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Application Type	Supplemental BLA
STN	125781/34
CBER Received Date	December 21, 2023
PDUFA Goal Date	June 21, 2024
Division / Office	DCGT/OTP
Committee Chair	Mike Singer, M.D.
Clinical Reviewer(s)	Mike Singer, M.D.
Project Manager	Rachel Duddy, M.S.
Priority Review	Yes
Reviewer Name(s)	Thomas Zhou, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Boguang Zhen, Ph.D., Branch Chief OBPV/DB/TEB1
	John Scott, Ph.D., Director OBPV/DB
Applicant	Sarepta Therapeutics, Inc.
Established Name	Delandistrogene moxeparvovec
(Proposed) Trade Name	ELEVIDYS
Pharmacologic Class	Adeno-associated virus (AAV) vector-based gene therapy
Formulation(s), including Adjuvants, etc	ELEVIDYS is a suspension for intravenous (IV) infusion, supplied in a single-dose 10 mL vial. Each 10 mL vial contains a nominal concentration of 1.33×10^{13} vg/mL of delandistrogene moxeparvovec formulated in 200 mM sodium chloride, 13 mM tromethamine HCl, 7 mM tromethamine, 1 mM magnesium chloride, 0.001% poloxamer 188.

Dosage Form(s) and Route(s) of Administration	ELEVIDYS is administered by IV infusion. The dosage is determined by patient body weight, with recommended dose of 1.33×10^{14} vector genomes (vg) per kg for patients weighing 10 to 70 kg, and a maximum of 9.31×10^{15} vg per kg for patients weighing 70 kg or greater.
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the DMD gene

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GLOSSARY

AAV	Adeno-Associated Virus
AE	Adverse Event
AESI	Adverse Event of Special Interest
BLA	Biologics License Application
CI	Confidence Interval
DMD	Duchenne Muscular Dystrophy
FDA	Food and Drug Administration
IR	Information Request
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IV	Intra-Venous
LSM	Least Squares Mean
MAR	Missing At Random
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
MWR	Meter Walk/Run
NSAA	North Star Ambulatory Assessment
PROMIS	Patient-Reported Outcomes Measurement Information System
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sBLA	Supplemental Biologics License Application
SE	Standard Error
SV95C	Stride Velocity 95th Centile
TEAE	Treatment-Emergent Adverse Event

1. Executive Summary

This is a supplemental Biologics Licensing Application (sBLA) for Sarepta Therapeutics' adeno-associated virus (AAV) vector-based gene therapy SRP-9001 with trade name ELEVIDYS, indicated for the treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the DMD gene. SRP-9001 was granted accelerated approval for ambulatory patients aged 4 through 5 years with DMD on June 22, 2023. The primary purpose of this sBLA is to justify expansion of the approved indication to all DMD patients and to convert the original Biologics Licensing Application (BLA) from accelerated approval to traditional approval.

In support of this sBLA, the applicant submitted the results from two studies: SRP-9001-301 (EMBARK) Part 1 and SRP-9001-103 (ENDEAVOR). Study SRP-9001-301 is a Phase 3, ongoing, global, randomized, double-blinded, placebo-controlled, two-part study in 125 male subjects with DMD who were ≥ 4 to < 8 years of age. Study SRP-9001-103 is a Phase 1b, ongoing, multicenter, single-arm, open-label, single-dose study in 48 male subjects with DMD across 5 cohorts of various inclusion criteria. For this review, Study SRP-9001-301 constitutes the primary source of evidence for safety and efficacy of SRP-9001. Results from Study SRP-9001-301 were based on the safety and efficacy data with a data cut-off date of September 13, 2023.

Study SRP-9001-301 Part 1 enrolled a total of 125 male subjects with DMD, who were ambulatory and ≥ 4 to < 8 years of age. The subjects were randomized in a 1:1 ratio, in which 63 subjects were assigned to SRP-9001 and 62 subjects to placebo. The primary efficacy endpoint was change in North Star Ambulatory Assessment (NSAA) total score from baseline to Week 52. The key secondary endpoints included: 1) quantity of micro-dystrophin protein expression at Week 12 as measured by Western blot, 2) change in time to rise from the floor from baseline to Week 52, and 3) change in time of 10-meter timed test from baseline to Week 52. The least squares mean (LSM) difference in change in NSAA total score from baseline to Week 52 between the two treatment arms was 0.65 (95% CI: -0.45, 1.74) and was not statistically significant (p = 0.244). The quantity of micro-dystrophin protein expression at Week 12 as measured by Western blot was 34.29% in the SRP-9001 arm and below the limit of quantification in the placebo arm. The LSM difference in change in time to rise from the floor from baseline to Week 52 was -0.64 (95% CI: -1.06, -0.23), and in time of 10-meter timed test was -0.42 (95% CI: -0.71, -0.13). Since the primary efficacy endpoint failed to demonstrate statistical significance, statistical inference was not made on the secondary endpoints.

No deaths occurred in Study SRP-9001-301 Part 1. No subjects with any adverse events (AE) discontinued from the study. Nineteen subjects reported serious adverse events (SAE), of which 14 (22.2%) subjects in SRP-9001 reported 21 SAEs and 5 (8.1%) subjects in placebo reported 9 SAEs. Seven (11.1%) subjects reported 10 treatment-related SAEs.

I have verified the primary efficacy and key secondary analyses results for study SRP-9001-301 Part 1 as pre-specified in the Statistical Analysis Plan (SAP). Subgroup analyses by age group were performed.

Study SRP-9001-301 Part 1 did not meet the success criterion for the primary clinical endpoint of a statistically significant greater improvement in NSAA total score from baseline to Week 52 in the SRP-9001 group compared with placebo group. This study therefore did not satisfy the accelerated approval letter requirement, that the study "describe and verify clinical benefit of SRP-9001 in ambulatory patients with DMD…evidenced by effects such as improved North Star Ambulatory Assessment (NSAA) Total Score from baseline to Week 52."

Substantial evidence of effectiveness has not been provided for the functional endpoint of 10-MWR timed test due to inconsistent and opposing results observed in Study SRP-9001-102 Part 1 reviewed in the original BLA submission. Although SRP-9001 showed a numerical advantage in the secondary endpoint of time to rise from floor, these results cannot be interpreted at face value due to the lack of pre-specification and control of type 1 error.

Post-hoc subgroup analyses by age group did not demonstrate that clinical benefit in the primary and key secondary efficacy endpoints were substantial and consistent across age subgroups. The results from the two randomized studies include only ambulatory subjects, so there is no evidence of effectiveness in non-ambulatory subjects with DMD.

Overall, the results in Study SRP-9001-301 Part 1 were comparable to the results of Study SRP-9001-102 Part 1 reviewed in the original BLA submission. These results do not suggest there is substantial evidence to support the effectiveness of SRP-9001 for the expanded indication to all DMD patients and do not support the conversion of accelerated to traditional approval.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

DMD is an X-linked degenerative neuromuscular disease caused by mutations in the dystrophin gene. The incidence of DMD is approximately 1 in 5000 males worldwide. Typically diagnosed between 3 to 5 years of age, DMD is a progressive disease leading to loss of ambulation by 10 to 14 years of age and death from cardiac or respiratory failure in the 20s.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently available FDA approved therapies for DMD include EMFLAZA for use in children > 5 years of age; EXONDYS 51, VYONDYS 53, AMONDYS 45, and

VILTEPSO for use in a small proportion of the DMD population (approximately 30% combined) who have amenable exon-skipping mutations.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre- and post-submission regulatory activities associated with the sBLA.

Table 1. Summary of major pre- and post-submission regulatory activities.

Date	Milestone	Background information
09/28/2022	Original BLA 125781 submission	
05/12/2023	Advisory committee meeting	Eight committee members voted "Yes" and six voted "No" for the voting question: "Do the overall considerations of benefit and risk, taking into account the current uncertainties, support Accelerated Approval of SRP-9001?"
06/22/2023	Accelerated Approval letter issued	The accelerated approval required completion of Study SRP-9001-301 Part 1, to "describe and verify clinical benefit of SRP-9001 in ambulatory patients with DMD". The approval letter states that "clinical benefit is evidenced by effects such as improved North Star Ambulatory Assessment (NSAA) Total Score from baseline to Week 52…If this required post-marketing trial fails to verify that clinical benefit is conferred by [SRP-9001]…we may withdraw this approval."
12/21/2023	sBLA submission	
02/14/2024	sBLA filed and granted priority review	
06/21/2024	PDUFA action due date	

Source: FDA reviewer.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

The studies were conducted with good clinical practices. There were no issues with data integrity.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

For this review, Study SRP-9001-301 constitutes the primary source of evidence for safety and efficacy of SRP-9001. This review focuses on verifying the clinical benefit of the product, as required in the Accelerated Approval letter. This review also evaluates the consistency in the results for the clinical endpoints between studies SRP-9001-301 Part 1 and SRP-9001-102 Part 1, of which the latter was used as the basis for accelerated approval. The key secondary endpoint of quantity of micro-dystrophin protein expression at Week 12 as measured by western blot is considered an intermediate endpoint and does not demonstrate clinical function, so is not an appropriate endpoint for traditional approval and will not be a focus of this review.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The documents considered for statistical review include:

- Original submission in BLA 125781/0
  - Module 2.5 Clinical Overview
  - Module 5.3 Clinical Study Reports
  - Module 5 Datasets
- Supplemental submission in BLA 125781/34
  - Module 1.14 Labeling
  - Module 2.5 Clinical Overview
  - Module 5.3 Clinical Study Reports
  - Module 5 Datasets
- Amendment in BLA 125781/34.7
  - Module 1.11 Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Table 2 summaries the overview of clinical studies submitted in sBLA 125781.

Table 2. Overview of clinical studies submitted in sBLA 125781 for treatment of DMD with SRP-9001.

Study Identifier (Study Phase)	Objective(s) of the Study	Study Design	Study Population	Number of Subjects	Hypothesis Testing
SRP-9001-301 Part	Evaluate the effect of SRP-9001 on physical	Randomized, double-blinded, placebo-	Ambulatory males, ≥ 4 to < 8 years of	125 subjects randomized to SRP-9001 (N =	Superiority

1 (Phase 3)	function as assessed by change in NSAA total score from baseline to Week 52	controlled, single dose	age, with DMD	63) or placebo (N = 62)	
SRP-9001-103 (Phase 1b)[1]	Evaluate micro-dystrophin expression from SRP-9001 as measured by western blot of biopsied muscle tissue at 12 weeks post infusion	Open-label, single-arm, single dose	Male subjects of various ages and ambulation with DMD (see 'Number of Subjects' column for details)	48 subjects across 5 cohorts: Cohort 1: 20 ambulatory subjects, aged ≥ 4 to < 8 years Cohort 2: 7 ambulatory subjects aged ≥ 8 to < 18 years Cohort 3: 6 non-ambulatory subjects Cohort 4: 7 ambulatory subjects aged ≥ 3 to < 4 years Cohort 5: 6 ambulatory subjects aged ≥ 4 to < 9 years (Cohort 5a) and 2 non-ambulatory subjects (Cohort 5b) with mutations involving exons 1-17	None

[1]Study SRP-9001-103 consists of a total of 7 cohorts. Cohort 6 is planned to consist of 6 ambulatory subjects aged ≥ 2 to < 3 years. Cohort 7 is planned to consist of 6 non-ambulatory subjects with moderate to severe pulmonary impairment. As of data cutoff on September 13, 2023, 1 subject in Cohort 7 has been enrolled and dosed, and no safety or efficacy are available for Cohorts 6 and 7.

Source: FDA reviewer.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

For the original BLA 125781 submission, an advisory committee meeting was held on May 12, 2023. The question posed to the committee was: "Do the overall considerations of benefit and risk, taking into account the existing uncertainties, support accelerated approval of SRP-9001, using as a surrogate endpoint expression of Sarepta's micro-dystrophin at Week 12 after administration, for the

treatment of ambulatory patients with DMD with a confirmed mutation in the DMD gene?" Eight committee members voted "Yes" and six voted "No" for the voting question. For further details, please refer to the statistical memo of the original BLA 125781 submission by Dr. Cong Wang.

5.5 Literature Reviewed (if applicable)

Pattern imputation with delta adjustment method for the tipping point analysis as described by Ratitch (2013) will be used:
Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics 2013; 121(6): 337-47.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom:
Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997; 53(3): 983-997.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study #1: SRP-9001-301 Part 1

Study SRP-9001-301 is the pivotal study which constitutes the primary evidence of safety and efficacy of SRP-9001 in the treatment of male ambulatory patients with DMD aged ≥ 4 to < 8 years old.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of this study is to evaluate the effect of SRP-9001 on physical function as assessed by the NSAA score.

Secondary objectives include:

- To evaluate the effect of SRP-9001 on physical function as assessed by the number of skills gained or improved on the NSAA
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 1) as measured by western blot of biopsied muscle tissue
- To evaluate the effect of SRP-9001 on timed function tests as assessed by measuring:
    - Time to rise from the floor
    - 100-meter walk/run (MWR)
    - Time to ascend 4 steps
    - 10-MWR
- To evaluate the effect of SRP-9001 on Stride velocity 95th centile (SV95C) as measured by a wearable device
- To evaluate subject (parent/caregiver proxy) reported Mobility and Upper Extremity Function using the Patient-Reported Outcomes Measurement Information System (PROMIS) tool

6.1.2 Design Overview

SRP-9001-301 is a Phase 3, randomized, double-blind, placebo-controlled, two-part study of systemic gene delivery of SRP-9001 in 125 male ambulatory subjects with DMD, who are ≥ 4 to < 8 years of age. The subjects are randomized in a 1:1 ratio to receive a single intravenous (IV) infusion of either SRP-9001 or placebo. The total duration of each subject's participation in the study is expected to be approximately 108 weeks, inclusive of an up to 4-week pre-infusion period and a 52-week treatment and follow-up period in Part 1 and Part 2 of the study. In Part 2, subjects who received placebo in Part 1 will receive SRP-9001, and subjects who received SRP-9001 in Part 1 will receive placebo in order to maintain blinding throughout the study.

6.1.3 Population

Key eligibility criteria are described below.

Selected inclusion criteria:

- Is male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of randomization.
- Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the DMD gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.
    - Mutations between or including exons 1-17 are not eligible.
    - In-frame deletions, in-frame duplications, and variants of uncertain significance ("VUS") are not eligible.
    - Mutations fully contained within exon 45 (inclusive) are not eligible.
- Able to cooperate with motor assessment testing.
- Has a NSAA score > 16 and < 29 at the Screening visit.
- Has a time to rise from floor < 5 seconds at the Screening visit.

Selected exclusion criteria:

- Has left ventricular ejection fraction < 40% on the screening ECHO or clinical signs and/or symptoms of cardiomyopathy.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study treatments are administered via a single IV infusion through a peripheral limb vein. The investigational product is SRP-9001 (1.33×10^{14} vg/kg). The control product is placebo (saline, 0.9% sodium chloride solution).

In addition, all subjects will be on a stable daily dose of oral corticosteroids for at least 12 weeks before the Screening visit. The day before the infusion (SRP-9001 or placebo), the subject will be started on additional steroid for

immunosuppression, continued at this level for at least 60 days after the infusion. Following these 60 days, subjects may be tapered off of the added steroid and return to their baseline dose of corticosteroids for DMD and will remain on their stable dose (except for modifications to accommodate changes in weight) through the remainder of the study.

6.1.6 Sites and Centers

This study is conducted at 42 centers in 9 countries (Belgium, Germany, Hong Kong, Italy, Japan, Spain, Taiwan, United Kingdom, United States).

6.1.7 Surveillance/Monitoring

A program-wide independent Data Monitoring Committee (DMC) will assist in the monitoring of safety, efficacy, data quality, and the integrity of study.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Change in NSAA total score from baseline to Week 52.
  The NSAA consists of 17 different functional activities, in which each activity is graded: 2 = achieves goal without any assistance, 1 = modified method but achieves goal independent of physical assistance from another person, and 0 = unable to achieve goal independently. The NSAA total score is defined as the sum of all 17 items ranges from 0 (worst) to 34 (best).

Key secondary endpoints:

- Quantity of micro-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 10-meter walk/run (10MWR) from baseline to Week 52

Other secondary endpoints:

- Change in SV95C from baseline to Week 52
- Change in time of 100-meter timed test from baseline to Week 52
- Change in time to ascend 4 steps from baseline to Week 52
- Change in PROMIS Mobility score from baseline to Week 52
- Change in PROMIS Upper Extremity score from baseline to Week 52
- Number of skills gained or improved at Week 52 as measured by the NSAA

6.1.9 Statistical Considerations & Statistical Analysis Plan

<u>Treatment Assignment:</u>
Subjects were randomized in a 1:1 ratio to either SRP-9001 or placebo arm. Randomization was stratified by age group at the time of randomization (≥ 4 to < 6 years or ≥ 6 to < 8 years) and NSAA total score (≤ 22 or > 22) at Screening.

Approximately 50% of subjects should be in the ≥ 4 to < 6 years age group at the time of randomization.

Statistical Hypotheses:
The null and alternative statistical hypotheses for the primary efficacy endpoint and key secondary endpoints are summarized in Table 3. Although the alternative hypotheses are two-sided, only superiority of SRP-9001 over placebo will be of interest.

Table 3. Statistical hypotheses for primary and key secondary efficacy endpoints in Study SRP-9001-301.

Type of Endpoint	Endpoint	Null	vs.	Alternative
Primary	Change in NSAA total score from baseline to Week 52[1]	$H_0: \mu_{SRP} = \mu_{placebo}$	vs.	$H_1: \mu_{SRP} \neq \mu_{placebo}$
Key secondary	Quantity of micro-dystrophin protein expression at Week 12 as measured by western blot[2]	$H_0: \theta_{SRP} = \theta_{placebo}$	vs.	$H_1: \theta_{SRP} \neq \theta_{placebo}$
Key secondary	Change in time to rise from the floor from baseline to Week 52[3]	$H_0: \lambda_{SRP} = \lambda_{placebo}$	vs.	$H_1: \lambda_{SRP} \neq \lambda_{placebo}$
Key secondary	Change in time of 10MWR from baseline to Week 52[4]	$H_0: \lambda_{SRP} = \lambda_{placebo}$	vs.	$H_1: \lambda_{SRP} \neq \lambda_{placebo}$

[1]Mean change in NSAA total score from baseline to Week 52 is denoted by μ_{SRP} in the SRP-9001 arm and $\mu_{placebo}$ in the placebo arm.
[2]Mean quantity of micro-dystrophin protein expression at Week 12 is denoted by θ_{SRP} in the SRP-9001 arm and $\theta_{placebo}$ in the placebo arm.
[3]Mean change in time to rise from the floor from baseline to Week 52 is denoted by λ_{SRP} in the SRP-9001 arm and $\lambda_{placebo}$ in the placebo arm.
[4]Mean change in time of 10MWR from baseline to Week 52 is denoted by λ_{SRP} in the SRP-9001 arm and $\lambda_{placebo}$ in the placebo arm.
Source: FDA reviewer.

Sample Size:
Sample size for this study was based on the power for the primary efficacy endpoint, change in NSAA total score from baseline to Week 52. Assuming a standard deviation of 3.5 in all subjects and a 10% dropout rate at Week 52, with a Type I error of 0.05 (2-sided), a sample size of 120 with 1:1 randomization ratio will provide approximately 90% power to detect a mean difference of 2.2 in change in NSAA total score from baseline to Week 52 between the SRP-9001 arm and placebo arm.

Analysis Population:
The analysis populations are summarized in Table 4. The primary and key secondary efficacy analyses were conducted on the Modified Intent-to-Treat (mITT) set.

Table 4. Analysis populations for statistical analyses in Study SRP-9001-301.

Population	Description
All subjects	All screened subjects (not including those enrolled under a regional addendum).
Intent-to-treat (ITT)	All randomized subjects (not including those enrolled under a regional addendum), with treatment group designated according to randomization.
Modified Intent-to-Treat (mITT)	All randomized subjects who receive study treatment (not including those enrolled under a regional addendum), with treatment group designated according to randomization. The mITT population will be the analysis population for efficacy endpoints.
Safety	All subjects who receive study treatment (not including those enrolled under a regional addendum), with treatment group designated according to the treatment they received.

Source: Adapted from BLA 125781/34; Module 5.3.5.1, Statistical Analysis Plan V2.0, p.19.

Statistical Methodology:

Primary efficacy endpoint: Change in NSAA total score from baseline to Week 52

A restricted maximum likelihood (REML)-based Mixed Model Repeated Measures (MMRM) will be used to compare SRP-9001 with placebo. In this model, the response vector consists of the change from baseline in NSAA total score at each post-baseline visit in Part 1 of Study SRP-9001-301. The model will include the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group at the time of randomization (categorical), baseline NSAA total score, age group at the time of randomization by visit interaction, 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 matrix. 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 (Kenward 1997) will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random.

Key secondary endpoint: Quantity of micro-dystrophin protein expression at Week 12 as measured by western blot

A re-randomization test will be performed, which will use a 2-sample Welch t-test as the test statistic. The Welch t-test statistic uses the variance estimated separately for each group. The null distribution of the Welch t-test statistic will be estimated using 10,000 re-randomization datasets based on the observed data set. In each re-randomization dataset, the probability of receiving either treatment or placebo is assigned 0.5 for every patient, and a 2-sample Welch t-test statistic

will be calculated from the resulting dataset. The 2-sided p-value will be calculated as twice the proportion of Welch t-test statistics from 10,000 re randomization datasets that are as extreme as or more extreme than the Welch t-test statistic obtained in the actual data set. In this re-randomization, seed for simulation will be fixed at 1100.

Key secondary endpoints: Change in timed functional tests from baseline to Week 52, rise from the floor and 10-MWR

An MMRM analysis similar to the one for the primary endpoint will be performed to compare the two treatment groups for each of the secondary endpoints for timed functional assessments, with baseline NSAA raw total score replaced with the corresponding baseline for the secondary timed functional endpoint, as well as NSAA group at the time of screening (≤ 22 vs. > 22) added as a covariate.

Supplementary analysis:

The same method used in primary analysis will be applied to the ITT set.

Handling of intercurrent events:

Since SRP-9001 is a single administration treatment and there is no rescue treatment for DMD, treatment discontinuation and start of rescue medication are not applicable. Any changes in corticosteroid treatment will be analyzed using a treatment policy estimand strategy. The data will be collected and analyzed regardless of whether an intercurrent event has occurred or not.

Handling of missing data:

Unless explicitly stated, missing data are not imputed.

- For NSAA assessment, if 3 or fewer of the 17 items are missing, the NSAA total score will be calculated as the average score of the completed items multiplied by 17. The total NSAA score will be treated as a missing value when 4 or more items are missing. No individual item score will be imputed even if it is missing unless specified otherwise.
- For time to rise from the floor assessment, if it is missing and the item score for item 12: rise from floor in NSAA assessment is equal to 0, the missing time to rise from the floor will be imputed as the maximum value for the reasonable range of time to rise from the floor (30 seconds).
- For 10-meter walk/run assessment, if it is missing and the item score for item 2: walk in NSAA assessment is equal to 0, the missing 10-meter walk/run will be imputed as the maximum value for the reasonable range of 10-meter walk/run (30 seconds).
- For time to ascend 4 steps assessment, if it is missing and the item scores for item 6: climb box step right and item 8: climb box step left in NSAA assessment are both equal to 0, the missing time to ascend 4 steps will be imputed as the maximum value for the reasonable range of time to ascend 4 steps (30 seconds).
- For 100-meter walk/run assessment, if it is missing and the item score for item 2: walk in NSAA assessment is equal to 0, the missing 100-meter

walk/run will be imputed as 240 seconds to approximate the largest value observed for this population in this program to date.

Sensitivity analysis to assess missing data impact:
Tipping point multiple imputation analysis will be conducted to assess the impact of missing data. Because this is a one-time [gene therapy] treatment, the applicant asserted that it can be assumed that treatment effect of patient discontinuing from the study or missing visits will remain the same had the patient stayed in the trial. When the delta-drift is assumed to be zero, the imputation corresponds to the missing at random (MAR) assumption and it can be assumed that treatment effect of patient discontinuing from the study or missing visits will remain the same had the patient stayed in the trial. Tipping Point Multiple-Imputation Analysis with non-zero delta-drift would be explored to assess the robustness of the primary analysis conclusions to deviations from the MAR assumption.

The Variant 3 of the pattern imputation with delta adjustment method for the tipping point analysis as described by Ratitch (2013) will be used. In this approach, missing data are first imputed for all visits under the MAR assumption, and then the worsening/shift is applied. This is repeated with increasing the delta-shift (worsening) until the result is no longer statistically significant. Specifically, for a given constant, c, the tipping-point analysis is conducted in a fashion similar to that used in standard multiple imputation, whereby m (= 20) complete datasets are randomly generated using the original observed dataset. These m complete datasets are subsequently analyzed using the primary model, and the results of those analyses are then combined using Rubin's rules. The construction and analysis of these m (= 20) datasets requires 4 primary steps:

1. Impute intermittent missing using Markov chain Monte Carlo (MCMC). This will be accomplished for each treatment group using "proc mi" within Statistical Analysis System (SAS) 9.4 or higher by utilizing the options "mcmc chain=multiple impute=monotone;" in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 90013011. This step will generate m monotone-missing datasets.
2. Impute monotone missing data. Applying parametric regression to the monotone-missing datasets generated from step 1, impute all the missing values. This will be accomplished for each treatment group using "proc mi" within SAS 9.4 or higher utilizing the option "monotone reg", in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 90013011. This step will generate m complete datasets.
3. Subtract a constant c from each of the imputed values of the active arm (to the detriment of active). The constant enables the assessment of the tipping-point aspect of the procedure.

4. Analyze each of the post-imputation complete datasets using the primary model, obtaining point estimate for the mean of interest (eg, change-from-baseline treatment difference at Week 52) and the associated variance.

This procedure will be repeated (using the same m imputed datasets) until the smallest c is found such that the significant result turns nonsignificant at the alpha level used for primary analysis. This tipping point value c provides a measure of robustness of the primary result. A relatively large value of c implies better robustness of the primary analysis against the impact of missing data in the study. It is noted that when c=0 the tipping point analysis described above corresponds to an analysis conducted under the assumption that the missing data are MAR. For values of c larger than 0, the tipping point analyses do not assume that the missing values follow a MAR mechanism. In fact, the analysis is based on a special missing not at random (MNAR) mechanism in which all missing data in the active arm are assumed to have a worse response by a constant amount of c than the values under MAR, while the missing data in the control group are assumed to be the same as that obtained under MAR.

Reviewer comment: The planned tipping point analyses were not applicable because there was no overall significant result to 'tip'.

Subgroup Analyses:
For the primary endpoint, subgroup analysis will be conducted with respect to all subgroup variables listed in Table 5. For the secondary endpoints, subgroup analysis will be conducted with respect to the age and NSAA group subgroup variables.

Table 5. Subgroups defined with baseline characteristics for subgroup analyses of primary and secondary endpoints in Study SRP-9001-301.

Subgroup Variable	Subgroups
Age group (at the time of randomization)	≥ 4 to < 6 years, ≥ 6 to < 8 years
NSAA group (at the time of screening)	NSAA total score ≤ 22, NSAA total score > 22
Race	White, Non-white (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander)
BMI group	< 20, ≥ 20 kg/m^2

Source: BLA 125781/34; Module 5.3.5.1, Statistical Analysis Plan V2.0, p.30.

For each category of a subgroup variable, an MMRM similar to the primary analysis model will be fitted using subset data. For age group subgroup analysis, age group and age group by visit interaction would be removed from the MMRM model as a covariate.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The analysis populations are summarized in Table 6. The ITT set consisted of 131 subjects. The mITT set and the safety set consisted of 125 subjects (63 subjects in SRP-9001 and 62 subjects in placebo).

Table 6. Subject disposition in each analysis set in Study SRP-9001-301.

Analysis set	SRP-9001, N	Placebo, N	Total, N
ITT	65	64	131[1]
mITT	63	62	125
Safety	63	62	125

[1]Two subjects were randomized but did not have treatment assignment recorded.
Source: FDA reviewer.

6.1.10.1.1 Demographics

The baseline demographics in the mITT population are summarized in Table 7. The median age was 6.20 years old in SRP-9001 group and 6.06 years old in placebo group. In the SRP-9001 group, 30 (47.6%) subjects were in the 4-5 years old age category and 33 (52.4%) in the 6-7 years old category. The SRP-9001 group consisted primarily of white (77.8%) and non-Hispanic (74.6%) subjects. The demographics were well balanced between the two treatment groups.

Table 7. Baseline demographics (mITT population) in Study SRP-9001-301.

Parameter	SRP-9001 N = 63	Placebo N = 62	Total N = 125
Age (years) at randomization, n	63	62	125
Mean (SD)	5.98 (1.06)	6.08 (1.05)	6.03 (1.05)
Median (Min, Max)	6.20 (4.07, 7.87)	6.06 (4.03, 7.99)	6.10 (4.03, 7.99)
Age group at randomization, n (%)	-	-	-
4-5 years old	30 (47.6%)	29 (46.8%)	59 (47.2%)
6-7 years old	33 (52.4%)	33 (53.2%)	66 (52.8%)
Sex, n (%)	-	-	-
Male	63 (100.0%)	62 (100.0%)	125 (100.0%)
Race, n (%)	-	-	-
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)
Asian	8 (12.7%)	11 (17.7%)	19 (15.2%)
Black or African American	0 (0%)	2 (3.2%)	2 (1.6%)

Native Hawaiian or other Pacific Islanders	0 (0%)	0 (0%)	0 (0%)
White	49 (77.8%)	46 (74.2%)	95 (76.0%)
Multiple	1 (1.6%)	0 (0%)	1 (0.8%)
Other	2 (3.2%)	1 (1.6%)	3 (2.4%)
Not Reported	3 (4.8%)	2 (3.2%)	5 (4.0%)
Race group, n (%)	-	-	-
White	49 (77.8%)	46 (74.2%)	95 (76.0%)
Non-white	11 (17.5%)	14 (22.6%)	25 (20.0%)
Missing	3 (4.8%)	2 (3.2%)	5 (4.0%)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	15 (23.8%)	8 (12.9%)	23 (18.4%)
Not Hispanic or Latino	47 (74.6%)	53 (85.5%)	100 (80.0%)
Not reported	0 (0%)	1 (1.6%)	1 (0.8%)
Unknown	1 (1.6%)	0 (0%)	1 (0.8%)

Abbreviations: SD = Standard Deviations; Min = Minimum; Max = Maximum
Source: FDA reviewer.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The baseline disease and medical characteristics in the mITT population are summarized in Table 8. On average, the subjects had 2.6 years since DMD diagnosis and 1.02 years since corticosteroid treatment started. The genetic mutation type was primarily large deletion, with 45 (71.4%) subjects in SRP-9001 group and 41 (66.1%) in placebo group, followed by small mutation, with 15 (23.8%) in SRP-9001 and 18 (29.0%) in placebo. In the SRP-9001 group, median NSAA total score at baseline was 23.5, median 10-MWR test was 4.6 seconds, and median time to rise from floor was 3.35 seconds. In the placebo group, the median NSAA total score at baseline was 22.5, median 10-MWR test was 4.9 seconds, and median time to rise from floor was 3.63 seconds. The disease and medical characteristics were well balanced between the two treatment groups.

Table 8. Baseline disease and medical characteristics (mITT population) in Study SRP-9001-301.

Parameter	SRP-9001 N = 63	Placebo N = 62	Total N = 125
Height (cm), n	63	62	125
Mean (SD)	108.64 (6.74)	110.68 (7.44)	109.65 (7.14)
Median (Min, Max)	109.00 (93.5, 127.0)	110.15 (95.2, 127.5)	109.30 (93.5, 127.5)
Weight (kg), n	63	62	125
Mean (SD)	21.29 (4.62)	22.37 (6.42)	21.83 (5.59)

Median (Min, Max)	20.20 (13.5, 38.5)	20.55 (14.1, 41.6)	20.20 (13.5, 41.6)
Body Mass Index (kg/m^2), n	63	62	125
Mean (SD)	17.85 (2.20)	17.89 (3.20)	17.87 (2.73)
Median (Min, Max)	17.36 (13.7, 24.9)	16.56 (13.5, 26.9)	17.26 (13.5, 26.9)
BMI (kg/m^2) category, n (%)	-	-	-
< 20	53 (84.1%)	52 (83.9%)	105 (84.0%)
≥ 20	10 (15.9%)	10 (16.1%)	20 (16.0%)
Years since diagnosis of DMD, n	63	62	125
Mean (SD)	2.62 (1.73)	2.60 (1.78)	2.61 (1.75)
Median (Min, Max)	2.40 (0.0, 6.7)	2.12 (0.2, 7.6)	2.27 (0.0, 7.6)
Years since corticosteroid treatment started, n	63	62	125
Mean (SD)	1.07 (0.92)	0.97 (0.83)	1.02 (0.88)
Median (Min, Max)	0.96 (0.23, 6.17)	0.66 (0.24, 4.01)	0.77 (0.23, 6.17)
Genetic mutation type, n (%)	-	-	-
Large deletion	45 (71.4%)	41 (66.1%)	86 (68.8%)
Large duplication	3 (4.8%)	3 (4.8%)	6 (4.8%)
Small mutation	15 (23.8%)	18 (29.0%)	33 (26.4%)
NSAA total score, n	63	62	125
Mean (SD)	23.10 (3.75)	22.82 (3.78)	22.96 (3.75)
Median (Min, Max)	23.5 (14.0, 32.0)	22.5 (15.5, 30.0)	23.0 (14.0, 32.0)
10-Meter timed test, n	63	62	125
Mean (SD)	4.82 (0.79)	4.92 (0.73)	4.87 (0.76)
Median (Min, Max)	4.60 (3.2, 6.9)	4.90 (3.7, 7.0)	4.80 (3.2, 7.0)
100-Meter timed test, n	63	59	122
Mean (SD)	60.67 (15.55)	63.00 (17.01)	61.80 (16.25)
Median (Min, Max)	58.40 (38.0, 129.2)	58.10 (38.7, 118.1)	58.20 (38.0, 129.0)
Time to rise from floor, n	63	62	125
Mean (SD)	3.52 (0.81)	3.60 (0.68)	3.56 (0.75)
Median (Min, Max)	3.35 (1.9, 5.8)	3.63 (2.3, 5.0)	3.50 (1.9, 5.8)
Time to ascend 4 steps, n	63	61	124
Mean (SD)	3.17 (1.01)	3.37 (1.09)	3.27 (1.05)
Median (Min, Max)	3.00 (1.6, 7.1)	3.10 (1.5, 7.1)	3.10 (1.5, 7.1)

SV95C, n	61	62	123
Mean (SD)	1.82 (0.30)	1.77 (0.29)	1.79 (0.29)
Median (Min, Max)	1.79 (1.1, 2.5)	1.79 (1.1, 2.4)	1.79 (1.1, 2.5)
PROMIS score in mobility, n	60	60	120
Mean (SD)	4.29 (0.42)	4.20 (0.40)	4.24 (0.41)
Median (Min, Max)	4.37 (3.0, 5.0)	4.20 (3.2, 5.0)	4.33 (3.0, 5.0)
PROMIS score in upper extremity, n	60	59	119
Mean (SD)	3.82 (0.94)	3.60 (0.93)	3.71 (0.93)
Median (Min, Max)	4.00 (1.8, 5.0)	3.75 (1.6, 5.0)	4.00 (1.6, 5.0)

Abbreviations: SD = Standard Deviations; Min = Minimum; Max = Maximum
Source: FDA reviewer.

Reviewer comment: Table 8 summarizes the descriptive statistics for NSAA total score at baseline, whereas Table 3 of the SRP-9001-301 CSR reports the NSAA total score at screening; the scores are similar. Because the primary efficacy endpoint is calculated as change from baseline, the NSAA total score at baseline is reported.

Because age is an important stratification factor in this study, NSAA total score at baseline was also examined by age group. The 4-5 year old age group had a median NSAA total score of 22 and the 6-7 year old group had a median of 24.25. The NSAA total score was balanced between treatment groups within each age group.

6.1.10.1.3 Subject Disposition
A total of 173 subjects were screened for the study, of which 42 subjects were screen failures. 131 subjects were randomized, of whom 6 subjects were not dosed. The 6 randomized but not dosed subjects all discontinued the study prior to dosing, and consisted of 2 subjects assigned to SRP-9001, 2 subjects assigned to placebo, and 2 subjects whose treatment assignment was not recorded. The reason for discontinuation included 2 subjects with infection, 3 subjects with COVID-19, and 1 subject withdrawal due to study schedule.

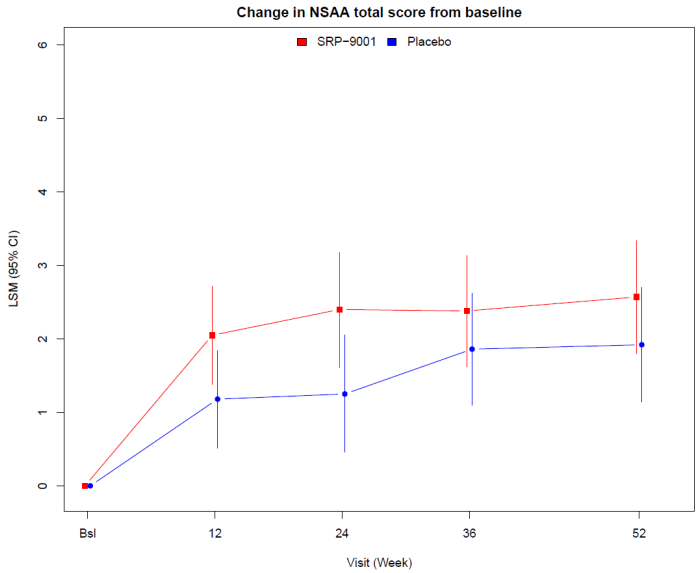
The mITT set is the primary analysis population, which consisted of 125 subjects (63 subjects in SRP-9001 and 62 subjects in placebo) who received study treatment and completed Part 1 of the study. No subjects discontinued from the study prior to Part 1 completion.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)
The primary efficacy endpoint of change in NSAA total score from baseline to Week 52 was analyzed using REML-based MMRM. The LSM change in NSAA total score from baseline at Week 52 was 2.57 (95% CI: 1.80, 3.34) in the SRP-

9001 group and 1.92 (95% CI: 1.14, 2.70) in the placebo group, respectively. The difference in LSM change from baseline at Week 52 between treatment groups was 0.65 (95% CI: -0.45, 1.74) and was not statistically significant (p = 0.244). Results of the MMRM analysis at each study visit are summarized in Table A1. Figure 1 illustrates the LSM change in NSAA total score from baseline over time in each treatment group.

Figure 1. LSM change in NSAA total score from baseline over time.



Source: FDA reviewer.

Because the ITT set includes the 6 subjects who are randomized but not dosed and who do not have any post-baseline assessments, a supplemental analysis based on the ITT set yields the same results as the primary analysis based on the mITT set.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary endpoint: Micro-dystrophin protein expression at Week 12 as measured by Western Blot

This is the first key secondary endpoint. For the SRP-9001 group, the mean micro-dystrophin level (% control) by Western blot adjusted to muscle content at Week 12 was 34.29%. For the placebo group, the mean micro-dystrophin level was below the level of quantification.

For traditional approval, the applicant intends to use the results of the other two key secondary endpoints, change in time to rise from the floor from baseline to Week 52 and change in time of 10-MWR from baseline to Week 52. An MMRM analysis similar to the one for the primary endpoint was performed to compare the two treatment groups for each of the two key secondary endpoints. Since the study did not demonstrate a statistically significant treatment effect on the

primary efficacy endpoint, statistical inference on the secondary endpoints was not performed. Treatment differences are summarized descriptively.

Key secondary endpoint: Time to rise from floor
The LSM change in time to rise from floor from baseline at Week 52 was -0.27 (95% CI: -0.56, 0.02) in the SRP-9001 group and 0.37 (95% CI: 0.08, 0.67) in the placebo group, respectively. The difference in LSM change from baseline at Week 52 between treatment groups was -0.64 (95% CI: -1.06, -0.23). Results of the MMRM analysis at each study visit are summarized in Table A2.

Key secondary endpoint: Time of 10-MWR test
The LSM change in time of 10-MWR test from baseline at Week 52 was -0.34 (95% CI: -0.55, -0.14) in the SRP-9001 group and 0.08 (95% CI: -0.13, 0.29) in the placebo group, respectively. The difference in LSM change from baseline at Week 52 between treatment groups was -0.42 (95% CI: -0.71, -0.13). Results of the MMRM analysis at each study visit are summarized in Table A3.

Reviewer comment: Analyses results for the two key secondary endpoints numerically favor SRP-9001. However, because the primary efficacy analysis was not statistically significant, the results for secondary endpoints are subject to inflated type 1 error rates.

The FDA's results for both key secondary endpoints, time to rise from floor (Table A2) and time of 10-MWR test (Table A3), were slightly different from the Applicant's results in CSR Tables 14.2.2.4.1.1 and 14.2.2.5.1.1, respectively. The applicant's analysis code to analyze these two key secondary endpoints for the overall population was slightly different from the one they used for the primary endpoint and the subgroup analyses for these two secondary endpoints. The Applicant also did not include an age group by visit interaction term in the MMRM model for the analyses of the overall population, which does not adhere to the SAP. The discrepancy in results is minor and does not change the overall statistical conclusions.

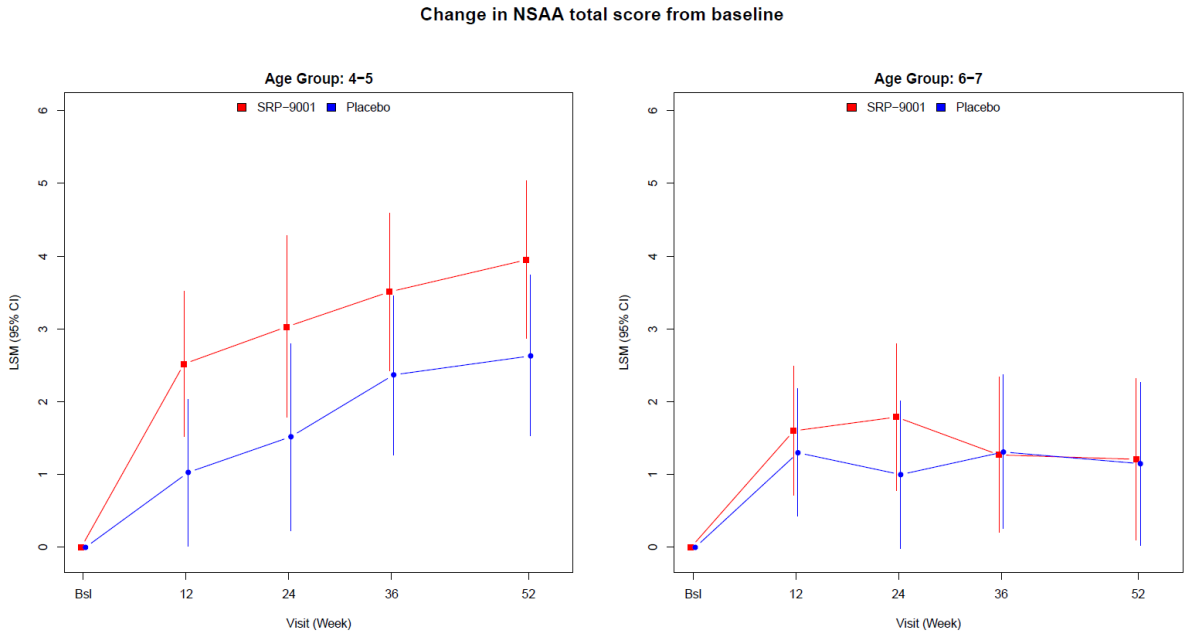
6.1.11.3 Subpopulation Analyses

Age is an important prognostic factor in the progression of DMD. The treatment effect on the primary and key secondary efficacy endpoints were further evaluated within the two age subgroups, 4-5 years old and 6-7 years old. Treatment effects seemed to result in contradictory conclusions between the primary and key secondary efficacy endpoints. For example, the primary endpoint of NSAA total score showed a greater qualitative improvement in the 4-5 age group, while the key secondary endpoint of time to rise from floor showed a greater treatment effect in the 6-7 age group. Results from the subgroup analyses are inconclusive.

Figure 2 illustrates the change from baseline in NSAA total score over visits by age subgroups. In the 4-5 age group, an increasing trend in NSAA total score

was observed in both SRP-9001 and placebo groups. The LSM treatment difference in change from baseline to Week 52 was 1.32 (95% CI: -0.23, 2.87) in this age subgroup; this treatment effect was observed to be consistent over time. There was no observable trend or treatment effect in the 6-7 age group.

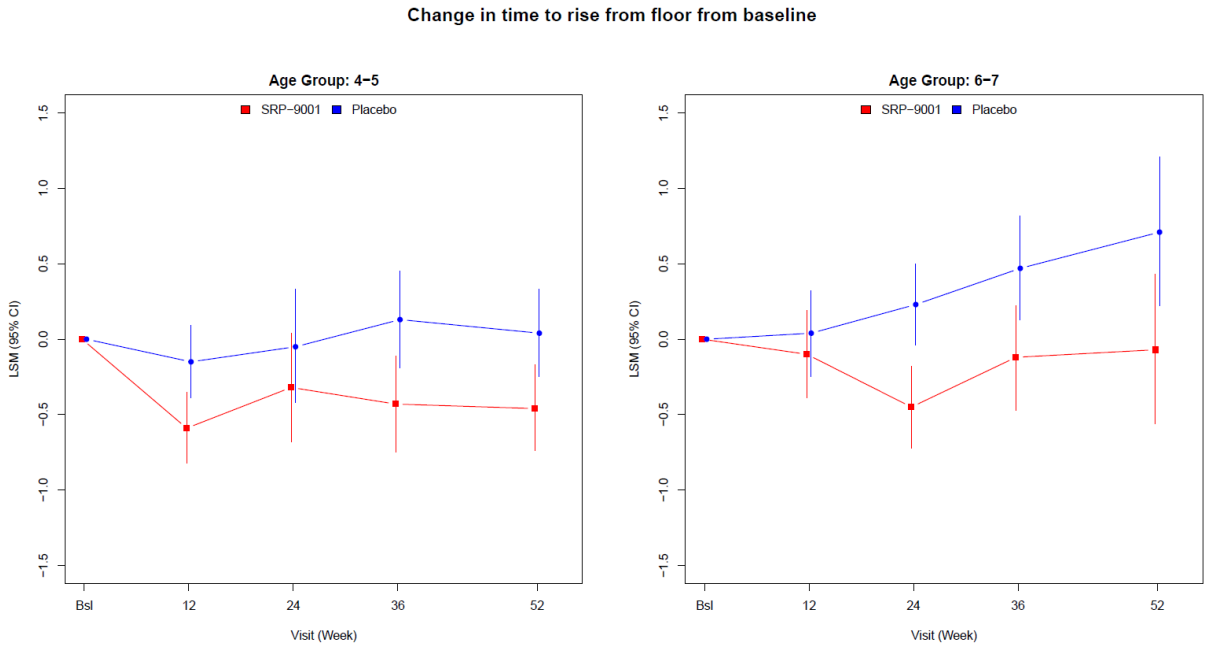
Figure 2. LSM change from baseline in NSAA total score over time by age subgroups.



Source: FDA reviewer.

Figure 3 illustrates the change from baseline in time to rise from floor over visits by age subgroups. In both the 4-5 age group and 6-7 age group, a treatment effect in time to rise from floor was observed between SRP-9001 and placebo. The LSM treatment difference in change from baseline to Week 52 was -0.50 (95% CI: -0.90, -0.09) in the 4-5 age group and -0.78 (95% CI: -1.48, -0.08) in the 6-7 age group.

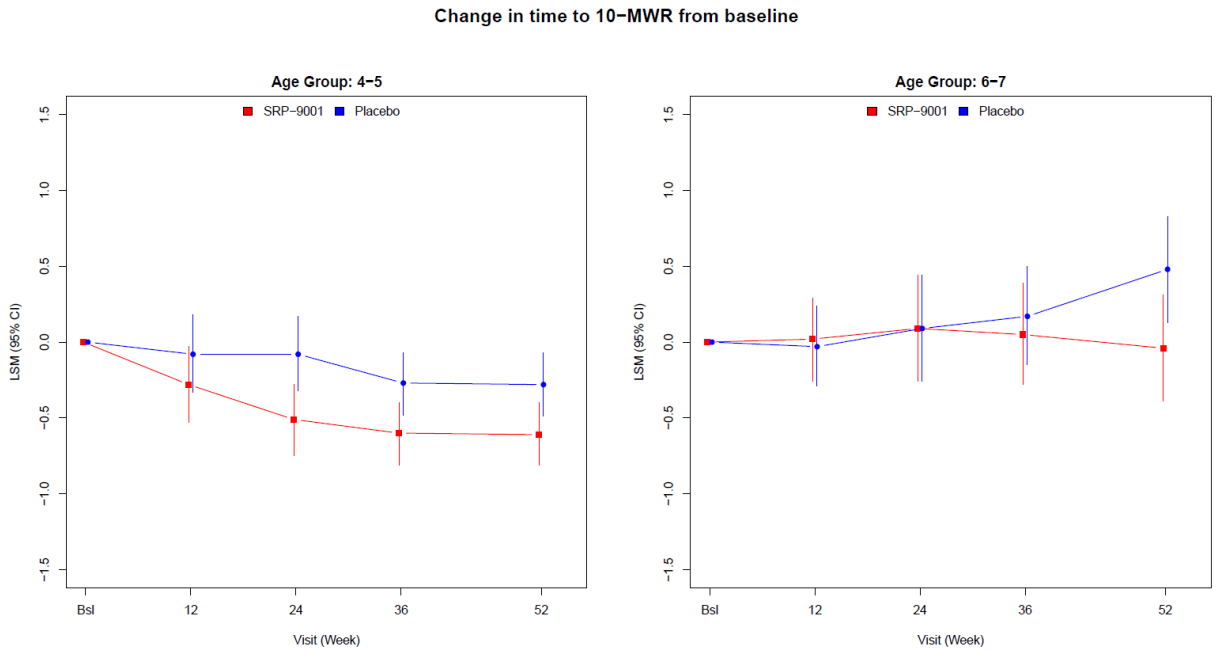
Figure 3. LSM change from baseline in time to rise from floor (seconds) over time by age subgroups.



Source: FDA reviewer.

Figure 4 illustrates the change from baseline in 10-MWR over visits by age subgroups. A consistent treatment effect was observed between SRP-9001 and placebo in the 4-5 age group over time, but a treatment difference was only observed in the 6-7 age group at Week 52. LSM treatment difference in change from baseline to Week 52 was -0.33 (95% CI: -0.62, -0.03) in the 4-5 age group and -0.52 (95% CI: -1.01, -0.03) in the 6-7 age group.

Figure 4. LSM change from baseline in time to 10-MWR (seconds) over time by age subgroups.



Source: FDA reviewer.

Reviewer comment: The subgroup analyses are exploratory in nature. The analyses were not pre-specified for hypothesis testing and are reported only descriptively. The analyses resulted in overlapping 95% CIs. In addition, no multiplicity adjustment for type 1 error control was applied.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.9 describes the planned strategy for handling intercurrent events and missing data due to loss to follow up. There were no treated subjects who discontinued from Study SRP-9001-301 Part 1.

6.1.12 Safety Analyses

Descriptive statistics were used to summarize safety data for Study SRP-9001-301 Part 1. AEs were reported from the time of informed consent through the data cutoff date of September 13, 2023. A total of 119 subjects (SRP-9001: 62; placebo: 57) reported at least 1 AE. In total, 1166 treatment emergent adverse events (TEAE) were reported (SRP-9001: 664; placebo: 502), of which 278 treatment-related TEAEs were reported (SRP-9001: 235; placebo: 43).

6.1.12.3 Deaths

No deaths occurred in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Nineteen subjects reported serious adverse events (SAE), of which 14 (22.2%) subjects in SRP-9001 reported 21 SAEs and 5 (8.1%) subjects in placebo reported 9 SAEs by September 13, 2023. Seven (11.1%) subjects reported 10 treatment-related SAEs.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Comparison of Study SRP-9001-301 Part 1 to Study SRP-9001-102 Part 1

Study SRP-9001-102 was used as the basis for accelerated approval for ambulatory patients aged 4 through 5 years with DMD. This review also evaluates the consistency in the results for the clinical endpoints between studies SRP-9001-301 Part 1 and SRP-9001-102 Part 1.

Study SRP-9001-102 Part 1 is a Phase 2, randomized, double-blind, placebo-controlled study. Forty-three males, 4 through 7 years of age, with molecular characterization of the DMD gene, were randomized in a 1:1 ratio to SRP-9001 and placebo group. The LSM treatment difference in the primary functional efficacy endpoint of change from baseline to Week 48 in NSAA total score was 0.82 (95% CI: -1.03, 2.67) and was not statistically significant (p = 0.37). The treatment difference in the primary biological endpoint of change in quantity of micro-dystrophin protein expression from baseline to Week 12 as measured by western blot was 3.1% (95% CI: 1.35%, 6.94%) and was statistically significant (p < 0.0001). The Accelerated Approval of ELEVIDYS was based on this intermediate biological endpoint of micro-dystrophin protein expression. For further details, please refer to the statistical memo of the original BLA 125781 submission by Dr. Cong Wang.

The study population in Study SRP-9001-102 differed in age and genetic diagnosis of DMD eligibility criteria from Study SRP-9001-301. In addition, Study SRP-9001-102 used study product that was not ready for commercial use and a dose that was different from Study SRP-9001-301, so they were not pooled for an efficacy analysis. Main efficacy results from the two randomized studies are summarized side by side in Table 9.

Table 9. Summary of main efficacy analysis results in comparing Study SRP-9001-301 Part 1 and SRP-9001-102 Part 1, overall and by age groups, in the mITT population.

Endpoint	Analysis	Difference in LSM (95% CI) at Week 52 in Study 301	Difference in LSM (95% CI) at Week 48 in Study 102
Primary Endpoint: NSAA total score	Overall	0.65 (-0.45, 1.74)	0.82 (-1.03, 2.67)
	4-5 years old	1.32 (-0.23, 2.87)	2.47 (0.52, 4.43)
	6-7 years old	0.06 (-1.52, 1.64)	-0.70 (-3.02, 1.62)
Key Secondary Endpoint:	Overall	-0.64 (-1.06, -0.23)	-0.50 (-1.22, 0.23)
	4-5 years old	-0.50 (-0.90, -0.09)	-0.30 (-1.32, 0.72)

Time to rise from floor (seconds)	6-7 years old	-0.78 (-1.48, -0.08)	-0.56 (-1.59, 0.47)
Key Secondary Endpoint: 10-MWR timed test (seconds)	Overall	-0.42 (-0.71, -0.13)	0.49 (-0.08, 1.06)
	4-5 years old	-0.33 (-0.62, -0.03)	0.16 (-0.69, 1.02)
	6-7 years old	-0.52 (-1.01, -0.03)	0.76 (-0.01, 1.54)

Abbreviations: LSM = Least Square Mean; SE = Standard Error; CI = Confidence Interval
Source: FDA Reviewer.

The overall primary efficacy analysis showed comparable numerical improvement in NSAA total score between Study SRP-9001-301 Part 1 and SRP-9001-102 Part 1. The subgroup analysis by age group showed that the difference between treatments was largely driven by the 4-5 year olds, while the 6-7 year old group showed no treatment difference in SRP-9001-301 and a treatment difference in favor of placebo in SRP-9001-102.

The overall and subgroup analysis results for the key secondary endpoint of time to rise from floor showed numerical advantages for SRP-9001 and were consistent between the two studies. The key secondary endpoint of 10-MWR test showed inconsistent results between the two studies, with an advantage for SRP-9001 in SRP-9001-301 but an advantage for placebo in SRP-9001-102. The subgroup analysis results by age group were consistent with the overall analysis results within each study.

Clinical benefit was not demonstrated in the primary efficacy endpoint of NSAA total score from baseline in both studies. The key secondary endpoint of 10-MWR timed test showed opposing treatment effects in the two studies, while time to rise from floor showed some evidence of advantage for SRP-9001. Interpretation of these results is challenging due to the lack of overall type 1 error control and lack of adjustment for multiple testing. As a result, these results cannot be attributed to an actual treatment effect. Without proper statistical considerations such as pre-specification of hypotheses and overall type 1 error control, these post-hoc analyses are considered exploratory in nature.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

SRP-9001 is an AAV vector-based gene therapy, indicated for the treatment of DMD patients with a confirmed mutation in the DMD gene. SRP-9001 was granted accelerated approval for ambulatory patients with DMD in 2023. The primary purpose of this sBLA is to justify expansion of the approved indication to all DMD patients and to convert the BLA from accelerated approval to traditional approval.

The primary source of evidence to support this application is from Study SRP-9001-301 Part 1. Study SRP-9001-301 is a Phase 3, ongoing, global, randomized, double-blinded, placebo-controlled, two-part study in 125 male subjects with DMD who were ≥ 4 to < 8 years of age. The subjects were randomized in a 1:1 ratio, in which 63 subjects were assigned to SRP-9001 and 62 subjects to placebo. The primary efficacy endpoint was change in NSAA total score from baseline to Week 52. The key secondary endpoints included change in time to rise from the floor from baseline to Week 52, and change in time of 10-MWR from baseline to Week 52.

The LSM difference in change in NSAA total score from baseline between the two treatment arms was 0.65 (95% CI: -0.45, 1.74) and was not statistically significant (p = 0.244). The LSM difference in change in time to rise from the floor from baseline to Week 52 was -0.64 (95% CI: -1.06, -0.23), and change in time of 10-MWR from baseline to Week 52 was -0.42 (95% CI: -0.71, -0.13).

Subgroup analyses by age group were performed on the primary efficacy endpoint of NSAA total score and the two key secondary functional timed endpoints. The descriptive statistics resulted in overlapping confidence intervals, and were mostly comparable to those shown in Study SRP-9001-102 Part 1 in the original BLA submission.

No deaths occurred in Study SRP-9001-301 Part 1. Nineteen subjects reported SAEs, of which 14 received SRP-9001 and 5 received placebo.

10.2 Conclusions and Recommendations

Study SRP-9001-301 Part 1 did not meet the success criterion for the primary clinical endpoint of a statistically significant greater improvement in NSAA total score from baseline to Week 52 in the SRP-9001 group compared with placebo group. This study therefore did not satisfy the accelerated approval letter requirement, that the study “describe and verify clinical benefit of SRP-9001 in ambulatory patients with DMD…evidenced by effects such as improved North Star Ambulatory Assessment (NSAA) Total Score from baseline to Week 52.”

Substantial evidence of effectiveness has not been provided for the functional endpoint of 10-MWR timed test due to inconsistent and opposing results in the two randomized, controlled studies. Although SRP-9001 showed a numerical advantage in the secondary endpoint of time to rise from floor, these results cannot be interpreted at face value due to the lack of pre-specification and control of type 1 error.

Post-hoc subgroup analyses by age group did not demonstrate that clinical benefit in the primary and key secondary efficacy endpoints were substantial and consistent across age subgroups. The results from the two randomized studies

include only ambulatory subjects, so there is no evidence of effectiveness in non-ambulatory subjects with DMD.

These results do not suggest there is substantial evidence to support the effectiveness of SRP-9001 for the expanded indication to all DMD patients and do not support the conversion of accelerated to traditional approval.

11. APPENDIX

11.1 Tables referred to but not included in text

Table A1. MMRM analysis of change in NSAA total score at each visit (mITT population) in Study SRP-9001-301.

Visit	Treatment	LSM (SE)	95% CI	Difference in LSM (SE)	95% CI of Difference
Week 12	SRP-9001	2.05 (0.34)	1.38, 2.72	0.88 (0.48)	-0.07, 1.82
	Placebo	1.18 (0.34)	0.51, 1.84		
Week 24	SRP-9001	2.40 (0.39)	1.61, 3.18	1.14 (0.56)	0.03, 2.26
	Placebo	1.25 (0.40)	0.46, 2.05		
Week 36	SRP-9001	2.38 (0.38)	1.62, 3.13	0.52 (0.54)	-0.55, 1.59
	Placebo	1.86 (0.38)	1.10, 2.62		
Week 52	SRP-9001	2.57 (0.39)	1.80, 3.34	0.65 (0.55)	-0.45, 1.74
	Placebo	1.92 (0.39)	1.14, 2.70		

Abbreviations: LSM = Least Square Mean; SE = Standard Error; CI = Confidence Interval
Source: FDA Reviewer.

Table A2. MMRM analysis of change in time to rise from floor (seconds) at each visit (mITT population) in Study SRP-9001-301.

Visit	Treatment	LSM (SE)	95% CI	Difference in LSM (SE)	95% CI of Difference
Week 12	SRP-9001	-0.35 (0.09)	-0.54, -0.16	-0.28 (0.13)	-0.54, -0.02
	Placebo	-0.07 (0.09)	-0.26, 0.11		
Week 24	SRP-9001	-0.40 (0.11)	-0.62, -0.18	-0.50 (0.16)	-0.81, -0.18
	Placebo	0.09 (0.11)	-0.13, 0.32		
Week 36	SRP-9001	-0.28 (0.12)	-0.51, -0.05	-0.58 (0.16)	-0.90, -0.25
	Placebo	0.29 (0.12)	0.06, 0.53		

Week 52	SRP-9001	-0.27 (0.15)	-0.56, 0.02	-0.64 (0.21)	-1.06, -0.23
	Placebo	0.37 (0.15)	0.08, 0.67		

Abbreviations: LSM = Least Square Mean; SE = Standard Error; CI = Confidence Interval

Source: FDA Reviewer.

Table A3. MMRM analysis of change in time of 10-MWR (seconds) test at each visit (mITT population) in Study SRP-9001-301.

Visit	Treatment	LSM (SE)	95% CI	Difference in LSM (SE)	95% CI of Difference
Week 12	SRP-9001	-0.14 (0.09)	-0.33, 0.04	-0.06 (0.13)	-0.32, 0.20
	Placebo	-0.08 (0.09)	-0.26, 0.10		
Week 24	SRP-9001	-0.22 (0.11)	-0.43, -0.01	-0.19 (0.15)	-0.49, 0.11
	Placebo	-0.03 (0.11)	-0.25, 0.18		
Week 36	SRP-9001	-0.29 (0.10)	-0.49, -0.09	-0.21 (0.14)	-0.49, 0.08
	Placebo	-0.08 (0.10)	-0.28, 0.12		
Week 52	SRP-9001	-0.34 (0.10)	-0.55, -0.14	-0.42 (0.15)	-0.71, -0.13
	Placebo	0.08 (0.10)	-0.13, 0.29		

Abbreviations: LSM = Least Square Mean; SE = Standard Error; CI = Confidence Interval

Source: FDA Reviewer.