Application Type	Original BLA
STN	125781
CBER Received Date	September 28th, 2022
PDUFA Goal Date	May 29th, 2023
Division / Office	DCGT/OTAT
Committee Chair	Emmanuel Adu-Gyamfi
Clinical Reviewer(s)	Mike Singer
Project Manager	Rachel Duddy
Priority Review	Yes
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
	John Scott, Ph.D. Director, FDA/CBER/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	SRP-9001 contains 1.33×10^{13} vg/mL of delandistrogene moxeparvovec formulated in 7 mM tromethamine, 13 mM tromethamine HCl, 200 mM sodium chloride, 1 mM magnesium chloride, 0.001% poloxamer 188, at (b) (4) .
Dosage Form(s) and Route(s) of Administration	Recommended weight-based dose, administered by intravenous infusion: 1.33×10^{14} vg/kg of body weight
Dosing Regimen	Target single dose of 1.33×10^{14} vg/kg
Indication(s) and Intended Population(s)	Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene

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GLOSSARY

Abbreviation	Definition
10MWR	10-Meter Walk/Run
AAV	Adeno-associated virus
AC	Advisory committee
ATT	Average Treatment Effect on the Treated
BL	Baseline
BLA	Biologics Licensure Application
CI	Confidence interval
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
EC	External control
FDA	Food and Drug Administration
IF	immunofluorescence
IND	Investigational new drug
ISE	Integrated summary of efficacy
ITT	Intent-to-treat
IV	Intravenous
LS	Least-square
mITT	Modified-ITT
MMRM	Mixed-Model for Repeated Measures
NA	Not applicable
NSAA	North Star Ambulatory Assessment
PDPF	Percent dystrophin positive fibers
PP	Per protocol
SAE	Serious adverse event
SE	Standard error
STD	Standard deviation
TEAE	Treatment-emergent adverse event
US	United States

1. Executive Summary

This Biologics Licensure Application (BLA) seeks licensure of SRP-9001 (Trade Name: ELEVIDYS), an adeno-associated virus (AAV) vector-based gene therapy, for the treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.

The applicant submitted three studies in this BLA: Study SRP-9001-101, 102 and 103. Study SRP-9001-101 and 103 are single-arm and open-label studies. Study SRP-9001-102 is a Phase 2 study conducted at 2 sites in the US with ambulatory patients with DMD aged 4-7 years at time of screening. Part 1 of the study is randomized, double-blind, and placebo-controlled. Placebo subjects in Part 1 crossed over to active treatment in Part 2. Therefore, the double-blind study, SRP-9001-102 Part 1, constitutes the primary source of evidence of safety and efficacy of SRP-9001 in the treatment of ambulatory patients aged 4-7 years old with DMD to support this application.

Study SRP-9001-102 Part 1 enrolled ambulatory patients aged 4-7 years old with DMD. The applicant proposed two primary endpoints in this study: a novel surrogate endpoint, change in micro-dystrophin protein expression from baseline to Week 12, and a clinical functional endpoint, change in North Star Ambulatory Assessment (NSAA) total score from baseline to Week 48. Forty-three (43) subjects were randomized with 1:1 ratio to SRP-9001 group and placebo group. Among these 43 randomized subjects, 41 subjects received study treatment (20 subjects in the SRP-9001 group and 21 subjects in the placebo group). Results summarized in this memo are based on the results from the 41 treated subjects with a data cut-off date of April 6, 2022.

In Study SRP-9001-102 Part 1, treatment with SRP-9001 resulted in a statistically significantly greater increase in micro-dystrophin expression by western blot from baseline to Week 12 compared to placebo (re-randomization test using 2-sample Welch t-test statistic $p < 0.0001$). However, the available clinical evidence that micro-dystrophin expression is reasonably likely to predict clinical benefit is very weak. Specifically, the residual R^2 from a Spearman correlation analysis associating change in micro-dystrophin expression from baseline to Week 12 as measured by western blot with change in NSAA total score at 1 Year, controlling for age and baseline NSAA total score, was 3% (excluding placebo patients). This means that only 3% of the residual variation in 1-year NSAA total score change can be explained by micro-dystrophin expression in subjects treated with SRP-9001. Therefore, this result does not provide substantial evidence of effectiveness.

For the NSAA primary endpoint, based on the mixed model repeated measures (MMRM) analysis, the least-square (LS) mean changes (standard error [SE]) in NSAA total score from baseline to Week 48 are 1.74 (0.62) and 0.92 (0.61) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference (0.82 [0.90]) at Week 48 between SRP-9001 group and placebo group is not statistically significant (95% CI: [-1.03, 2.67]; $p = 0.37$). In this memo, the primary efficacy evaluation is based on the clinically meaningful endpoint, change in NSAA total score from baseline to Week 48.

No deaths occurred in Study SRP-9001-102 Part 1. Five subjects (12.2%) had at least one severe treatment-emergent adverse event (TEAE): Three subjects (15.0%) in the SRP-9001 group and two subjects (9.5%) in the placebo group.

The applicant also performed exploratory analyses comparing SRP-9001 data with external control (EC) data for functional endpoints among DMD patients. The LS mean of treatment difference in NSAA total score from baseline to 1 Year between the two groups is 2.5 (95% CI: [1.6, 3.5]), showing an improvement in NSAA total score for subjects receiving SRP-9001. However, when comparing placebo data from Study SRP-9001-102 Part 1 with EC data, the LS mean of treatment difference in NSAA total score from baseline to 1 Year between two groups is 0.7 (95% CI: [-0.3, 1.6]) which indicates that placebo subjects in the randomized trial numerically outperformed the external controls on NSAA total score, calling into question the comparability of the external control group.

Study SRP-9001-102 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 48 in the SRP-9001 group compared with placebo group. The results from the comparison study with external control are of doubtful interpretability given inherent limitations of the external comparison approach as well as observed heterogeneity of outcome between external controls and concurrent placebo subjects. Therefore, the statistical analysis results do not provide substantial evidence to support the effectiveness of SRP-9001 for the proposed indication in this BLA. I didn't identify any notable safety issues, but there are risks associated with any AAV vector gene therapy; discussion of these risks is deferred to the clinical review team.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

DMD is an invariably fatal, X-linked, monogenic, degenerative neuromuscular disease caused by mutations within the dystrophin gene that cause disruption of the reading frame resulting in an absence or deficiency of functional dystrophin, an important structural protein critical to muscle health and function. The incidence of DMD is approximately 1 in 5000 live male births worldwide (Mendell 2012, Crisafulli 2020). DMD patients have a median life expectancy of 28.1 years (Broomfield 2021).

The first clinical symptoms of DMD are delay in motor developmental milestones, such as walking, seen around 2 years of age but often there is a delay in diagnosis until the age of 3 to 5 years (Ciafaloni 2009, van Ruiten 2014) as patients get evaluated by appropriately knowledgeable healthcare professionals. Peak gains in DMD boys are achieved by 6.3 years of age (Muntoni 2019) and begin to decline after that. 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. On average, by 10 to 14 years of age, patients lose ambulation and are wheelchair dependent.

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. The prevalence of cardiomyopathy in DMD patients increases with age and disease progression, with most patients affected by age 18 (Gulati 2005, Spurney 2014). 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).

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 this BLA.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Milestone	Background information
10/05/2017	IND 17763 received from Dr. Jerry Mendell (Nationwide Children's Hospital)	
10/11/2018	IND transferred to Sarepta Therapeutics, Inc.	
12/20/2018	Type B multidisciplinary meeting	FDA stated that expression of Sarepta's micro-dystrophin protein is not currently accepted as a surrogate endpoint considered "reasonably likely to predict clinical benefit" to support accelerated approval. FDA recommended that Sarepta choose an endpoint that assesses clinically meaningful benefit, as manifested by how a patient feels, functions, or survives.
06/04/2020	Fast track designation granted	
09/04/2020	Type C CMC and clinical meeting	FDA expressed concern about the lack of correlation between clinically meaningful benefit and the primary efficacy endpoint, expression of Sarepta's micro-dystrophin at Week 12 after SRP-9001 administration.
07/27/2021	Type B end of Phase 2 teleconference	FDA stated that based on the results of Study SRP-9001-101 and Study SRP-9001-102, the Agency is not convinced that there is a clear correlation between expression of Sarepta's micro-dystrophin and clinical benefit.

02/14/2022	Request for pre-BLA meeting denied	FDA denied the pre-BLA meeting request and decided to convert this meeting to a Type C meeting
04/29/2022	Type C meeting to discuss possible accelerated approval pathway	FDA expressed concerns regarding the predictive relationship of expression of Sarepta's micro-dystrophin to clinical benefit.
09/28/2022	BLA 125781 submission	
11/25/2022	BLA filed. Filing letter issued to the applicant	
05/12/2023	Advisory committee meeting	Eight committee members voted "Yes" and six voted "No" for the voting question.
05/29/2023	PDUFA action due date	

(Source: FDA regulatory project manager review/BLA 125781 AC Briefing Document)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from the Study SRP-9001-102 Part 1, which is the focus of this review memo.

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

The basis of this statistical memo is the review of clinical study reports and data sets submitted in modules 2 and 5 of BLA 125781/0.

5.3 Table of Studies/Clinical Trials

A safety dataset was provided in this BLA for a total of 153 subjects with DMD treated with SRP-9001. Table 2 summarizes the 7 studies (4 ongoing, 3 planned) included in the BLA submission.

Table 2. Studies in the BLA application

Study code	Study population	Study design	# Subjects treated*
SRP-9001-101	Ambulatory aged 4-7 years	First-in-human, open-label, single-arm	4
SRP-9001-102	Ambulatory aged 4-7 years	Phase 2, 1:1 randomized, double-blind with blinded crossover in Part 2	41
SRP-9001-103 Cohort 1	Ambulatory aged 4-7 years	Phase 1b, open-label, single-arm, single-dose	20
SRP-9001-301	Ambulatory aged 4-7 years	Phase 3, global, randomized, double-blind	88
SRP-9001-302	Ambulatory aged 6 months-4 years	Phase 3, global, open-label, single-arm	0
SRP-9001-303	Cohort 1: non-ambulatory with no age restriction Cohort 2: ambulatory aged 8-18 years	Phase 3, global, randomized, double-blind	0
SRP-9001-305	Refer to Studies SRP-9001-301 and 303	Open-label, global, long-term extension study in subjects who have previously participated in Studies SRP-9001-301 or 303.	0

* All subjects in Studies SRP-9001-101, 102 and 103 Cohort 1 have completed enrollment and dosing. The data cutoff dates for Studies SRP-9001-101, 102, 103 Cohort 1 and 301 are April 26, 2022, April 1, 2022, April 6, 2022 and August 12, 2022, respectively. Enrollment has not started for other studies.
(Source: Clinical Overview Table 1, p. 18; FDA statistical reviewer's summary)

5.4 Consultations

5.4.1 Advisory Committee Meeting

An advisory committee (AC) meeting was held on May 12, 2023. The following voting question was posed to the committee:

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 (8) committee members voted "Yes", and 6 members voted "No".

Reviewer Comment:
Due to the following reasons, I continue to think substantial evidence of effectiveness has not been provided, despite the narrow majority vote of the AC in favor of accelerated approval.

- *Multiple AC members cited patient videos presented during public comment or to the meeting docket, as well as their general trust in the investigators' expertise, as persuasive in their decision-making. Although the patient videos and testimonies at the AC were compelling, it is difficult to determine whether the individual patients actually benefitted from treatment given the high variability in disease course in the short term. In addition, the majority of videos had no pre-treatment comparisons. Finally, some videos and anecdotes presented during the open public hearing reported dramatic benefits on a time scale (e.g., within a few days) incompatible with the mechanism of action of an AAV vector-based gene therapy.*
- *There was limited support from AC members for the proposition that change in micro-dystrophin can be considered as a surrogate endpoint reasonably likely to predict clinical benefit.*
- *SRP-9001 is a single-chance product; once exposed to SRP-9001, patients will be unable to benefit from additional doses or any subsequent AAV-based gene therapy (of which there are multiple in clinical development, some in late stage).*
- *High-quality data on the clinical effectiveness of SRP-9001 will be available within months, as the applicant's confirmatory trial reaches its data cut-off date in early Fall, 2023. Approving based on extremely inconclusive evidence before seeing these data is difficult to justify.*

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study # SRP-9001-102 Part 1

Study SRP-9001-102 Part 1 is the pivotal study that the applicant proposes to constitute the primary evidence of safety and efficacy of SRP-9001 in the treatment of ambulatory patients aged 4-7 years old with DMD.

6.1.1 Objectives

Primary:
- To evaluate the safety of SRP-9001
- To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks post dosing as measured by western blot of biopsied muscle tissue
- To evaluate the effect of SRP-9001 on physical functional assessments as assessed by NSAA over 48 weeks

Secondary objectives included evaluating the effect of SRP-9001 on physical functional assessments over 48 weeks measured by other assessments (e.g., 100-meter timed test, rise from floor test, etc.), micro-dystrophin expression at 12 weeks as measured by immunofluorescence (IF) fiber intensity of biopsied muscle tissue and IF percent dystrophin positive fibers (PDPF) of biopsied muscle tissue.

6.1.2 Design Overview

Study SRP-9001-102 Part 1 is a 48-week randomized, double-blind, placebo-controlled trial of systemic gene delivery of SRP-9001 in up to 44 DMD patients aged 4 to 7 years

(inclusive) who either have a confirmed frameshift (deletion or duplication) between exons 18 to 58 or premature stop codon mutation between exons 18 to 58. Subjects meeting all eligibility criteria were randomized to receive intravenous (IV) SRP-9001 or placebo (lactated Ringer's solution) in a 1:1 allocation ratio. Randomization was stratified by age group at baseline (4-5 vs. 6-7 years old).

6.1.3 Population

Key elements of eligibility criteria for Study SRP-9001-102 Part 1 are listed below.
- Eligible subjects were male, 4 to 7 years of age, at the time of screening
- Subjects were required to have molecular characterization of the DMD gene with either frameshift (deletion or duplication) between exons 18 to 58, or premature stop codon mutation between exons 18 to 58
- Subjects with signs of cardiomyopathy, including ECHO with ejection fraction < 40% were excluded from this study

6.1.4 Study Treatments or Agents Mandated by the Protocol

SRP-9001 was administered as a single IV infusion through a peripheral limb vein.
- Dose Level 1: 6.29×10^{13} vg/kg
- Dose Level 2: 8.94×10^{13} vg/kg
- Target Dose Level: 1.33×10^{14} vg/kg

Note: By design, all subjects were to be randomized to a target dose level of SRP-9001 or placebo. However, due to differences among lots of the drug product and the adoption of Sarepta's quantitative polymerase chain reaction method with a linear standard to reassign or assign the dose level, there were 3 dose levels being assigned and received.

6.1.6 Sites and Centers

Two (2) study sites in US.

6.1.7 Surveillance/Monitoring

An independent Data Monitoring Committee (DMC) was established to periodically review the safety and study progress for the clinical trial and provide recommendations to the applicant.

6.1.8 Endpoints and Criteria for Study Success

- *Primary biological endpoint*: Change in quantity of micro-dystrophin protein expression from baseline to Week 12 as measured by western blot.
- *Primary functional endpoint*: Change in NSAA total score from baseline to Week 48.

The study protocol also included several secondary efficacy endpoints:
- *Secondary functional endpoint:*
  a. Change in time of 100-meter timed test from baseline to Week 48
  b. Change in time to ascend 4 steps from baseline to Week 48
  c. Change in time to rise from the floor from baseline to Week 48
  d. Change in time of 10-meter timed test from baseline to Week 48

- *Secondary biological endpoint:*
  e. Change in micro-dystrophin expression from baseline to Week 12 as measured by IF fiber intensity
  f. Change in micro-dystrophin expression from baseline to Week 12 as measured by IF PDPF

Reviewer Comment:
According to the SAP, the 2-sided alpha of 0.05 was split, with 0.01 allocated to the primary biological endpoint and 0.04 allocated to the primary functional endpoint to control the overall type I error rate. However, FDA had conveyed concerns regarding use of the micro-dystrophin expression as a surrogate endpoint to support the accelerate approval and had not reached an agreement with the applicant on the primary endpoint. Since the proposed biological endpoint is not considered as a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval and the primary functional endpoint (i.e., NSAA total score change from baseline to Week 48) is considered clinically meaningful, I only rely on the primary NSAA endpoint to support effectiveness conclusions in this memo.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

Statistical hypothesis:
- H_{10}: $d_{11} = d_{12}$ vs. H_{11}: $d_{11} \neq d_{12}$, where d_{11} and d_{12} are mean change in quantity of micro-dystrophin expression from baseline to Week 12, as measured by western blot, for SRP-9001 group and placebo group, respectively.
- H_{20}: $d_{21} = d_{22}$ vs. H_{21}: $d_{21} \neq d_{22}$, where d_{21} and d_{22} are mean change in NSAA total score from baseline for SRP-9001 group and placebo group, respectively.

Analysis populations:
- *Intent-to-treat (ITT) analysis set* included all randomized subjects
- *Modified-ITT (mITT) analysis set* included all randomized subjects who received the study treatment
- *Per Protocol (PP) analysis set* included subjects in the mITT analysis set who do not have important protocol deviations that may substantially affect the study results
- *Safety analysis set* has the same definition as mITT set in this study

Reviewer Comments:
In the protocol and SAP, the applicant defined the ITT analysis set as all randomized subjects who received the study treatment. However, this definition is not a true ITT analysis set, but instead is a mITT analysis set. The mITT analysis set, as defined above, was used for the primary efficacy analysis in this study. From the statistical perspective, an ITT analysis set is preferred as it can prevent bias and provide a secure foundation for statistical tests[1], however FDA agreed with the use of the mITT analysis set in this case.

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1 Guidance for Industry: E9 Statistical Principles for Clinical Trials

Statistical methods:
Primary efficacy analyses were conducted on the mITT analysis set.

- Analysis method for primary endpoint
  o *Biological endpoint*: A re-randomization test was performed using the 2-sample Welch t-test as the test statistic.
  o *Functional endpoint*: A MMRM method was used to compare the SRP-9001 group with placebo group. In this model, the response variable is the NSAA total score change from baseline at each post-baseline visit and the mean function includes the covariates of treatment group, visit, treatment group by visit interaction, age group (4-5 and 6-7 years old), baseline NSAA total score, and baseline NSAA total score by visit interaction. A random intercept is incorporated to account for the within-subject correlations and an unstructured covariance matrix is used to model the within-subject variance-covariance structure. The LS estimates and SE on the treatment difference at Week 48 with corresponding p-value was provided for statistical inference.

- Analysis method for secondary endpoints
  o *Functional endpoint:* similar analysis as the primary functional endpoint. A hierarchical testing procedure was used in the order shown in Section 6.1.8, to control the overall type I error rate.
  o *Biological endpoint:* correlations between muscle biopsy measures at Week 12, and relationship between muscle biopsy endpoints and change from baseline in NSAA total score were summarized.

Sample size and power calculation:
The following assumptions were used to determine the sample size based on the functional efficacy endpoint of change in NSAA total score from baseline to Week 48:
- a mean treatment difference of 5 between SRP-9001 group and placebo group
- standard deviation of 5
- two sample t-test was used
- two-sided alpha level of 0.05
- target power of 90%
- no dropout assumed
Given the assumptions above, 44 (22 per arm) subjects were needed.
Note: According to the applicant, a dramatic treatment difference is expected for the biological efficacy endpoint of change from baseline to Week 12 in quantity of micro-dystrophin protein expression as measured by western blot. Therefore, the study was only sized based on the functional efficacy endpoint, NSAA total score change from baseline to Week 48, to ensure adequate power.

Sensitivity analyses for efficacy:
- *Primary biological endpoint:* Two-sample Wilcoxon rank sum test was performed for efficacy analysis

- *Primary functional endpoint:* A sensitivity analysis based on the PP analysis set was performed

Subgroup analyses:
Subgroup analyses were performed based on the following baseline characteristics in the mITT analysis set. Some grouping of classes was considered if there were too few subjects in some subgroups.
- Age: 4-5 vs. 6-7 years old at the time of screening
- Race: white vs. non-white
- BMI: <20, >=20 kg/m^2
- Steroid type: use of deflazacort at baseline vs. others
- Lot group: G02A0918-1 (Dose level 1), G02A0918-2 (Dose level 2), Other lots (Target dose level)
- Baseline NSAA: NSAA baseline total score >= median score vs. NSAA baseline total score < median score

Missing data handling for primary analysis and sensitivity analysis:
- For NSAA assessment, if 5 or fewer of the 17 items are missing, the NSAA total score would be calculated as the average score of the completed items times 17. The total NSAA score would be treated as missing values when 6 or more items are missing.
- In the primary analysis of NSAA, if in-clinic NSAA assessment at Week 48 is missed or out of protocol-defined visit window, interpolated NSAA total score using neighboring in-clinic assessments would be used[2]. For missing NSAA at other visits, the missing data mechanism is assumed to be missing at random.
- Tipping-point multiple-imputation analysis was performed to assess the robustness of the primary analysis conclusions to deviations from missing at random assumption used in the MMRM.
- A sensitivity analysis of NSAA was performed using out-of-window in-clinic assessments directly for the assigned time points without interpolation.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
For analyses of efficacy and safety in Study SRP-9001-102 Part 1, Table 3 summarizes the study analysis sets. Forty-three (43) subjects were randomized, constituting the ITT analysis set; 2 subjects (1 each from the 2 groups) withdrew consent before dosing. Forty-one (41) subjects were treated, constituting the mITT analysis set: 20 subjects in the SRP-9001 group and 21 subjects in the placebo group.

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2 Missed NSAA total score at Week 48 in Part 1 was made up via out-of-window in-clinic visits and then was imputed by linear interpolation with 2 neighboring in-clinic visits (prior to Part 1 Week 48 and out-of-window visit after Part 1 Week 48 [prior to dosing in Part 2]) based on the actual study day.

Table 3. Analysis sets

Analysis Set	SRP-9001, n	Placebo, n	Total, n
ITT	21	22	43
mITT	20 (95.2%)	21 (95.5%)	41 (95.3%)
PP	10 (47.6%)	16 (72.7%)	26 (60.5%)

(Source: FDA statistical reviewer's summary)

6.1.10.1.1 Demographics
Table 4 shows the demographic information for subjects in the SRP-9001 and placebo groups based on the mITT analysis set. The two groups had similar demographics.

Table 4. Demographics in mITT analysis set

	SRP-9001, n=20	Placebo, n=21	Total, n=41
Age (years)			
Mean (STD)	6.3 (1.2)	6.2 (1.1)	6.3 (1.1)
Median (min, max)	6.5 (4.5, 7.9)	6.0 (4.3, 8.0)	6.1 (4.3, 8.0)
Age group n (%)			
4-5 years	8 (40.0%)	8 (38.1%)	16 (39.0%)
6-7 years	12 (60.0%)	13 (61.9%)	25 (61.0%)
Race n (%)			
White	13 (65.0%)	17 (80.9%)	30 (73.2%)
Black or African American	0	0	0
Asian	4 (20.0%)	1 (4.8%)	5 (12.2%)
Other	3 (15.0%)	3 (14.3%)	6 (14.6%)
Ethnicity n (%)			
Hispanic or Latino	1 (5.0%)	4 (19.0%)	5 (12.2%)
Other	19 (95.0%)	17 (81.0%)	36 (87.8%)

(Source: FDA statistical reviewer's summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Table 5 shows the baseline clinical characteristics for subjects in the SRP-9001 and placebo groups based on the mITT analysis set. There were no notable differences with respect to subject baseline characteristics between two groups except baseline NSAA total score. The SRP-9001 group had a lower baseline NSAA total score than the placebo group, but the difference between groups was within one standard deviation.

Given that age is a stratification factor in this study, a further analysis for baseline NSAA total score by age group was performed. For subjects aged 4-5 years old, baseline NSAA total scores were well balanced between two groups. However, for subjects aged 6-7 years old, an imbalance in baseline NSAA total score was observed between treatment groups: the average score was 19.6 for the SRP-9001 group and 24.0 for the placebo group.

Table 5. Baseline characteristics in mITT analysis set

	SRP-9001, n=20	Placebo, n=21	Total, n=41
Years since diagnosis of DMD			
n	20	21	41
Mean (STD)	2.5 (1.3)	2.7 (1.3)	2.6 (1.3)
Median (min, max)	2.6 (0.4, 5.1)	2.6 (0.7, 5.4)	2.6 (0.4, 5.4)
BMI (kg/m^2)			
n	20	21	41
Mean (STD)	17.9 (1.7)	17.2 (2.0)	17.6 (1.9)
Median (min, max)	17.5 (16.1, 22.7)	17.3 (12.9, 21.2)	17.4 (12.9, 22.7)
BMI group			
<20	17 (85.0%)	19 (90.5%)	36 (87.8%)
>=20	3 (15.0%)	2 (9.5%)	5 (12.2%)
Height (cm)			
n	20	21	41
Mean (STD)	113.3 (7.7)	111.6 (6.2)	112.5 (7.0)
Median (min, max)	112.7 (102.4, 124.6)	112.0 (97.0, 125.5)	112.0 (97.0, 125.5)
Weight (kg)			
n	20	21	41
Mean (STD)	23.2 (4.3)	21.5 (3.4)	22.3 (4.0)
Median (min, max)	22.4 (17.8, 34.5)	20.5 (15.0, 29.3)	21.5 (15.0, 34.5)
Baseline NSAA total score			
n	20	21	41
Mean (STD)	19.8 (3.3)	22.6 (3.3)	21.2 (3.6)
Median (min, max)	20 (13, 26)	22 (15, 29)	21 (13, 29)
Steroid type			
Use of deflazacort at BL	7 (35.0%)	7 (33.3%)	14 (34.1%)
others	13 (65.0%)	14 (66.7%)	27 (65.9%)

BMI = body mass index; BL=baseline
(Source: FDA statistical reviewer's summary)

6.1.10.1.3 Subject Disposition
At the time of the data cutoff date April 6, 2022, all 41 subjects who received treatment
(20 received SRP-9001 and 21 received placebo) had completed the Study SRP-9001-102
Part 1; no subjects discontinued from the study apart from the two randomized subjects
who withdrew consent before treatment.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint
According to the SAP, for the primary biological endpoint, the null hypothesis was to be
rejected if the two-sided p-value associated with the test was ≤ 0.01; for the primary
functional endpoint, the null hypothesis was to be rejected if the two-sided p-value
associated with the test was ≤ 0.04.

- *Biological endpoint: Change in quantity of micro-dystrophin protein expression from
  baseline to Week 12 as measured by western blot*

Table 6 summarizes the micro-dystrophin level at Week 12 by western blot based on mITT analysis set. Both a re-randomization test (using two-sample Welch t-test statistic) and a Wilcoxon rank sum test were conducted.

Table 6. Summary of micro-dystrophin level by western blot in the mITT analysis set

	SRP-9001, n=20			Placebo, n=21		
	baseline	Week 12	change	baseline	Week 12	Change
Mean (STD)	2.4 (4.1)	17.4 (26.2)	15.0 (26.0)	1.1 (0.7)	1.3 (0.8)	0.2 (0.7)
Median (min, max)	1.1 (0.2, 18.3)	5.3 (1.2, 85.4)	3.1 (-0.1, 84.3)	1.2 (0.1, 2.8)	1.1 (0.1, 2.9)	0.02 (-1.0, 1.5)
Re-randomization test using 2-sample Welch t-test statistic						
2-sided p-value				<0.0001		
Wilcoxon rank sum test						
2-sided p-value				<0.0001		

(Source: FDA statistical reviewer's analysis)

In the mITT analysis set of 41 subjects (20 in the SRP-9001 group and 21 in the placebo group), the 2-sided p-values based on both the re-randomization test and Wilcoxon rank sum test (adjusted for the stratification factor age) were < 0.0001, which shows a statistically significantly greater increase in micro-dystrophin expression by western blot from baseline to Week 12 in the SRP-9001 group than the placebo group.

Reviewer Comments:
The applicant has provided mechanistic rationales, pre-clinical studies, and clinical data to support change in micro-dystrophin expression by western blot as a surrogate endpoint reasonably likely to predict clinical benefit. I defer detailed interpretation of the mechanistic and pre-clinical support to other review disciplines. However, the clinical evidence of surrogacy is quite weak, and this evidence is most salient to the application.

The partial Spearman correlation coefficient, adjusted for age and baseline NSAA total score, between change in micro-dystrophin expression at Week 12 and change in NSAA total score at 1 Year for the overall treated population including placebo subjects is 0.33 (80 total subjects from Study 102 Part 1, Part 2 and Study 103 Cohort 1)[3]. This corresponds to a partial R^2 of 0.11, meaning that change in micro-dystrophin accounts for 11% of the residual variance in NSAA total score after accounting for age and baseline NSAA score.

I also calculated the same correlation excluding placebo subjects, because theoretically any variability in placebo subject micro-dystrophin expression is due to assay limitations; placebo subjects have no micro-dystrophin. Therefore, including them in the analysis can introduce bias (e.g., if there are non-SRP-9001 mediated differences in clinical outcome between investigational and placebo groups) and add noise. I calculated the partial Spearman correlation coefficient using this approach to be 0.18 (based on 60

3 FDA BLA 125781.0 Clinical review memo; CDER Pharmacometric Consult review memo

total SRP-9001-treated subjects from Study 102 Part 1, Part 2 and Study 103 Cohort 1). This corresponds to a partial R^2 of 0.03, meaning that change in micro-dystrophin accounts for 3% of the residual variance in NSAA total score after accounting for age and baseline NSAA total score. The evidence is extremely weak no matter whether including or excluding placebo subjects and, in my opinion, shows that micro-dystrophin expression is not reasonably likely to predict clinical benefit.

Because micro-dystrophin protein expression measured by western blot has not been shown to be reasonably likely to predict clinical benefit as a surrogate endpoint suitable to support accelerated approval in this application, the analysis for micro-dystrophin level is not relevant to my conclusions regarding effectiveness of SRP-9001.

- *Functional endpoint: Change in NSAA total score from baseline to Week 48*

Table 7 summarizes the results of the MMRM analysis of change in NSAA total score at each visit in the mITT analysis set. Figure 1 shows the LS mean change in NSAA total score from baseline over time in the SRP-9001 group and placebo group, respectively.

Table 7. The LS mean estimate of treatment effect at each visit based on the MMRM analysis in the mITT analysis set

visit	Treatment	LSM change from baseline (SE)	LSM treatment difference (SE)	95% CI
Week 4	SRP-9001	1.38 (0.46)	0.73 (0.67)	(-0.63, 2.09)
	Placebo	0.65 (0.45)		
Week 8	SRP-9001	2.17 (0.49)	1.26 (0.72)	(-0.20, 2.72)
	Placebo	0.91 (0.48)		
Week 12	SRP-9001	2.19 (0.57)	1.53 (0.83)	(-0.16, 3.22)
	Placebo	0.66 (0.56)		
Week 24	SRP-9001	2.06 (0.65)	0.55 (0.95)	(-1.40, 2.50)
	Placebo	1.52 (0.64)		
Week 36	SRP-9001	1.66 (0.72)	0.70 (1.02)	(-1.38, 2.78)
	Placebo	0.96 (0.67)		
Week 48	SRP-9001	1.74 (0.62)	0.82 (0.90)	(-1.03, 2.67)
	Placebo	0.92 (0.61)		

(Source: FDA statistical reviewer's analysis)

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

NSAA Total Score: LS Mean Change From Baseline Over Time
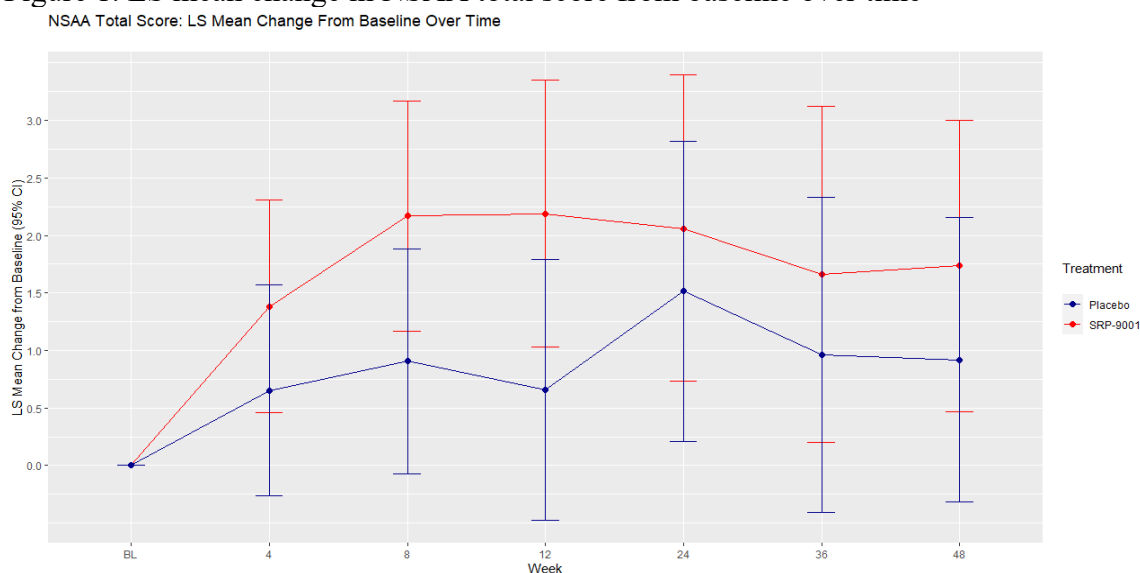
(Source: FDA statistical reviewer's analysis)

Based on the MMRM analysis in the mITT analysis set, the LS mean changes (SE) in NSAA total score from baseline to Week 48 are 1.74 (0.62) and 0.92 (0.61) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference estimated as 0.82 (0.90) at Week 48 between SRP-9001 group and placebo group is not statistically significant (95% CI: [-1.03, 2.67]; p = 0.37).
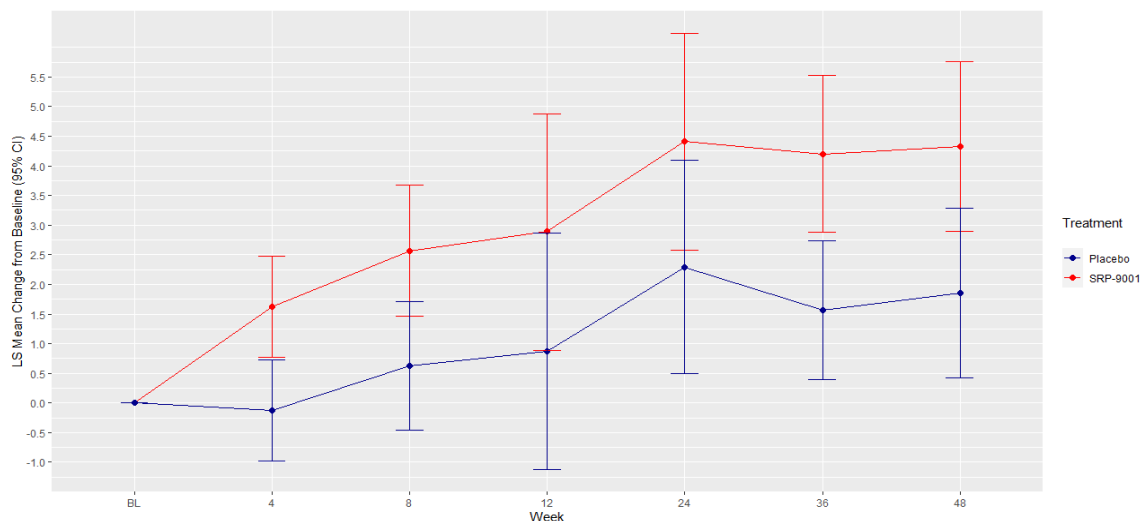
6.1.11.2 Analyses of Secondary Endpoints

Overall, the SRP-9001 group did not show improvement in functional assessments (e.g., 100-meter timed test, time to ascend 4 steps, time to rise from the floor, and 10-meter timed test) from baseline to Week 48 compared to the placebo group. As the primary functional endpoint, NSAA total score change from baseline to Week 48, failed, the secondary endpoints in this study were not formally tested.
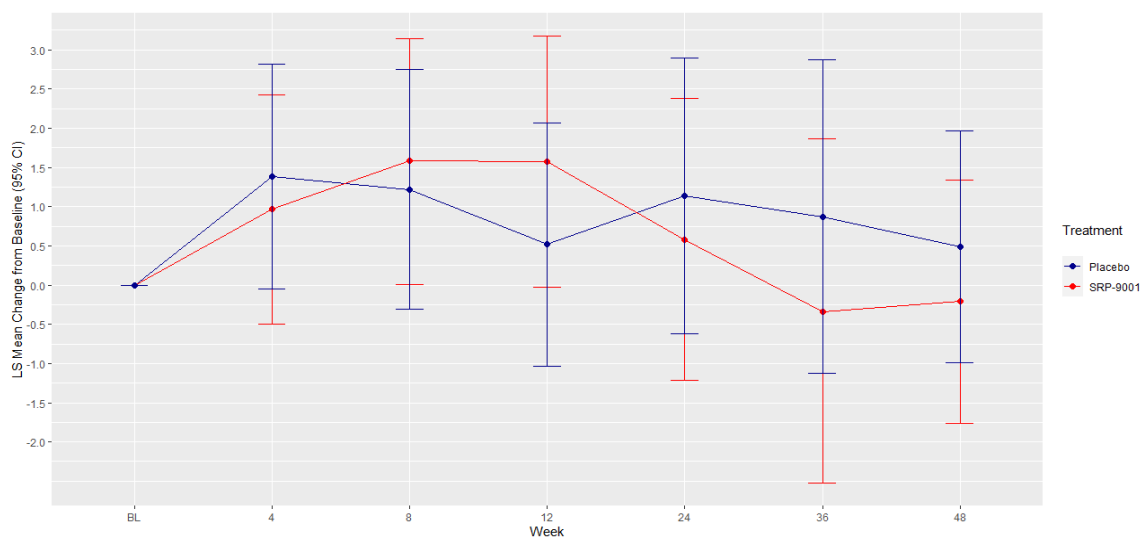
6.1.11.3 Subpopulation Analyses

Age is an important prognostic factor in the progression of DMD and thus the treatment effect on the outcome was further evaluated by analyzing results within two age subgroups, 4-5 years old and 6-7 years old. Figures 2 and 3 show the LS mean change in NSAA total score from baseline over time in age groups 4-5 and 6-7 years old.

Figure 2. LS mean change in NSAA total score from baseline over time in Age 4-5 Years

(Source: FDA statistical reviewer's analysis)

Figure 3. LS mean change in NSAA total score from baseline over time in Age 6-7 Years

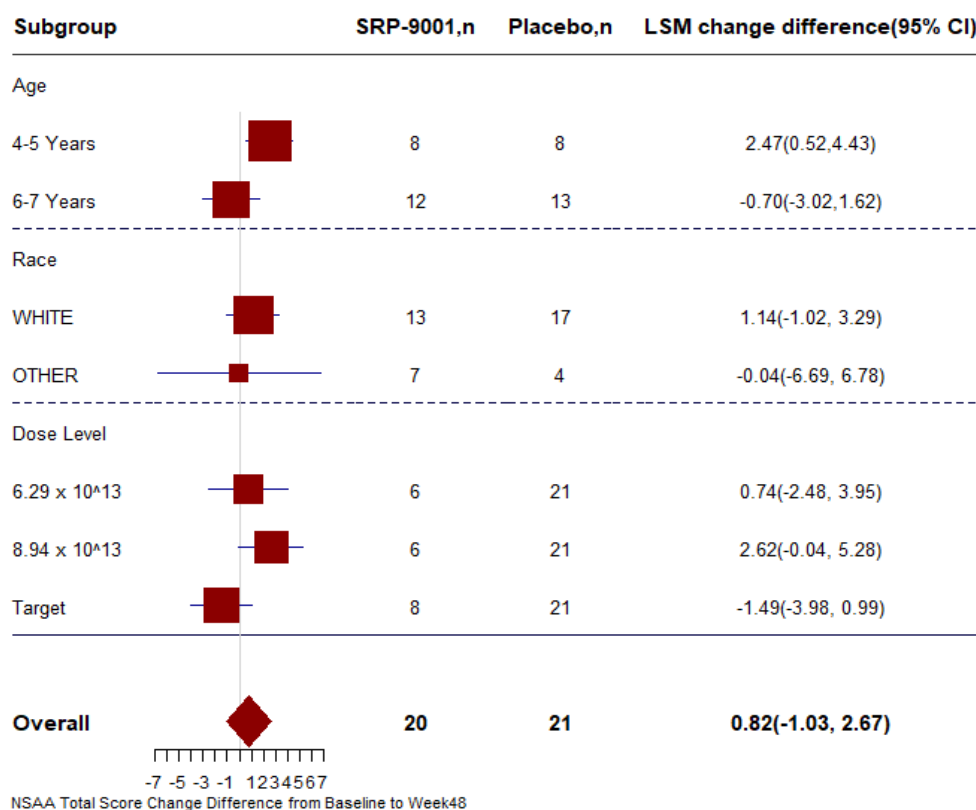(Source: FDA statistical reviewer's analysis)

For subjects aged 4-5 years old, the LS mean changes (SE) in NSAA total score from baseline to Week 48 are 4.32 (0.68) and 1.85 (0.68) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference at Week 48 between SRP-9001 group and placebo group is 2.47 (0.91) with a 95% CI of (0.52, 4.43). For subjects with age 6-7 years old, the LS mean changes (SE) in NSAA total score from baseline to Week 48 are -0.21 (0.75) and 0.49 (0.71) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference is -0.70 (1.12) at Week 48 between SRP-9001 group and placebo group with a 95% CI of (-3.02, 1.62).

Reviewer Comments:

It is important to note that this subgroup analysis is exploratory in nature. The analysis was not pre-specified for hypothesis testing and no pre-specified multiplicity adjustment strategy was employed. Therefore, these subgroup results are not reliable. Moreover, the imbalance in baseline NSAA total score between treatment groups might have influenced the study findings.

In addition, Figure 4 shows the forest plot of change in NSAA total score from baseline to Week 48 by age group, race, and dose level.

Figure 4. Forest plot of change in NSAA total score from baseline to Week 48 by subgroups

Subgroup		SRP-9001,n	Placebo,n	LSM change difference(95% CI)
Age				
4-5 Years		8	8	2.47(0.52,4.43)
6-7 Years		12	13	-0.70(-3.02,1.62)
Race				
WHITE		13	17	1.14(-1.02, 3.29)
OTHER		7	4	-0.04(-6.69, 6.78)
Dose Level				
6.29 x 10^13		6	21	0.74(-2.48, 3.95)
8.94 x 10^13		6	21	2.62(-0.04, 5.28)
Target		8	21	-1.49(-3.98, 0.99)
Overall		20	21	0.82(-1.03, 2.67)

-7 -5 -3 -1 1234567
NSAA Total Score Change Difference from Baseline to Week48

(Source: FDA statistical reviewer's analysis)

Due to the small sample sizes in each race and dose level subgroup and overall non-significant result in the combined analysis set, it is not possible to draw any strong conclusions from this subgroup analysis. However, there are no notable qualitative differences between subgroups.

6.1.11.4 Dropouts and/or Discontinuations

Among 43 randomized subjects, 2 subjects (1 each from the 2 groups) discontinued from the study before dosing due to withdrawal of consent. All 41 treated subjects completed the Study SRP-9001-102 Part 1 and no treated subject discontinued from the study.

6.1.12 Safety Analyses

This section summarizes safety results of Study SRP-9001-102 Part 1.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data for Study SRP-9001-102 Part 1. The safety analysis set in this section includes a total of 41 treated subjects (20 in the SRP-9001 group and 21 in the placebo group).

6.1.12.3 Deaths

No deaths occurred in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Five (12.2%) subjects had at least 1 severe TEAE: Three (15.0%) subjects in the SRP-9001 group and two (9.5%) subjects in the placebo group. The subjects with serious TEAEs are as follows:
- Subject (b) (6) in the SRP-9001 group (rhabdomyolysis)
- Subject (b) (6) in the SRP-9001 group (liver injury and rhabdomyolysis)
- Subject (b) (6) in the SRP-9001 group (transaminases increased)
- Subject (b) (6) in the placebo group (rhabdomyolysis)
- Subject (b) (6) in the placebo group (humerus fracture)

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Comparison of SRP-9001 Treated Subjects to External Control Subjects

7.1.1 Methods of Integration

The applicant performed comparisons of SRP-9001 data to external control (EC) data for functional endpoints among DMD patients. The comparative analyses included both study-level and integrated analysis, based on SRP-9001 treated subjects from Studies SRP-9001-101, 102 and 103. In this review memo, only the integrated-level analysis is presented; the analysis including only study-level data does not add important information to affect my conclusions.

EC data source:
- CINRG (Cooperative International Neuromuscular Research Group) Duchenne Natural History Study (DNHS) data
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) data
- Lilly Study (H6D-MC-LVJJ) data
All databases contain 3 functional assessments which overlap with the variables collected in Studies SRP-9001-101, 102 and 103: NSAA total score, 10-meter walk/run (10MWR) and rise from the floor.

7.1.4 Analysis of Primary Endpoint

Primary analysis set:
Integrated summary of efficacy (ISE) Target Dose (i.e., 1.33×10^{14} vg/kg) 1-year analysis set, including 4 subjects from Study SRP-9001-101, 29 subjects in Study SRP-9001-102 (8 subjects with target dose from Part 1 and 21 subjects from Part 2), and 20 subjects who completed the Week 52 assessment in Cohort 1 of Study SRP-9001-103, for a total of 53 subjects.

Primary endpoint:
1-year change in NSAA total score from baseline.

Statistical method:
The primary EC analysis was conducted using a propensity score weighting method. Propensity scores were estimated through a logistic regression model, where the dependent variable is the probability of receiving SRP-9001 and model covariates include the baseline age group (4-5 vs. 6-7 vs. 8 years old), baseline NSAA total score, baseline time to rise from the floor, and baseline 10MWR. The propensity score weighting scheme was then implemented in subsequent modeling, where SRP-9001 treated subjects were given a weight of 1, and EC patients were weighed by propensity score divided by (1 minus propensity score).

A weighted linear regression model was then fitted on the weighted data, to assess the treatment effect of SRP-9001 while accounting for the baseline covariates of baseline age group, baseline NSAA total score, and baseline age group by baseline NSAA total score interaction. The estimated treatment effect, along with the 95% CI, are presented.

Reviewer Comments:
It is important to note that the EC comparison has the following limitations/weakness:
- *The disease course of DMD is highly heterogeneous across this age range, increasing the likelihood of non-comparable patients across data sources*
- *The intended treatment effect is unlikely to be more than moderate, and thus the analysis will not provide results persuasive enough to overcome potential biases in non-concurrent analysis*
- *It is difficult to determine that the external population is similar to the study population with regard to all key baseline characteristics, including unobserved baseline characteristics.*
- *Outcome measures (e.g., NSAA total score) are process-dependent[4], so data generated from different studies are not directly comparable.*
  The validity of the propensity score weighting method depends on critical and unverifiable assumptions, including the incorporation of all important confounding factors (and some important confounding factors may not even be measured) and appropriate specification of the functional form of the relationship between confounding factors and probability of SRP-9001 treatment.

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

Due to the limitations/weakness shown above, the comparison of SRP-9001 data to EC data can only serve as exploratory.

Reviewer Comments:
The interaction term of baseline age group by baseline NSAA total score was included in the weighted linear regression model to assess the treatment effect of SRP-9001; however, this term was not included in the MMRM model when assessing the treatment effect of SRP-9001 from Study SRP-9001-102 Part 1 (Section 6.1.11.1). I re-conducted the MMRM analysis including the interaction term as one of the covariates from Study SRP-9001-102 Part 1 and obtained a p-value for treatment difference between two groups of 0.41.

7.1.11 Efficacy Conclusions

According to the applicant, among a total of 765 subjects from the CINRG, FOR-DMD, and Lilly datasets, 131 met all the applied entry criteria to be consistent with the characteristics of subjects enrolled in the SRP-9001 studies and were followed for at least 1 year for outcomes. Of 53 subjects included in the ISE Target Dose 1-year dataset, 52 subjects were included in the primary analysis. One subject did not have the Week 48 assessment in Study SRP-9001-102 Part 2, due to recovery from heel cord surgery.

The LS mean of treatment difference in NSAA total score from baseline to 1 Year between the two groups was 2.5 (95% CI: [1.6, 3.5]), suggesting improved functional outcomes for patients treated with SRP-9001 compared to external controls.

Reviewer comment:
To provide additional context for the comparison of SRP-9001 subjects to external controls, I performed an analogous propensity score-adjusted analysis comparing placebo subjects from Study SRP-9001-102 Part 1 to EC. In this analysis, the LS mean of treatment difference in NSAA total score from baseline to 1 Year between the two groups was 0.7 (95% CI: [-0.3, 1.6]), indicating potentially improved functional outcomes also for placebo subjects in SRP-9001-102 Part 1 compared to EC. This analysis is subject to all the same limitations as the applicant's analysis and serves only to provide evidence of the non-comparability of the SRP-9001 study population with the external control population. This reinforces the exploratory nature and limited interpretability of the applicant's EC comparison.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This BLA seeks licensure of SRP-9001, an AAV vector-based gene therapy, for the treatment of ambulatory patients with DMD with a confirmed mutation in the DMD gene.

The primary source of evidence to support this application comes from Study SRP-9001-102 Part 1. Study SRP-9001-102 Part 1 was a randomized, double-blind, placebo-controlled, Phase 2 study of ambulatory subjects with DMD aged 4-7 years at time of screening. Forty-three subjects were randomized in a 1:1 ratio to SRP-9001 group and placebo group. Among 43 subjects, 41 subjects received the study treatment (20 subjects in the SRP-9001 group and 21 subjects in the placebo group).

In Study SRP-9001-102 Part 1, the LS mean changes (SE) in NSAA total score from baseline to Week 48 are 1.74 (0.62) and 0.92 (0.61) for the SRP-9001 group and placebo group, respectively. The LS mean (SE) treatment difference (0.82 [0.90]) at Week 48 between SRP-9001 and placebo groups is not statistically significant (95% CI: [-1.03, 2.67]; p = 0.37).

In Study SRP-9001-102 Part 1, treatment with SRP-9001 resulted in a statistically significantly greater increase in micro-dystrophin expression by western blot from baseline to Week 12 compared to placebo (re-randomization test using 2-sample Welch t-test statistic p < 0.0001). However, the available clinical evidence that micro-dystrophin expression is reasonably likely to predict clinical benefit is very weak. Specifically, the residual R^2 from a Spearman correlation analysis associating change in micro-dystrophin expression from baseline to Week 12 as measured by western blot with change in NSAA total score at 1 Year, controlling for age and baseline NSAA total score, was 3% (excluding placebo patients). This means that only 3% of the residual variation in 1-year NSAA total score change can be explained by micro-dystrophin expression in subjects treated with SRP-9001.

No deaths occurred in Study SRP-9001-102 Part 1. Five subjects (12.2%) had at least 1 severe TEAE: Three subjects (15.0%) in the SRP-9001 group and two subjects (9.5%) in the placebo group.

The applicant performed an exploratory analysis comparing SRP-9001 data with EC data for functional endpoints among DMD patients. The LS mean of treatment difference in NSAA total score from baseline to 1 Year between two groups is 2.5 (95% CI: [1.6, 3.5]), showing an improvement in NSAA total score for subjects receiving the gene therapy. However, when comparing placebo data from Study SRP-9001-102 Part 1 with EC data, the LS mean of treatment difference in NSAA total score from baseline to 1 Year between two groups is 0.7 (95% CI: [-0.3, 1.6]), indicating that placebo subjects in the randomized trial numerically outperformed the external controls on NSAA total score improvement, calling into question the comparability of the external control group.

10.2 Conclusions and Recommendations

Study SRP-9001-102 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 48 in the SRP-9001 group compared with placebo group. The results from the comparison study with external control are of doubtful interpretability given inherent limitations of the external comparison approach as well as observed heterogeneity of outcome between external controls and concurrent placebo subjects.

Similarly, the statistically significant increase in micro-dystrophin expression seen in SRP-9001-treated subjects does not provide substantial evidence of effectiveness because the clinical evidence that micro-dystrophin expression is reasonably likely to predict clinical benefit is very weak. Therefore, the statistical analysis results do not provide substantial evidence to support the effectiveness of SRP-9001 for the proposed indication in this BLA. I did not identify any safety issues in my review. However, there are risks associated with any AAV vector-based gene therapy; discussion of these risks is deferred to the clinical reviewer.