Min, max	4.38, 7.94	8.00, 12.05	9.86, 20.23	3.24, 3.95
4 to 5 years, n (%)	11 (55.0)	0	0	0
6 to 7 years, n (%)	9 (45.0)	0	0	0
Race, n (%)				
White	15 (75.0)	5 (71.4)	6 (100.0)	6 (85.7)
Non-white	5 (25.0)	2 (28.6)	0	1 (14.3)
Weight, kg				
Mean (SD)	21.15 (4.23)	37.06 (7.64)	59.93 (15.17)	15.16 (1.60)
Min, max	15.2, 33.1	28.0, 50.5	36.1, 80.1	12.5, 16.5
BMI, kg/m^2				
Mean (SD)	17.76 (2.26)	22.09 (3.51)	29.86 (8.43)	17.61 (1.82)
Min, max	15.00, 24.60	18.12, 27.30	18.42, 43.81	14.77, 20.46

BMI: body mass index; SD: standard deviation
a Efficacy data presented for n: 6 patients with Baseline and post-baseline biopsy data

5.4.6.3 Patient Baseline Characteristics and Medications

The *DMD* mutations were mostly whole-exon deletions in each cohort (Table 17). All patients in Cohorts 1–3 were taking oral corticosteroids prior to enrollment, mostly prednisolone in Cohort 1 (90.0%), deflazacort in Cohort 2 (100.0%), and prednisone in Cohort 3 (83.3%).

Table 17: Study 103 Patient Baseline Characteristics

Category	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)
Years since diagnosis of DMD [a]				
Mean (SD)	2.36 (1.37)	4.89 (2.01)	9.92 (3.96)	1.32 (1.40)
Min, Max	0.87, 6.74	2.08, 8.13	5.50, 16.92	0.06, 3.23
Years since corticosteroid treatment started [b]				
Mean (SD)	0.99 (0.94)	1.89 (1.14)	5.70 (5.16)	0
Min, Max	0.10, 4.10	0.35, 3.38	1.03, 13.98	0
Genetic mutation type, n (%)				
Exon 45 Deletion Only	0	0	0	3 (42.9)
Other	20 (100.0)	7 (100.0)	6 (100.0)	4 (57.1)
Genetic mutation type, n (%)				
Whole-Exon Deletion Mutation	12 (60.0)	6 (85.7)	3 (50.0)	6 (85.7)
Whole-Exon Duplication Mutation	5 (25.0)	1 (14.3)	1 (16.7)	0
Premature Stop Codon Mutation	3 (15.0)	0	2 (33.3)	0
Canonical Splice Site Mutation	0	0	0	1 (14.3)
Mutation status, n (%)				
Mutations in Exons 1–17	5 (25.0)	3 (42.9)	1 (16.7)	0
Other	15 (75.0)	4 (57.1)	5 (83.3)	7 (100)
Time since loss of ambulation [c]				
Mean (SD)	NA	NA	2.54 (2.45)	NA
Min, Max	NA	NA	0.00, 6.85	NA

DMD: Duchene muscular dystrophy; NA: not applicable; SD: standard deviation

As required by the study protocol, patients in Cohorts 1, 2, and 3 were to receive stable weekly dose equivalent of oral corticosteroids for at least 12 weeks before the Screening visit, with the dose remaining constant (except for modifications to accommodate changes in weight) throughout the first year of the study.

5.4.6.4 Functional Assessments

The mean Baseline NSAA total score for Cohort 1 was 22.1 (range: 18–26; Table 18).

Table 18: Study 103 Cohort 1 Baseline Functional Assessments

Assessment	Cohort 1 (N=20)
NSAA Total Score	
Mean (SD)	22.1 (3.0)
Median	22.0
Min, max	18, 26
Time of 100-meter timed test (sec)	
Mean (SD)	64.11 (20.72)
Median	59.10
Min, max	42.7, 119.8
Time to Ascend 4 Steps (sec)	
Mean (SD)	3.55 (0.96)
Median	3.60
Min, max	1.9, 5.5
Time to Rise From Floor (sec)	
Mean (SD)	4.17 (1.43)
Median	3.85
Min, max	2.4, 8.2
Time of 10-meter timed test (sec)	
Mean (SD)	5.11 (0.82)
Median	4.95
Min, max	3.5, 6.7

NSAA: North Star Ambulatory Assessment; SD: standard deviation

5.4.7 Efficacy Results

5.4.7.1 Biologic Primary Endpoint Results: 12-Week SRP-9001 Dystrophin Expression by Western Blot for Cohort 1

Treatment with SRP-9001 resulted in a statistically significant mean increase from Baseline to Week 12 in SRP-9001 dystrophin expression level by western blot with a mean change from baseline (SD) SRP-9001 dystrophin level (expressed as % normal) of 54.21 (42.57, $p < 0.0001$) at 12 Weeks.

Complete results for other key biologic efficacy measures such as transduction efficiency, localization, and measures of biologic activity such as DAPC reconstitution and serum CK reduction are described in Section 3.2.2.

5.4.7.1.1 Functional Efficacy Results: the North Star Ambulatory Assessment Total Score Over 52 Weeks

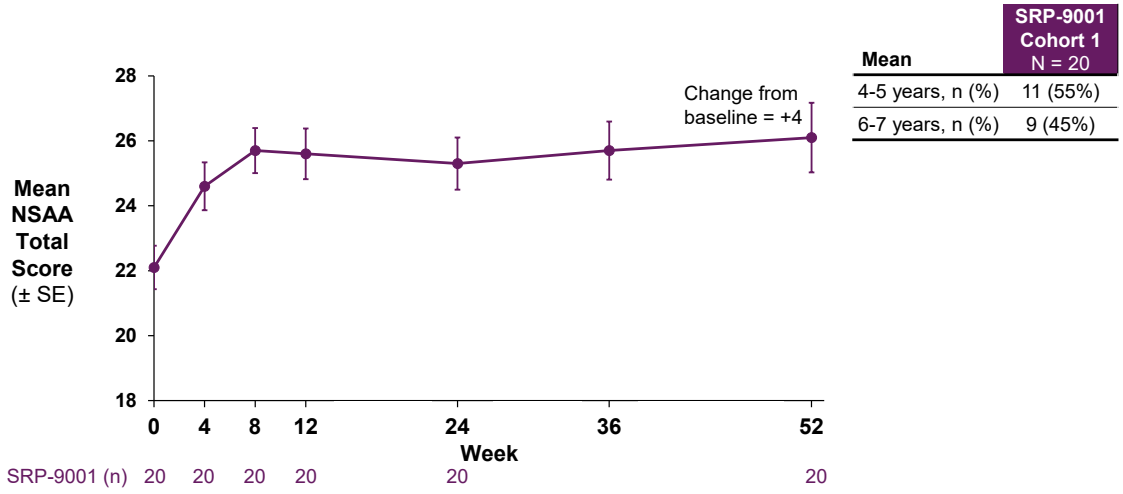
All patients in Cohort 1 completed 52 weeks of follow-up. A mean increase (improved) in NSAA total score of 4.0 from Baseline to Week 52 post-infusion was observed in Cohort 1 patients (Table 19). NSAA total score was observed to increase as early as Week 4 (2.5) post-infusion, which was maintained through Week 52 (Figure 25).

Table 19: Study 103 Summary of North Star Ambulatory Assessment Total Score for Cohort 1

	Cohort 1 (N=20)	
Visit/Statistics	**Value**	**Change**
Baseline		
N	20	20
Mean NSAA (SD)	22.1 (3.0)	
Min, Max	18, 26	
Week 52		
N	20	20
Mean NSAA (SD)	26.1 (4.8)	4.0 (3.5)
Min, Max	16, 33	-3, 10

NSAA: North Star Ambulatory Assessment SD: standard deviation

Figure 25: Study 103 Cohort 1: Mean NSAA Total Score Over Time



NSAA: North Star Ambulatory Assessment; SE: standard error

5.4.7.1.2 Change in NSAA Timed Functional Tests Over 52 Weeks

The mean decreases (improved) from Baseline to Week 52 of the following timed functional tests for Cohort 1 patients were: -12.02 seconds (100-meter timed test), -0.79 seconds (time to ascend 4 steps), -0.48 seconds (time to rise from the floor), and -0.77

seconds (10 meter timed test; Table 20). Timed functional tests were observed to decrease as early as Week 4 post-SRP-9001 infusion, which were maintained through Week 52.

Table 20: Study 103 Change in Timed Function Tests From Baseline to Week 52 in Cohort 1

Visit / Statistics	Time of 100-meter Timed Test (Sec) (N=20)		Time to Ascend 4 Steps (Sec) (N=20)		Time to Rise From Floor (Sec) (N=20)		Time of 10-meter Timed Test (Sec) (N=20)	
	Value	Change	Value	Change	Value	Change	Value	Change
Baseline								
Mean (SD)	64.11 (20.72)		3.55 (0.96)		4.17 (1.43)		5.11 (0.82)	
Median	59.10		3.60		3.85		4.95	
Min, Max	42.7, 119.8		1.9, 5.5		2.4, 8.2		3.5, 6.7	
Week 52								
Mean (SD)	52.10 (13.72)	-12.02 (18.37)	2.76 (1.28)	-0.79 (0.88)	3.70 (2.10)	-0.48 (1.47)	4.35 (1.04)	-0.77 (0.84)
Median	50.55	-8.85	2.40	-1.20	2.95	-0.70	4.00	-0.90
Min, Max	36.0, 88.9	-64.5, 19.9	1.1, 5.9	-2.0, 1.0	1.7, 9.6	-3.8, 3.7	3.1, 7.5	-2.2, 1.9

SD: standard deviation

5.5 Comparison of Efficacy in SRP-9001-Treated Patients to External Control Data

5.5.1 Study Objectives

Given that Studies 101 and 103 are open-label, that concurrent placebo control was available only in Part 1 of Study 102, and that the interpretation of the efficacy data in the 6–7 year-old age stratum was limited based on an imbalanced randomization in Study 102, Sarepta conducted EC comparative analyses on physical function data to contextualize study level results and inform the Phase 3 confirmatory study design. In the absence of placebo-controlled data in all studies, the primary purpose of the EC comparative analyses was to provide an estimate of treatment effect over a 1-year period. The 1-year period represents change from Baseline to Week 48 for Study 102 and change from Baseline to Week 52 for Study 103. EC comparisons were made to the individual study 1 year datasets as well as the integrated 1.33×10^{14} vg/kg dose analysis set. To ensure the integrity of the EC analyses, the SAP for the EC comparisons was finalized and submitted to the FDA prior to the database lock for 102 Part 2 and 5 months before the database lock for 103 Cohort 1 Week 52 data.

The EC comparison was also used to provide additional data on durability over 2 years by comparison to the cohort of patients who were dosed in Part 1 of Study 102 and followed up for 2 years (received placebo in Part 2). Furthermore, an EC comparison

was conducted to contextualize treatment effect in patients 6 to 7 years old as a means of addressing the imbalance in patient characteristics between placebo and SRP-9001 at Baseline in Study 102.

5.5.2 External Comparators

For the integrated analysis, the EC dataset consisted of propensity score weighted controls from the CINRG Duchenne Natural History Study (DNHS), Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD), and Lilly Study (H6D-MC-LVJJ) datasets who met all the applied entry criteria to be consistent with the characteristics of patients enrolled in the SRP-9001 studies. These data sources were identified as the only appropriately representative, high-quality patient level data with the necessary permissions to be used by the sponsor in a regulatory filing. The 3 EC studies were conducted in a time period that was close to the time period and same standard of care of Studies 101, 102 and 103 Cohort 1 (EC 2005–2019 with > 90% of patients after 2013 vs SRP-9001 2018–2022).

Additional detail on each of the datasets is provided in Appendix Section 10.4.

5.5.3 Entry Criteria

The following entry criteria were applied to reduce the pool of potential ECs to be consistent with the observed characteristics of patients with DMD enrolled in the SRP-9001 studies (Study 101, Study 102, and Cohort 1 of Study 103) taking into consideration the availability of these characteristics across databases:

- Age at Baseline was between 4 to 7 years old or 4 to 8 years old, inclusive.
- On a stable dose or dose equivalent of oral corticosteroids for at least 12 weeks before Baseline. Patients on an intermittent (10 day on/10 day off) regime were excluded.
- NSAA score ≥ 13 and ≤ 30 at Baseline (minimum and maximum values of the NSAA total score at the time of dosing with SRP-9001 for treated patients).
- Time to rise from the floor ≤ 10.4 seconds at Baseline (the maximum value of the Time to Rise from the Floor prior to dosing with SRP-9001 for treated patients).
- 10-meter walk/run ≤ 9.1 seconds at Baseline (the maximum value of the 10-meter walk/run at the time of dosing with SRP-9001 for treated patients).

5.5.4 Propensity Score Weighted Analysis

Propensity scores were estimated by logistic regression analyses with a dependent variable of treated or not (whether patients received SRP-9001 treatment in this case). Covariates in the logistic regression model included the Baseline age group (4–5 years vs 6–7 years vs 8 years), the Baseline NSAA total score, the Baseline time to rise from the floor, and the Baseline 10-meter walk/run. The choice of the covariates is consistent with the known prognostic factors in DMD (Goemans 2016; Goemans 2020; Muntoni

2022) which include age, Baseline function (including NSAA and timed function tests) and steroid use. To enhance the similarity of control patients to SRP-9001-treated patients across all prognostic factors jointly, the pool of EC patients was further reduced to those whose propensity scores lie in the range of the propensity scores for the SRP-9001-treated patients. The average treatment effect on the treated weight of each patient was implemented, which means the SRP-9001-treated patients had weight equal to 1 and the EC patient had weight equal to PS/(1-PS) where PS represents the propensity score.

For the comparison, a weighted linear regression model was used to assess the treatment effect of SRP-9001 with the covariates of treatment group, Baseline age group, Baseline NSAA total score, and Baseline age group by Baseline NSAA total score interaction. Estimated treatment effect, the 95% CI, and p-value are presented for the between group comparison (Stuart 2010).

To assess the robustness of results of the propensity score weighted linear regression, 2 sensitivity analyses were specified in the SAP and carried out: optimal 1:1 matching and predictive control model. The latter was based on predictions using distinctly different EC data sources and a distinctly different method that was developed by Collaborative Trajectory Analysis Project (cTAP).

5.5.5 Planned Analyses

The EC analyses were defined and described prior to the analyses of Study 102 Part 2 data and Study 103 Cohort 1 Week 52 data. The analyses were prospectively specified in the SAP submitted to the FDA prior to the unblinding of Study 102 and the completion of the 1-year visits in Study 103.

The primary analysis was 1-year change from Baseline in NSAA total score for the integrated SRP-9001 1.33×10^{14} vg/kg 1-year analysis set based on propensity score weighting. The primary endpoint was tested for a 2-sided statistical significance level of 0.05. The null hypothesis was that the population means for the SRP-9001-treated patients and EC patients were equal. The alternative hypothesis was that the population means for the SRP-9001-treated patients and the EC patients were not equal.

5.5.6 Baseline Characteristics

At Baseline, the integrated SRP-9001 1.33×10^{14} vg/kg integrated 1-year analysis set and EC groups were well balanced with respect to propensity weighted age and functional assessments (Table 21). The mean (SD) ages for the SRP-9001 1.33×10^{14} vg/kg 1-year analysis set and the EC groups were 6.44 (1.32) years and 6.67 (0.68) years, respectively, with a standardized difference of -0.19 year. The mean (SD) NSAA total scores at Baseline for the SRP-9001 1.33×10^{14} vg/kg integrated 1-year analysis set and the EC groups were 22.1 (3.8) and 21.4 (3.1), respectively, with a standardized difference of 0.18.

Table 21: Weighted Summary For Baseline Age and Functional Endpoints Based on Propensity Score Weighting (Integrated 1-year Analysis Set and External Control Dataset)

Parameter	Integrated SRP-9001 1.33×10^{14} vg/kg 1-year (N=52)	External Control (N=105)	Standardized Difference
Age (years)			
n	52	105	
Mean (SD)	6.44 (1.32)	6.67 (0.68)	-0.19
Median	6.39	6.55	
Min, Max	4.02, 8.89	4.24, 8.92	
NSAA Total Score			
n	52	105	
Mean (SD)	22.1 (3.8)	21.4 (3.1)	0.18
Median	22.0	21.0	
Min, Max	13, 30	13, 30	
Time to Rise from the Floor (sec)			
n	52	105	
Mean (SD)	4.48 (1.83)	4.49 (1.15)	0.00
Median	3.95	4.30	
Min, Max	2.40, 10.40	1.90, 10.20	
Time of 10MWR (sec)			
n	52	105	
Mean (SD)	5.14 (1.10)	5.17 (0.70)	-0.03
Median	4.90	5.10	
Min, Max	3.50, 9.10	3.03, 8.00	

10MWR : 10-meter walk/run; NSAA: North Star Ambulatory Assessment; SD: standard deviation
Note: Propensity score (PS) are estimated by logistic regression analyses with covariates of Baseline age group (4–5 years vs 6–7 years vs 8 years), Baseline NSAA total score, Baseline Time to Rise from the Floor, and Baseline 10MWR. SRP-9001 patients have weight of 1 and EC have weight of PS/(1-PS) where PS represents the propensity score.

5.5.7 Primary Analysis Results: 1-Year Change from Baseline in NSAA Total Score

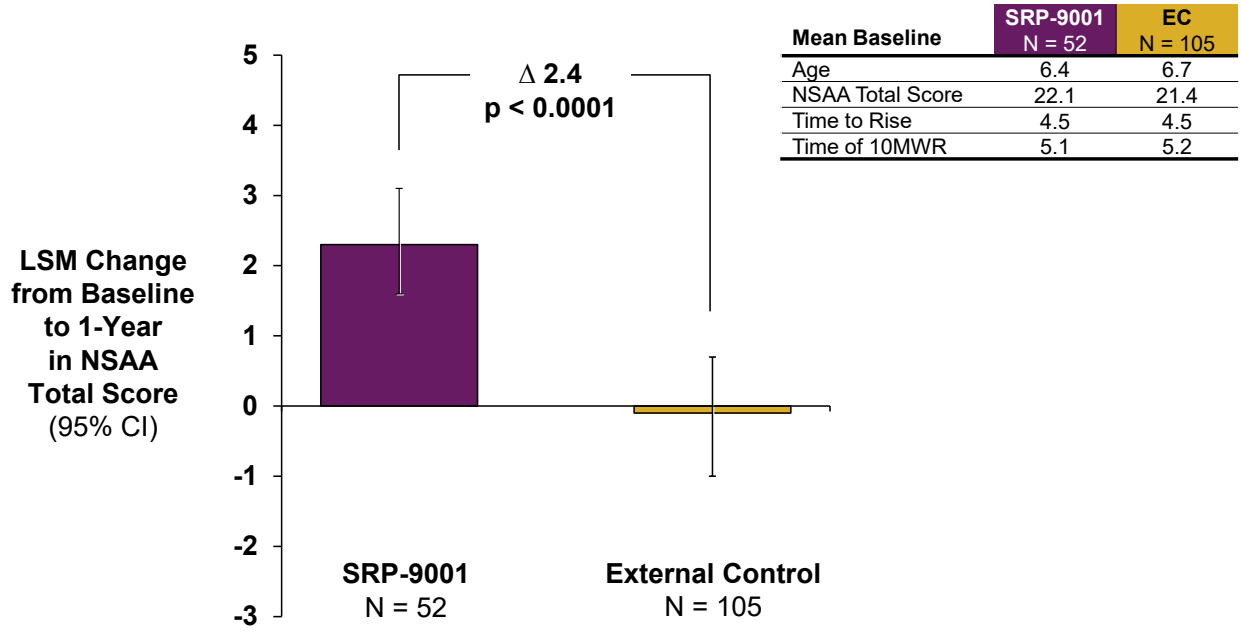
A statistically significant difference was observed between the 1.33×10^{14} vg/kg integrated 1-year analysis set (N=52) and the propensity score weighted EC dataset (N=105) in the mean change from Baseline to 1 year post-SRP-9001 infusion in NSAA total score (LSM change difference 2.4, $p < 0.0001$), favoring SRP-9001 (Table 22 and Figure 26). The sensitivity analyses for the primary endpoint (optimal 1:1 matching and a predictive control model) both showed a similar 1-year change in NSAA total score from Baseline demonstrating that results were consistent across different analyses.

Table 22: Comparison of Change in NSAA Total Score From Baseline to Year 1 Between Integrated SRP-9001 1-Year Analysis Set and External Control

Visit Statistic	Integrated SRP-9001 1.33×10^{14} vg/kg 1 Year N=52	External Control N=105
Baseline		
Mean (SD)	22.1 (3.8)	21.4 (3.1)
Median	22.0	21.0
Year 1		105
Mean (SD)	24.6 (5.2)	20.7 (4.9)
Median	25.0	22.0
Change from Baseline		
Mean (SD)	2.4 (3.4)	-0.6 (2.8)
Median	2.0	0.0
Weighted Linear Regression Analysis Results		
LSM Change (95% CI)	2.3 (1.6, 3.1)	-0.1 (-0.8, 0.6)
LSM Change Difference (95% CI)	2.4 (1.4, 3.4)	
P-value	< 0.0001	

CI: confidence interval; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SD: standard deviation

Figure 26: Change in NSAA Total Score From Baseline to Year 1 Between Integrated SRP-9001 1-Year Analysis Set and External Control



Mean Baseline	SRP-9001 N = 52	EC N = 105
Age	6.4	6.7
NSAA Total Score	22.1	21.4
Time to Rise	4.5	4.5
Time of 10MWR	5.1	5.2

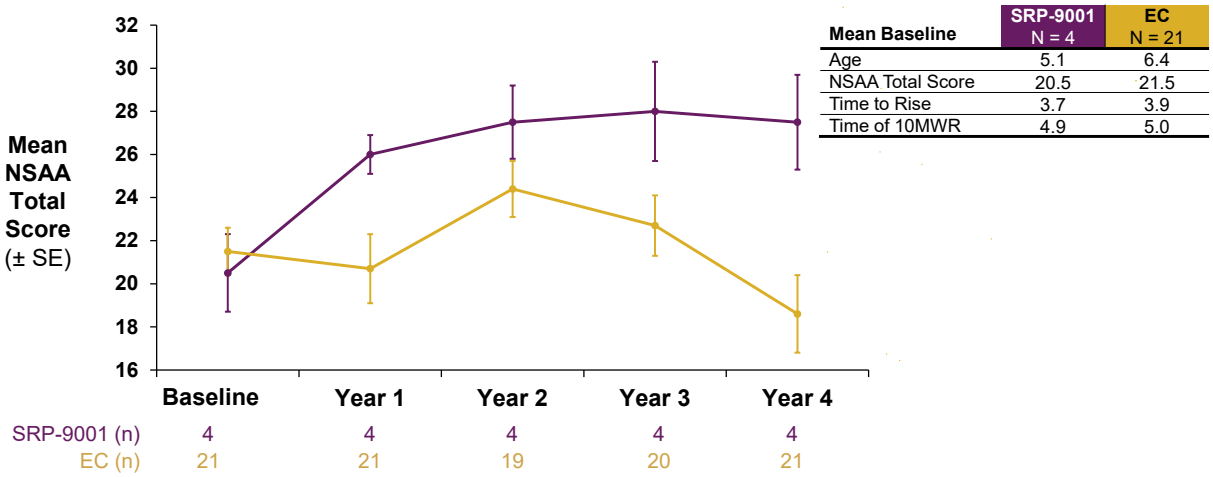
10MWR : 10-meter walk/run; CI: confidence interval; EC: external control; LSM: least squares mean; NSAA: North Star Ambulatory Assessment

5.5.8 Supportive Analyses

5.5.8.1 Study 101

A post hoc analysis was also performed using the same propensity weighting methodology as Section 5.5.4. A statistically significant difference was observed between Study 101 4-year analysis set (N=4) and the propensity score weighted EC cohort (N=21) in the mean change from Baseline in NSAA total score at Year 4, favoring SRP-9001 (LSM change 6.4 vs -3.1, respectively; LSM change difference 9.4, p=0.0125; Figure 27).

Figure 27: Study 101 Mean NSAA Total Score Over Time Comparison to External Controls



Mean Baseline	SRP-9001 N = 4	EC N = 21
Age	5.1	6.4
NSAA Total Score	20.5	21.5
Time to Rise	3.7	3.9
Time of 10MWR	4.9	5.0

10MWR: 10-meter walk/run; EC: external control; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

5.5.8.2 Study 102

In contrast to the Study 102 Part 1 result (Section 5.3.8), which had limited interpretability due to both the Baseline functional imbalance and different dose levels based on the retrospective linear standard qPCR, a statistically significant mean difference in NSAA total score from Baseline over 48 or 52 weeks was observed in the Study 102 study level analysis set (N=28) compared to the propensity score weighted EC cohort (N=91) (LSM change difference 1.8, p=0.0036), favoring SRP-9001 (Table 23). This analysis provides consistent estimates to the integrated 1.33×10^{14} vg/kg 1-year analysis set, as well as the subgroup results in 4- to 5-year-olds in Study 102 Part 1, where baseline function further strengthening their validity.

In Study 102 Part 2, a statistically significant difference was also observed between the Placebo Crossover analysis set (N=20) and the propensity score weighted EC cohort

(N=103) in the mean change from Baseline in NSAA total score over 48 weeks (LSM change difference 2.0, p=0.0009), favoring SRP-9001.

Table 23: Comparison of Change in NSAA Total Score From Baseline to Year 1 Between SRP-9001 Groups and External Control

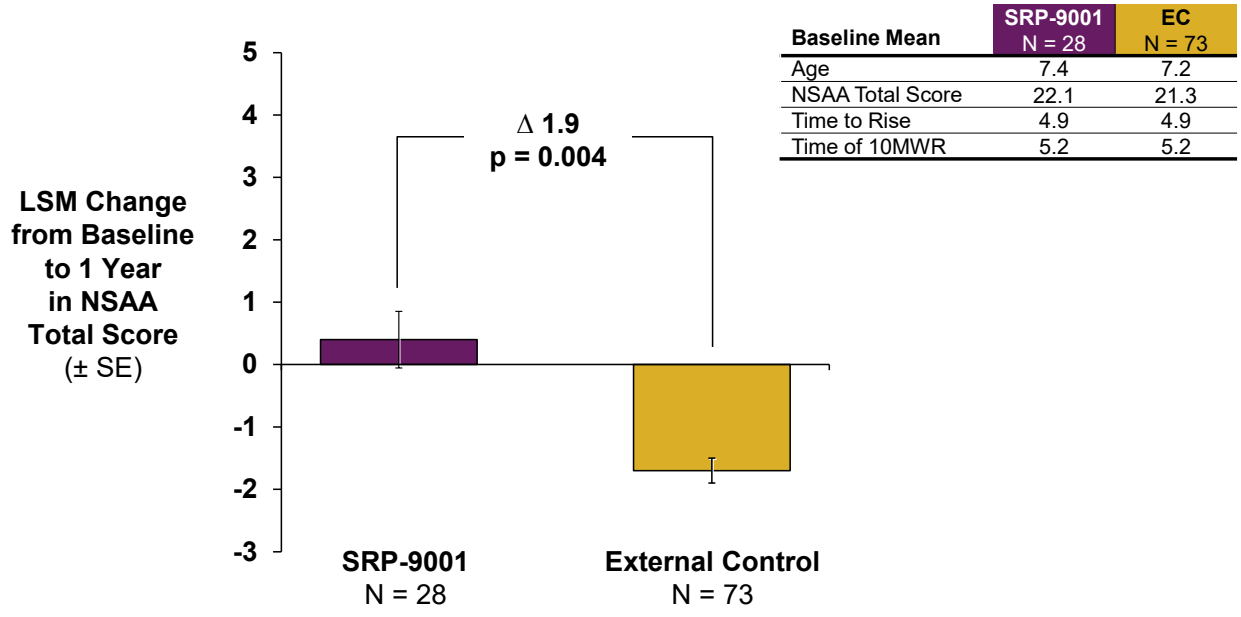
Visit Statistic	Study 102 Placebo Crossover 1 Year	Study 102 6–8-year-old 1-Year	Study 102 SRP-9001 1.33×10^{14} vg/kg 1 Year
NSAA			
SRP-9001 analysis sets	**N=20**	**N=28**	**N=28**
Baseline			
Mean (SD)	23.8 (3.7)	22.1 (4.4)	22.4 (4.3)
Median	24.5	22.5	22.5
Year 1			
Mean (SD)	25.1 (4.9)	22.4 (5.6)	23.3 (5.6)
Median	25.0	22.5	24.0
Change from Baseline			
n	20	28	28
Mean (SD)	1.3 (2.7)	0.4 (2.4)	0.9 (2.7)
Median	1.5	0.5	1.0
External control datasets	**N=103**	**N=73**	**N=91**
Baseline			
Mean (SD)	23.5 (1.9)	21.3 (2.8)	22.4 (2.0)
Median	24.0	21.0	22.0
Endpoint, n	103	73	91
Mean (SD)	22.8 (2.8)	19.6 (4.4)	21.5 (3.3)
Median	23.0	20.0	22.0
Change from Baseline			
Mean (SD)	-0.7 (1.8)	-1.7 (2.5)	-0.9 (2.2)
Median	0.0	-1.0	0.0
Weighted Linear Regression Analysis Results			
LSM Change (95% CI) SRP-9001	1.4 (0.6, 2.2)	0.5 (-0.4, 1.4)	1.0 (0.2, 1.8)
LSM Change (95% CI) External Control	-0.6 (-1.4, 0.2)	-1.4 (-2.3, -0.5)	-0.8 (-1.7, 0.1)
LSM Change Difference (95% CI)	2.0 (0.8, 3.2)	1.9 (0.6, 3.2)	1.8 (0.6, 3.0)
P-value	0.0009	0.0040	0.0036

CI: confidence interval; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SD: standard deviation

Given the Baseline functional imbalance in the 6–7-year-old age stratum, an EC analysis was undertaken to contextualize the results for this age group. For this analysis, the treated group (N=28, middle column of Table 23) comprised eleven 6–7-year-olds treated in Part 1, as well as seventeen 6–8-year-olds dosed in the crossover Part 2. As demonstrated in the inset table in Figure 28, the baseline physical functional characteristics of the treated and external comparator cohorts were comparable. As shown in the bar chart, the mean change from baseline in NSAA score for the treated

group was 0.4 points, while the external comparator cohort declined an average of 1.7 points, resulting in an LSM change difference of 1.9 points (Figure 28).

Figure 28: Study 102 External Control Analysis of 6–8 Year Olds



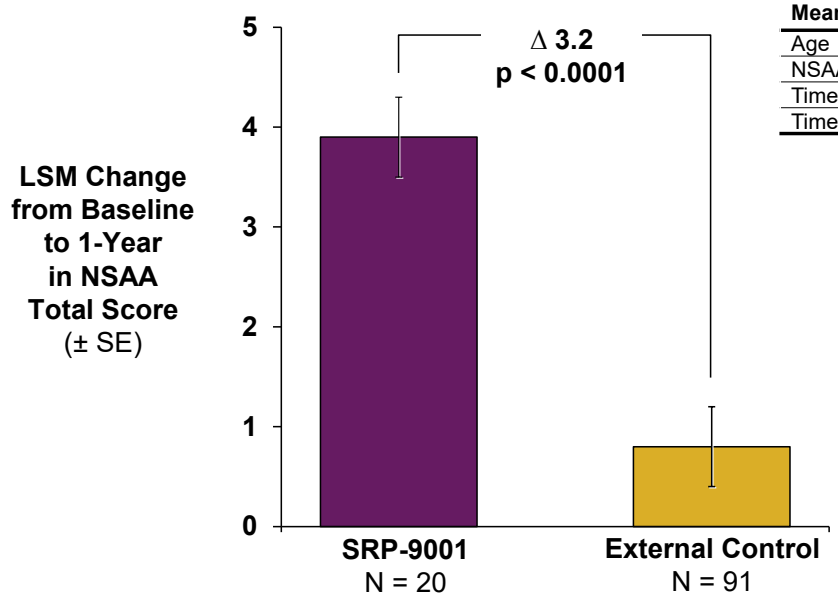
Baseline Mean	SRP-9001 N = 28	EC N = 73
Age	7.4	7.2
NSAA Total Score	22.1	21.3
Time to Rise	4.9	4.9
Time of 10MWR	5.2	5.2

10MWR: 10-meter walk/run; EC: external control; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

5.5.8.3 Study 103

In the Study 103 analysis set (N=20), a statistically significant increase in NSAA total score from Baseline to 1 year post-SRP-9001 infusion was observed compared to the propensity score weighted EC cohort (N=91) (LSM change difference 3.2, $p < 0.0001$), favoring SRP-9001 (Figure 29).

Figure 29: Study 103 External Control Analysis



Mean Baseline	SRP-9001 N = 20	EC N = 91
Age	5.8	6.2
NSAA Total Score	22.1	21.9
Time to Rise	4.2	4.2
Time of 10MWR	5.1	5.1

10MWR: 10-meter walk/run; EC: external control; LSM: least squares mean; NSAA: North Star Ambulatory Assessment; SE: standard error

5.6 Efficacy Conclusions

Studies 101, 102, and 103 demonstrated that treatment with SRP-9001 resulted in a significant mean increase in SRP-9001 dystrophin expression by western blot from Baseline to Week 12 and that SRP-9001 dystrophin expression was associated with clinical benefit as measured by NSAA total score change at 1 year.

- Vector genome copies per nucleus were detected by ddPCR at Week 12 for patients treated with SRP-9001 in all 3 studies demonstrating biodistribution and successful transduction with the treatment.
- Significant increases were observed in SRP-9001 dystrophin expression by IF fiber intensity and IF PDPF from Baseline to Week 12 in all 3 studies, demonstrating correct and consistent localization of the SRP-9001 dystrophin protein to the sarcolemma membrane.
- Treatment with SRP-9001 resulted in clinical reductions of serum CK levels in almost all patients to levels below the median CK level for placebo patients, which is supportive of normalization of the muscle micro-environment induced by the biological activity of SRP-9001, again confirming a similar effect seen in the nonclinical setting.
- While Study 102 missed its primary efficacy endpoint, analysis of the 2 age strata used in the randomization showed evidence of benefit in the 4–5-year-old

stratum where baseline prognostic factors were well balanced but not in the 6–7-year-old. stratum where placebo treated patients had more favorable baseline prognosis. A pre-specified EC analysis was performed to provide additional context around these findings which supported a consistent benefit across both age groups.

- In Study 103, an LSM change difference of 3.2 points in NSAA score was seen at 1 year when treated patients were compared to a propensity score weighted EC cohort.
- In an integrated analysis across the 3 clinical studies of 52 patients dosed at 1.33×10^{14} vg/kg, the results of an LSM change difference in NSAA score of 2.4 points ($p < 0.0001$) at 1 year support the clinical efficacy of SRP-9001 in the context of accelerated approval pending the results of larger confirmatory study, Study 301.
- Maintenance of improvements in NSAA total score were observed up to 4-years following SRP-9001 infusion in Study 101.

6 CLINICAL SAFETY

6.1 Safety Populations

Two analysis sets were used to evaluate the safety of SRP-9001:

- Primary Analysis Set: all patients who received study treatment in Study 102 during Part 1 (SRP-9001 N=20; placebo N=21)
    - Total of 19.4 patient-years of exposure (SRP-9001 group)
    - Mean follow-up observation time: 0.97 patient-years (SRP-9001 group)
- Exposure Analysis Set: all patients who received SRP-9001 in Studies 101, 102, and 103 (Cohorts 1–4) (N=85)
    - Total of 182.75 patient-years of exposure
    - Mean follow-up observation time: 2.15 patient-years

The safety data for patients receiving the SRP-9001 dose of 1.33×10^{14} vg/kg (N=73) are presented in the Exposure Analysis Set.

6.2 Overview of Adverse Events

For the Primary Analysis Set, a total of 528 AEs were observed; 303 AEs in the SRP-9001 group and 225 AEs in the placebo group. Four hundred and ninety-seven were treatment-emergent AEs (TEAEs); 288 TEAEs in the SRP-9001 group and 209 TEAEs in the placebo group. More patients in the SRP-9001 group than the placebo group had treatment-related TEAEs (85.0% versus 38.1%). The majority of events were mild or moderate in intensity (Table 24).

Three (15.0%) patients in the SRP-9001 group and 2 (9.5%) patients in the placebo group had a total of 6 SAE. These SAEs are described in detail in Section 6.4. There were no deaths or AEs leading to study discontinuation.

Table 24: Overview of Treatment-Emergent Adverse Events – Primary Analysis Set

Statistics	SRP-9001 1.33×10^{14} (N=8) n (%)	SRP-9001 (N=20) n (%)	Placebo (N=21) n (%)
Patients with any TEAE	8 (100.0)	20 (100.0)	21 (100.0)
Mild	1 (12.5)	1 (5.0)	3 (14.3)
Moderate	6 (75.0)	16 (80.0)	16 (76.2)
Severe	1 (12.5)	3 (15.0)	2 (9.5)
Patients with any SAE	1 (12.5)	3 (15.0)	2 (9.5)
Patients with any AEs Leading to Discontinuation	0	0	0
Deaths	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse events

In the Exposure Analysis Set, there was a total of 1230 TEAEs with 98.5% being mild or moderate. 96.5% of patients experiencing at least 1 TEAE (Table 25). There were no AEs leading to study discontinuation; however, 2 patients who were treated with SRP-9001 in Part 1 of Study 102 did not receive treatment (placebo) in Part 2 due to AEs but remained in the study for follow-up.

- One patient had a non-serious TEAE of irritability that was considered by the Investigator to be moderate in severity and not related to SRP-9001 treatment. The TEAE was considered to be steroid-related, and the patient was tapered off corticosteroids.
- One patient had a serious TEAE of femur fracture that was considered by the Investigator to be severe and not related to SRP-9001 treatment. The fracture required surgery and a significant recovery time; therefore, the patient moved back to his home country.

No deaths occurred during any of the studies.

Table 25: Overview of Treatment-Emergent Adverse Events – Exposure Analysis Set

Statistics	SRP-9001 1.33×10^{14} (N=73) n (%) [EAIR]	All Patients (N=85) n (%) [EAIR]
Patients with any TEAEs	70 (95.9) [14.78]	82 (96.5) [16.93]
Mild	19 (26.0)	19 (22.4)
Moderate	42 (57.5)	50 (58.8)
Severe	9 (12.3)	13 (15.3)
Patients with any Treatment-related TEAEs	63 (86.3) [3.52]	73 (85.9) [2.90]
Patients with any SAEs	7 (9.6) [0.05]	11 (12.9) [0.07]
Patients with any Treatment-related SAEs	5 (6.8) [0.04]	7 (8.2) [0.04]
Patients with any AEs Leading to Discontinuation	0	0
Deaths	0	0

AE: adverse event; EAIR: exposure-adjusted incidence rate; SAE: serious adverse event; TAR: time at risk; TEAE: treatment-emergent adverse events
Percentages calculated as 100 × (n / N).
EAIR: (number of patients with event / total TAR).

6.3 Common Adverse Events

In the Primary Analysis Set, the most frequently reported TEAEs in both the SRP-9001 and placebo groups were upper respiratory tract infection, vomiting, and viral infection (Table 26). More SRP-9001-treated patients experienced vomiting than patients receiving placebo. Vomiting is further discussed in Section 6.6.6.

Table 26: Commonly Reported (> 10%) Treatment-Emergent Adverse Events – Primary Analysis Set

Preferred term	SRP-9001 (N=20) n (%)	Placebo (N=21) n (%)
Upper respiratory tract infection	13 (65.0)	13 (61.9)
Vomiting	13 (65.0)	7 (33.3)
Cough	9 (45.0)	6 (28.6)
Decreased appetite	8 (40.0)	0
Viral infection	8 (40.0)	9 (42.9)
Ecchymosis	7 (35.0)	4 (19.0)
Nausea	7 (35.0)	2 (9.5)
Abdominal pain upper	6 (30.0)	4 (19.0)
Incision site haemorrhage	6 (30.0)	4 (19.0)
Abdominal pain	5 (25.0)	2 (9.5)
Arthralgia	5 (25.0)	1 (4.8)
Gamma-glutamyltransferase increased	5 (25.0)	0
Pain in extremity	5 (25.0)	5 (23.8)
Procedural pain	5 (25.0)	7 (33.3)
Pyrexia	4 (20.0)	1 (4.8)
Rhinorrhoea	4 (20.0)	3 (14.3)
Skin abrasion	4 (20.0)	2 (9.5)
Constipation	3 (15.0)	0
Diarrhoea	3 (15.0)	2 (9.5)
Gastroenteritis	3 (15.0)	2 (9.5)
Headache	3 (15.0)	6 (28.6)
Irritability	3 (15.0)	1 (4.8)
Limb injury	3 (15.0)	1 (4.8)
Nasal congestion	3 (15.0)	2 (9.5)
Sleep disorder	3 (15.0)	1 (4.8)

Of the patients who experienced an AE, 100% of the patients in the SRP-9001 group and 81.0% patients in the placebo group experienced the first event within the first 2 weeks after study drug administration. There were temporal patterns for gastrointestinal (GI) and ALI events. Most GI events (ie, vomiting) were experienced within 60 days (majority within 2 weeks) of study drug administration (see Section 6.6.6). ALI events were all experienced within 60 days of study drug administration (typically between 2 weeks and 60 days). These are further described in Section 6.6.1.

In the Exposure Analysis Set, the most common TEAEs overall were vomiting, decreased appetite, nausea, and upper respiratory tract infection (Table 27). Of the

patients who experienced an AE in the Exposure Analysis Set, 94.0% experienced their first event within the first 2 weeks after study drug administration. The temporal pattern for GI and hepatotoxicity events was similar to the Primary Analysis Set.

Table 27: Commonly Reported (> 10%) Treatment-Emergent Adverse Events – Exposure Analysis Set

Preferred Term	SRP-9001 1.33×10^{14} (N=73) n (%)	All Patients (N=85) n (%)
Vomiting	45 (61.6)	52 (61.2)
Decreased appetite	35 (47.9)	40 (47.1)
Nausea	31 (42.5)	34 (40.0)
Upper respiratory tract infection	25 (34.2)	36 (42.4)
Abdominal pain upper	18 (24.7)	23 (27.1)
Irritability	16 (21.9)	22 (25.9)
Pain in extremity	18 (24.7)	28 (32.9)
Pyrexia	16 (21.9)	20 (23.5)
Procedural pain	15 (20.5)	23 (27.1)
Headache	14 (19.2)	18 (21.2)
Fatigue	14 (19.2)	17 (20.0)
Glutamate dehydrogenase increased	16 (21.9)	16 (18.8)
Cough	15 (20.5)	20 (23.5)
Gamma-glutamyltransferase increased	13 (17.8)	15 (17.6)
COVID-19	24 (32.9)	29 (34.1)
Thrombocytopenia	10 (13.7)	10 (11.8)
Diarrhoea	10 (13.7)	15 (17.6)
Constipation	12 (16.4)	14 (16.5)
Incision site haemorrhage	8 (11.0)	13 (15.3)
Gastrooesophageal reflux disease	9 (12.3)	11 (12.9)
Viral infection	9 (12.3)	15 (17.6)
Rhinorrhoea	5 (6.8)	13 (15.3)
Arthralgia	6 (8.2)	10 (11.8)
Ecchymosis	3 (4.1)	10 (11.8)
Gastroenteritis viral	7 (9.6)	9 (10.6)

6.4 Serious Adverse Events

In the Primary Analysis Set, 5 patients experience a total of 6 SAEs (3 patients in the SRP-9001 group and 2 patients in the placebo group). The SAEs reported in the SRP-9001 group were rhabdomyolysis (n=2), liver injury (n=1) and transaminases increased (n=1). The SAEs reported in placebo group were rhabdomyolysis and humerus fracture.

In the Exposure Analysis Set, 11 patients experienced a total of 13 SAEs. Hypertransaminasaemia and vomiting were the only preferred terms reported in more than 1 patient at the dose of 1.33×10^{14} vg/kg (Table 28).

Table 28: Serious Adverse Events – Exposure Analysis Set

Preferred Term	SRP-9001 1.33×10^{14} (N=73) n (%)	All Patients (N=85) n (%)
Hypertransaminasaemia	2 (2.7)	2 (2.4)
Vomiting	2 (2.7)	2 (2.4)
Appendicitis	1 (1.4)	1 (1.2)
Immune-mediated myositis	1 (1.4)	1 (1.2)
Liver injury	0	1 (1.2)
Myocarditis	1 (1.4)	1 (1.2)
Femur fracture	1 (1.4)	3 (3.5)
Rhabdomyolysis	0	2 (2.4)

Of these 11 patients who experienced a SAE, 7 (8.2%) of these patients had a total of 9 SAEs that were assessed by the Investigator to be related to study treatment (Table 29). Seven of the related SAEs recovered/resolved while 2 recovered/resolved with sequelae (due to residual weakness in the immune-mediated myositis case; additional long-term cardiac medication in the myocarditis case).

Additional details are provided in Appendix Section 10.3.

Table 29: Serious Related Adverse Events – Exposure Analysis Set

Preferred Term	SRP-9001 1.33×10^{14} (N=73) n (%)	All Patients (N=85) n (%)
Hypertransaminasaemia	2 (2.7)	2 (2.4)
Vomiting	2 (2.7)	2 (2.4)
Myocarditis	1 (1.4)	1 (1.2)
Immune-mediated myositis	1 (1.4)	1 (1.2)
Liver injury	0	1 (1.2)
Rhabdomyolysis	0	2 (2.4)

6.5 Deaths

No deaths have occurred during the studies.

6.6 Adverse Events of Special Interest

6.6.1 Acute Liver Injury

Transient elevations in liver biomarkers has been identified as a class effect for AAV gene therapy and with SRP-9001 liver enzymes routinely increase between 4 to 8 weeks following infusion and resolve without complications (Figure 30).

Serum ALT and AST levels are commonly used to assess hepatocellular health. However, in patients with DMD, high transaminase levels (ALT and AST up to ~22 × ULN) originating from muscle are often observed (McMillan 2011) and can confound safety assessments. Thus, in the SRP-9001 clinical program, the Sponsor, leveraging the Council for International Organizations of Medical Sciences Working Group's Consensus definition and FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (CIOMS 2020, FDA 2009), defined ALI as GGT > 3 × ULN, or GLDH > 2.5 × ULN, or alkaline phosphatase (ALP) > 2 × ULN, or ALT > 3 × baseline excluding ALT elevation from muscle.

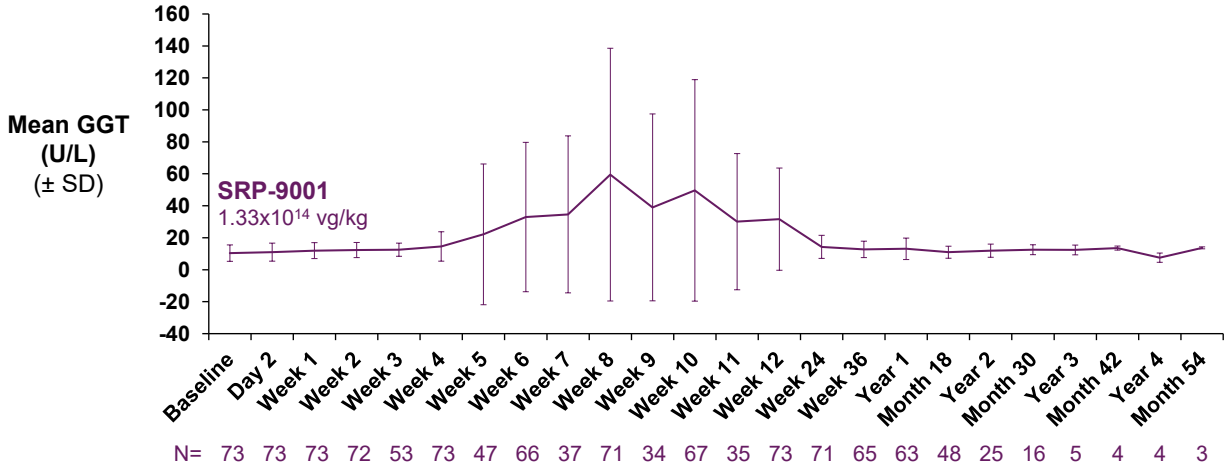
ALI, as defined by the Sponsor and based upon review of reported Preferred Terms, was observed in 31 (36.5%) patients treated with SRP-9001 (Table 30). Twenty-five (80.6%) patients had ALI events assessed as mild/moderate and resolved spontaneously or with corticosteroids. Of these 31 patients, 26 patients had laboratory value changes deemed clinically significant by the Investigator which were reported as a coded liver AE (ie, GGT increased, transaminases increased, hepatic enzymes increased, etc.). Three of these were assessed as serious due to hospitalization but none of the patients demonstrated any clinically important liver dysfunction, or coagulation abnormalities (ie, no abnormal international normalized ratio [INR]), or subsequent liver failure. All 3 SAEs resolved with corticosteroid treatment. The 2 most severe cases of ALI had an increase in total bilirubin (1 patient with jaundice) and were found to be complicated by previously unknown infection with H. pylori and Parvovirus. These 3 serious cases are described in Appendix Section 10.3.

Based upon the FDA's Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, ALI events were assessed for new onset (ie, timing coinciding with the changes in hepatic enzymes) of an AE potentially related to hepatic inflammation. No events met this criterion; however, there was 1 report of stomach pain most likely related to concurrent *H. pylori* infection. In the ongoing, blinded Study 301, there is 1 report of right upper quadrant tenderness to palpation.

In patients with liver enzyme elevations, increases began within 60 days of infusion, with a mean time to onset of ALI of 51 days, and mean time to peak of 8 days after onset.

The relatively predictable onset (within 60 days) and duration, along with resolution following a temporary increase in corticosteroid dose differentiate the ALI observed with SRP-9001 from that associated with small molecules which tends to be idiosyncratic.

Figure 30: GGT Elevations Over Time



GGT: Gamma-glutamyl transferase; SD: standard deviation

The pattern of liver enzyme changes observed with SRP-9001 resembles those associated with viral infections (EASL 2019, Kumar 2014, Temple 2006).

Overall, ALI occurrence, clinical course, and outcome were predictable. All ALI cases were manageable and resolved spontaneously or with corticosteroid treatment, and none were associated with elevated INR or any other signs of liver failure or global liver dysfunction.

Table 30: Patients Meeting Criteria for ALI Laboratory Parameters and Other Related Criteria – Exposure Analysis Set

Category	All Patients (N=85) n (%)
Meeting x-fold definition of ALI	31 (36.5)
GGT > 3 × ULN	15 (17.6)
GLDH > 2.5 × ULN	22 (25.9)
ALT > 3 × Baseline	14 (16.5)
ALP > 2 × ULN	0
Total bilirubin > 2 × ULN	3 (3.5)
Total Bilirubin > 2 mg/dL	3 (3.5)
GGT increases triggered additional steroid use (identified by medical review)	19 (22.4)
ALI onset during steroid tapering (identified by medical review)	5 (5.9)
IV use of steroids by ALI patients (x-fold definition) for adverse events	7 (8.2)

ALI: acute liver injury; ALP: alkaline phosphatase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; GLDH: glutamate dehydrogenase; IV: intravenous; ULN: upper limit of normal.
GLDH was only collected in Study 102 Part 2.

6.6.2 Immune-Mediated Myositis

Immune-mediated myositis is defined as an immune reaction to SRP-9001 dystrophin. A single SAE of immune-mediated myositis has been observed with SRP-9001. This patient, with a deletion of exons 3–43 mutation, approximately 1 month SRP-9001 administration developed muscle weakness, dysphagia, dysphonia, difficulty sitting and walking. Cardiac function was preserved (LVEF of 65%) and a pathology report from a muscle biopsy listed a diagnosis of inflammatory myopathy in background of chronic dystrophinopathy. The patient was treated with supportive care, plasmapheresis, steroids and on discharge tacrolimus. The patient recovered with sequelae (weakness; strength returned but not completely to baseline).

After this SAE, the Sponsor classified immune-mediated myositis as an important identified risk with the risk related to the nature of a patient's dystrophin mutation. The SRP-9001 dystrophin transgene contains portions of the N-terminus (exons 1–17 are present in the SRP-9001 construct) and C-terminus (exons 59–71 are present in the SRP-9001 construct) of the naturally occurring full-length dystrophin gene. Mutations in the transgene portion of the construct may impart higher immunogenic risk, as mutations in these exons can result in a lack of immune tolerance. In particular, mutations that delete a portion of that genetic sequence (known as deletions) may confer risk, due to the inability to activate known alternative transcription mechanisms potentially present within the deleted region that would allow for production of low levels of dystrophin protein that, while not functional, may induce immunological self-tolerization. These mechanisms include exogenous exon skipping, cryptic splice site activation, and spontaneous read-through of premature termination codons (Adachi 2003, Juan-Mateu 2013, Wein 2014). The potential risk applies to the transgene region (exons 1–17 and 59–71) because this is the only portion of the dystrophin gene sequence present in the SRP-9001 construct.

To date, 13 patients with mutations in the transgene region (exons 1–17 and 59–71) have been dosed with SRP-9001. Only 1 of these patients, that patient with a deletion of exons 3–43, had an SAE of immune-mediated myositis. The other 8 patients with mutations in exons 1–17, including 2 patients who had smaller mutations involving exons 8 and 9, as well as the 4 patients with mutations in exons 59–71 did not have any evidence of immune-mediated myositis.

Based upon additional investigations done after this index case, the Sponsor has proposed a contraindication in patients with any deletion that fully includes exons 9–13 in the *DMD* gene. The contraindication is based upon the following observations:

- The mechanism is currently understood to be a lack of self-tolerance to antigenic epitopes within the N-terminal region of transgene-expressed dystrophin protein in persons whose *DMD* mutations would prevent them from natively expressing these epitopes,

- Ex vivo mapping indicated that peptides from exons 8 and 9 appear to be immunogenic,
- Exons 1–7 have high homology to utrophin, while homology diverges at exons 8 and 9,
- Patients with deletions of exons 8–12 and exons 10–11 did not have an event, and
- Patients with duplications and point mutations did not have an event.

Note that the proposed contraindication of patients with full deletion of exons 9–13 will, by definition, include larger deletions such as 8–13, 3–43, and 8–17. While no patient dosed with SRP-9001 outside of the proposed contraindication has had an immune-mediated myositis event, ELISpot positivity in exons 8 and 9 indicates that patients with other deletions in the transgene region may be at risk. For these reasons the Sponsor proposes a warning and precaution that patients with any deletion in any transgene region (exons 1–17 or 59–71) may be at risk for a severe immune-mediated myositis reaction. Finally, the Sponsor also informs that there is limited data available for patients with other mutations between exons 1 to 17 and exons 59 to 71.

6.6.3 Myocarditis

Two cases of myocarditis, 1 in the ongoing, blinded Study 301 study (therefore not included in the SAE Table 33), have been observed within the SRP-9001 clinical trial program. Myocarditis was reported by the Investigators and confirmed by external expert medical review. Both myocarditis events occurred within 3–4 days after infusion of SRP-9001 therapy (or placebo for the Study 301 event) and were detected based on elevated troponin levels on blood samples that were draw during patient admission to hospital for another reason (vomiting in the unblinded case, vomiting and fever for the Study 301 case. Neither event was associated with acute cardiac dysfunction or imaging changes from baseline. One event recovered, while the other recovered with sequala (residual changes on myocardial MRI scan which required adjustment of medication for chronic cardiomyopathy, specifically the addition of aldosterone and carvedilol).

One of the events was confounded by pre-existing cardiomyopathy (11-year-old boy in Study 103). For the SRP-9001 program the AE of special interest of “troponin elevations” is defined as an elevation of troponin-I greater than 3 × ULN or 3 × baseline for patients with elevated baseline values which does occur in patients with DMD. Considering both myocarditis events being detected by incidental troponin increases during hospitalization for another condition, monitoring of troponin-I is recommended prior to SRP-9001 infusion and weekly for the first month and should be continued weekly as medically indicated. There was no identifiable, predicable temporal pattern of troponin elevations within the SRP-9001 clinical program. The cases were reviewed with an external cardiologist who noted that “to be effective in delivering its therapeutic

'pay-load,' AAVs carrying shortened dystrophin are designed and intended to target and penetrate skeletal and cardiac myocytes. By definition, therefore, gene therapy causes an iatrogenic 'viral myocarditis' with a non-pathological / non-replicating virus. Viewed in this light, the 'myocarditis,' constituting a pre-defined study SAE, could contribute to a more dramatic troponin release than occurs to some degree in many patients with DMD receiving gene therapy rather than requiring separate explanation."

6.6.4 Thrombocytopenia

Thrombocytopenia, both recorded as a laboratory parameter and or reported as an AE, has been observed in clinical studies with SRP-9001. The reduction in platelet number is seen within the first 1–2 weeks following infusion with a nadir at day 7–8. These mild asymptomatic decreases resolved without treatment by week 2 post-SRP-9001 infusion and without associated clinical impact.

In the Exposure Analysis Set, a total of 10 (11.8%) patients had 1 or more AEs of thrombocytopenia and no patient experienced a TEAE of thrombocytopenia after 60 days post-infusion. All events were considered by the Investigator to be treatment related. None of these were SAEs or associated with clinical consequences. Based on laboratory parameters 41 (48.2%) of patients had thrombocytopenia with 5 (5.9%) patients meeting the criteria (platelet count < 75,000/ µL) for moderate thrombocytopenia. There were no decreases below 50,000/ µL.

6.6.5 Thrombotic Microangiopathy

TMAs are complement-mediated clinical syndromes defined by the presence of hemolytic anemia (destruction of red blood cells), low platelets (thrombocytopenia), and organ damage due to the formation of microscopic blood clots in capillaries and small arteries.

No events of TMA and no microangiopathy with kidney injury was observed in any patient following SRP-9001 administration.

Predictable, transient, complement reduction has been seen post-administration of SRP-9001. Complement decrease (C3 and C4) were observed at Week 1 without any associated symptoms and returned to normal by Week 2. In the Exposure Analysis Set, 2 (2.4%) patients had a C4 level decrease of 0–25% of baseline, 20 (23.5%) patients had a decrease of 26–50%, 23 (27.1%) patients had a decrease of 51–75%, and 4 patients had a decrease of > 75% of baseline. For C3, 40 (47.1%) patients had a C3 level decrease of 0–25%, 6 (7.1%) patients had a decrease of 26–50%, and 1 (1.2%) patient had a decrease of 51–75% of baseline; no patients had a C3 level decrease of greater than 75% of baseline. Note that patients were counted in 1 category only based on their maximum grade/change.

6.6.6 Vomiting

Vomiting has been observed in all clinical studies with SRP-9001.

Events of vomiting generally occurred in the first 2 weeks after infusion with the majority within the first week. In the Exposure Analysis Set, 52 (61.2%) patients had an AE of vomiting (Table 27). Two patients had SAEs of vomiting. Both patients were proactively admitted for administration of IV corticosteroids due to concern that oral administration would not be tolerated and to ensure hydration. Incidentally both had pre-existing history of cardiomyopathy and experienced asymptomatic troponin increase.

6.7 Long-Term Safety

There are no long-term safety issues through ≥ 2 years of follow-up; no evidence of late-onset or latent events has been observed.

In general, the number of patients with AEs was similar across the time periods: 96.5% of patients had AEs in < 1 year following infusion; 57.1% of patients had AEs in 1 to < 2 years following infusion; and 67.6% patients had AEs in ≥ 2 years following infusion. The most common AEs within 1 year of SRP-9001 infusion were vomiting (61.2% of patients), decreased appetite (47.1% of patients), and nausea (40.0% of patients). After 1 to < 2 years following infusion, the most common AEs were upper respiratory tract infection (14.3% of patients), pain in extremity (13.0% of patients), and cough (11.7% of patients). AEs occurred infrequently after ≥ 2 years following infusion with each reported AE occurring in < 10% of patients.

In alignment with FDA guidance, Sarepta is following all clinical trial patients for at least 5 years post SRP-9001 administration in the clinical trial setting as well as the initial commercial patients via a 10-year long-term Phase 4 post-marketing trial.

6.8 Safety Conclusions

DMD is a rare disease and based on the extensive experience from 85 patients dosed with SRP-9001 across 3 clinical studies with 182.75 patient-years of exposure, SRP-9001 was generally safe and well tolerated.

The majority (98.5 %) of treatment-related AEs were mild or moderate in severity and occurred within the first 60 days of administration of SRP-9001. All were monitorable, manageable, reversible, and consistent across studies. No new event was seen in the SRP-9001 program relative to other AAV gene therapies. ALI, immune-mediated myositis, myocarditis, thrombocytopenia, TMA (not seen in SRP-9001), and vomiting have been identified as important identified risks and important potential risks.

7 CONFIRMATORY STUDY 301

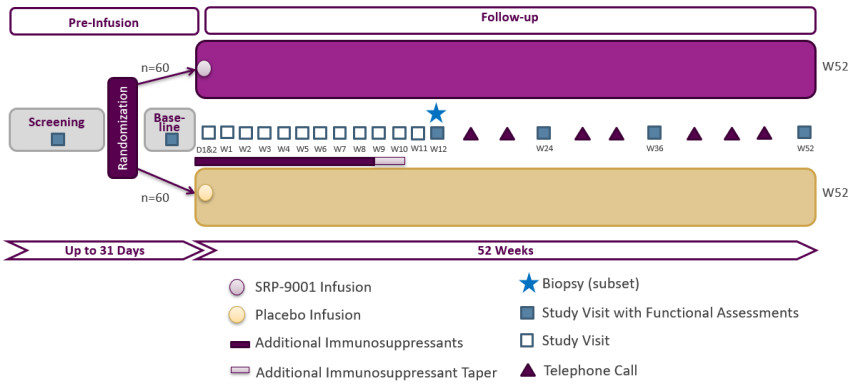
7.1 Design Overview

Study 301 (Embark) is a global Phase 3, randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 (1.33×10^{14} vg/kg) in approximately 120 male patients with DMD who are ≥ 4 to < 8 years of age. Data from Studies 101, 102, and 103 informed the design of the confirmatory Phase 3 study, including inclusion/exclusion criteria, study population, endpoints and sample size to ensure that this study will generate definitive results with high probability of success. Specifically, based on findings from Study 102 inclusion criteria in Study 301 include patients having a NSAA score > 16 and < 29 and a time to rise from floor < 5 seconds at the Screening visit. Randomization is also stratified by age group (≥ 4 to < 6 years vs ≥ 6 to < 8 years) and NSAA total score at Screening (≤ 22 vs > 22).

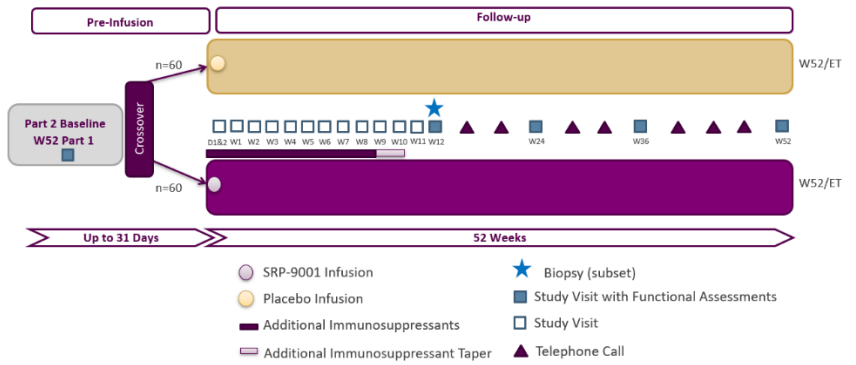
Eligible patients were randomized 1:1 to receive either SRP-9001 or placebo in Part 1 and will be followed for 52 weeks (Figure 31). In Part 2, patients who received placebo in Part 1 will receive SRP-9001, and those who received SRP-9001 in Part 1 will receive placebo; with a follow-up duration of 52 weeks.

Figure 31: Study 301 Schematic

Part 1



Part 2



Patients must be on a stable daily dose of oral corticosteroids for at least 12 weeks before the initial Screening visit, with the dose remaining constant (except for modifications to accommodate changes in weight) throughout the study. The day before the infusion (SRP-9001 or placebo) and for 60 days following infusion, patients are started on an additional 1 mg/kg/day of glucocorticoid (prednisone equivalent).

The primary objective of Study 301 Part 1 is to evaluate the effect of SRP-9001 on physical function as assessed by change in NSAA total score from Baseline to Week 52. Patients remain blinded during both Part 1 and Part 2 of the study. The primary assessment of Study 301 is based on Part 1 data.

The first patient was screened for the study in October 2021, and the study is fully enrolled having recruited a total of 125 patients. By the end of May 2023, just under half of the US patients will have completed their week 52 visits. Given that all patients in this study will have guaranteed access to SRP-9001 by the end of September (the majority significantly earlier), and all patients are blinded to their current treatment allocation, the Sponsor sees the risk of US patients dropping out to access commercial therapy with associated uncertainties on eligibility, access, and timing to be extremely low. Any residual risk to this study is further mitigated by having 45 patients recruited ex-US and conservative estimations on dropouts within the power calculations.

7.2 Enrollment Criteria

Male patients with DMD who met the following are criteria were eligible for enrollment:

- Ambulatory and are ≥ 4 to < 8 years of age at time of randomization.
- Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing.
- Ability to cooperate with motor assessment testing.
- Stable daily dose of oral corticosteroids for at least 12 weeks prior to Screening, and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
- rAAVrh74 antibody titers are not elevated as per protocol-specified requirements.
- A pathogenic frameshift mutation or premature stop codon contained between exons 18 and 79 (inclusive), with the exception of mutation fully contained within exon 45.

Exclusions criteria included:

- Exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression within protocol-specified time limits.
- Abnormality in protocol-specified diagnostic evaluations or laboratory tests.

- Presence of any other clinically significant illness, medical condition, or requirement for chronic drug treatment that in the opinion of the Investigator creates unnecessary risk for gene transfer.
- Mutations between or including exons 1–17, in-frame deletions/duplications, and variants of uncertain significance.
- Mutations fully contained within exon 45 (inclusive).

7.3 Endpoints

The primary objective of Study 301 Part 1 is to evaluate the effect of SRP-9001 on physical function as assessed by:

- Change in NSAA total score from Baseline to Week 52.

Key secondary endpoints include:

- Quantity of SRP-9001 dystrophin protein expression at Week 12 as measured by western blot
- Change in time to rise from the floor from Baseline to Week 52
- Change in time of 100- and 10-meter timed test from Baseline to Week 52
- Change in time to ascend 4 steps from Baseline to Week 52
- Change in Stride Velocity 95th Centile from Baseline to Week 52 measured by a wearable device
- Change from Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) score in mobility and upper extremity function to Week 52
- Number of skills gained or improved at Week 52 as measured by the NSAA

AEs, SAEs, and AEs of Special Interest will also be evaluated throughout the study.

7.4 Statistical Methods

The primary endpoint and some secondary endpoints will be tested in a hierarchical manner using an appropriate multiple-testing approach that provides strong control of the familywise Type 1 error rate at a 2-sided 0.05 level. The details of the testing procedure will be specified in the SAP.

For the primary endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), summary statistics will be provided by treatment group for NSAA total score at Baseline, each post-baseline visit in Part 1, and for change from Baseline to each post-baseline visit in Part 1. For the Baseline and Week 52 (Part 1) visits where 2 scores of NSAA will be collected, the mean NSAA score will be used in the analysis.

As the primary analysis, a restricted maximum likelihood-based mixed model repeated measures analysis will be used to compare the 2 treatment groups for change in NSAA total score from Baseline to Week 52 (Part 1). In this model, the response vector consists of the change from Baseline in NSAA total score at each post-baseline visit in Part 1. The model will include the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group at randomization (categorical), Baseline NSAA total score, and Baseline NSAA total score by visit interaction. All covariates will be fixed effects in this analysis.

An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure results in a lack of convergence, the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random.

The superiority of SRP-9001 over placebo will be concluded if the test achieves statistical significance based on the multiplicity-adjusted testing procedure that will be specified in the SAP.

8 BENEFIT-RISK CONCLUSIONS

DMD is a rare, progressive and fatal x-linked, neuromuscular monogenetic disease. Despite treatment advances, a significant unmet medical need exists for patients with DMD, who still have a median life expectancy of 28 years.

One-time infusion of SRP-9001, a recombinant AAV rh74 vector-based gene transfer therapy, addresses the root cause of DMD by providing functional SRP-9001 dystrophin protein, resulting in improved or preserved muscle function, prevention of muscle loss, and stabilization of DMD disease progression.

Studies 101, 102, and 103 demonstrated that treatment with SRP-9001 resulted in a significant mean increase in SRP-9001 dystrophin protein expression by western blot from Baseline to Week 12. Similarly, significant increases were observed in SRP-9001 dystrophin expression by IF fiber intensity and IF PDPF from Baseline to Week 12 in all 3 studies. SRP-9001 dystrophin protein expression was associated with significant decreases from Baseline in CK levels post-treatment and improvements in the muscle micro-environment. These observations are supportive of disease stabilization of the sarcolemma membrane consistent with the mechanism of action and biological effect of SRP-9001.

Collectively, these empirical data confirm the mechanism of action of SRP-9001 and strongly support that the key functional regions of the dystrophin protein selected for inclusion in the SRP-9001 vector construct establish a functional SRP-9001 dystrophin protein.

The empirical evidence is supported by the observed group level clinical benefit, after controlling for key prognostic factors of baseline age and motor function. When compared to properly score weighted ECs, a 2.4-point NSAA change at 1-year was observed in the pre-specified primary analysis of an integrated set of patients across trials 101, 102 and 103. The magnitude of NSAA gain at 1-year predicted by SRP-9001 dystrophin is clinically meaningful. With the natural history of DMD showing a mean loss of approximately 3 NSAA points a year after the age of 6 (Muntoni 2019), this level of treatment effect is in keeping with the hypothesis that SRP-9001 stabilizes disease progression. The treatment effect would be predicted to grow year on year as the treated trajectory diverges from natural history. This is supported by Study 101 in which a 9-point NSAA difference is seen at 4 years.

The treatment goal is to beneficially modify disease trajectory compared to the expected course of DMD, slowing disease progression and, over the long-term, extending preservation of critical functions such as ambulation, upper limb mobility, pulmonary capacity, and myocardial health.

Safety data from the clinical studies with SRP-9001 have shown that treatment with SRP-9001 was generally safe and well tolerated. The observed AEs and identified risks

are monitorable, manageable, and reversible. The observed AEs have been mild to moderate in severity without any deaths.

ALI, immune-mediated myositis, thrombocytopenia, myocarditis, thrombotic microangiopathy, and vomiting are identified safety concerns for SRP-9001. ALI was adequately monitored with GGT levels and managed with corticosteroids throughout the studies. No cases of ALI, including the serious cases, have included signs of hepatic failure. There was 1 SAE of immune-mediated myositis reported. The event appears to be related to the patient's proximate DMD mutation (deletion mutation involving exons 3–43 in the DMD gene) and has led to changes in which patients are and will be eligible for treatment. Thrombocytopenia (none < 50,000 µL) has been observed with all events spontaneously resolving within the second week following SRP-9001 infusion. Two patients were diagnosed with myocarditis following hospitalization for other events and incidental finding of elevated troponin without acute cardiac changes or compromise. Troponin monitoring is being proposed in the time frame immediately following SRP-9001 treatment. Thrombotic microangiopathy has been observed with other AAV gene-based therapies but not with SRP-9001. Vomiting, typically within the first 2 weeks post-infusion, is commonly observed and responds to standard of care. In context of the progressive debilitating and eventually fatal course of DMD, the ability to easily monitor, manage, and reverse identified safety concerns, the risk-benefit profile of SRP-9001 is approvable.

The patient and caregiver perspective are of central importance when judging the acceptability of a given benefit-risk for a treatment. This perspective has been formally assessed and published by Patient Project Muscular Dystrophy, a global patient organization (Peay 2021). In 2021, following research with caregivers and adult patients with DMD, an assessment of the MAR in the first week after gene therapy was published. In this research gene therapy was described as a therapy that could be given only once, something likely to help the patient's muscles, to slow progression but not cure the disease, and to have a durability of around 10 years. A higher MAR was associated with dosing at a later disease state with the mean MAR ranging from 2.1% if dosed as a newborn, up to 6.3% if given in the last year of being able to lift hand to mouth. Looking specifically at those caregivers willing to accept the highest risk of mortality in the first week after dosing (≥ 200/2,000), 13% would accept this risk to dose as a newborn rising to 36% if dosing was in the last year of the patient being able to lift their hand to their mouth.

The high unmet medical need in DMD, the totality of biological and clinical evidence generated across 3 clinical trials, and the ongoing fully enrolled confirmatory study, support use of the Accelerated Approval Pathway for SRP-9001 to treat patients affected by this universally progressive, fatal disease. Further, the SRP-9001 accelerated approval evidence set exceeds that of the 4 approved anti-sense oligonucleotides and the standard set for an accelerated approval.

In the absence of functional dystrophin, myocytes of patients with DMD continue to die and are replaced by fat and fibrosis leading to irreversible paralysis and death. Therefore, the urgency of treatment is high and any delay in availability of therapy that provides functional dystrophin to patients with DMD will result in irreversible progression of disease. With a total of 182.75 patient-years of follow-up and nearly 5 years of follow-up for individual patients, SRP-9001 has demonstrated efficacy and an acceptable and manageable safety profile. The benefit-risk assessment is positive for the proposed indication.

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10 APPENDICES

10.1 Summary of Functional Assessment Clinical Relevance

Table 31: Overview of Timed Function Tests and Clinical Relevance

Test	Description	Validation	Clinical Relevance
Time to rise from floor (EC data available)	The test is an individual item in NSAA and assesses the ability to stand from a supine position and the time the patient needs to complete the task. Performance is rated with a score of 2 when there is no evidence of Gower's maneuver. When a patient exhibits at least one of the Gower's components, in particular rolling towards the floor, and/or using hand(s) on legs, his ability is rated with 1 point. The performance is scored with 0 points when the patient needs external support of an object (eg, chair) or is unable to complete stand from the floor task. The longer time spent for the accomplishment of the task indicates poor performance.	Time to stand from a supine position is a reliable measure of functional ability and has been systematically used in clinical practice and trials (Bushby 2011). Test-retest reliability has been proved for rise from floor assessment in DMD (McDonald 2013a). The natural history data indicate that the time patients with DMD need to rise from the floor increases with the progression of disease (Mazzone 2016, Muntoni 2019). Multiple lines of evidence show that the timed score to rise from supine task is sensitive to therapeutic interventions (Mendell 1989, Biggar 2006b, McDonald 2020)	Losing the ability to rise from the floor is a milestone of disease progression in DMD. Progressive muscle weakness results in functional impairment captured by an increased time for complex motor actions such as the sequence of maneuvers employed in the stand from supine task (Biggar 2006b). The timed score of the rise from supine can have a predictive value for other motor daily activities such as the ascension of stairs or walking longer distances (Mazzone 2016, Goemans 2020). Additionally, the test is considered as an important prognostic factor in predicting loss of ambulation and disease progression within 12 months (Mazzone 2016, Zambon 2022).
10-meter walk/run (EC data available)	The test is the last item in the NSAA. The test measures the time it takes a patient to complete a 10-meter distance as fast as possible. The performance is scored with 2 points when both feet take off the ground (no double stance phase during running), with 1 point when the 'Duchenne jog'/ fast walk is observed, and with 0 points when the patient walks.	The test is a reliable measure of gross motor ability assessed in clinical trials of DMD (McDonald 2013a, McDonald 2013b). Natural history of 10-meter run/walk performance in boys with DMD has been published (Mazzone 2010, McDonald 2013b, Fowler 2018). The test has documented responses to therapeutic interventions (Bushby 2014).	Changes in 10-meter walk/run timed test results over 1-year interval are clinically meaningful (Henricson 2013, Mazzone 2013). Children who are capable of running would achieve higher speeds on the 10-meter walk/run test, and they walk at higher cadences during their daily activities. The 10-meter walk/run test is valuable because it provides high sensitivity, a strong predictive value, and the ability to be performed in a large proportion of ambulatory boys (Arora 2018, Muntoni 2019).

Test	Description	Validation	Clinical Relevance
Time to ascend 4 steps	The test measures the time it takes for a patient to ascend 4 standardized stairs.	The test has been used as an important assessment in clinical practice and in clinical trials (Goemans 2020). Of the timed functional tests, the time to ascend 4 steps shows the highest test-retest reliability (McDonald 2013a). Data delineating the natural history of test performance in boys with DMD has been published (McDonald 2013b, Pane 2014). The test is a sensitive measure that can capture therapeutic interventions effects on change over time in functional ability (McDonald 2020).	The time to climb 4 stairs reflects lower and upper extremity muscle power. In particular, the test is able to assess lower extremity motor strength, which is reflective of underlying muscle health/size. The performance in time to ascend 4 steps is correlated with knee extension strength (McDonald 2013a). Additionally, the test does not require children to understand the concept of time. For example, it is difficult for young boys to grasp the concept of how much 6 minutes are in the 6-minute walk test. Therefore, the time to ascend 4 steps test may be more reliably performed by children within the age range enrolled in Studies 101, 102, and 103.
100-meter run/walk	The test is a fixed-distance ambulatory assessment used to quantify maximal ambulatory ability in children. The child is instructed to walk/run 100 meters as fast as safely possible on a 25-meter track. Time to complete the test is recorded to one-tenth of a second. A percent predicted score can be calculated based on age and BMI (Alfano 2017).	The test is a reliable measure and has normative values and proved test-retest reliability (Alfano 2017). Therapeutic efficacy has been shown: DMD boys under treatment can complete the test significantly faster compared with DMD treatment-naïve boys (Alfano 2017). Natural history studies indicate that the test score is sensitive to disease progression over time (Miller 2017, Alfano 2018).	As a distance-based test, the task is more attainable and improves understanding compared to the abstract concept of the time-based assessments (Alfano 2017). Given that the test measures maximal speed over a fixed-distance, it eliminates ambiguity and allows the young children to better assess the feasibility of test completion at maximal performance. Although the most able boys with DMD may walk as fast as age-matched peers, their running speed is significantly slower (Miller 2017). Moreover, in the early disease phase, some boys with DMD can accomplish everyday tasks such as stair climbing similarly to their peers. However, none of the boys with DMD matches the maximum 100-meter performance of peers

Test	Description	Validation	Clinical Relevance
			(Miller 2020). Therefore, change in test performance has high predictive value of loss of ambulation over time (Miller 2017, Alfano 2018).

BMI: Body Mass Index; DMD: Duchenne muscular dystrophy; EC: external control; NSAA: North Star Ambulatory Assessment

10.2 Study 102 Summary of Timed Functional Tests

Table 32: Summary of Change From Baseline in Timed Functional Tests Based on In-clinic Assessments and Interpolated Part 1 Week 48 Assessments – ITT Population (Part 1 and Part 2)

	SRP-9001 in Part 1 (N=20)		SRP-9001 in Part 2 (N=21)		
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**	**Change from Part 2 Baseline**
Time of the 100-meter timed test (seconds)					
Baseline					
n	20		21		
Mean (SD)	61.04 (12.71)		53.86 (8.30)		
Median	57.10		55.60		
Min, Max	42.3, 99.3		40.6, 69.1		
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	70.17 (38.19)	8.67 (27.98)	56.35 (10.00)	2.49 (7.52)	
Median	59.20	3.50	55.00	0.90	
Min, Max	44.8, 218.7	-8.2, 119.4	41.5, 80.1	-8.9, 20.0	
Part 2 Baseline					
n	19		21		
Mean (SD)	70.06 (38.34)		55.98 (10.21)		
Median	59.20		55.00		
Min, Max	42.9, 218.7		41.5, 80.1		
Part 2 Week 48					
n	17	17	20	20	20
Mean (SD)	69.15 (26.62)	10.44 (19.10)	54.60 (11.57)	0.84 (8.84)	-1.19 (3.76)
Median	62.30	3.20	53.25	0.50	-1.80
Min, Max	44.7, 129.0	-14.8, 55.8	38.6, 82.3	-12.7, 17.6	-9.7, 5.5
Time of the 100-meter timed test (seconds) percent predicted					
Baseline					
n	20		21		
Mean (SD)	54.11 (10.67)		60.21 (8.53)		
Median	54.73		58.93		
Min, Max	29.9, 73.8		45.9, 77.1		

	SRP-9001 in Part 1 (N=20)		SRP-9001 in Part 2 (N=21)		
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**	**Change from Part 2 Baseline**
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	50.05 (14.84)	-3.72 (7.53)	55.99 (9.67)	-4.22 (7.24)	
Median	52.26	-4.43	56.40	-5.57	
Min, Max	13.8, 73.0	-16.1, 9.1	38.1, 71.6	-20.9, 8.4	
Part 2 Baseline					
n	19		21		
Mean (SD)	50.24 (15.28)		56.35 (10.02)		
Median	52.26		56.43		
Min, Max	13.8, 73.0		38.1, 71.6		
Part 2 Week 48					
n	17	17	20	20	20
Mean (SD)	48.07 (15.31)	-8.03 (8.14)	56.22 (12.15)	-4.09 (8.88)	-0.35 (4.68)
Median	45.55	-7.51	54.69	-4.69	0.04
Min, Max	21.4, 66.6	-19.4, 10.8	36.0, 79.1	-19.7, 14.0	-6.8, 12.9
Time to ascend 4 steps (seconds)					
Baseline					
n	20		21		
Mean (SD)	3.69 (1.46)		3.10 (0.98)		
Median	3.30		3.00		
Min, Max	2.1, 6.5		1.9, 5.8		
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	3.96 (2.15)	0.26 (1.35)	3.12 (1.08)	0.03 (0.87)	
Median	3.20	-0.30	2.90	-0.10	
Min, Max	1.6, 9.0	-1.6, 3.2	1.8, 6.2	-1.7, 2.1	
Part 2 Baseline					
n	19		21		
Mean (SD)	4.02 (2.14)		3.09 (1.09)		
Median	3.20		2.80		
Min, Max	1.6, 9.0		1.8, 6.2		
Part 2 Week 48					
n	17	17	20	20	20
Mean (SD)	5.34 (6.30)	1.89 (5.43)	2.93 (1.39)	-0.20 (1.08)	-0.18 (0.70)
Median	3.10	-0.30	2.45	-0.45	-0.10
Min, Max	1.8, 23.9	-2.3, 18.4	1.5, 7.2	-1.8, 2.0	-1.4, 1.0

	SRP-9001 in Part 1 (N=20)		SRP-9001 in Part 2 (N=21)		
Visit / Statistics	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**	**Change from Part 2 Baseline**
Time to rise from the floor (Seconds)					
Baseline					
n	20		21		
Mean (SD)	5.10 (2.17)		3.56 (0.65)		
Median	4.30		3.40		
Min, Max	3.2, 10.4		2.7, 4.8		
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	4.95 (2.13)	-0.21 (1.13)	4.00 (1.29)	0.44 (0.91)	
Median	3.80	-0.40	3.80	0.30	
Min, Max	2.3, 9.6	-1.8, 2.8	2.4, 7.2	-0.9, 2.5	
Part 2 Baseline					
n	19		21		
Mean (SD)	4.86 (2.19)		4.02 (1.30)		
Median	3.80		3.90		
Min, Max	2.3, 10.0		2.4, 7.2		
Part 2 Week 48					
n	15	15	20	20	20
Mean (SD)	4.51 (2.42)	0.31 (2.12)	3.74 (1.72)	0.18 (1.33)	-0.28 (0.70)
Median	3.60	-0.50	3.15	-0.25	-0.30
Min, Max	2.7, 10.9	-1.4, 5.9	1.8, 8.1	-1.4, 4.2	-1.3, 2.0
Time of the 10-meter timed test (seconds)					
Baseline					
n	20		21		
Mean (SD)	5.35 (1.14)		4.83 (0.72)		
Median	5.00		4.70		
Min, Max	4.1, 8.9		4.0, 7.2		
Part 1 Week 48					
n	19	19	21	21	
Mean (SD)	6.08 (1.94)	0.70 (1.16)	4.85 (1.13)	0.01 (0.69)	
Median	5.50	0.38	4.60	-0.20	
Min, Max	4.1, 12.4	-0.6, 3.5	3.8, 9.1	-0.8, 1.9	
Part 2 Baseline					
n	19		21		
Mean (SD)	5.91 (1.89)		4.84 (1.12)		
Median	5.40		4.70		

Visit / Statistics	SRP-9001 in Part 1 (N=20)		SRP-9001 in Part 2 (N=21)		
	Value	Change from Baseline	Value	Change from Baseline	Change from Part 2 Baseline
Min, Max	4.0, 12.4		3.8, 9.1		
Part 2 Week 48					
n	16	16	20	20	20
Mean (SD)	5.61 (2.08)	0.56 (1.63)	4.71 (1.00)	-0.14 (0.75)	-0.14 (0.55)
Median	4.95	0.15	4.45	-0.15	-0.05
Min, Max	3.9, 12.1	-1.2, 5.2	3.3, 7.8	-1.9, 1.2	-1.5, 0.5

Max: maximum; Min: minimum; SD: standard deviation.
a N includes the patients with data points assessed at the specified time point
b Part 2 Baseline was defined as the last available assessment before Part 2 dosing (if no dosing in Part 2, then Part 1 Week 48 was used as the Baseline). Part 1 Baseline was used to calculate the change from Baseline

10.3 Serious Adverse Events

Table 33: Summary of Serious Adverse Events – Exposure Analysis Set

Age at Screening (years) [a]	Preferred Term (Verbatim Term)	Start Day [b]/ End Day [b]	Severity/ Relatedness	Outcome
Study 101 **–** No serious adverse events occurred during this study				
Study 102 – Part 1				
7.79	Rhabdomyolysis (Rhabdomyolysis)	16 / 20	Severe/ Yes	Recovered/ Resolved
4.96[c]	Liver injury (Acute liver injury)	50 / 83	Severe/ Yes	Recovered/ Resolved
4.96[c]	Rhabdomyolysis (Rhabdomyolysis)	156/ 158	Severe/ Yes	Recovered/ Resolved
7.85	Transaminases increased (Transaminitis [elevated LFT])	43 / 86	Severe/ Yes	Recovered/ Resolved
Study 102 – Part 2				
6	Femur fracture (Mid-shaft right femur fracture)	1197/	Severe/No	Not recovered/not resolved
8.82	Appendicitis (Appendicitis)	506 / 521	Severe/ No	Recovered/ Resolved
7.18	Femur fracture (Closed torus fractur of L femur)	479 / 635	Severe/ No	Recovered/ Resolved
6.08	Femur fracture (Closed nondisplaced subtrochaenteric fracture of left femur)	358 / 427	Severe/ No	Recovered/ Resolved
Study 103				
7.14	Transaminases increased (Transaminitis)	50 / 106	Severe/ Yes	Recovered/ Resolved
7.85	Vomiting (Vomiting secondary to AAV transfer)	1 / 7	Severe/ Yes	Recovered/ Resolved
8.95	Immune-mediated myositis (Muscle weakness secondary to immune-mediated adverse reaction)	35 / 100	Severe/ Yes	Recovered/ Resolved with sequelae
11.75[d]	Vomiting (Vomiting)	3 / 12	Severe/ Yes	Recovered/ Resolved
11.75[d]	Myocarditis (Myocarditis)	4 / 12	Severe/ Yes	Recovered/ Resolved with sequelae

AAV: adeno-associated virus; TEAE: treatment-emergent adverse event
a. Screening age = (date of informed consent – date of birth + 1)/365.25; for Study 102 Part 2, age at SRP 9001 infusion is used.
b. Day = Start date – First dose date + 1. If start date < first dose date, day = Start date – First dose date.
c. These events occurred in the same patient.
d. These events occurred in the same patient.

10.4 Datasets Used to External Control Analysis

10.4.1 CINRG Duchenne Natural History Study (DNHS)

The CINRG DNHS (NCT00468832) was a worldwide 20-center longitudinal study that prospectively collected the comprehensive natural history data of patients with DMD aged 2 to 28 years (McDonald 2013b). Assessments obtained every 3 months for 1 year, at 18 months, and annually thereafter included: clinical history, manual muscle testing, timed function tests, pulmonary function, and patient-reported outcomes/health-related quality of life instruments. The study was launched in 2006 and recruited patients in 2006–2009 and again in 2012–2016 (N=440).

10.4.2 Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD)

FOR-DMD (NCT01603407) was a multicenter, double-blind, parallel group, 36–60-month study, comparing 3 corticosteroid regimens in wide clinical use in DMD: daily prednisone (0.75 mg/kg/day), intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off), and daily deflazacort (0.9 mg/kg/day). Boys aged 4–7 years (n=225) were randomized to the 3 groups and completed a minimum of 3 years of treatment period with the expectation to remain on study drug (steroids) for up to 5 years. Assessments were collected once during screening period (1 to 3 months prior to Baseline visit), then again at Baseline (Month 0), Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. The study started in November 2012, and completed in November 2019. Patients on the daily regime (prednisone or deflazacort) were included as EC patients for the analysis (n=194).

10.4.3 Lilly Study (H6D-MC-LVJJ)

The Eli Lilly and Company-sponsored “A Study of Tadalafil for Duchenne Muscular Dystrophy” (NCT01865084) was a Phase 3 randomized, placebo-controlled, parallel 3-arm trial of tadalafil in patients with DMD in 63 sites in 15 countries. Patients with DMD (n=331), 7 to 14 years of age and taking glucocorticoids were randomized to the following groups: tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo (Victor 2017). Assessments were collected every 12 weeks up to 96 weeks; however, placebo-controlled data were only collected up to 48 weeks. The study started in September 2013 and completed in March 2016. Only placebo-treated patients were included as ECs for the analysis (n=131) as this was the only data available.