

BLA Clinical Review Memorandum

Application Type	Original Application
STN	125781/0
CBER Received Date	September 29, 2022
PDUFA Goal Date	May 29, 2023
Division / Office	DCEGM/OCE/OTP
Priority Review (Yes/No)	Yes
Reviewer Name	Mike Singer, MD, PhD (Efficacy) Rosa Sherafat-Kazemzadeh, MD (Safety and Team Lead)
Review Completion Date	June 22, 2023
Supervisory Concurrence Branch Chief	Lei Xu, MD, PhD
Division and Office Director (Acting)	Celia Witten, PhD, MD
Applicant	Sarepta Therapeutics, Inc.
Established Name	Delandistrogene moxeparvovec-rokl
(Proposed) Trade Name	ELEVIDYS
Pharmacologic Class	Adeno-associated virus (AAV) vector-based gene therapy
Formulation(s), including Adjuvants, etc.	Suspension with a nominal concentration of 1.33×10^{13} vector genomes (vg) per mL and excipients 200mM sodium chloride, 13 mM tromethamine HCl, 7 mM tromethamine, 1mM magnesium chloride, 0.001% poloxamer 188
Dosage Form(s) and Route(s) of Administration	Recommended weight-based dose, administered by intravenous infusion: 1.33×10^{14} vg per kg of body weight
Dosing Regimen	Single dose
Proposed Indication(s) and Population(s)	For treatment of ambulatory patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the <i>DMD</i> gene
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY	1
1. EXECUTIVE SUMMARY	2
1.1 Demographic Information: Subgroup Demographics and Analysis Summary	8
1.2 Patient Experience Data	8
2. CLINICAL AND REGULATORY BACKGROUND	12
2.1 Disease or Health-Related Condition(s) Studied	12
2.1.1 Duchenne Muscular Dystrophy	12
2.1.2 Clinical Outcome Measure for DMD: North Star Ambulatory Assessment	12
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)	13
2.3 Safety and Efficacy of Pharmacologically Related Products	14
2.4 Previous Human Experience with the Product (Including Foreign Experience)	14
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	14
2.6 Other Relevant Background Information	16
2.6.1 FDA Approval Pathways and the Role of Surrogate Endpoints	16
2.6.2 Special Risks of AAV Vector-Based Gene Therapy Products	17
3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES	18
3.1 Submission Quality and Completeness	18
3.2 Compliance With Good Clinical Practices and Submission Integrity	18
3.3 Financial Disclosures	18
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	19
4.1 Chemistry, Manufacturing, and Controls	19
4.1.1 SRP-9001	19
4.1.2 Manufacturing Processes	20
4.1.3 Concerns Regarding Increased Percentage of Empty Capsids	21
4.2 Assay Validation	21
4.3 Nonclinical Pharmacology/Toxicology	21
4.4 Clinical Pharmacology	23
4.4.1 Mechanism of Action	23
4.4.2 Pharmacodynamics	27
4.4.3 Relationship Between Expression of ELEVIDYS Micro-dystrophin Protein and Clinical Efficacy Outcome on the NSAA	29
4.4.4 Human Pharmacokinetics (PK)	31
4.5 Statistical	31
4.6 Pharmacovigilance	31
5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW ...	32
5.1 Review Strategy	32
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review	32
5.3 Table of Studies/Clinical Trials	33
5.4 Consultations	36
5.4.1 Advisory Committee Meeting	36
5.5 Literature Reviewed	40
6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS	40
6.1 Trial #1: SRP-9001-101 (Study 101)	40
6.1.1 Objectives (Primary and Secondary)	40

6.1.2 Design Overview	40
6.1.3 Population.....	41
6.1.4 Study Treatments or Agents Mandated by the Protocol	41
6.1.5 Directions for Use	42
6.1.6 Sites and Centers	42
6.1.7 Surveillance/Monitoring	42
6.1.8 Endpoints and Criteria for Study Success.....	44
6.1.9 Statistical Considerations and Statistical Analysis Plan	44
6.1.10 Study Population and Disposition.....	44
6.1.11 Efficacy Analyses	45
6.1.12 Safety Analyses	46
6.1.13 Study Summary and Conclusions	49
6.2 Trial #2: SRP-9001-102 (Study 102)	49
6.2.1 Objectives (Primary, Secondary).....	50
6.2.2 Design Overview	50
6.2.3 Population.....	51
6.2.4 Study Treatments or Agents Mandated by the Protocol	52
6.2.5 Sites and Centers	52
6.2.7 Surveillance/Monitoring	52
6.2.8 Endpoints and Criteria for Study Success.....	57
6.2.9 Statistical Considerations and Statistical Analysis Plan	57
6.2.10 Study Population and Disposition.....	59
6.2.11 Efficacy Analyses	60
E6.2.12 Safety Analyses	66
6.2.13 Study Summary and Conclusions	71
6.3 Trial #3: SRP-9001-103 (Study 103)	72
6.3.1 Objectives (Primary and Secondary).....	72
6.3.2 Design Overview	73
6.3.3 Population.....	73
6.3.4 Study Treatments or Agents Mandated by the Protocol	74
6.3.6 Sites and Centers	75
6.3.7 Surveillance/Monitoring	75
6.3.8 Endpoints and Criteria for Study Success.....	80
6.3.9 Statistical Considerations & Statistical Analysis Plan	80
6.3.10 Study Population and Disposition.....	80
6.3.11 Efficacy Analyses	81
6.3.12 Safety Analyses	82
6.3.13 Study Summary and Conclusions	85
7. INTEGRATED OVERVIEW OF EFFICACY	85
7.1 Indication #1	85
7.1.1 Methods of Integration.....	85
7.1.4 Analysis of Primary Endpoint(s)	86
7.1.11 Efficacy Conclusions	87
8. INTEGRATED OVERVIEW OF SAFETY	88
8.1 Safety Assessment Methods	88
8.2 Safety Database	88
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	88
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	88
8.2.3 Categorization of Adverse Events	89
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	90
8.4 Safety Results	90
8.4.1 Deaths	90
8.4.2 Nonfatal Serious Adverse Events.....	90

8.4.3 Study Dropouts/Discontinuations	92
8.4.4 Common Adverse Events	92
8.4.5 Clinical Test Results	96
8.4.6 Systemic Adverse Events	96
8.4.7 Adverse Events of Special Interest	96
8.5 Additional Safety Evaluations	99
8.5.1 Dose Dependency for Adverse Events	99
8.5.2 Time Dependency for Adverse Events	101
8.5.3 Product-Demographic Interactions	102
8.5.6 Human Carcinogenicity	102
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound	102
8.5.8 Immunogenicity (Safety)	102
8.5.9 Person-to-Person Transmission, Shedding	102
8.6 Safety Conclusions	102
9. ADDITIONAL CLINICAL ISSUES	103
9.1 Special Populations	103
9.1.1 Human Pregnancy Data	103
9.1.2 Use During Lactation	103
9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations	103
9.1.4 Immunocompromised Patients	103
9.1.5 Geriatric Use	103
10. CONCLUSIONS	103
11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS	104
11.1 Risk-Benefit Considerations	104
11.2 Risk-Benefit Summary and Assessment	107
11.3 Discussion of Regulatory Options	107
11.4 Recommendations on Regulatory Actions	108
11.5 Labeling Review and Recommendations	108
11.6 Recommendations on Postmarketing Actions	108
APPENDIX 1. CTGTAC MEMBERS AND THEIR VOTES REGARDING ACCELERATED APPROVAL OF ELEVIDYS	110
APPENDIX 2. EXPLORATORY ASSESSMENTS OF SECONDARY FUNCTIONAL ENDPOINTS IN STUDY 102 PART 1	112

GLOSSARY

10MWR	10-meter walk/run test
AAV	adeno-associated virus
AAVrh74	adeno-associated virus serotype rhesus type 74
AE	adverse event
ALI	acute liver injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIMO	BioResearch Monitoring
BLA	Biologics License Application
BMD	Becker muscular dystrophy
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Device and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
DAPC	dystrophin-associated protein complex
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EC	external control
ELISA	enzyme-linked immunosorbent assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
HCP	health care professional
IF	immunofluorescence
ITT	Intent to Treat
kg	kilogram
LDT	laboratory developed test
LS	least square
MHCK7	chimeric alpha-myosin heavy chain/creatine kinase 7 promoter
mITT	modified-Intent to Treat
MMRM	mixed model for repeated measures
NSAA	North Star Ambulatory Assessment
PI	prescribing information
PMA	Premarketing Approval
rAAVrh74	recombinant adeno-associated virus serotype rhesus type 74
SAE	serious adverse event
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
vg	vector genome
WB	Western blot

1. EXECUTIVE SUMMARY

Delandistrogene moxeparvovec-rokl (also known as SRP-9001; proprietary name: ELEVIDYS) is a gene therapy which utilizes a nonreplicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) vector. ELEVIDYS encodes a novel protein, ELEVIDYS micro-dystrophin (also known as Sarepta's micro-dystrophin).

Sarepta Therapeutics, Inc. (the Applicant) submitted Biologics License Application (BLA) 125781 to seek Accelerated Approval for ELEVIDYS, based on the proposed surrogate endpoint of expression of ELEVIDYS micro-dystrophin at Week 12 following administration of SRP-9001.

The proposed indication for ELEVIDYS is for treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. The proposed dose, administered via intravenous infusion, is 1.33×10^{14} vector genomes (vg) per kg of body weight (vg/kg) in patients weighing 10 to 70 kg, and 9.31×10^{15} vg in patients weighing >70 kg.

DMD is a serious, progressive condition for which there is an urgent, unmet medical need. DMD results from deficiency of the cytoskeletal protein dystrophin due to mutation of the *DMD* (also known as *Dystrophin*) gene, which is carried on the X chromosome and is the largest known human gene. DMD affects about 1 in 3,300 boys. Generalized weakness is usually apparent in early childhood, typically leading to diagnosis by approximately age 5 years. Weakness is progressive, with loss of ambulation commonly occurring by early adolescence. Patients experience a progressive and parallel loss of cardiorespiratory reserve, with death by about age 30 years.

Deflazacort (Emflaza) is the only available therapy approved by FDA via the traditional approval pathway. Deflazacort is a corticosteroid which delays loss of motor strength and loss of ambulation. Four antisense oligonucleotide exon-skipping drugs have received approval via the FDA Accelerated Approval pathway, based on the surrogate endpoint of expression of internally-truncated dystrophin protein, for a subset of patients with specific *DMD* mutations; clinical benefit of all four of these drugs remains to be verified.

Proposed Surrogate Endpoint and Clinical Trials

Treatment with ELEVIDYS is intended to slow or stabilize progression of DMD, to alter the disease trajectory to a milder, Becker muscular dystrophy (BMD)-like phenotype. To qualify for Accelerated Approval, the Applicant proposes to utilize as primary evidence of effectiveness expression of ELEVIDYS micro-dystrophin protein at Week 12 after administration of ELEVIDYS. This biomarker is intended to serve as the required surrogate endpoint considered "reasonably likely to predict clinical benefit" for Accelerated Approval.

ELEVIDYS micro-dystrophin (138 kDa) is a novel, engineered protein that contains selected domains of normal, wild-type dystrophin (427 kDa). No epidemiologic or pathophysiologic evidence of function of ELEVIDYS micro-dystrophin is available. The protein differs in important ways from both the endogenous shortened forms of dystrophin in patients with BMD, and the internally-truncated dystrophins expressed through treatment with exon-skipping drugs. Measurement of levels of ELEVIDYS micro-

dystrophin in muscle tissue therefore provides information only about expression of the transgene product in cells transduced by ELEVIDYS, rather than insight into a pharmacologic effect on a known biomarker in the pathway of the disease.

To support use of expression of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval, an effect on this candidate surrogate endpoint is expected to correlate with an effect on a clinical outcome measure that evaluates how a patient feels, functions, or survives. The clinical outcome measure in this case is the North Star Ambulatory Assessment (NSAA), a validated, 17-item instrument frequently used in DMD clinical trials.

In contrast to an objective endpoint such as survival, functional measures such as the NSAA have important limitations. First, they are effort-dependent: performance can be affected by motivation and effort, and by encouragement from family, caregivers, and the clinicians scoring the exam. Consequently, NSAA results from open-label studies are challenging to interpret; patients typically score better than in double-blind studies. Second, the NSAA and similar measures are process-dependent: results can differ based on how consistently the test is administered and scored by the clinical staff. Therefore, NSAA scores from a clinical study cannot be rigorously compared to scores from external sources, such as natural history studies, registries, or even to scores from clinical trials of other drugs for that condition.

The BLA submission includes data from three clinical studies: Study SRP-9001-101 (Study 101), Study SRP-9001-102 (Study 102) Part 1 and Part 2, and Study SRP-9001-103 (Study 103). Study 101 and Study 103 are open-label. Study 102 includes a randomized, double-blind, placebo-controlled Part 1, and a “cross-over” Part 2 (i.e., subjects who received ELEVIDYS in Part 1 were then administered placebo in Part 2, and vice-versa). Although the blind was maintained in Part 2, by that point the subjects, caregivers, and evaluators were aware that all subjects had now received SRP-9001, rendering Part 2 effectively an open-label study.

Study design has important implications for the interpretability of efficacy data for ELEVIDYS. Under certain circumstances, data obtained from open-label studies are readily interpretable: when the disease being studied is homogeneous, the treatment has a large effect, and the clinical endpoint can be objectively assessed. That was the situation, for example, with onasemnogene abeparvovec-xioi (Zolgensma), the gene therapy approved for patients less than 2 years old with spinal muscular atrophy. In contrast, progression of DMD is heterogeneous; improvement on the NSAA occurs with standard of care alone in patients aged about 4 to 6 years, such as those in the Applicant’s studies; any effect of ELEVIDYS is likely to be moderate; and the NSAA is effort-dependent and process-dependent. Thus, randomized, double-blind, placebo-controlled studies are necessary to clearly ascertain the effect of ELEVIDYS. The only data available that can provide reliable assessment of NSAA performance are those from Study 102 Part 1.

The primary objectives of Study 102 were to evaluate expression of ELEVIDYS micro-dystrophin in skeletal muscle at Week 12, and to evaluate the effect of ELEVIDYS on the NSAA Total Score in Part 1. Study 102 Part 1 enrolled 41 ambulatory male subjects with DMD, aged 4 to 7 years, who either had a confirmed frameshift mutation or a premature stop codon mutation between exons 18 to 58 in the *DMD* gene.

These subjects were randomized in a 1:1 ratio and received a single intravenous infusion of either ELEVIDYS (N = 20) or placebo (N = 21). However, the Applicant retrospectively determined that in the ELEVIDYS group, only 8 subjects actually received the intended dose (1.33×10^{14} vg/kg), while 6 subjects received approximately two-thirds of the intended dose (8.94×10^{13} vg/kg; middle dose) and 6 subjects received about half of the intended dose (6.29×10^{13} vg/kg; low dose). This discrepancy was identified following a change in the analytical method for dose determination.

Randomization was stratified by age (4-5 years versus 6-7 years). Key demographic data are presented in Table 1 below. All subjects were on a stable dose of corticosteroids as standard of care treatment for DMD, for at least 12 weeks prior to infusion of ELEVIDYS or placebo. All subjects had baseline titers of anti-AAVrh74 total binding antibodies of <1:400, as determined by an investigational ELISA assay. The day prior to treatment, the subject's background dose of corticosteroid was increased to at least 1 mg/kg (prednisone equivalent) daily, and was continued at this level for at least 60 days after the infusion, unless earlier tapering was indicated clinically.

Efficacy

Change in the NSAA Total Score was assessed from baseline to Week 48 after infusion of ELEVIDYS or placebo. The difference between the overall ELEVIDYS group and the placebo group was not statistically significant ($p = 0.37$). The least squares (LS) mean change (standard error, SE) in the NSAA Total Score from baseline to Week 48 was 1.7 (0.6) points for the SRP-9001 group and 0.9 (0.6) points for the placebo group. The difference between the ELEVIDYS and placebo groups at all time points is well within the uncertainty bounds, also demonstrated by the absence of even a trend toward statistical significance.

Exploratory subgroup analysis suggests a benefit for ELEVIDYS in subjects aged 4 to 5 years: the LS mean change (SE) in NSAA Total Score from baseline to Week 48 was 4.3 (0.7) points for the ELEVIDYS group, versus 1.9 (0.7) points for the placebo group. Subjects aged 6-7 years, however, showed the opposite result: the LS mean change (SE) in NSAA Total Score from baseline to Week 48 was -0.2 (0.7) points for the ELEVIDYS group compared to 0.5 (0.7) points for the placebo group. In addition, subjects aged 6 to 7 years in the ELEVIDYS group showed no improvement from baseline. There are several important caveats associated with the exploratory subgroup analysis: it was based on limited sample size; it was not prespecified for hypothesis testing; and no prespecified multiplicity adjustment strategy was employed. Such post hoc subgroup analysis following an overall nonsignificant test in the population as a whole therefore can only be considered hypothesis-generating. Results of the subgroup analysis consequently must be interpreted with caution. Significance tests such as p-values from an exploratory analysis after an overall nonsignificant test in the population as a whole are inherently misleading. For this reason, significance tests from these exploratory analyses have not been included in this review.

Levels of ELEVIDYS micro-dystrophin in subjects from Study 102 Part 1 at Week 12 following ELEVIDYS infusion were determined by Western blot performed on biopsied muscle tissue, adjusted for muscle content, and expressed as a percent of control (i.e., relative to levels of normal dystrophin in muscle tissue from healthy individuals).

Expression of ELEVIDYS micro-dystrophin increased with increasing dose of ELEVIDYS: the mean level (standard deviation, SD) was 3.6% (5.7), 28.2% (52.2), and 43.4% (48.6) for subjects who received the low dose, middle dose, and intended dose, respectively. However, no clear association was evident overall between expression of ELEVIDYS micro-dystrophin at Week 12, and NSAA Total Score change at Week 48. The limited data (n = 8) from subjects aged 4 to 5 years suggest improvement in the NSAA Total Score with increased expression of ELEVIDYS micro-dystrophin; no such association was observed in subjects aged 6-7 years (n = 11).

The Applicant also performed exploratory analyses comparing change in the NSAA Total Score for subjects treated with ELEVIDYS from the three studies, versus NSAA results for patients with DMD from external control data sources. The LS mean of the treatment difference in NSAA Total Score from baseline to Year 1 was 2.5 points higher in the ELEVIDYS subjects compared to the external control patients. These results, however, cannot provide confirmatory evidence of effectiveness to support clinical benefit of ELEVIDYS: the same considerations which limit interpretability of open-label studies also preclude use of external controls.

Safety

The safety database consists of the 85 subjects with a confirmed mutation in the *DMD* gene who received a single intravenous infusion of ELEVIDYS in the three clinical studies described in the BLA submission. At the time of ELEVIDYS administration, subjects had a mean age of 7.1 years (range: 3-20) and mean weight of 25.9 kg (range: 12.5-80.1). Seventy-three subjects received the intended dose of ELEVIDYS (1.33×10^{14} vg/kg), and 12 received one of two lower doses. Of the 85 subjects, 45 subjects (Study 101 and Study 102) received ELEVIDYS manufactured by Process A, and 40 subjects received ELEVIDYS manufactured by Process B. ELEVIDYS is not analytically comparable to Process A ELEVIDYS, due to the higher percentage of empty-capsid impurities in Process B ELEVIDYS.

There were no deaths. Two cases of immune-mediated myositis, including one life-threatening case, were observed approximately 1 month after ELEVIDYS infusion. The subject who experienced life-threatening immune-mediated myositis had a deletion mutation involving exons 3-43 in the *DMD* gene. The other subject, a newly-reported case, was not part of the 85-subject safety database; he had a deletion mutation involving exons 8 and 9 in the *DMD* gene. These immune reactions may have resulted from a T-cell-based response due to lack of self-tolerance to a specific region encoded by the transgene. ELEVIDYS therefore is contraindicated in patients with any deletion in exons 8 and/or 9 in the *DMD* gene. Acute serious myocarditis and troponin-I elevations, and acute liver injury (ALI)—defined as gamma-glutamyl transferase (GGT) $>3 \times$ the upper limit of normal (ULN), glutamate dehydrogenase (GLDH) $>2.5 \times$ ULN, alkaline phosphatase $>2 \times$ ULN, or alanine aminotransferase (ALT) $>3 \times$ baseline excluding ALT elevation from degenerating muscle—have been observed following ELEVIDYS infusion. The cases of myositis and myocarditis occurred in subjects receiving ELEVIDYS manufactured by Process B. The most common adverse reactions (incidence $\geq 5\%$) include vomiting (61%), nausea (40%), ALI (37%), pyrexia (24%), and thrombocytopenia (12%).

All clinical trials enrolled only subjects with baseline titers of anti-AAVrh74 total binding antibodies of <1:400, measured using an investigational enzyme-linked immunosorbent assay (ELISA). Following ELEVIDYS infusion, increase in anti-AAVrh74 total binding antibody titers occurred in all subjects. Anti-AAVrh74 total binding antibody titers reached at least 1:409,600 in every subject, and titers exceeded 1:26,214,400 in some subjects. The safety of re-administration of ELEVIDYS has not been evaluated in humans.

Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) met on May 12, 2023, to discuss BLA 125781. The committee voted 8 to 6 in favor of Accelerated Approval of SRP-9001. Several committee members who voted in favor of Accelerated Approval did so despite reservations about the clinical study results and use of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit.”

Testimony by clinical investigators involved in the Applicant’s studies, and videos of several study subjects, suggest that SRP-9001 may provide benefit to some patients. While certainly compelling, these data do not address FDA’s broader concerns of how to identify which patients may benefit and which may not, and whether ELEVIDYS micro-dystrophin is a suitable surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval. Those issues instead are expected to be informed by evidence indicating effectiveness from adequate and well-controlled studies, which is lacking in this BLA submission.

Conclusions

The Applicant has provided substantial evidence that ELEVIDYS infusion leads to expression of ELEVIDYS micro-dystrophin, the proposed surrogate endpoint for Accelerate Approval. However, to support Accelerated Approval, the surrogate endpoint must be “reasonably likely to predict clinical benefit.” Determination of whether a candidate surrogate endpoint is “reasonably likely to predict clinical benefit” is a matter of judgment, dependent on biological plausibility; empirical evidence (which may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data); and sufficient supportive clinical data.

Since ELEVIDYS micro-dystrophin is a novel protein that does not occur in nature, epidemiologic data are not available, and the effect of ELEVIDYS micro-dystrophin on the pathophysiology of DMD is not known. The data in the BLA submission do not indicate a persuasive correlation between expression of ELEVIDYS micro-dystrophin and clinical benefit. Thus, there is insufficient evidence that expression of ELEVIDYS micro-dystrophin is “reasonably likely to predict clinical benefit.” Expression of ELEVIDYS micro-dystrophin therefore is not a suitable surrogate endpoint to support Accelerated Approval of ELEVIDYS for the treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene.

Available data from exploratory analysis suggests improved NSAA Total Score with increased expression of ELEVIDYS micro-dystrophin in subjects aged 4 to 5 years (with the caveat of limited data, from only 8 subjects), and no clear association in subjects aged 6 to 7 years. Exploratory subgroup analysis suggests that the ELEVIDYS group

may have had a better NSAA outcome compared to the placebo group for ambulatory subjects aged 4 to 5 years. The same exploratory analysis, however, also suggests that for ambulatory subjects aged 6 to 7 years, no difference was present between the SRP-9001 group and the placebo group; moreover, the ELEVIDYS 1 group did not even demonstrate improvement from baseline. However, these exploratory subgroup analyses following an overall nonsignificant test in the population as a whole can only be considered hypothesis-generating. These data therefore are insufficient to support expression of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval of ELEVIDYS for even a limited patient population, such as ambulatory patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.

Moreover, available data do not provide clear evidence that ELEVIDYS is likely beneficial for ambulatory patients with DMD. It is challenging to conclude with reasonable confidence from data provided by the Applicant either that ELEVIDYS is likely effective for younger patients, or that it is likely ineffective for older patients or patients with somewhat poorer functional status.

The clinical reviewer has significant concerns related to the possibility of administering an ineffective gene therapy. Because of the high anti-AAVrh74 antibody levels after ELEVIDYS infusion, and possible immunologic cross-reactivity with other AAV subtypes, patients who do not benefit from ELEVIDYS likely will not be able to receive an effective AAV-based gene therapy for DMD in the future.

The clinical reviewer recommends Complete Response for BLA 125781, because expression of ELEVIDYS micro-dystrophin is not a suitable surrogate endpoint that is “reasonably likely to predict clinical benefit,” and the overall potential benefit associated with the Accelerated Approval of ELEVIDYS does not outweigh the known and unknown risks of ELEVIDYS. The clinical reviewer recommends inclusion of the following in the Complete Response letter to the Applicant:

Your BLA submission for Accelerated Approval of SRP-9001 provides data from three clinical studies (SRP-9001-101, SRP 9001-102, and SRP-9001-103) involving subjects with Duchenne muscular dystrophy (DMD). Your proposed primary evidence of effectiveness is based on the candidate surrogate endpoint of expression of ELEVIDYS micro-dystrophin protein following administration of SRP-9001.

To support Accelerated Approval, the surrogate endpoint must be “reasonably likely to predict clinical benefit.” Determination of whether a candidate surrogate endpoint is “reasonably likely to predict clinical benefit” is a matter of judgment, depending on biological plausibility; empirical evidence (which may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data); and sufficient supportive clinical data.

Since ELEVIDYS micro-dystrophin is a novel protein that does not occur in nature, epidemiologic data are not available, and the effect of ELEVIDYS micro-dystrophin on the pathophysiology of DMD is not known. The data in your BLA do not indicate a persuasive correlation between expression of ELEVIDYS micro-dystrophin and improvement on the North Star Ambulatory Assessment. Thus, there is insufficient

evidence that expression of ELEVIDYS micro-dystrophin is “reasonably likely to predict clinical benefit” to support Accelerated Approval of SRP-9001.

We recommend that you complete Study SRP-9001-301 to assess the effectiveness of SRP-9001 based on the prespecified clinically meaningful endpoints. After completing the study, and depending on the results, you may request a meeting with us to discuss the future clinical development plan of SRP-9001 for the treatment of DMD, including readiness for submission of a BLA.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for the 41 subjects in Study 102 are shown in Table 1.

Table 1. Key Demographic Characteristics, Study SRP-9001 (Part 1)

Characteristic	SRP-9001 (n=20)	Placebo (n=21)	Total (N=41)
Age, mean (SD), year	6.3 (1.2)	6.2 (1.1)	6.3 (1.1)
Age, median (min, max), year	6.5 (4.5, 7.9)	6.0 (4.3, 8.0)	6.1 (4.3, 8.0)
Age 4-5 years, n (%)	8 (40%)	8 (38%)	16 (39%)
Age 6-7 years, n (%)	12 (60%)	13 (62%)	25 (61%)
Race, n (%)			
White	13 (65%)	17 (81%)	30 (73%)
Black or African American	0	0	0
Asian	4 (20%)	1 (5%)	5 (12%)
Other	3 (15%)	3 (14%)	6 (15%)
Ethnicity, n (%)			
Hispanic or Latino	1 (5%)	4 (19%)	5 (12%)
Other	19 (95%)	17 (81%)	36 (88%)

Source: SRP-9001 Revised USPI

Abbreviation: max, maximum; min, minimum; NSAA, North Star Ambulatory Assessment; SD, standard deviation

Reviewer Comment:

The Applicant proposes to use expression of ELEVIDYS micro-dystrophin as the surrogate endpoint for Accelerated Approval. Therefore, no pivotal studies were submitted to the BLA. The review team’s analysis of whether expression of ELEVIDYS micro-dystrophin is suitable as a surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval is based on the data collected from Study 102 Part 1, the only randomized, double-blind, placebo-controlled study for which data are available.

Randomized, double-blind, placebo-controlled studies are necessary to clearly ascertain the effect of SRP-9001. There are several reasons why data from other study designs are difficult to interpret: progression of DMD is heterogeneous; improvement on the NSAA occurs with standard of care alone in patients aged about 4 to 7 years, such as those in the Applicant’s studies; any effect of SRP-9001 is likely to be moderate; and the NSAA is effort-dependent and process-dependent.

1.2 Patient Experience Data

Please see Patient Experience Data reviewed in this BLA, summarized in Table 2 below.

Table 2. Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input checked="" type="checkbox"/>	Clinician-reported outcome	6.1.1, 6.2.1, 6.3.1
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input checked="" type="checkbox"/>	Natural history studies	6.2.11.5
<input type="checkbox"/>	Patient preference studies	
<input checked="" type="checkbox"/>	Other: Activities Outside of the Clinic (videos of subjects submitted to the BLA in module 1.15.1.4)	1.2
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
	Perspectives shared at patient stakeholder meeting	1.2
<input type="checkbox"/>	Patient-focused drug development meeting	
	FDA Patient Listening Session	
<input checked="" type="checkbox"/>	Other stakeholder meeting summary report	1.2
<input type="checkbox"/>	Observational survey studies	
<input checked="" type="checkbox"/>	Other: External Advisory Committee, 74 th Cellular, Tissue, and Gene Therapy Advisory Committee (CTGTAC) held on May 12, 2023: Open Public Hearing session and comments submitted to the Docket No. FDA-2023-N-1190	5.4.1

Reviewer Comment:

In addition to the clinical outcome data from the clinical trials and natural history studies data, this reviewer considered the following patient experience materials of subjects who received SRP-9001 in the setting of clinical trials:

- (1) A selection of videos of study subjects with DMD at different aged and timepoints following treatment with SRP-9001 was submitted to the BLA in Module 1.15.1.4. These videos, taken by family members, were shared by parents and include the viewpoint of a subject matter expert experienced in treatment of children with DMD. The videos showed the children during social engagement or participation in daily activities such as gym class, doing “the floss” at a basketball game, or playing a carnival pitch game.

The videos, while impressive, pose several limitations for scientific analysis, such as lack of baseline for comparison; tools (e.g., stairs) used at baseline and after SRP-9001 treatment that are not comparable; and use of non-standardized recording methods.

- (2) In response to an FDA Information Request (March 20, 2023), the Applicant identified one additional subject for whom the parents provided a pre-treatment and post-treatment video of their son descending stairs. The new video was submitted to the BLA in Module 1.15.1.4. The Applicant emphasized that “these are home videos not associated with the clinical trial or the formal clinical effect assessments in the trial.” This reviewer concurs with the Applicant that the interpretation of the videos can be challenging due to the non-standardized manner of recording.
- (3) This reviewer also considered the comments and videos submitted by parents and clinicians to Docket No. FDA-2023-N-1190, including pre-treatment and post-treatment videos of five study subjects submitted by a study investigator. Pre-treatment and post-treatment NSAA Total Scores were obtained, as well as expression levels of ELEVIDYS micro-dystrophin in these subjects.

This reviewer noted the following limitations:

- (1) All boys in the videos were subjects in an open-label study. Despite showing improved function in the videos, two boys experienced worsening of NSAA Total Score over time, while three had improvement in NSAA Total Score.
- (2) Expression of ELEVIDYS micro-dystrophin in these subjects varied from 20% to 133%, suggesting lack of a clear relationship between ELEVIDYS micro-dystrophin and improved clinical performance.
- (3) Two subjects showed improvement 4 and 8 weeks after treatment. This improvement cannot be explained by the mechanism of action of SRP-9001, which requires several weeks for transgene expression.
- (4) One subject with NSAA improvement, from 23 points at baseline to 27 at Week 12 and 28 at Week 52), received a higher dose of corticosteroid on Days 1 through 45 after treatment. In assessing his observed functional improvement, it is challenging to distinguish the effects of high-dose corticosteroids from effects of SRP-9001.
- (5) Three subjects had mutations amenable to Exon 45 skipping. Natural history data suggest that boys with this type of mutation may maintain ambulation longer.

Table 3 summarizes FDA interactions with external stakeholder organizations since 2019.

Table 3. FDA Meetings With Patients and Advocacy Organizations

Date	Meeting	Organization	Discussion Topic
January 23-25, 2019	PPMD Duchenne Healthcare Professionals Summit: Addressing Challenges and Seeking Solutions in Duchenne	PPMD https://www.parent2projectmd.org	FDA speakers presented on “Platform Clinical Trials” and “Regulatory Challenges in CBER”
March 4, 2019	PPMD Duchenne Gene Therapy Policy Forum	PPMD	Discussion of the Applicant’s gene therapy in development; CBER speaker provided an update on efforts to facilitate development and approval of gene therapy products
May 13, 2019	PPMD Duchenne Outcomes Meeting	PPMD	DMD research landscape; clinical outcome data being collected by DMD researchers and registries; gaps in those data; potential approaches and opportunities to facilitate collection of data that would help fill the identified gaps
December 26, 2019	Informal conference call with CBER	Cure Duchenne https://www.cureduchenne.org	Cure Duchenne biobank project
January 5, 2021	PPMD/FDA Meeting	PPMD	Development of new Duchenne gene therapy clinical trial preference study
May 24, 2021	PPMD/CBER Meeting	PPMD	Update to community- led Duchenne guidance and considerations for gene therapies
September 19, 2022	Informal conference call with CBER	One Rare https://onerare.org PPMD	Discussion of patient and caregiver concerns and preferences regarding gene therapy products for DMD

Source: FDA

Abbreviations: CBER, Center for Biologics Evaluation and Research; DMD, Duchenne muscular dystrophy; FDA, Food and Drug Administration; PPMD, Parent Project Muscular Dystrophy.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

2.1.1 Duchenne Muscular Dystrophy

DMD is a serious condition with an urgent unmet medical need. DMD results from mutation of the *DMD* (also known as *Dystrophin*) gene, the largest known human gene, which is carried on the X chromosome. DMD affects about 1 in 3,300 boys. Although histologic and laboratory evidence of myopathy may be present at birth, the clinical onset of skeletal muscle weakness usually does not become evident until early childhood. The average age at diagnosis is approximately 5 years.

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

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

2.1.2 Clinical Outcome Measure for DMD: North Star Ambulatory Assessment

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

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

Performance on the NSAA can be affected both by the consistency of administration (process-dependence), and by the motivation of the subject and coaching or encouragement by family members, caregivers, or medical staff (effort-dependence).² Therefore, in clinical studies employing the NSAA, blinding to treatment assignment is crucial for clear interpretation of results.

Natural history data of 395 subjects selected from the North Star Clinical Network database showed heterogeneous disease progression and identified four general

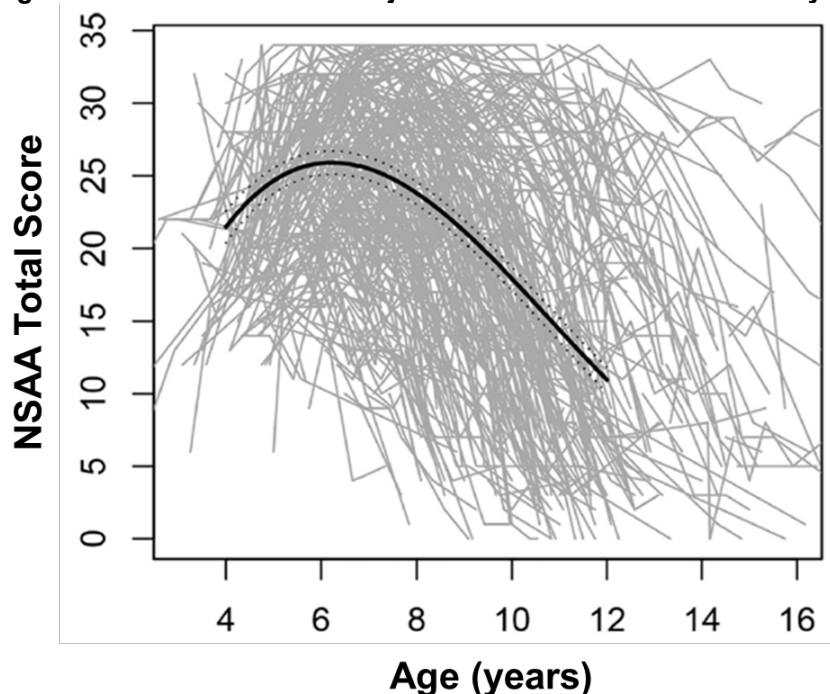
1. Wahlgren, L, AK Krokmark, M Tulinius, and K Sofou, 2022, One in five patients with Duchenne muscular dystrophy dies from other causes than cardiac or respiratory failure, *Eur J Epidemiol*, 37(2):147-156.

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

trajectories of ambulatory function, measured by the NSAA Total Score, over time. Twenty-five percent of the boys were in cluster 1 (NSAA falling to ≤ 5 at age ~ 10 years), 35% were in cluster 2 (NSAA ≤ 5 at age ~ 12 years), 21% were in cluster 3 (NSAA ≤ 5 at age ~ 14 years), and 19% were in cluster 4 (NSAA > 5 up to 15 years). Mean ages at diagnosis of DMD were similar across clusters (4.2, 3.9, 4.3, and 4.8 years, respectively).³

The overall mean trajectory of NSAA Total Score versus age initially increased at a rate of about 3 points per year, peaking at age 6.3 years with a mean NSAA Total Score of 26. Following the peak, scores eventually approached a rate of decline of approximately 3 points per year (Figure 1).

Figure 1. NSAA Total Score Trajectories for Individual Patients by Age



Source: Modified from Muntoni et al (2019) *PLoS ONE* 14(9): e0221097.
Abbreviation: NSAA, North Star Ambulatory Assessment

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

There is no cure for DMD. The main pharmacologic treatment is corticosteroids (usually deflazacort or prednisone), typically initiated in boys aged 4 years or older. In addition, effort is made to control symptoms using physical therapy, surgery to correct progressive scoliosis, medications for cardiac function, assisted ventilation, and tracheostomy.⁴

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

4. MedLine Plus, 2022, Duchenne muscular dystrophy, accessed April 4, 2023, 2023, <https://medlineplus.gov/ency/article/000705.htm>.

Deflazacort received FDA approval in 2017 for the treatment of patients with DMD.⁵ Data from a Phase 3 randomized, double-blind, placebo-controlled trial evaluating muscular strength in 196 boys aged 5 to 15 years showed a significant change compared with placebo, on par with the efficacy observed with prednisone, in the primary outcome measure, muscle strength at 12 weeks. Subjects receiving deflazacort demonstrated less weight gain than those receiving prednisone, although deflazacort still has multiple side effects associated with long-term corticosteroid use.⁶

Four exon-skipping drugs have received FDA approval through the Accelerated Approval pathway based on surrogate endpoints. Therefore, for regulatory purposes, they are not considered available therapies. These drugs are intended to treat the minority of patients with DMD harboring amenable mutations in the *DMD* gene: eteplirsen (Exondys 51, approved September 19, 2016; ~13% of patients), golodirsen (Vyondys 53, approved December 12, 2019; ~8% of patients), viltolarsen (Viltepso, approved August 12, 2020; ~8% of patients), and casimersen (Amondys 45, approved February 25, 2021; ~8% of patients).^{7,8,9,10} All are antisense oligonucleotides which modify splicing of DMD mRNA to promote translation of a shortened forms of the dystrophin protein retaining some function. All four require periodic intravenous administration. Importantly, none of the required confirmatory clinical studies have been completed for these products, so their clinical benefit remains unknown.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically related products currently available.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The product is not approved in any country. A global Phase 3 clinical trial (Study 301 [EMBARC], NCT05096221) is ongoing.

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

Table 4 below is a brief summary of the main regulatory milestones and interactions between the FDA and the Applicant.

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

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

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

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

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

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

Table 4. Key Regulatory History of SRP-9001

Date	Milestone	Background Information
November 16, 2016	Pre-IND meeting	—
October 5, 2017	IND 17763 received from Dr. Jerry Mendell (Nationwide Children's Hospital)	—
November 3, 2017	IND may proceed	—
June 27, 2018	IND placed on Clinical Hold – Clinical Hold letter issued July 22, 2018	IND placed on clinical hold because human subjects were or could have been exposed to an unreasonable and significant risk of illness or injury, and the IND did not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies. Specific deficiencies in CMC were communicated.
September 21, 2018	Clinical Hold removed – study may proceed	—
October 11, 2018	IND transferred to the Applicant	—
(b) (4)	(b) (4)	—
December 20, 2018	Type B multidisciplinary meeting	FDA stated that expression of ELEVIDYS 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 the Applicant choose an endpoint that assesses clinically meaningful benefit, as manifested by how a patient feels, functions, or survives.
(b) (4)	(b) (4)	—
June 4, 2020	Request for Fast Track designation granted	—
September 4, 2020	Type C CMC and Clinical Meeting	FDA expressed concern about the lack of correlation between clinically meaningful benefit and the primary efficacy endpoint, expression of ELEVIDYS micro-dystrophin at Week 12 after SRP-9001 administration. FDA recommended that the Applicant revise the design of Study SRP-9001-103 (the first study to utilize SRP-9001 manufactured by Process B) from a single-arm, open-label study to a randomized, blinded, and concurrent-controlled design, to better serve as a bridging study.
July 27, 2021	Type B End-of-Phase 2 teleconference	FDA stated that based on the results of Study SRP-9001-101 and Study SRP-9001-102, the Agency is not convinced that a clear correlation

Date	Milestone	Background Information
		exists between expression of ELEVIDYS micro-dystrophin and clinical benefit.
August 6, 2021	IND placed on Clinical Hold due to SAE – letter issued September 1, 2021	IND placed on Clinical Hold as it did not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies. An unexpected SAE of asthenia in a 9-year-old subject was reported, requiring hospitalization and respiratory support after he received therapy in Study 103.
October 1, 2021	Clinical Hold removed – study may proceed	—
April 29, 2022	Type C Meeting to discuss possible Accelerated Approval	FDA expressed concerns regarding the ability of expression of ELEVIDYS micro-dystrophin to predict clinical benefit. the Applicant stated that regulatory precedent exists for granting Accelerated Approval to drugs promoting expression of “shortened forms of dystrophin.” FDA replied that “shortened forms of dystrophin” constitute a diverse group, which are not equivalent regarding their ability to serve as surrogate endpoints considered “reasonably likely to predict clinical benefit” for Accelerated Approval.
September 28, 2022	Original BLA submission	—

Source: FDA

Abbreviations: BLA, Biologics License Application; CFR, Code of Federal Regulations; CMC, chemistry, manufacturing, and controls; FDA, Food and Drug Administration; IND, Investigational New Drug; RMAT, Regenerative Medicine Advanced Therapy; SAE, serious adverse event.

2.6 Other Relevant Background Information

2.6.1 FDA Approval Pathways and the Role of Surrogate Endpoints

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

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

Before a surrogate endpoint can be accepted in place of a clinical outcome, the surrogate endpoint must be supported by sufficient clinical evidence indicating that it can be relied upon to predict, or to correlate with, clinical benefit. When extensive evidence

is available, including results of epidemiologic investigation and clinical studies, such surrogate endpoints are termed validated surrogate endpoints. Validated surrogate endpoints may be accepted by FDA in place of clinical endpoints for approval of new drugs via the Traditional Approval pathway.

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

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

- Biological plausibility of the relationship of the disease, the candidate surrogate endpoint, and the desired effect;
- Empirical evidence, which “may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data” (although evidence of pharmacologic activity alone is not sufficient)^{12, 13, 14}; and
- Clinical data supporting the relationship of an effect on the candidate surrogate endpoint to an effect on the clinical outcome. An effect on the surrogate endpoint is expected to correlate with a clinical outcome measure that directly assesses benefit in clinical studies by evaluating how a patient feels, functions, or survives.

2.6.2 Special Risks of AAV Vector-Based Gene Therapy Products

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

Accelerated Approval of an ineffective gene therapy product poses an additional, unique risk. Patients receiving a systemically-administered AAV vector-based gene therapy mount an immune response against the AAV vector carrying the transgene. Patients for whom the dose is inadequate are therefore unable to receive additional doses of the same medication. Moreover, that immune response has been found to cross-react

11. FDA-NIH Biomarker Working Group, 2016, Reasonably Likely Surrogate Endpoint, Food and Drug Administration, accessed April 13, 2023, <https://www.ncbi.nlm.nih.gov/books/NBK453485/>.

12. Under section 506(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

13. 57 FR 58942

14. FDA, 2014, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, <https://www.fda.gov/media/86377/download>.

against other AAV vectors of different serotypes. As a result, patients likely have only one opportunity to receive a systemically-administered AAV vector-based gene therapy.

In this case, patients for whom ELEVIDYS is ineffective would be unable to receive a different, beneficial AAV vector-based gene therapy product in the future.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was filed on November 25, 2022. The submission was adequately organized and integrated to accommodate conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices and Submission Integrity

All three studies (Study 101, Study 102, and Study 103) enrolled only subjects in the United States. The studies were conducted under Center for Biologics Evaluation and Research (CBER) IND 017763, in accordance with the regulations specified in 21 CFR 312 and were compliant with Good Clinical Practice international ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human subjects. The clinical trials included provisions for informed consent by parents or guardians of all study subjects, and for ethical treatment of study subjects.

Bioresearch Monitoring (BIMO) inspection assignments were issued for two domestic clinical investigator sites. One site participated in the conduct of Study 102 and Study 103, while the other site participated solely in the conduct of Study 103. These two sites were selected based upon Applicant-reported adverse events, protocol deviations, total number of enrolled subjects, and previous BIMO inspection histories. The inspections did not reveal significant problems impacting the data submitted in support of this BLA (Table 5).

Table 5. Summary of Bioresearch Monitoring Inspections at Two Clinical Investigator Sites

Site ID	Number of Subjects Randomized	Investigator and Location	Form 483 Issued	Final Inspection Classification
201	14 (Study 102) 37 (Study 103)	Jerry R. Mendell, MD Columbus, OH	No	NAI
210	8 (Study 103)	Craig Zaidman, MD St. Louis, MO	No	NAI

Source: BLA 125781, BIMO Review

Note: An FDA Form 483 is issued at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic Act and related Acts.

Abbreviations: BIMO, Bioresearch Monitoring; NAI, no action indicated.

3.3 Financial Disclosures

No significant issues with financial disclosures were identified that could suggest undue bias in the data submitted in support of this BLA.

Covered clinical study (name and/or number): SRP-9001-101 (Study 101) SRP-9001-102 (Study 102) SRP-9001-103 (Study 103)
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: 6
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <div style="margin-left: 40px;"> Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: X Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant) </div>
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 <div style="margin-left: 40px;"> Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant) </div>

All studies included in this application were conducted in accordance with FDA regulations, the International Council for Harmonization E6 Guideline for Good Clinical Practice, Declaration of Helsinki, and applicable local, state, and federal laws. Each study was reviewed and approved by the appropriate institutional review boards, as required.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

4.1.1 SRP-9001

SRP-9001 is an AAV-based gene therapy designed to deliver the gene encoding ELEVIDYS micro-dystrophin protein. SRP-9001 is a nonreplicating, recombinant, adeno-associated virus serotype rh74 (rAAVrh74)-based vector containing the ELEVIDYS micro-dystrophin transgene under the control of the chimeric MHCK7 (alpha-myosin heavy chain/creatine kinase 7) promote. The genome within the ELEVIDYS AAVrh74

vector includes no viral genes, and consequently ELEVIDYS is incapable either of replication or reversion to a replicating form. The micro-dystrophin protein encoded by ELEVIDYS is a rationally designed protein which contains selected domains of normal human dystrophin expressed in healthy muscle cells and is about one-third the size of normal dystrophin.

ELEVIDYS is delivered in a preservative-free, sterile, clear, colorless liquid that may have some opalescence and may contain white to off-white particles. ELEVIDYS is a suspension for intravenous infusion, with a nominal concentration of 1.33×10^{13} vg/mL and is supplied in single-use 10 mL vials. Each vial contains an extractable volume of 10 mL, which includes the following excipients: 200 mM sodium chloride, 13 mM tromethamine HCl, 7 mM tromethamine, 1mM magnesium chloride, and 0.001% poloxamer 188.

4.1.2 Manufacturing Processes

To produce purified Good Manufacturing Practice-grade ELEVIDYS drug product for the clinical program, the Applicant utilized two different manufacturing processes: Process A for the early clinical studies (Study 101 and Study 102), and Process B for the later clinical studies (Study 103 and the Phase 3 study, Study 301). The changes in manufacturing from Process A to Process B affected the purity of the ELEVIDYS product, such that the products made by the two manufacturing processes are not analytically comparable for the critical quality attribute of full viral capsids.


Process A used a purification method that allows near-complete removal of empty AAV capsids (i.e., capsids lacking the viral genome encoding ELEVIDYS micro-dystrophin) from the final formulated product. Process A product was manufactured at Nationwide Children's Hospital (Ohio State University, Columbus, OH).

Process B, the to-be-commercial manufacturing process, utilizes a scaled-up purification technique that incorporates chromatography-based methods for separation of empty capsid residuals from the full capsids. The Process B purification method results in poor separation of empty AAV capsids from full AAV capsids. Process B is manufactured by Catalent Pharma Solutions (Baltimore, MD).

Comparability of Process A and Process B Products

Based on assessment by both the Applicant and FDA, the Process A and Process B products were determined to not be analytically comparable regarding levels of empty capsid residuals. The percent of full capsids in Process A and Process B products were found to be significantly different (t-test, $p = 0.0002$), with Process B product containing more empty-capsid impurities.

(b) (4)



4.1.3 Concerns Regarding Increased Percentage of Empty Capsids

The dose of the drug product is reported as vector genomes per kilogram body weight (vg/kg), and does not take into account the level of empty-capsid impurities in each lot.

Because of the high dose of vector administered (proposed doses: 10-70 kg, 1.33×10^{14} vg/kg; ≥ 70 kg, 9.31×10^{15} vg/kg) and the proposed acceptance criterion for percent full capsids, subjects treated with Process B SRP-9001 may receive drug product lots containing a substantial number of empty capsids, potentially resulting in administration of more than 100% additional viral particles, compared with subjects who received Process A SRP-9001. For example, a subject weighing 50 kg who is administered SRP-9001 with 50% full capsids will receive 6.7×10^{15} capsids containing the vector genome, and 6.7×10^{15} empty capsids with no potential therapeutic benefit.

This difference may have important clinical implications. Reports show that immune responses and associated adverse events (e.g., T-cell mediated liver injury, thrombocytopenic microangiopathy associated with complement activation) are directly related to vector dose.^{15,16} Empty capsids may contribute an increased antigenic load, with the potential to enhance recognition and clearance of AAV-transduced cells by activated capsid-specific cytotoxic CD8+ T cells.^{17,18,19,20} These properties may result in decreased overall safety and efficacy of treatment with ELEVIDYS. The effects on long-term safety and efficacy of such high levels of empty-capsid impurities cannot be determined by analytical testing, and instead require clinical data.

4.2 Assay Validation

Please see the Chemistry, Manufacturing and Controls review for details.

4.3 Nonclinical Pharmacology/Toxicology

Proof-of-concept studies for ELEVIDYS were conducted in *Dmd^{mdx}* mice, an animal model which manifests a milder clinical phenotype than that of patients with DMD.

Assessment of function of ELEVIDYS micro-dystrophin in these studies was limited to isolated measurements of muscle force in the tibialis anterior and diaphragm, which showed variable increases in specific force, with partial correction of the deficit. The Applicant provided post hoc correlation analyses of data across these studies and concluded that the functional outcome measured by relative specific force did not correlate with expression of ELEVIDYS micro-dystrophin protein as measured by

15. Kishimoto, TK and RJ Samulski, 2022, Addressing high dose AAV toxicity - 'one and done' or 'slower and lower'?, Expert Opin Biol Ther, 22(9):1067-1071.

16. Mingozi, F and KA High, 2013, Immune responses to AAV vectors: overcoming barriers to successful gene therapy, Blood, 122(1):23-36.

17. Hui, DJ, SC Edmonson, GM Podsakoff, GC Pien, L Ivanciu, RM Camire, H Ertl, F Mingozi, KA High, and E Basner-Tschakarjan, 2015, AAV capsid CD8+ T-cell epitopes are highly conserved across AAV serotypes, Mol Ther Methods Clin Dev, 2:15029.

18. Pien, GC, E Basner-Tschakarjan, DJ Hui, AN Mentlik, JD Finn, NC Hasbrouck, S Zhou, SL Murphy, MV Maus, F Mingozi, JS Orange, and KA High, 2009, Capsid antigen presentation flags human hepatocytes for destruction after transduction by adeno-associated viral vectors, J Clin Invest, 119(6):1688-1695.

19. Finn, JD, D Hui, HD Downey, D Dunn, GC Pien, F Mingozi, S Zhou, and KA High, 2010, Proteasome inhibitors decrease AAV2 capsid derived peptide epitope presentation on MHC class I following transduction, Mol Ther, 18(1):135-142.

20. Mingozi, F and KA High, 2013, Immune responses to AAV vectors: overcoming barriers to successful gene therapy, Blood, 122(1):23-36.

Western blot, but did correlate with percentage of ELEVIDYS micro-dystrophin-positive fibers determined by immunofluorescence

Two nonclinical studies were performed using *Dmd^{mdx}* rats. Treatment with ELEVIDYS led to different responses, despite broad expression of ELEVIDYS micro-dystrophin. In the study conducted in younger (3-4-week-old) rats, administration of ELEVIDYS resulted in increased spontaneous activity, and decreased dystrophic pathology in muscle tissue, compared with control animals. However, in the study conducted in older (3-5 month-old) rats, no improvement in any of these parameters was observed.

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

The Applicant nevertheless cites the functional improvement observed in nonclinical studies as supportive evidence that expression of ELEVIDYS micro-dystrophin can be considered a surrogate endpoint “reasonably likely to predict clinical benefit” in patients. Important factors, however, further limit extrapolation of clinical benefit from these nonclinical studies:

- (1) Study design limitations (e.g., lack of robustness, missing data, potential for bias, noncompliance with principles of Good Laboratory Practice), since the studies were intended for proof of concept, and therefore were not designed or powered to assess correlation between expression of ELEVIDYS micro-dystrophin and functional outcomes;
- (2) Differences between the *Dmd^{mdx}* rodent models and patients with DMD, since these models show a milder phenotype, with less motor impairment and cardiac dysfunction compared with patients with DMD;
- (3) Species-specific differences in disease pathophysiology in these models compared with humans, including differences in compensatory mechanisms, and increased regenerative capacity of muscle fibers in the rodents;
- (4) Physiological differences between rodents and humans, such as relative differences in muscle volumes and physiological loads sustained; and
- (5) Unknown clinical significance of the functional endpoints assessed (e.g., muscle specific force) and the magnitude of change observed.

Reviewer Comment:

The limited nonclinical data for ELEVIDYS, and the differences between the rodent models and human disease, underscore the need for well-controlled clinical studies to determine whether the ELEVIDYS micro-dystrophin protein has clinically meaningful function in humans, and whether it is suitable as a surrogate endpoint “reasonably likely to predict clinical benefit.”

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Because *DMD* is the largest known human gene—spanning over 2,200 kb in the genome,²¹ resulting in a complementary DNA of about 11 kb that encodes a protein of about 427 kDa—the normal (wild-type) gene cannot be delivered via AAV-based gene therapy vectors, whose size limits their capacity to a genome of about 4.7 kb. This constraint led to the design of various novel, much smaller transgenes encoding “micro-dystrophin” proteins containing selected domains of normal dystrophin (Figure 4). The transgene encoding ELEVIDYS micro-dystrophin, delivered by SRP-9001, is one such engineered micro-dystrophin. It is based on a mutant, shortened form of dystrophin identified in a patient with milder disease (BMD; Figure 3). Unlike the shortened form of dystrophin in that patient or in other patients with BMD, or those generated by treatment with exon-skipping drugs, none of these micro-dystrophin proteins—including ELEVIDYS micro-dystrophin—are naturally expressed in any patients.

The goal of treatment with SRP-9001 is to slow or stabilize progression of DMD, so as to alter the disease trajectory to a milder, BMD-like phenotype. The Applicant is seeking Accelerated Approval of SRP-9001 for treatment of ambulatory patients with DMD. For Accelerated Approval, the Applicant proposes to utilize a surrogate endpoint—expression of ELEVIDYS micro-dystrophin at Week 12 after administration of SRP-9001—to provide primary evidence of effectiveness. This biomarker thus is intended to serve as the required surrogate endpoint considered “reasonably likely to predict clinical benefit” of SRP-9001.

SRP-9001 (rAAVrh74.MHCK7.micro-dystrophin, ELEVIDYS) consists of a 4.7 kb codon-optimized DNA vector genome within a simian AAV serotype rh74 capsid. Each virion potentially contains a single copy of the vector genome. The vector genome expression cassette contains essential elements to control gene expression, including AAV2 inverted terminal repeats, a chimeric (SV40) intron, and a synthetic polyadenylation signal (Figure 2). Expression of the gene encoding ELEVIDYS micro-dystrophin is driven by the chimeric *MHCK7* (α -myosin heavy chain/creatine kinase 7) promoter to restrict expression to skeletal and cardiac muscle.

Figure 2. ELEVIDYS Design



Source: Modified from BLA 125782.

Abbreviations: AAVrh74, adeno-associated virus vector rhesus serotype 74; ITR, inverted terminal repeat; MHCK7, chimeric α -myosin heavy chain/creatine kinase 7; pA, polyadenylation signal.

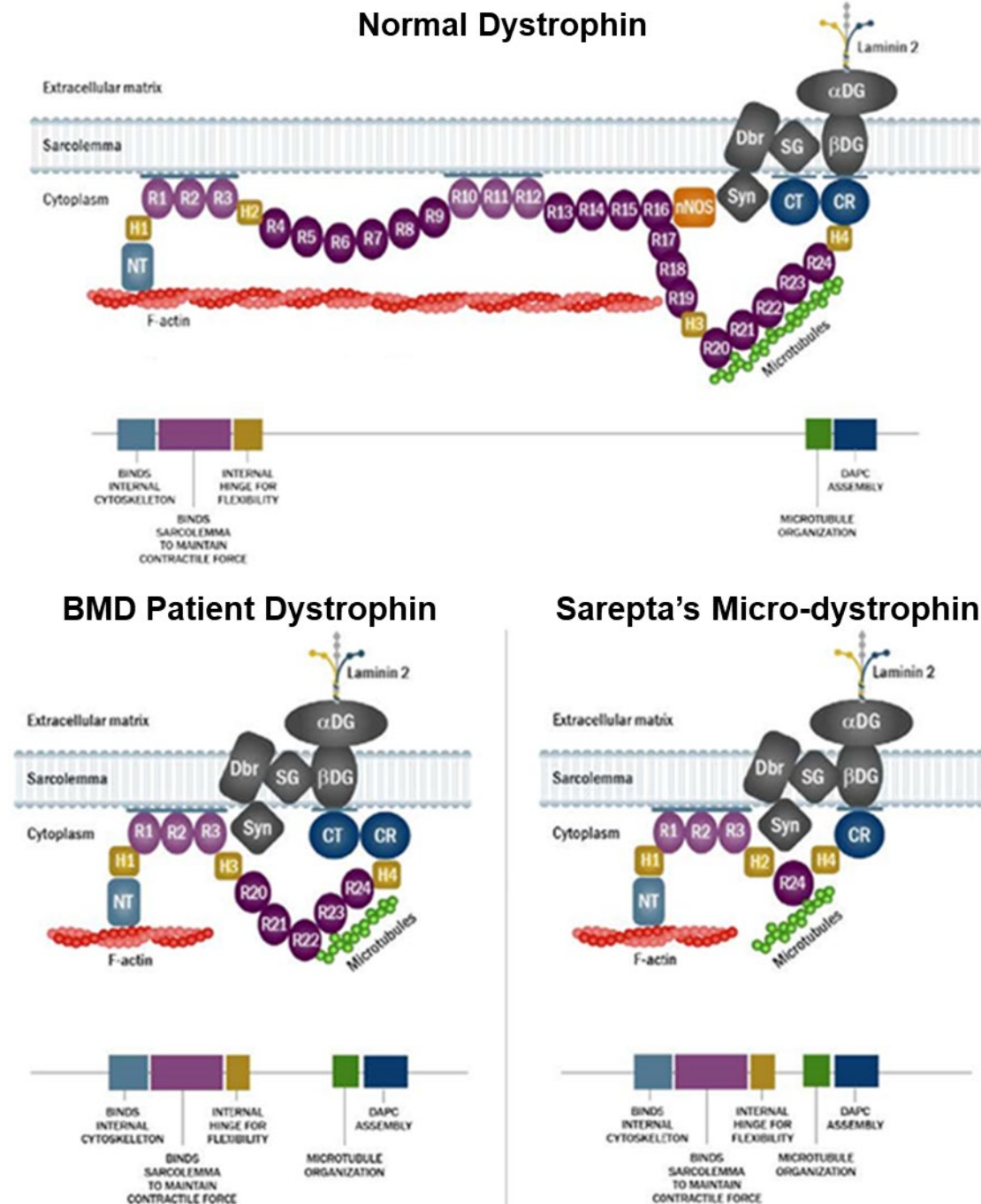
21. Koenig, M, EP Hoffman, CJ Bertelson, AP Monaco, C Feener, and LM Kunkel, 1987, Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals, *Cell*, 50(3):509-517.

The schematic in Figure 3 summarizes the structure and corresponding established functions of normal dystrophin (427 kDa); the partially-functional mutant dystrophin protein (200 kDa) from the patient with mild BMD reported by England and colleagues²²; and ELEVIDYS micro-dystrophin (138 kDa).

Normal dystrophin forms part of the dystrophin-associated protein complex (DAPC), a transmembrane oligomeric complex of proteins that spans the sarcolemma of skeletal and cardiac muscle cells. The other components of the DAPC are the sarcoglycan complex, sarcospan, the dystroglycan complex, syntrophins, and dystrobrevins.

²² England, S., Nicholson, L., Johnson, M. et al. Very mild muscular dystrophy associated with the deletion of 46% of dystrophin. *Nature* 343, 180–182 (1990). <https://doi.org/10.1038/343180a0>

Figure 3. Structure and Corresponding Functions of Normal Dystrophin, Mutant Dystrophin in a Patient with BMD (England et al., 1990), and ELEVIDYS Micro-dystrophin



Source: Modified from Applicant. (adapted from Zhao J, et al. Hum Mol Genet. 2016; 25:3647-3653).

Note: ELEVIDYS micro dystrophin is also known as Sarepta's micro-dystrophin

Abbreviations: αDG, α-dystroglycan; βDG, β-dystroglycan; BMD, Becker muscular dystrophy; CR, cysteine-rich region; DAPC, dystrophin-associated protein complex; Dbr, dystrobrevin; H, hinge region; nNOS, neuronal nitric oxide synthase; NT, N-terminus; R, rod domain; SG, sarcoglycan; Syn, syntrophin.

The DAPC connects to the extracellular protein laminin, thereby linking the cytoskeleton to the extracellular matrix. The DAPC helps to transmit and absorb the shock associated

with muscle contraction, thereby maintaining sarcolemmal integrity during muscle use. In the absence of a functional DAPC, muscle contraction in patients with DMD compromises sarcolemmal integrity, leading to leakage of intracellular contents such as creatine kinase (CK), and ultimately to loss of muscle function.

Notably, recent reports indicate that the role of normal dystrophin extends beyond serving as a spring or shock absorber. Evidence strongly suggests that the 24 spectrin-like repeats in dystrophin (Figure 4) play an important scaffolding role, helping to recruit proteins including sodium channels, potassium channels, and calcium channels; neuronal nitric oxide synthase; and multiple signaling molecules, such as kinases.²³ Due to the limited DNA-carrying capacity of the AAV vector, the gene for ELEVIDYS micro-dystrophin does not include the sequences encoding important functional domains present in normal dystrophin (Figure 4). For example, ELEVIDYS micro-dystrophin lacks the domains which bind neuronal nitric oxide synthase and α -syntrophin, two proteins known to protect muscle cells by functioning synergistically to modulate blood flow. Recruitment of neuronal nitric oxide synthase at the sarcolemma by normal dystrophin through spectrin-like repeats 16 and 17 (R16/17) and α -syntrophin helps control local blood flow by antagonizing sympathetic vasoconstriction.^{24,25,26} Because of such differences, the extent to which ELEVIDYS micro-dystrophin can function similarly to normal dystrophin, or to the various shortened forms of dystrophin in patients with BMD, is unclear.

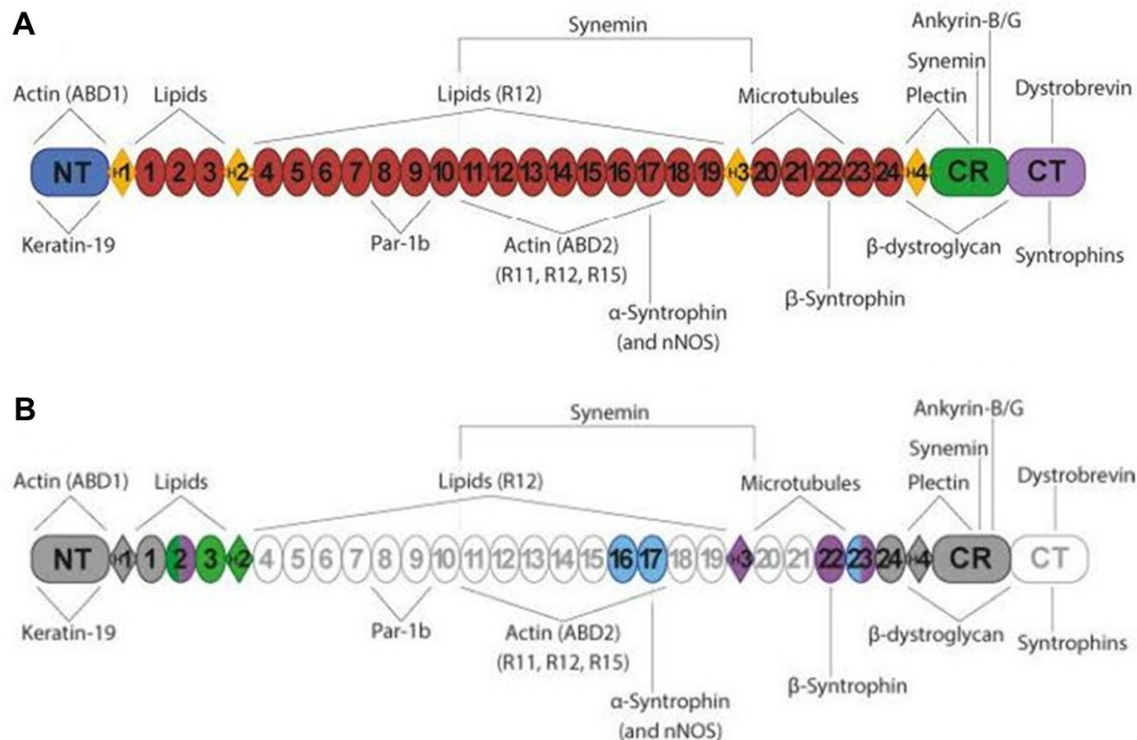
23. Adams, ME, GL Odom, MJ Kim, JS Chamberlain, and SC Froehner, 2018, Syntrophin binds directly to multiple spectrin-like repeats in dystrophin and mediates binding of nNOS to repeats 16-17, *Hum Mol Genet*, 27(17):2978-2985.

24. Cirak, S, L Feng, K Anthony, V Arechavala-Gomeza, S Torelli, C Sewry, JE Morgan, and F Muntoni, 2012, Restoration of the dystrophin-associated glycoprotein complex after exon skipping therapy in Duchenne muscular dystrophy, *Mol Ther*, 20(2):462-467.

25. Lai, Y, GD Thomas, Y Yue, HT Yang, D Li, C Long, L Judge, B Bostick, JS Chamberlain, RL Terjung, and D Duan, 2009, Dystrophins carrying spectrin-like repeats 16 and 17 anchor nNOS to the sarcolemma and enhance exercise performance in a mouse model of muscular dystrophy, *J Clin Invest*, 119(3):624-635.

26. Nelson, DM and JM Ervasti, 2021, Structural proteins: Dystrophin: A multifaceted protein critical for muscle health, *Encyclopedia of Biological Chemistry: Third Edition*, 3rd edition: Elsevier, 3: 625-638.

Figure 4. Dystrophin Domains



Source: Nelson, DM and JM Ervasti, 2021, Structural Proteins: Dystrophin—A multifaceted protein critical for muscle health, Encyclopedia of Biological Chemistry: Third Edition, 3rd edition: Elsevier, 3: 625-638.

Note: Figure A represents dystrophin regions and their associated protein- and lipid-binding partners; Figure B represents the dystrophin domains present in three clinical-stage micro-dystrophin gene therapy constructs, manufactured by Sarepta Therapeutics (ELEVIDYS), Solid Biosciences, and Pfizer. Gray domains are present in all three micro-dystrophins. Green domains are present only in ELEVIDYS micro-dystrophin, blue only in Solid Biosciences' micro-dystrophin, and purple only in Pfizer's micro-dystrophin. Two-color dystrophin domains are present in both indicated companies' constructs. Semi-transparent, white domains are missing from all three micro-dystrophins. Diamonds represent hinge regions, and ovals represent spectrin-like repeats.

Abbreviations: ABD2, actin-binding domain 2; CR, cysteine-rich domain; CT, C-terminus; nNOS, neuronal nitric oxide synthase; NT, N-terminus.

4.4.2 Pharmacodynamics

In subjects who received SRP-9001 in clinical studies, expression of ELEVIDYS micro-dystrophin protein in muscle tissue (from biopsy of the gastrocnemius or biceps femoris) was quantified by Western blot and localized by immunofluorescent staining (reported as fiber intensity and percentage ELEVIDYS micro-dystrophin-positive fibers).

Muscle biopsies for all subjects were obtained at baseline prior to ELEVIDYS infusion, and at Week 12 after ELEVIDYS infusion. The absolute quantity of ELEVIDYS micro-dystrophin in muscle biopsy samples was measured by Western blot assay, then adjusted for muscle content and expressed as a percent of control (i.e., of levels of normal dystrophin in muscle tissue from healthy individuals without DMD or BMD). Results for subjects receiving 1.33×10^{14} vg/kg ELEVIDYS are presented in Table 6. For subjects aged 4 to 5 years, the mean (range) expression level of ELEVIDYS micro-dystrophin at Week 12 in Study 102 was 95.7% (N = 3, range 85.2% to 116.3%), and in Study 103 was 54.6% (N = 10, range 4.8% to 133.4%).

Table 6. Expression of ELEVIDYS Micro-dystrophin in Study 102 and Study 103 (measured via Western blot assay)

Western blot (percent of control expression)	Study 102 (Week 12) Part 1 & 2 (n = 29)	Study 103 (Week 12) Cohort 1 (n = 20)
Mean change from baseline (range)	38.6 (-1.1–114.7)	54.2 (4.8–153.9)

Source: FDA

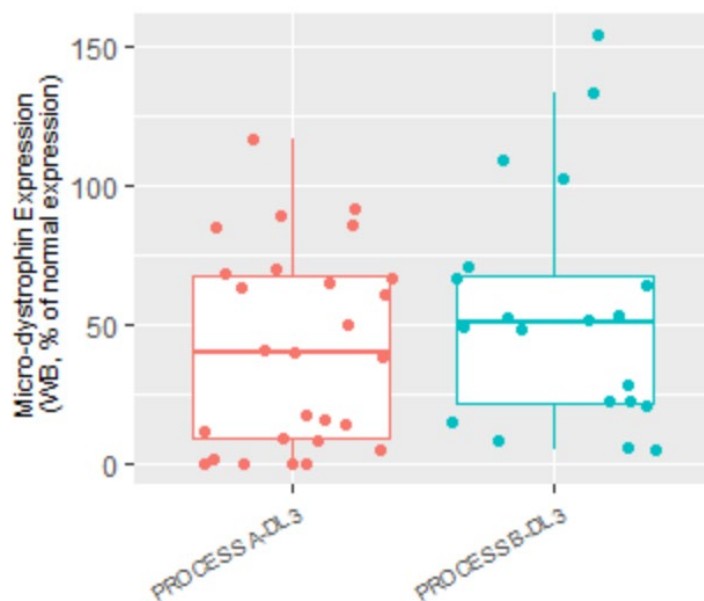
Results for Study 101 are not included here because expression of ELEVIDYS micro-dystrophin was quantified using a different method, for which the reliability is uncertain.

Two subjects in Study 102 Part 1 had substantially high baseline values; according to the Applicant, those results may have been due to baseline expression of a nonfunctional, truncated form of dystrophin resulting from the subjects' specific mutations. ELEVIDYS micro-dystrophin expression results from those two subjects were excluded from this analysis.

As shown in

Figure 5, expression of ELEVIDYS micro-dystrophin protein was slightly higher in subjects who received SRP-9001 manufactured by Process B (Process B SRP-9001), compared with that in subjects who received SRP-9001 manufactured by Process A (Process A SRP-9001). The mean (SD) and median (min, max) of ELEVIDYS micro-dystrophin levels (percent of control) in muscle biopsy samples from subjects receiving Process A SRP-9001 (n = 27) were 41.3% (35.4) and 39.7% (0.0, 116.3), respectively. The mean (SD) and median (min, max) of ELEVIDYS micro-dystrophin levels (percent of control) in muscle tissue biopsy samples from subjects receiving Process B SRP-9001 (n = 20) were 54.2% (42.6) and 50.6% (4.8, 153.9), respectively.

Figure 5. Boxplot of ELEVIDYS Micro-dystrophin Expression (measured by Western blot) in Muscle Biopsy Tissue of Subjects Receiving Process A ELEVIDYS Versus Process B ELEVIDYS



Source: FDA Clinical Pharmacology Review.

Note: PROCESS A-DL refers to subjects in Study 102 who received placebo in Part 1, and received SRP-9001 in Part 2 at the dose of 1.33×10^{14} vg/kg.

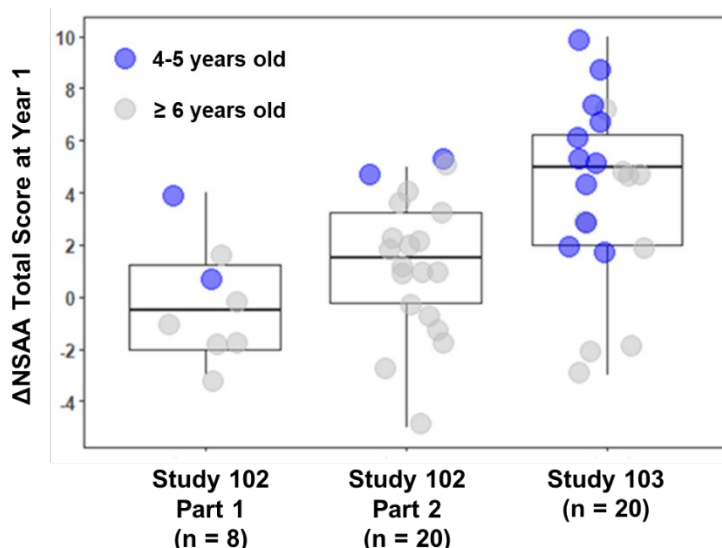
Abbreviation: DL, dose level; WB, Western blot.

4.4.3 Relationship Between Expression of ELEVIDYS Micro-dystrophin Protein and Clinical Efficacy Outcome on the NSAA

The relationship between expression of ELEVIDYS micro-dystrophin protein (measured by Western blot) and functional outcome on the NSAA was evaluated using two sources of data: (i) data from Study 102 Part 1, the only randomized, double-blinded, placebo-controlled study, and (ii) pooled data from Study 102 Part 1 and Part 2, and Study 103 Cohort 1.

The analysis of the pooled data assumes that the difference in study design (open-label, single-arm, versus randomized, double-blind, concurrent-controlled) did not affect subjects' performance on the effort-driven functional outcome measure (NSAA), or influence the relationship between expression of ELEVIDYS micro-dystrophin and the functional outcome. That assumption, however, is problematic. As shown in Figure 6, for subjects who received the proposed dose (1.33×10^{14} vg/kg), the change in NSAA Total Score for those in the randomized, double-blind, placebo-controlled Study 102 Part 1 was lower than that for those in the functionally open-label Study 102 Part 2 or the open-label Study 103.

Figure 6. Boxplot of Change in NSAA Total Score From Dosing (1.33×10^{14} vg/kg) to 1 Year after Treatment with ELEVIDYS, Across Study 102 Part 1, Study 102 Part 2, and Study 103



Source: FDA Briefing Document, CTGTAC, 2023

Note: Solid circles represents subjects; color indicates age group. The bottom of the lower vertical line indicates the minimum value; the top of the upper vertical line indicates the maximum value; the bottom of the box corresponds to the first quartile; the horizontal line through the box represents the median value; and the top of the box indicates the third quartile.

Abbreviations: NSAA, North Star Ambulatory Assessment.

Analysis Based on Study 102 Part 1 Data

- Data from Study 102 Part 1 show no clear association between expression of ELEVIDYS micro-dystrophin protein at Week 12, and change in NSAA Total Score at Week 48.
- Study 102 Part 1 data suggest improved NSAA Total Score with increased expression of ELEVIDYS micro-dystrophin in subjects aged 4 to 5 years; the limited data (n = 8 subjects), however, is an important caveat. In subjects aged 6 to 7 years, no clear association was present between expression of ELEVIDYS micro-dystrophin at Week 12, and change in NSAA Total Score at Week 48.

Analysis Based on Pooled Data From Study 102 and Study 103

- Increase in expression of ELEVIDYS micro-dystrophin protein at Week 12 is associated with change in NSAA Total Score at Year 1 (Week 48 for Study 102, and Week 52 for Study 103).
- ELEVIDYS micro-dystrophin accounts for approximately 11% of the variation in change in NSAA Total Score, after adjustment for baseline age and NSAA Total Score (i.e., $R^2 = 0.11$)
- Even accepting the flawed assumption that study design did not affect subjects' NSAA performance, this correlation is not sufficiently persuasive to consider expression of ELEVIDYS micro-dystrophin "reasonably likely to predict clinical benefit."

4.4.4 Human Pharmacokinetics (PK)

Vector Distribution and Vector Shedding

Following intravenous administration of ELEVIDYS, the vector genome is transported via the systemic circulation and distributes into target muscle tissues, followed by elimination in the urine and feces. ELEVIDYS biodistribution and tissue transduction were detected in the target muscle tissue groups and quantified in biopsies of the gastrocnemius or biceps femoris. Evaluation of ELEVIDYS vector genome exposure (expressed as copies per nucleus) in muscle biopsies at Week 12 after infusion revealed ELEVIDYS drug distribution and transduction with a mean observed value of 3.00 copies per nucleus for the recommended dose of 1.33×10^{14} vg/kg across Study 102 and Study 103 Cohort 1.

The estimated elimination half-life of the ELEVIDYS vector genome in the serum is approximately 12 hours, and majority of the drug is expected to be cleared from the serum by 1 week after dosing. The estimated elimination half-life of the ELEVIDYS vector genome is 40 hours, 55 hours, and 60 hours in urine, feces, and saliva, respectively.

Following entry into target cells, ELEVIDYS capsid proteins are broken down through proteasomal degradation. Consequently, ELEVIDYS is not likely to exhibit the drug-drug interaction potential mediated by known drug-metabolizing enzymes (e.g., cytochrome P450-based enzymes) and drug transporters.

For further details, please see the Clinical Pharmacology Review.

4.5 Statistical

Study 102 Part 1 did not meet the success criterion for the primary clinical endpoint: statistically significant greater improvement in the NSAA Total Score from baseline to Week 48 for the ELEVIDYS group, compared to placebo. The results from the comparison to external controls are of doubtful interpretability, given the inherent limitations of the external comparison approach, as well as the observed differences of outcome between the external control patients and the concurrent placebo subjects. Therefore, the statistical analysis results do not provide substantial evidence to support the safety and effectiveness of ELEVIDYS for the indication proposed in this BLA.

Please see the Statistical Review for details.

4.6 Pharmacovigilance

The Applicant proposed the following postmarketing measures:

- (1) Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
- (2) Enhanced pharmacovigilance:
 - (a) Follow-up of spontaneously reported cases with targeted questionnaires; monthly review of cases; and analysis of aggregate data in periodic safety reports for the following safety concerns: acute liver injury, immune-mediated

myositis, myocarditis (including troponin increased), thrombocytopenia, thrombotic microangiopathy, and rhabdomyolysis.

- (b) Expedited (15-day) reporting (regardless of seriousness or expectedness) to the FDA Adverse Event Reporting System for three years following approval, for the following safety concerns: acute liver injury, immune-mediated myositis, myocarditis (including troponin increased), and thrombotic microangiopathy.

The Applicant will conduct a voluntary long-term follow-up postmarketing safety study (Study SRP-9001-401) to provide 10-year safety and effectiveness data for ELEVIDYS in the postmarketing setting. Study SRP-9001-401 is a prospective cohort study that will include a comparator group. Subjects will be prospectively recruited into two cohorts: 1) an exposed group (subjects who were first recruited and then received commercial ELEVIDYS); and 2) an unexposed or standard-of-care group (subjects who were receiving or prescribed chronic glucocorticoid treatment at the time of recruitment). The Applicant plans to recruit a total of 454 subjects, with 227 subjects in each cohort.

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

5.1 Review Strategy

The sources for this review are: (1) the licensing application, which includes data from three ongoing clinical trials (Study 101, Study 102, and Study 103); (2) sources external to the application, such as videos and other information submitted to the Cellular, Tissue, and Gene Therapies Advisory Committee Docket No. FDA-2023-N-1190; and (3) publications submitted by the Applicant and from other sources.

For evaluation of efficacy, the clinical reviewer focused on data from Study 102 Part 1, the only randomized, double-blind, placebo-controlled clinical trial. In addition, the reviewer worked closely with the Clinical Pharmacology reviewer to determine whether expression of ELEVIDYS micro-dystrophin can serve as surrogate endpoint that is “reasonably likely to predict clinical benefit” for Accelerated Approval of ELEVIDYS for the proposed indication.

Safety of ELEVIDYS was evaluated in the Exposure Analysis Set, consisting of data from 85 male subjects with DMD with a confirmed mutation in the *DMD* gene, who received a one-time intravenous infusion of ELEVIDYS in the three clinical studies.

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

Data provided in the licensing application include results from three US studies (Table 7) and the relevant modules in the BLA submission:

- The Administrative and Prescribing Information (PI) in Module 1
- Summary Clinical Information in Modules 2.5 and 2.7
- Clinical study reports in Module 5, including the narrative clinical study reports, appendices, tabulation and analysis datasets, case report forms, and literature references submitted by the Applicant.
- Applicant Briefing Document for the Cellular, Tissue, and Gene Therapies Advisory Committee meeting, May 12, 2023

- Comments and videos submitted to Docket No. FDA-2023-N-1190

In addition, the reviewer used publicly-available resources, including UpToDate and PubMed, to understand the disease of interest.

5.3 Table of Studies/Clinical Trials

The BLA includes data from three interventional clinical trials of SRP-9001 (Table 7):

- (1) NCT03375164 (Study SRP-9001-101), "Systemic Gene Delivery Phase 1/2a Clinical Trial for Duchenne Muscular Dystrophy Using rAAVrh74.MHCK7.Micro-dystrophin (microDys-IV-001)," a single-arm, parallel-assignment, first-in-human study
Start date: January 4, 2018
Estimated completion date: April 25, 2023
- (2) NCT03769116 (Study SRP-9001-102), "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial for Duchenne Muscular Dystrophy Using SRP-9001," an ongoing, two-part "cross-over" study
Start date: December 22, 2018
Estimated completion date: April 2, 2026
- (3) NCT04626674, (Study SRP-9001-103), "An Open-Label, Systemic Gene Delivery Study Using Commercial Process Material to Evaluate the Safety of and Expression From SRP-9001 in Subjects with Duchenne Muscular Dystrophy (ENDEAVOR)," an ongoing, single-arm "bridging" study
Start date: November 23, 2020
Estimated completion date: January 31, 2028

All ELEVIDYS-treated subjects currently are being followed as per the respective protocols.

Table 7. Clinical Studies Submitted in the Biologics License Application

Study Identifier	Study Population	Study Design	Treatment with ELEVIDYS (vg/kg)	Primary and Key Secondary Endpoints	Number of Subjects	Number of Centers
SRP-9001-101	Ambulatory boys with DMD, aged 4-7 years	Open-label, single-arm	$1.33 \times 10^{14,a}$	Primary: • Safety Secondary: • Expression of ELEVIDYS micro-dystrophin at Week 12; • 100-meter timed walk test	4	Single US site
SRP-9001-102	Ambulatory boys with DMD, aged 4-7 years	Part 1: Randomized (1:1), double-blind, placebo-controlled (48 weeks) Part 2: “Cross-over,” with blinding from Part 1 maintained (48 weeks) Part 3: Open-label follow-up (5 years)	Part 1a: • 1.33×10^{14} (n = 8; intended dose) • 6.29×10^{13} (n = 6) • 8.94×10^{13} (n = 5) • Placebo (n = 21) Part 2a: • 1.33×10^{14} (n = 20; intended dose)	Primary: • Expression of ELEVIDYS micro-dystrophin at Week 12 • Change in NSAA at Week 48 Secondary: • Time to rise from floor at Week 48 • Time to ascend 4 steps at Week 48 • 100-meter timed walk test at Week 48 • 10-meter timed walk test at Week 48	41	2 US sites

Study Identifier	Study Population	Study Design	Treatment with ELEVIDYS (vg/kg)	Primary and Key Secondary Endpoints	Number of Subjects	Number of Centers
SRP-9001-103	Boys with DMD <ul style="list-style-type: none"> • Cohort 1: 20 ambulatory boys aged 4-7 years • Cohort 2: 7 ambulatory boys aged 8-17 years • Cohort 3: 6 non-ambulatory boys; no age restriction • Cohort 4: ambulatory boys aged 3-4 years 	Open-label, single-arm	$1.33 \times 10^{14,b}$	<p>Primary:</p> <ul style="list-style-type: none"> • Expression of ELEVIDYS micro-dystrophin at Week 12 <p>To support use of ELEVIDYS micro-dystrophin as surrogate endpoint “reasonably likely to predict clinical benefit,” change in NSAA Total Score from baseline to Week 52 for subjects from Cohort 1 was compared to corresponding data for DMD patients obtained from external sources.</p>	40 total (Cohort 1: 20)	5 US sites

Source: Sarepta BLA

^a ELEVIDYS manufactured using Process A

^b ELEVIDYS manufactured using Process B

Abbreviations: BLA, Biologics License Application; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; US, United States

5.4 Consultations

Studies 101, 102, and 103 only enrolled subjects with anti-rAAVrh74 antibody titers <1:400, as determined using an investigational enzyme-linked immunosorbent assay (ELISA). To assess the validity, reliability, and accuracy of the assay, the review team consulted colleagues in the FDA Center for Device and Radiological Health (CDRH) Office of In Vitro Diagnostics, within the Office of Product Evaluation and Quality. The CDRH team provided the following comments:

- (1) The documents provided to CDRH from CBER for review regard a single-site AAVrh74 ELISA assay conducted at the Applicant's facility. On December 6, 2022, the Applicant provided CBER a document entitled "AOM [Application Overview Meeting] final slides." On Slide 7, the proposed indication for the therapeutic product includes the statement "[Tradename for delandistrogene moxeparvovec] administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers (>1:400)." Since the indication for use of the therapeutic product specifies a patient population for whom the therapy is not universally recommended, and determination of suitable patients requires use of a diagnostic test, a companion diagnostic to identify this population is appropriate. A companion diagnostic thus should be approved with this therapeutic product, ideally contemporaneously. To date, (b) (4)

- (2) The validation studies for the Applicant's anti-AAVrh74 ELISA assay included in the documentation provided by CBER do not adequately support premarket submission or approval.

- (3) According to the FDA guidance document *In Vitro Companion Diagnostic Devices*:

"FDA may decide to approve a therapeutic product even if an [in vitro companion diagnostic device] is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared [in vitro companion diagnostic device]."

Additionally, the guidance document states that:

"In general, if a therapeutic product is approved without approval or clearance of an [in vitro companion diagnostic device], FDA expects that an [in vitro companion diagnostic device] that is intended for use with the therapeutic product will be subsequently approved or cleared through an appropriate device submission, and the therapeutic product labeling will be revised to stipulate the use of the [in vitro companion diagnostic device]."

5.4.1 Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) met on May 12, 2023. The Committee was asked to address the following issues, and to vote on the final question:

- 1) Discussion Topic 1: Please discuss the strengths and limitations of the available evidence supporting the use of measurement of ELEVIDYS micro-dystrophin, expressed through administration of ELEVIDYS, as a surrogate endpoint “reasonably likely to predict clinical benefit” in ambulatory patients with DMD with a confirmed mutation in the *DMD* gene.

FDA Summary of Discussion:

The Committee considered the difficulties of assessing the clinical correlation between expression of ELEVIDYS micro-dystrophin and clinical outcome data. These difficulties are due to limitations of the metrics used; variability in the data; level of transduction observed; and differences in interpretation of the data. A subset of patients perhaps may benefit from SRP-9001, but the efficacy of the treatment may depend on multiple factors, including age at the time of treatment. Although ELEVIDYS micro-dystrophin may have a structural effect in muscle cells, its physiological meaningfulness remains unclear. Members noted concern regarding the differences in both structure and tissue distribution between ELEVIDYS micro-dystrophin and shortened forms of dystrophin produced in patients with BMD or treated with exon-skipping drugs. Overall, the Committee felt that the clinical significance of the findings is difficult to interpret, as is whether ELEVIDYS micro-dystrophin is a reasonable predictor of clinical benefit.

- 2) Discussion Topic 2: Part 1 of Study 102 was the only randomized, double-blind, placebo-controlled clinical study for which data currently are available. The study failed to demonstrate a statistically significant effect of treatment with ELEVIDYS versus placebo on the primary clinical outcome measure, change in the NSAA Total Score from baseline to Year 1. Exploratory subgroup analyses suggest that the ELEVIDYS group may have had a better NSAA outcome compared to the placebo group among ambulatory patients aged 4 to 5 years; however, among ambulatory patients aged 6 to 7 years, there appeared to be no difference between the ELEVIDYS group and the placebo group, and the ELEVIDYS group showed no improvement from baseline.

Please discuss the clinical significance of these findings.

FDA Summary of Discussion:

The Committee discussed that the clinical significance of the exploratory subgroup analysis is difficult to interpret. The analysis was not prespecified for hypothesis testing, and no prespecified multiplicity adjustment strategy was employed. The members also noted that while the NSAA is a well-established tool for assessing patients, its use in an open-label setting introduces challenges in interpreting the resulting data; many qualifying statements may be needed, such as the age of the patient, how the data were measured, or how the data were analyzed.

- 3) Discussion Topic 3: Please discuss the potential benefits, risks, and uncertainties that may be associated with administration of ELEVIDYS for treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene.

FDA Summary of Discussion:

The Committee felt that the most commonly-identified safety events are manageable. Members discussed the persistence of anti-AAV antibodies following ELEVIDYS infusion, and the opportunity cost to patients of forgoing any future AAV-based treatment.

- 4) Discussion Topic 4: If ELEVIDYS were to be approved under Accelerated Approval provisions, the Applicant proposes that Part 1 of Study 301 (the Phase 3 randomized, double-blind, placebo-controlled 52-week crossover clinical study) may serve as the required postmarketing confirmatory trial to verify and describe clinical benefit. Please note that the last patient last clinical visit for the 52-week primary endpoint is expected to be completed by the end of September 2023. Please discuss the potential impact of marketing approval on completion of Part 1 of Study 301.

FDA Summary of Discussion:

The Committee noted that the data from Study 301 are critical, as that study is the first controlled trial using SRP-9001 manufactured by Process B. Members expressed the concern that, if SRP-9001 receives Accelerated Approval, patients may drop out of the study to obtain the commercially-available product sooner, which may confound the results of Study 301. Without clear evidence to the contrary, patients may be receiving an ineffective product, and patients who have received SRP-9001 will not be able to receive a future AAV-based treatment.

Members also considered whether it would be ethical to keep patients who have not received SRP-9001 in the study until study completion, if the product is approved. Study 301 is currently fully enrolled. It is difficult to predict whether patients who have not received SRP-9001 would continue in the study. Some committee members indicated that based on the current enrollment status, there may be a good chance that patients who have not yet received ELEVIDYS will remain in the trial.

- 5) Discussion Question, Then Voting: 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 ELEVIDYS micro-dystrophin at Week 12 after administration of ELEVIDYS—for the treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene?
- (a) Yes
 - (b) No
 - (c) Abstain

FDA Summary of Discussion:

The committee voted 8 to 6 in favor of Accelerated Approval of ELEVIDYS.

Several committee members who voted in favor of Accelerated Approval nevertheless expressed concern regarding the clinical study results and use of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit.”

The names, affiliations, and votes of the individual committee members are provided in Appendix 1. CTGTAC Members and .

Reviewer Comment:

Mr. Cassidy, the patient representative, voted in favor of Accelerated Approval. He eloquently conveyed the patients' experience of DMD, and the willingness of patients and their caregivers to accept the higher level of risk associated with new drugs approved via the Accelerated Approval pathway. He also noted that individual patient outcomes should be considered as data, even when statistical analysis is not possible. Ms. O'Sullivan-Fortin, the consumer representative, also voted in favor of Accelerated Approval. She underscored the urgent need for better treatments for DMD. This reviewer shares both their sentiments.

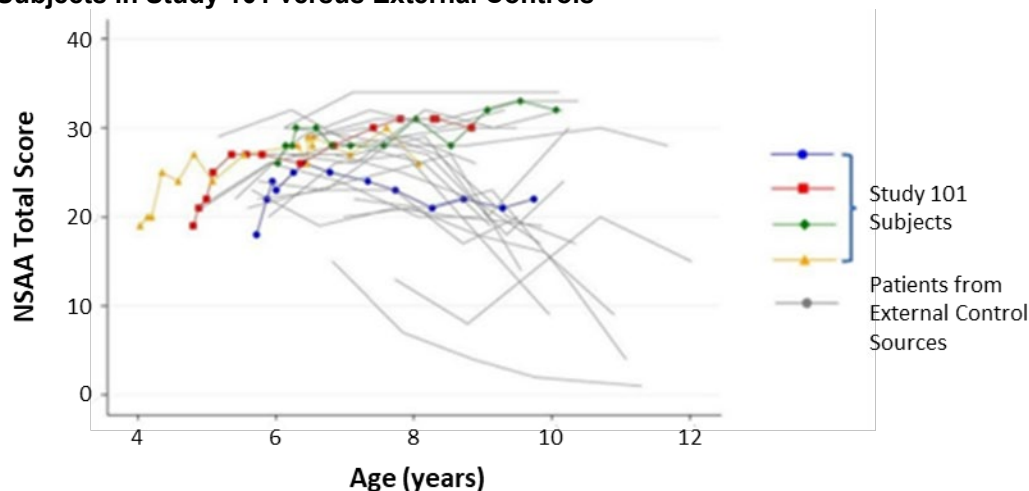
Several committee members who voted in favor of Accelerated Approval did so despite reservations about the clinical study results and use of ELEVIDYS micro-dystrophin as a surrogate endpoint. For example:

- Dr. Pavlakis expressed disappointment with the clinical study data and did not feel that the proposed surrogate endpoint had been demonstrated to be “reasonably likely to predict clinical benefit.” He based his YES vote on the testimony of the outstanding investigators involved in the ELEVIDYS clinical studies.
- Dr. Chiorini also did not find persuasive the data in support of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit.” However, he felt that the most compelling data were those from the 4-year follow-up of the four subjects in Study 101.
- Dr. Kohn also considered the most compelling data those from the 4-year follow-up of the four subjects in Study 101.

This reviewer agrees that the testimony of clinicians including Dr. Craig McDonald and Dr. Jerry Mandell, both of whom are clinical investigators in the ELEVIDYS clinical studies, was compelling, as was their February 24, 2023, letter to Dr. Witten and Dr. Marks. While supporting the conclusion that ELEVIDYS provides benefit to some patients, their testimony and letter cannot address the broader regulatory issues of which patients may benefit and which may not, and whether ELEVIDYS micro-dystrophin is a suitable surrogate endpoint for Accelerated Approval. Those issues instead are informed by evidence of effectiveness from adequate and well-controlled studies, which is lacking in this case.

The 4-year follow-up data from the four subjects in Study 101 similarly is of limited utility here. An important consideration in interpreting those results is that for all four subjects, their NSAA scores remain within the expected range of natural history for DMD (Figure 7).

Figure 7. Longitudinal Comparison of North Star Ambulatory Assessment Results for Subjects in Study 101 versus External Controls



Source: Modified from Applicant
Abbreviation: NSAA, North Star Ambulatory Assessment.

5.5 Literature Reviewed

References are indicated in footnotes throughout this document.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: SRP-9001-101 (Study 101)

Study title: Systemic Gene Delivery Phase 1/2a Clinical Trial for Duchenne Muscular Dystrophy Using rAAVrh74.MHCK7.Micro-dystrophin (microDys-IV-001)

Clinical Trial Registry Identifier: NCT03375164

6.1.1 Objectives (Primary and Secondary)

The primary objective of this study was assessment of the safety of intravenous administration, via a peripheral limb vein, of ELEVIDYS (rAAVrh74.MHCK7.micro-dystrophin; SRP-9001) to subjects with DMD.

Secondary objectives were to evaluate: (1) expression of ELEVIDYS micro-dystrophin expression, as quantified by Western blot and immunofluorescence assays; and (2) the effect of treatment with ELEVIDYS on a physical functional assessment (the 100-meter timed test).

6.1.2 Design Overview

Study 101 was the first-in-human, proof-of-concept study. The study design was open-label, single-arm, and single-dose.

Figure 8. Schematic Diagram of Study 101 Design



Source: Applicant's Briefing Document for the Cellular, Tissue and Gene Therapies Advisory Committee.

6.1.3 Population

Key Inclusion Criteria

- Ambulatory boys aged 4 to 7 years, inclusive
- Molecular characterization: frameshift (deletion or duplication) or premature stop codon mutation between exons 18 to 58 of the *DMD* gene
- Anti-rAAVrh74 antibody titer $\leq 1:400$ per ELISA²⁷
- Serum creatine kinase level >1000 U/L
- Below-average score (defined as $\leq 80\%$ predicted for age) on the 100-meter timed test
- Corticosteroid dose: stable dose equivalent of oral corticosteroids for at least 12 weeks prior to screening, with the dose expected to remain constant throughout the first year of the study (except for potential modifications to accommodate changes in weight)

Key Exclusion Criteria

- Signs of cardiomyopathy, including echocardiogram demonstrating ejection fraction $< 40\%$
- Received any investigational medication (other than corticosteroids) or exon-skipping drugs, experimental or otherwise (including eteplirsen), in the 6 months prior to screening for this study
- Abnormal laboratory values considered clinically significant:
 - GGT $> 3 \times$ upper limit of normal
 - Bilirubin ≥ 3.0 mg/dL
 - Creatinine ≥ 1.8 mg/dL
 - Hemoglobin < 8 or > 18 g/dL
 - White blood cell count $> 18,500/\mu\text{L}$

6.1.4 Study Treatments or Agents Mandated by the Protocol

All subjects received a single intravenous infusion of ELEVIDYS manufactured by Process A at Nationwide Children's Hospital (Ohio State University, Columbus, OH).

27. The Gene Therapy Center of Excellence (GTCOE) ELISA assay was used for Studies SRP-9001-101.

All four subjects received ELEVIDYS at a dose of 2×10^{14} vg/kg, as measured by a quantitative polymerase chain reaction method using a supercoiled plasmid standard in 10 mL/kg. (That dose is considered as equivalent to 1.33×10^{14} vg/kg as measured with linear standard.)

Reviewer Comment:

This study was originally designed to enroll a total 12 subjects, in two cohorts: 6 subjects in Cohort B (aged 4 to 7 years), followed by 6 subjects in Cohort A (aged 3 months to 3 years). However, after 4 subjects were enrolled into Cohort B, enrollment was stopped to allow subsequent subjects in the 4- to 7-years-old age range to enroll in Study 102. No subjects were enrolled in Cohort A.

6.1.5 Directions for Use

After pretreatment of the infusion site with either a lidocaine/prilocaine eutectic mixture incorporated in a cream base (EMLA cream), or a cellulose disk (EMLA patch), two intravenous catheters were placed: one catheter for infusion, and one as a secondary catheter in the event of complications at the first site.

The total dose of ELEVIDYS was infused over approximately one to two hours. Vital signs were monitored during infusion. Subjects were discharged one day after ELEVIDYS infusion.

6.1.6 Sites and Centers

Nationwide Children's Hospital (Ohio State University, Columbus, OH).

6.1.7 Surveillance/Monitoring

Subjects were followed on Days 7, 14, 30, and 60; Month 3; then every 3 months until Month 12, then every 6 months until Year 5. The detailed monitoring schedule is provided in Table 8.

Physical therapy assessments were performed during screening, and at all visits from Day 30 onward.

Muscle biopsies of the gastrocnemius muscle were performed during screening and on Day 90.

Table 8. Schedule of Events for Study SRP-9001-101 (Study 101)

STUDY TIMELINE																					
Study Interval	BI Scr	Vector Infusion (Inpatient)			Follow Up																
Visit #	1	2			3	4	5	6	7	Opt	8	9	10	11	12	13	14	15	16	17	18
Study Interval	-60 to -2	-1 d	0 d	1 d	7 d	14 d	30 d	60 d	90 d	1-2 w post biopsy	180 d	9 m	1 y	18 m	2 y	30 m	3 y	42 m	4 y	54 m	5 y
Visit Window (days)					±7	±7	±7	±14	±14	±14	±14	±14	±14	±21	±21	±21	±21	±21	±21	±21	±21
Informed Consent	x																				
Medical History	x																				
Vitals	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECHO/ECG	x						x						x		x		x		x		x
Chest X-Ray	x																				
MRI ^a	x										x		x								
Hepatitis B & C, HIV	x																				
Biomarker Testing	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety Labs ^b	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Therapy Assessments	x						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Gene Transfer			x																		
Immunology Studies	x				x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x
Muscle Biopsy	x								x												
Photograph of Injection Site	x	x	x	x	x	x	x														
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications	To be collected from time of consent until final study visit, recorded on separate CRF																				

Source: Applicant's Protocol SRP-9001-101, Version 9.0 (August 25, 2020)

^a MRIs will only be performed on the subjects greater than 3 years of age (Cohort B) at the time of enrollment. Only conscious sedation will be used during the cardiac MRI. If general anesthesia is required, the cardiac MRI will not be performed.

^b Safety labs: CBC with differential and platelets with smear, PT/PTT/INR, electrolytes, ALT, AST, alkaline phosphatase, amylase, BUN, CK (preferably on Day 2 visits but may be tested on a Day 1 visit per discretion of principal investigator), creatinine, cystatin C, GGT, glucose, total protein, total bilirubin, and urinalysis.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BI, baseline; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; CRF, case report form; d, day; ECG, electrocardiogram; ECHO, echocardiogram; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; INR, international normalized ratio; m, month; MRI, magnetic resonance imaging; Opt, optional; PT, prothrombin; PTT, partial thromboplastin time; Scr, screening; y, year.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint

Safety, as assessed by adverse events, changes in laboratory parameters (hematology, serum chemistry, and urinalysis), immunologic response to rAAVrh74 and ELEVIDYS micro-dystrophin, and reported history and observations of symptoms.

Secondary Endpoints

- Expression of ELEVIDYS micro-dystrophin
- Bayley-III Gross Motor Subtest (Cohort A only)
- 100-meter timed test (Cohort B only)

Reviewer Comment:

Since no subjects were enrolled in Cohort A, the Bayley-III Gross Motor Subtest assessment was not performed.

6.1.9 Statistical Considerations and Statistical Analysis Plan

The Full Analysis Set (FAS), which included all subjects who received ELEVIDYS, was used as the analysis population for Study 101. Analyses were descriptive; no formal statistical tests were performed, due to the small sample size and open-label design of the study. Descriptive statistics were presented for all endpoints, and included the number of subjects, mean and standard deviation, minimum and maximum for continuous variables, and number and percentage for categorical variables. No inferential statistical analyses were conducted in this trial.

6.1.10 Study Population and Disposition

All subjects were ambulatory, had a confirmed *DMD* mutation, and had a baseline anti-AAVrh74 total binding antibody titer < 1:400 as determined by investigational ELISA.

6.1.10.1 Populations Enrolled/Analyzed

Analyses of efficacy and safety included all four subjects in Study 101, all of whom received the investigational product.

6.1.10.1.1 Demographics

The four subjects were all ambulatory, and had a mean age of 4.8 years (range, 4 to 6 years), mean weight of 18.1 kg (range, 13.7 to 21.4 kg), mean NSAA Total Score of 20.5 (range, 18.0 to 26.0), and mean time to rise from floor of 3.7 seconds (range, 3.0 to 4.1).

All subjects were on a stable dose of corticosteroids for at least 12 weeks prior to ELEVIDYS infusion, as well as throughout the first year of the study.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The *DMD* mutations in the four subjects are as follows:

- Subject 1: Deletion of exons 46-50

- Subject 2: Deletion of exons 46-49
- Subject 3: Premature stop codon in exon 27
- Subject 4: Partial deletion of exon 44

6.1.10.1.3 Subject Disposition

All subjects have been followed for more than 4 years; follow-up is ongoing.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objective and corresponding endpoints in this study were safety-related. Efficacy assessments were associated with the secondary and exploratory objectives.

6.1.11.2 Analyses of Secondary Endpoints

Quantity of ELEVIDYS micro-dystrophin was measured by Western blot of biopsied muscle. Levels are described as change from baseline, in order to remove any background signal in the assay. Levels are expressed as a percent of control (i.e., as a percent of the level of normal, wild-type dystrophin present in muscle tissue of healthy individuals without DMD or Becker muscular dystrophy).

The change from baseline in ELEVIDYS micro-dystrophin level at the Day 90 visit were 38.8%, 13.5%, 47.2%, and 182.6%, for Subjects 1, 2, 3 and 4, respectively.

Reviewer Comment:

The Western blot method used for quantification in Study 101 was of uncertain reliability compared to the method employed in Study 102 and Study 103. This review therefore generally excludes data from Study 101 in discussion of Western blot results.

At Year 1 following treatment with ELEVIDYS, a mean decrease from baseline of 9 seconds (range, 2 to 24) was observed in time to walk 100 meters. At Year 4 after ELEVIDYS infusion, a mean decrease from baseline of 7 seconds (range: 0 to 14) was seen in time to walk 100 meters.

Table 9. Subject-Level Data for Time to Walk 100 Meters (Baseline to Year 4), Study 101

Subjects	Baseline	Year 1	Year 2	Year 3	Year 4	Change from Baseline to Year 4
1	49.3	42.9	41.8	45.4	45.2	-4.1
2	49.8	47.4	40.9	- ^a	39.7	-10.1
3	59.3	55.5	50.7	48.8	59.2	-0.1
4	67.2	43.6	- ^a	50.7	53.7	-13.5

Source: BLA Study 101 report.

^a Data not collected

Reviewer Comment:

NSAA was assessed as an exploratory endpoint in Study 101. At Year 1, a mean increase (improvement) from baseline of 5.5 points (range, 2 to 8) was observed in NSAA Total Score. At Year 4, a mean increase from baseline of 7 points (range, 4 to 11) was also observed. Subject-level data from baseline through Year 4 after ELEVIDYS infusion are presented in Table 10 below:

Table 10. Subject-Level Data for North Star Ambulatory Assessment Total Score From Baseline to Year 4

Subject	Baseline	Year 1	Year 2	Year 3	Year 4	Change in NSAA Total Score from Baseline to Year 4
1	18	25	23	22	22	4
2	19	27	28	31	30	11
3	26	28	31	32	32	6
4	19	24	- ^a	27	26	7

Source: BLA 125781 Study 101 report.

^a Data not collected

Abbreviation: NSAA, North Star Ambulatory Assessment.

In the absence of blinding, clinical outcomes such as time to walk 100 meters and NSAA are highly susceptible to bias. Therefore, caution is warranted in interpreting these data. In addition, at the subject level, the quantity of ELEVIDYS micro-dystrophin does not appear to predict clinical outcomes; in addition, there does not appear to be a correlation between change in the NSAA Total Score and the time to walk 100 meters, despite both assessments serving to gauge lower-extremity function.

6.1.11.3 Subpopulation Analyses

Due to small sample size, subpopulation analysis was not performed.

6.1.11.4 Dropouts and/or Discontinuations

No subjects dropped out or discontinued the study.

6.1.12 Safety Analyses

6.1.12.1 Methods

All 4 subjects were included in the safety population (Exposure Analysis Set). For discussion, please see Section 8 Integrated Analysis of Safety.

6.1.12.2 Overview of Adverse Events

Table 11 provides the percentage of subjects reporting any treatment-related treatment-emergent adverse events (TEAEs). Three of the four subjects experienced at least one TEAE. Seventy-five percent of the subjects experienced increased hepatic enzyme and vomiting; 50% experienced decreased appetite; and 25% experienced asthenia, fatigue, or nausea.

Table 11. Treatment-Related Adverse Events in Study 101

Preferred Term	ELEVIDYS N = 4 n (%)
Any treatment-related AE	3 (75.0)
Asthenia	1 (25.0)
Decreased appetite	2 (50.0)
Fatigue	1 (25.0)
Hepatic enzyme increased	3 (75.0)
Nausea	1 (25.0)
Vomiting	3 (75.0)

Source: FDA

Abbreviation: AE, adverse event.

6.1.12.3 Deaths

No deaths occurred in this study.

6.1.12.4 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) observed in this study.

6.1.12.5 Adverse Events of Special Interest

No subjects in Study 101 experienced adverse events defined in the Study 101 protocol as Adverse Events of Special Interest.

Reviewer Comment:

Based on the SAEs observed with AAV vector-based gene therapy products as a class, and SAEs reported in other clinical trials of ELEVIDYS, the following adverse events were considered Adverse Events of Special Interest: acute serious liver injury, immune-mediated myositis, myocarditis and increased troponin-I, thrombocytopenia, and potential immunologic cross-reactivity with AAV vectors of other serotypes.

These Adverse Events of Special Interest are discussed in Section 8.2.

6.1.12.6 Clinical Test Results

Table 12 and Table 13, respectively, provide the proportion of subjects with potentially clinically significant abnormalities in laboratory parameters and on cardiac tests. All subjects had at least one clinically significant abnormal laboratory parameter. The majority of subjects had GGT > 3 times baseline or > ULN (100%), ALT and aspartate aminotransferase (AST) ≥ 2 times baseline level (75%), and white blood cell count > 1.5 times ULN or below the lower limit of normal (75%).

One subject had potentially clinically significant abnormalities on electrocardiogram: corrected QT interval (by Fridericia formula) of < 320 msec (Table 13).

Reviewer Comment:

Troponin-I level was not assessed in Study 101.

Table 12. Proportion of Subjects With Potentially Clinically Significant Abnormalities in Laboratory Parameters in Study 101

Parameter	Abnormality Criteria	Subjects (N = 4) % (n)
Chemistry	-	-
Subjects with any potentially clinically significant abnormalities	-	100.0 (4)
Alanine aminotransferase (U/L)	$\geq 2 \times$ baseline value	75.0 (3)
Alkaline phosphatase (U/L)	$> 1.5 \times$ ULN	0
Amylase (U/L)	$> \text{ULN}$	25.0 (1)
Aspartate aminotransferase (U/L)	$\geq 2 \times$ baseline value	75.0 (3)
Blood urea nitrogen (mmol/L)	$> 1.5 \times$ baseline and $> \text{ULN}$	0
Creatinine (micromol/L)	$> \text{ULN}$	0
Cystatin C (mg/L)	$> \text{ULN}$	0
GGT (U/L)	$> 3 \times$ baseline or $> \text{ULN}$	100.0 (4)
Potassium (mmol/L)	$> 5.5 \text{ mmol/L}$ or $< 3 \text{ mmol/L}$	25.0 (1)
Total bilirubin (mg/dL)	$> 1.5 \times \text{ULN}$	25.0 (1)
Total protein (g/dL)	$< \text{LLN}$	50.0 (2)
Hematology	-	-
Subjects with any potentially clinically significant abnormalities	-	100.0 (4)
Basophils ($10^9/\text{L}$)	$< \text{LLN}$ or $> \text{ULN}$	25.0 (1)
Eosinophils ($10^9/\text{L}$)	$> 1.5 \times \text{ULN}$ or $< \text{LLN}$	0
Hematocrit (Proportion of 1)	$< \text{LLN}$	0
Hemoglobin (g/L)	$< \text{LLN}$	25.0 (1)
Lymphocytes ($10^9/\text{L}$)	$< \text{LLN}$	0
Monocytes ($10^9/\text{L}$)	$< \text{LLN}$	0
Neutrophils ($10^9/\text{L}$)	$> 1.5 \times \text{ULN}$ or < 0.000001	50.0 (2)
Platelets ($10^9/\text{L}$)	< 150 or < 200 with a decrease of at least 100	50.0 (2)
Red blood cell count ($10^{12}/\text{L}$)	$< \text{LLN}$	0
White blood cell count ($10^9/\text{L}$)	$> 1.5 \times \text{ULN}$ or $< \text{LLN}$	75.0 (3)
Urinalysis	-	-
Subjects with any potentially clinically significant abnormalities	-	25.0 (1)
Protein in urine	$> 1 +$	25.0 (1)

Source: Adapted from BLA 125781.0, Study 101 Clinical Study Report

Cutoff Date: December 20, 2021

Abbreviations: GGT, gamma-glutamyl transferase; LLN, lower limit of normal; ULN, upper limit of normal.

Table 13. Proportion of Subjects With Potentially Clinically Significant Abnormalities on Electrocardiogram and Echocardiogram, Study 101

Parameter	Subjects (N=4) % (n)
Subjects with any potentially clinically significant abnormality	25.0 (1)
Heart rate (beats/minute)	-
< 50	0
> 120	0

Parameter	Subjects (N=4) % (n)
QTcF interval (msec)	-
Prior to treatment > 450	0
Postbaseline	N/A
< 320	25.0 (1)
Increase >30	0
Increase >60	0
> 450	0
> 480	0
> 500	0
LVEF (%)	-
< 55	0

Source: Adapted from BLA 125781, Study101 Clinical Study Report

Abbreviation: LVEF, left ventricular ejection fraction; QTcF, QT interval corrected by Fridericia formula.

6.1.12.7 Dropouts and/or Discontinuations

None of the subjects dropped out or were discontinued from this study due to adverse events.

6.1.13 Study Summary and Conclusions

Treatment with ELEVIDYS in four ambulatory subjects with DMD, aged 4 to 6 years (mean age of 4.8 years), appeared to be well-tolerated. Subjects demonstrated a mean decrease from baseline of 9 seconds (range, 2 to 24) in time to walk 100 meters, and a mean increase from baseline in NSAA Total Score of 5.5 points (range, 2 to 8). At Year 4, the mean decrease from baseline in time to walk 100 meters was 7 seconds (range, 0 to 14) and the mean increase from baseline in NSAA Total Score was 7 points (range, 4 to 11).

Reviewer Comment:

Considering natural history data for this age group regarding the heterogeneity of DMD progression and the general trajectory of the NSAA Total Score, it is challenging to discern a clear, meaningful clinical benefit of ELEVIDYS in this open-label, single-arm, limited study of four subjects.

Additionally, Study 101 utilized ELEVIDYS manufactured by Process A, (b) (4) compared to ELEVIDYS manufactured using Process B. Therefore, in considering the overall clinical development program, caution is warranted in extrapolating from safety data collected in Study 101.

6.2 Trial #2: SRP-9001-102 (Study 102)

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

Clinical Trial Registry Identifiers: NCT03769116

6.2.1 Objectives (Primary, Secondary)

Primary

- Evaluate safety of ELEVIDYS
- Part 1: evaluate expression of ELEVIDYS micro-dystrophin, measured by Western blot, at Week 12 after dosing
- Part 1: evaluate the effect of ELEVIDYS on physical function, measured by change in NSAA Total Score from baseline to Week 48

Secondary

- Part 1: evaluate the effect of ELEVIDYS on physical function over 48 weeks, measured by other assessments (e.g., 100-meter timed test, time to rise from floor test, etc.)
- Part 1: evaluate expression of ELEVIDYS micro-dystrophin Week 12, as measured by immunofluorescence of biopsied muscle tissue (fiber intensity and percent ELEVIDYS micro-dystrophin positive fibers)

Reviewer Comment:

Biomarker assessments (e.g., expression of ELEVIDYS micro-dystrophin expression, immunofluorescent fiber intensity) and functional assessments in Study 102 Part 2 were exploratory objectives. Because of the functional open-label nature of Study Part 2, this review will focus on results from Study 102 Part 1.

6.2.2 Design Overview

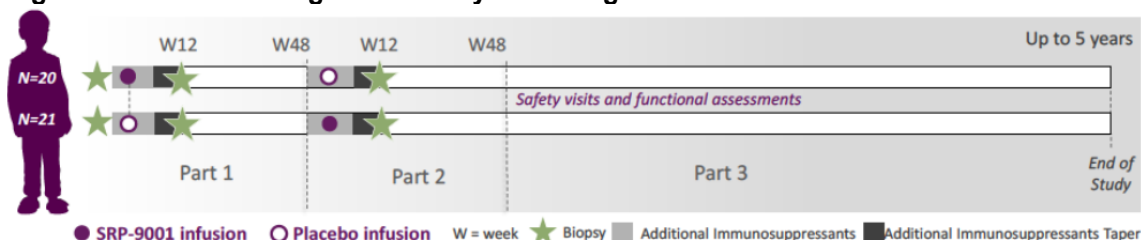
Study 102 is an ongoing, three-part, multicenter clinical trial. Data from Study 102 Part 1 and Study 102 Part 2 are included in the BLA submission.

Study 102 Part 1 was a 48-week randomized, double-blind, placebo-controlled trial of systemic gene delivery of ELEVIDYS in up to 44 subjects with DMD aged 4 to 7 years (inclusive) who have either a confirmed frameshift (deletion or duplication) between exons 18 to 58 or a premature stop codon mutation between exons 18 to 58 of the *DMD* gene. Subjects meeting all eligibility criteria were randomized in a 1:1 allocation ratio to receive intravenous infusion of either ELEVIDYS or placebo (lactated Ringer's solution). Randomization was stratified by age group at baseline (age 4 to 5 years versus 6 to 7 years).

Study 102 Part 2 was a 48-week "cross-over" trial initiated after the subject completed Study 102 Part 1. Subjects randomized to placebo during Study 102 Part 1 received intravenous ELEVIDYS (1.33×10^{14} vg/kg) in Study 102 Part 2. Subjects treated with ELEVIDYS in Study 102 Part 1 received placebo in Study 102 Part 2, in order to maintain blinding to the initial treatment assignment.

Part 3 is an ongoing long-term follow-up study.

Figure 9. Schematic Diagram of Study 102 Design



Source: Applicant's Briefing Document for the Cellular, Tissue and Gene Therapies Advisory Committee

Reviewer Comment:

Unlike for cross-over studies with small-molecule drugs, no wash-out period is possible for gene therapies. Therefore, although the blind was maintained in Study 102 Part 2, by that point the subjects, caregivers, and evaluators were aware that all subjects had now received ELEVIDYS, rendering Study 102 Part 2 effectively an open-label study. Thus, the only data available from a randomized, double-blind, placebo-controlled study are those from Study 102 Part 1.

6.2.3 Population

Key Inclusion Criteria

- Ambulatory boys aged 4 to 7 years, inclusive
- Molecular characterization: frameshift (deletion or duplication) or premature stop codon mutation between exons 18 to 58 of the *DMD* gene
- Anti-rAAVrh74 antibody titer $\leq 1:400$ per ELISA
- Serum creatine kinase level >1000 U/L
- Time < 95 th percentile predicted for age on the 100-meter timed walk test
- Corticosteroid dose: stable dose equivalent of oral corticosteroids for at least 12 weeks prior to screening, with the dose expected to remain constant throughout the first year of the study (except for potential modifications to accommodate changes in weight)

Key Exclusion Criteria

- Signs of cardiomyopathy, including echocardiogram demonstrating ejection fraction $< 40\%$
- Received any investigational medication (other than corticosteroids) or exon-skipping drugs, experimental or otherwise (including eteplirsen), in the 6 months prior to screening for this study
- Abnormal laboratory values considered clinically significant:
 - GGT $> 3 \times$ upper limit of normal
 - Bilirubin ≥ 3.0 mg/dL
 - Creatinine ≥ 1.8 mg/dL
 - Hemoglobin < 8 or > 18 g/dL
 - White blood cell count $> 18,500/\mu\text{L}$

6.2.4 Study Treatments or Agents Mandated by the Protocol

ELEVIDYS was administered as a single intravenous infusion through a peripheral limb vein. The intended dose of SRP-9001 was 1.33×10^{14} vg/kg. However, the Applicant retrospectively determined that in the ELEVIDYS group, only 8 subjects actually received the intended dose, while 6 subjects received approximately two-thirds of the intended dose (8.94×10^{13} vg/kg; Dose Level 2/middle dose) and 6 subjects received about half of the intended dose (6.29×10^{13} vg/kg; Dose Level 1/low dose). This discrepancy was identified following a change in the analytical method for dose determination.

All subjects were on a stable dose of corticosteroids, as standard of care treatment for DMD, for at least 12 weeks prior to infusion of ELEVIDYS or placebo. All subjects had baseline titers of anti-AAVrh74 total binding antibodies of <1:400 as determined by an investigational ELISA assay. The day prior to treatment, the subject's background dose of corticosteroid was increased to at least 1 mg/kg (prednisone equivalent) daily and continued at this level for at least 60 days after the infusion, unless earlier tapering was indicated clinically.

6.2.5 Sites and Centers

- David Geffen School of Medicine at UCLA, Los Angeles, CA
- Nationwide Children's Hospital, Ohio State University, Columbus, OH

6.2.7 Surveillance/Monitoring

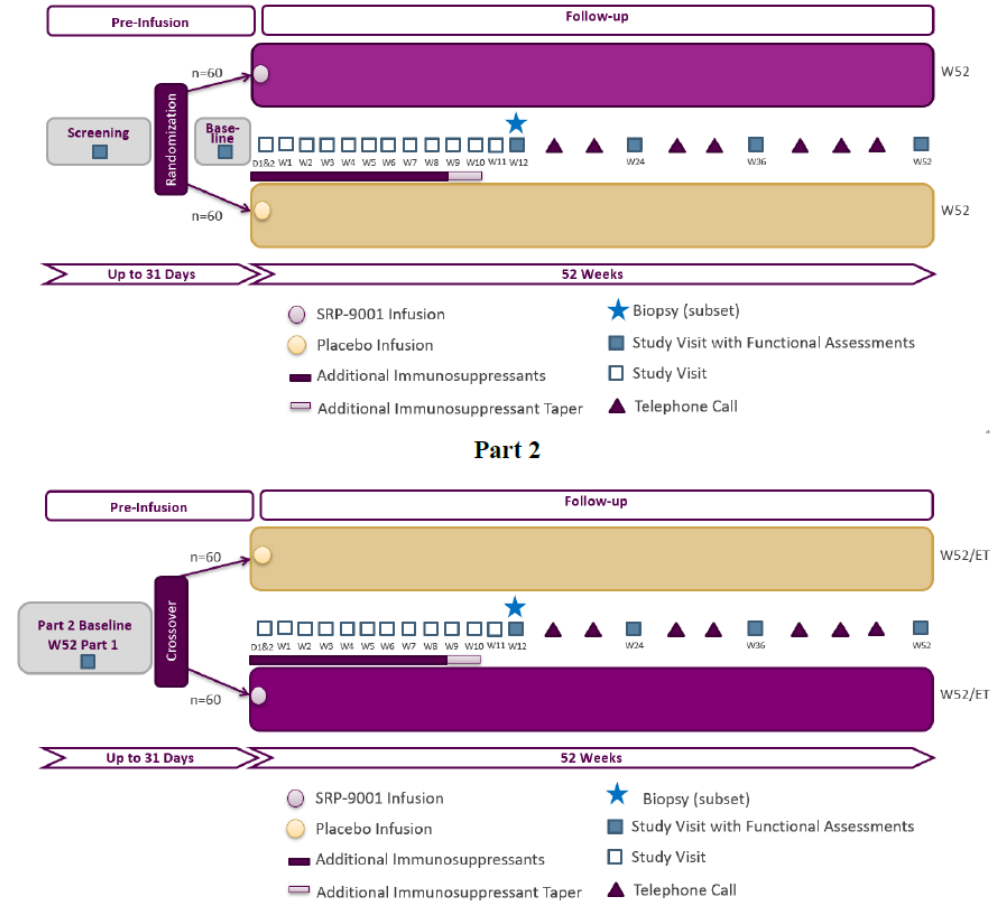
An independent Data Monitoring Committee was established to periodically review the safety and study progress of the study, and to provide recommendations to the Applicant.

Study 102 follow-up visits are summarized in Figure 10,

Table 14 and Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D/d, day; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; HIV, human immunodeficiency virus; Scr, screening; W/w, week.

Table 15.

Figure 10. Schematic Diagram of Visits for Study 102 Part 1 and Study 102 Part 2



Source: BLA 126781 Summary of Clinical Efficacy.
Abbreviations: D, day; ET, early termination; W, week.

Table 14. Schedule of Events for Study 102 Part 1

Study Interval	Scr / Baseline	Part 1 - Inpatient			Part 1 - Follow Up											
Study Interval	W-4 to D-2	D-1	D1	D2	W1	W2	W3 ^a	W4	W5 ^a	W6	W8	W10	W12	W24	W36	W48
Visit Window					±3d	± 3d	±3d	±3d	±3d	±3d	±1w	±1w	±1w	±6w	±6w	±6w
Informed consent	X															
Medical history	X															
Vitals	X	X	X	X	X	X		X		X	X	X	X	X	X	X
Height	X	X			X	X		X			X		X	X	X	X
Weight	X	X			X	X		X			X		X	X	X	X
Physical exam	X	X		X	X	X		X		X	X	X	X	X	X	X
Electrocardiogram	X							X								X
Echocardiogram	X							X								X
Chest X-ray	X															
Hepatitis B & C, HIV	X															
Clinical lab assessments ^b	X	X		X	X	X		X		X	X	X	X	X	X	X
GLDH ^c	X	X		X	X	X		X		X	X	X	X	X	X	X
Liver function tests ^a							X		X							
Functional assessments ^d	X							X			X		X	X	X	X
Patient-reported outcomes	X							X					X	X	X	X
Immunology ^e	X				X	X		X		X	X	X	X	X	X	X
Sample for targeted DNA analysis	X															
Sample for RNA analysis	X							X			X		X	X	X	X
Muscle biopsy	X												X			
Study treatment infusion			X													
Adverse events	To be collected from time of consent until final study visit.															
Concomitant medications	To be collected from time of consent until final study visit.															

Source: Protocol SRP-9001-102, Version 9.0 (submitted to IND 17763)

^a Liver function tests were performed at all clinic visits as part of the clinical lab assessments. However, from the Week 3 and 5 visits, only liver function tests, including GGT, ALT, AST, total bilirubin, albumin, and alkaline phosphatase were performed. The Weeks 3 and 5 visits were performed either at the clinic or a local laboratory; if collected at the clinic, GLDH should also be collected and processed via a central laboratory.

^b Clinical laboratory assessments: Complete blood count/differential/platelet with smear, prothrombin time, partial thromboplastin time, international normalized ratio electrolytes, ALT, AST, alkaline phosphatase, amylase, lactate dehydrogenase, C-reactive protein, blood urea nitrogen, creatine kinase (preferably on 2-day visits but may be tested on a 1-day visit at discretion of the principal investigator), creatinine, cystatin C, GGT, glucose, total protein, albumin, total bilirubin, urinalysis, complement (CH50, C3, C4, and factor B). Note that CH50 may be collected and analyzed by the clinical site; however, C3, C4, and factor B will be collected and analyzed by the central laboratory only.

^c GLDH assay will be performed by a central laboratory and only collected at the clinic visit. If the Week 3 and 5 visits occur in the clinic, a blood sample for the assessment of GLDH will be collected.

^d Functional Assessments: Time to rise from floor, time to ascend 4 steps, North Star Ambulatory Assessment, 10-meter timed test, 100-meter timed test.

^e Antibodies to rAAVrh74 and antigen-specific T-cells to rAAVrh74 capsid or ELEVIDYS micro-dystrophin.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D/d, day; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; HIV, human immunodeficiency virus; Scr, screening; W/w, week.

Table 15. Schedule of Events for Study 102 Part 2

Study Interval	Part 2 - Inpatient			Part 2 - Follow-Up											
Study Interval	D-1 ^a	D1	D2	W1	W2	W3 ^b	W4	W5 ^b	W6	W8	W10	W12	W24	W36	W48
Visit Window				±3d	±3d	±3d	±3d	±3d	±3d	±1w	±1w	±1w	±6w	±6w	±6w
Vitals	X	X	X	X	X		X		X	X	X	X	X	X	X
Height	X			X	X		X			X		X	X	X	X
Weight	X			X	X		X			X		X	X	X	X
Physical exam	X		X	X	X		X		X	X	X	X	X	X	X
ECG							X								X
ECHO							X								X
Clinical lab assessments ^c	X		X	X	X		X		X	X	X	X	X	X	X
GLDH ^d	X		X	X	X		X		X	X	X	X	X	X	X
Liver function tests ^b						X		X							
Functional assessments ^e	X						X			X		X	X	X	X
Patient-reported outcomes					X										X
Immunology ^f	X			X	X		X		X	X	X	X	X	X	X
Study treatment infusion		X													
Whole-genome DNA sequence analysis ^g	X														
Sample for RNA analysis							X			X		X	X	X	X
Muscle biopsy ^h												X			
Vector shedding ⁱ	X	X	X	X	X	X	X	X	X	X	X	X			
Cardiac MRI (sub-study) ^j	X														X
Musculoskeletal MRI (sub-study) ^j	X														X
Adverse events	To be collected from time of consent until final study visit.														
Concomitant medications	To be collected from time of consent until final study visit.														

Source: Protocol SRP-9001-102, Version 9.0 (submitted to IND 17763)

^a If the period between the Week 48 (Part 1) visit and the Day 1 (Part 2) visit is ≤4 weeks, only the following assessments are required at the Day 1 (Part 2) visit: vital signs, height, weight, physical exam; clinical and laboratory assessments; total bilirubin, alkaline phosphatase, amylase, ALT, AST, GGT, lactate dehydrogenase, CRP, CK, serum cystatin C, glucose, complement (CH50, C3, C4, and factor B), GLDH; and, in a subset of patients, vector shedding (saliva, urine, and stool) sample collection. If the period between the Week 48 (Part 1) visit and the Day 1 (Part 2) visit is >30 days, all immunology samples need to be repeated and titer results confirmed prior to the Day 1 visit.

^b Liver function tests will be performed at all clinic visits as part of the clinical lab assessments. However, for the Week 3 and Week 5 visits, only liver function tests, including GGT, ALT, AST, total bilirubin, albumin, and alkaline phosphate will be performed. The Week 3 and Week 5 visits will be performed either at the clinic or at a local laboratory; if collected at the clinic, GLDH should also be collected and processed via a central laboratory.

^c Clinical laboratory assessments: Complete blood count/differential/platelet with smear, prothrombin time, partial thromboplastin time, international normalized ratio, electrolytes, ALT, AST, alkaline phosphatase, amylase, lactate dehydrogenase, CRP, blood urea nitrogen, CK (preferably on 2-day visits but may be tested on a 1-day visit per Principal Investigator discretion), creatinine, cystatin C, GGT, glucose, total protein, albumin, total bilirubin, urinalysis, complement (CH50, C3, C4, and factor B). Note that CH50 may be collected and analyzed by the clinical site; however, C3, C4, and factor B will be collected and analyzed only by the central laboratory.

^d GLDH assay will be performed by a central laboratory and only at clinic visits. If the Week 3 and Week 5 visits occur in the clinic, a blood sample for the assessment of GLDH will be collected.

^e Functional assessments: Time to rise from floor, time to ascend 4 steps, North Star Ambulatory Assessment, 10-meter timed test, 100-meter timed test.

^f Ant bodies to rAAVrh74 and antigen-specific T-cells to rAAVrh74 capsid or ELEVIDYS micro-dystrophin.

^g Blood sample for whole-genome sequencing is optional based upon local regulations and Institutional Review Board approval. An additional informed consent/assent form must be signed prior to collection of samples.

^h Biopsy samples should be collected at least 12 weeks after infusion and by the end of Part 2 (no later than the Week 48 visit).

ⁱ Vector shedding assessments will be performed in a subset of subjects. For any single subject, samples will be collected at select pre-determined visits as allocated in the Vector Shedding Manual. Thus, subject will not undergo collection of samples at all time points during the study; for Week 3 and Week 5, samples will be collected only if the visit occurs in the clinic. Samples to be collected will include saliva, urine, and stool, and will be stored until analysis. For subjects in whom samples will be obtained on Day 1, the samples will be collected ≥ 6 hours following completion of the infusion. Further details are noted in the Vector Shedding Manual.

^j Imaging assessments will be performed in a subset of subjects. The first collection must occur after the Part 1 Week 48 visit, but not later than the Part 2 Day 1 visit. Further details are noted in the MRI Study Manual.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; D/d, day; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; MRI, magnetic resonance imaging; W/w, week.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoints for Study 102 Part 1

- Change in quantity of ELEVIDYS micro-dystrophin protein from baseline to Week 12, as measured by Western blot (biological endpoint)
- Change in NSAA Total Score from baseline to Week 48 (functional endpoint)

Secondary Efficacy Endpoints for Study 102 Part 1

- Change in time of 100-meter timed test from baseline to Week 48
- Change in time to ascend 4 steps from baseline to Week 48
- Change in time to rise from the floor from baseline to Week 48
- Change in time of 10-meter timed test from baseline to Week 48
- Change in expression of ELEVIDYS micro-dystrophin from baseline to Week 12, as measured by immunofluorescence (fiber intensity)
- Change in ELEVIDYS micro-dystrophin expression from baseline to Week 12 as measured by immunofluorescence (percent ELEVIDYS micro-dystrophin positive fibers)

6.2.9 Statistical Considerations and Statistical Analysis Plan

Statistical Hypothesis

- H_{10} : $d_{11} = d_{12}$ versus H_{11} : $d_{11} \neq d_{12}$, where d_{11} and d_{12} are mean change in quantity of ELEVIDYS micro-dystrophin from baseline to Week 12, as measured by Western blot, for the ELEVIDYS and placebo groups, 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 the ELEVIDYS and placebo groups, respectively.

Analysis Method for Primary Endpoint

- *Biological endpoint*: A re-randomization test was performed using the 2-sample Welch t-test as the test statistic.
- *Functional endpoint*: A mixed model for repeated measures (MMRM) method was used to compare the ELEVIDYS group with the placebo group.

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 ELEVIDYS 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 dropouts

Based on these assumptions, a total of 44 subjects (22 subjects per study arm) were needed.

Reviewer Comment:

The study was powered based only on the functional primary efficacy endpoint, change in the NSAA Total Score from baseline to Week 48.

No subgroup analyses were prespecified for hypothesis testing, and no prespecified multiplicity adjustment strategy was employed.

Subgroup Analyses

Subgroup analyses were performed post hoc, based on the following baseline characteristics in the modified-Intent to Treat (mITT) analysis set:

- Age: 4 to 5 years versus 6 to 7 years at the time of screening
- Race: white versus non-white
- Body mass index: $< 20 \text{ kg/m}^2$ versus $\geq 20 \text{ kg/m}^2$
- Corticosteroid type: use of deflazacort at baseline versus use of other steroids
- Lot group: G02A0918-1 (Dose Level 1), G02A0918-2 (Dose Level 2), versus other lots (Target Dose Level)
- Baseline NSAA: baseline NSAA Total Score greater than the median score, versus baseline NSAA Total Score less than the median score

Missing Data Handling for Primary Analysis and Sensitivity Analysis

- For NSAA scoring, 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 multiplied by 17. The NSAA Total Score would be treated as a missing value when 6 or more items are missing.
- In the primary analysis of NSAA results, if in-clinic NSAA score at Week 48 is missed or performed out of the protocol-defined visit window, an interpolated NSAA Total Score would be used, based on neighboring in-clinic measurements. 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.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Analysis Populations

- Intent-to-Treat (ITT) analysis set: all randomized subjects
- Modified Intent-to-Treat (mITT) analysis set: all randomized subjects who received the study treatment; this analysis set was used for primary efficacy analyses
- Per Protocol analysis set: subjects in the mITT analysis set who did not have important protocol deviations that may substantially affect the study results
- Safety analysis set: same definition as mITT set

Table 16. Analysis Sets

Analysis Set	ELEVIDYS, n	Placebo, n	Total, n
Intent-to-Treat	21	22	43
Modified Intent-to-Treat	20	21	41
Per Protocol	10	16	26

Source: FDA Statistical Review.

Reviewer Comment:

The ITT population consists of 43 subjects. The mITT population consists of 41 subjects. Since the primary and secondary efficacy assessments were based on the mITT population, the demographic and baseline characteristics below focus on the mITT population.

6.2.10.1.1 Demographics

Key demographics of the mITT population are presented in Table 17.

Baseline clinical characteristics for subjects in the ELEVIDYS and placebo groups, based on the mITT analysis set, are shown in Table 17. There were no notable differences between the two groups, except for lower baseline NSAA Total Score in the ELEVIDYS group. The difference between the two groups, however, was within one standard deviation.

Table 17. Baseline Characteristics of the Modified Intent-to-Treat Analysis Set

Characteristics	ELEVIDYS (n = 20)	Placebo (n = 21)	Total (N = 41)
Years since DMD diagnosis			
Mean (SD)	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)			
Mean (SD)	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)			
Mean (SD)	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)

Characteristics	ELEVIDYS (n = 20)	Placebo (n = 21)	Total (N = 41)
Weight (kg)			
Mean (SD)	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			
Mean (SD)	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 baseline	7 (35.0%)	7 (33.3%)	14 (34.1%)
Other corticosteroid	13 (65.0%)	14 (66.7%)	27 (65.9%)

Source: FDA Statistical Reviewer's summary

Abbreviation: BMI, body mass index; DMD, Duchene muscular dystrophy; max, maximum; min, minimum; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

Since 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 to 5 years, baseline NSAA Total Scores were well-balanced between the ELEVIDYS group and the placebo group. However, for subjects aged 6 to 7 years, an imbalance in baseline NSAA Total Score was present between the groups: the mean baseline NSAA Total Score was 19.6 points for the ELEVIDYS group, and 24.0 points for the placebo group.

6.2.10.1.3 Subject Disposition

At the April 6, 2022 data cutoff date, all 41 subjects who received treatment (of whom 20 subjects received ELEVIDYS and 21 subjects received placebo) had completed Study 102 Part 1; no subjects discontinued the study aside from the two randomized subjects who withdrew consent before treatment.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

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

Table 18 summarizes level of ELEVIDYS micro-dystrophin, based on the mITT analysis set.

Table 18. Summary of ELEVIDYS Micro-dystrophin Level Measured by Western Blot in the Modified Intent-to-Treat Analysis Set

Level by Western Blot	ELEVIDYS Baseline (n = 20)	ELEVIDYS Week 12 (n = 20)	ELEVIDYS Change	Placebo Baseline (n = 21)	Placebo Week 12 (n = 21)	Placebo Change
Mean (SD)	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)

Source: FDA Statistical Reviewer's analysis

Abbreviation: max, maximum; min, minimum; mITT, modified Intent-to-Treat; SD, standard deviation.

In the mITT analysis set of 41 subjects, the 2-sided p-values based on both the re-randomization test (using two-sample Welch t-test statistic) and Wilcoxon rank sum test

(adjusted for the stratification factor of age) were <0.0001, indicating as expected a statistically significant greater increase in expression of ELEVIDYS micro-dystrophin (measured by Western blot) from baseline to Week 12 in the ELEVIDYS group compared to the placebo group.

- Functional endpoint: Change in NSAA Total Score from baseline to Week 48

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

Table 19 summarizes the results of the MMRM analysis of change in NSAA Total Score at each visit for the mITT analysis set. Figure 11 shows the LS mean change in NSAA Total Score from baseline over time in the ELEVIDYS group and the placebo group, respectively.

Table 19. LS Mean Estimate of Treatment Effect at Each Visit, Based on the Mixed Model for Repeated Measurements Analysis in the Modified Intent-to-Treat Analysis Set

Visit	LS Mean Change From Baseline (SE)	LSM Treatment Difference (SE)	95% CI
Week 4	-	-	-
ELEVIDYS	1.38 (0.46)	0.73 (0.67)	(-0.63, 2.09)
Placebo	0.65 (0.45)	—	—
Week 8	-	-	-
ELEVIDYS	2.17 (0.49)	1.26 (0.72)	(-0.20, 2.72)
Placebo	0.91 (0.48)	—	—
Week 12	-	-	-
ELEVIDYS	2.19 (0.57)	1.53 (0.83)	(-0.16, 3.22)
Placebo	0.66 (0.56)	—	—
Week 24	-	-	-
ELEVIDYS	2.06 (0.65)	0.55 (0.95)	(-1.40, 2.50)
Placebo	1.52 (0.64)	—	—
Week 36	-	-	-
ELEVIDYS	1.66 (0.72)	0.70 (1.02)	(-1.38, 2.78)
Placebo	0.96 (0.67)	—	—
Week 48	-	-	-
ELEVIDYS	1.74 (0.62)	0.82 (0.90)	(-1.03, 2.67)
Placebo	0.92 (0.61)	—	—

Source: FDA Statistical Reviewer's analysis.

Abbreviation: CI, confidence interval; LS, least squares; mITT, modified Intent-to-Treat; MMRM, Mixed Model for Repeated Measurements; SE, standard error.

Source: FDA Statistical Reviewer's analysis
Abbreviation: LS, least squares; NSAA, North Star Ambulatory Assessment.

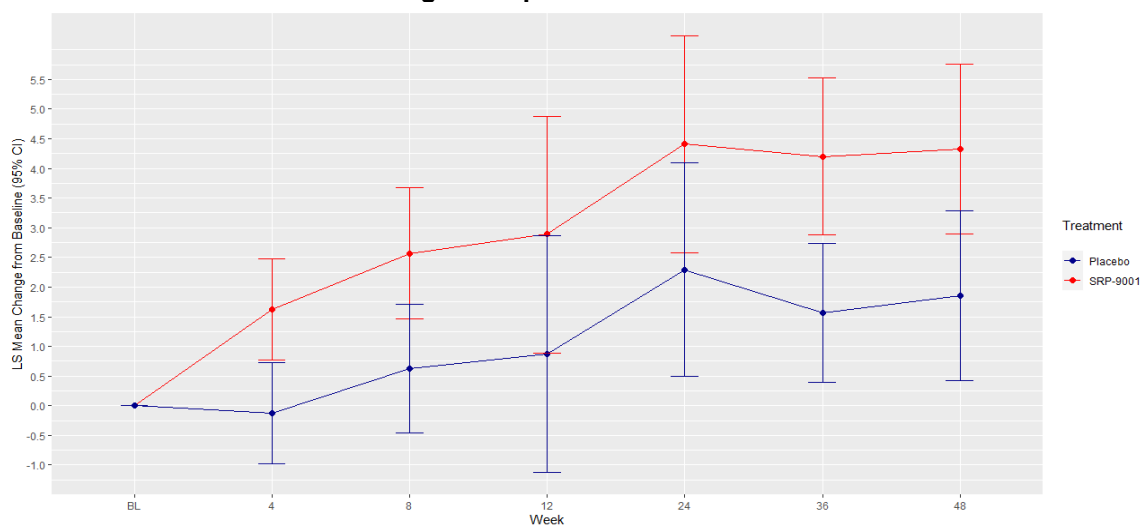
Based on the MMRM analysis in the mITT analysis set, the LS mean change (SE) in NSAA Total Score from baseline to Week 48 are 1.74 (0.62) for the ELEVIDYS group, and 0.92 (0.61) for the placebo group. The LS mean (SE) treatment difference estimated as 0.82 (0.90) at Week 48 between the ELEVIDYS group and the placebo group is not statistically significant (95% confidence interval: -1.03, 2.67; $p = 0.37$).

6.2.11.3 Subpopulation Analyses

Because age is an important prognostic factor for functional abilities in patients with DMD, the Applicant further evaluated the effect of ELEVIDYS treatment by analyzing results within two age subgroups: subjects aged 4 to 5 years, and subjects aged 6 to 7 years. Figure 12 and For subjects aged 4 to 5 years, the LS mean changes (SE) in NSAA Total Score from baseline to Week 48 are 4.3 (0.7) for the ELEVIDYS group, and 1.9 (0.7) for the placebo group. The LS mean (SE) treatment difference at Week 48 between the two groups is 2.5 (0.9), numerically favoring the ELEVIDYS group.

Figure 13 show the LS mean change in NSAA Total Score from baseline over time for each those age groups in Study 102 Part 1.

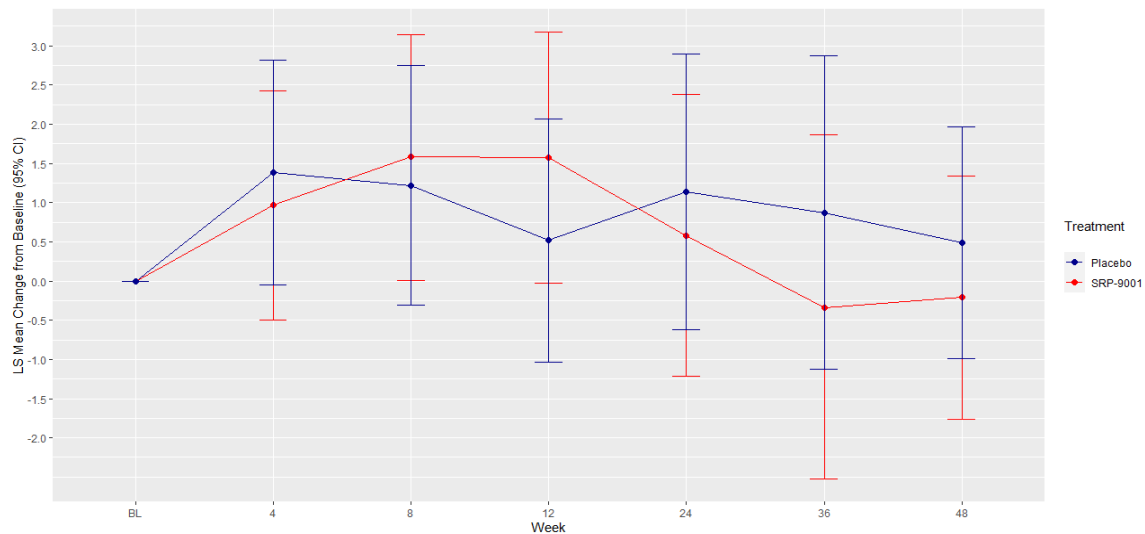
Figure 12. LS Mean Change in North Star Ambulatory Assessment Total Score From Baseline Over Time in 4-5 Year Age Group



Source: FDA Statistical Reviewer's analysis
Abbreviation: LS, least squares; NSAA, North Star Ambulatory Assessment.

For subjects aged 4 to 5 years, the LS mean changes (SE) in NSAA Total Score from baseline to Week 48 are 4.3 (0.7) for the ELEVIDYS group, and 1.9 (0.7) for the placebo group. The LS mean (SE) treatment difference at Week 48 between the two groups is 2.5 (0.9), numerically favoring the ELEVIDYS group.

Figure 13. LS Mean Change in North Star Ambulatory Assessment Total Score From Baseline Over Time in 6-7 Year Age Group



Source: FDA Statistical Reviewer's analysis
Abbreviation: LS, least squares; NSAA, North Star Ambulatory Assessment.

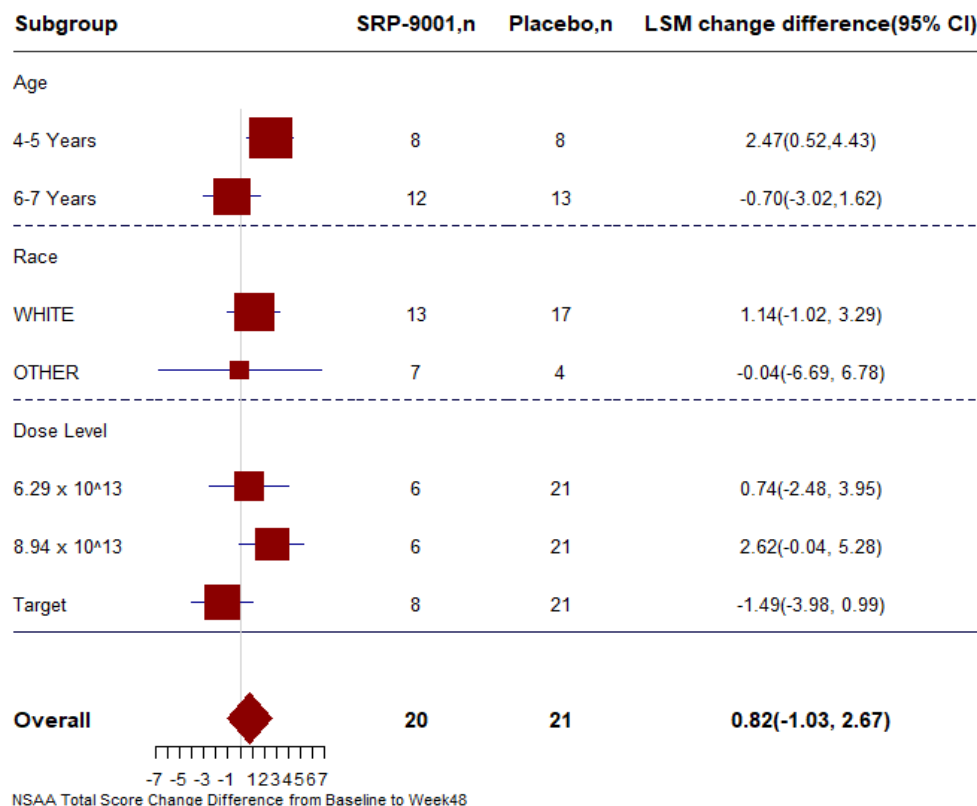
For subjects aged 6 to 7 years, the LS mean changes (SE) in NSAA Total Score from baseline to Week 48 are -0.2 (0.8) for the ELEVIDYS group, and 0.5 (0.7) for the placebo group. The LS mean (SE) treatment difference at Week 48 between the two groups is -0.7 (1.1), numerically favoring the placebo group.

Reviewer Comments:

It is important to note that this subgroup analysis is exploratory. The analysis was not pre-specified for hypothesis testing, and no pre-specified multiplicity adjustment strategy was employed. Post hoc subgroup tests following an overall nonsignificant test in the population as a whole can only be considered hypothesis-generating, and results of the subgroup analysis must be interpreted with caution. Significance tests such as p-values from such exploratory analysis therefore are not included here, because under these circumstances they are misleading, and cannot guide any stakeholders—including patients, family members and caregivers, and prescribers—in making informed decisions about the potential benefit of treatment with ELEVIDYS.

Figure 14 is a forest plot of change in NSAA Total Score from baseline to Week 48, by age group, race, and dose level.

Figure 14. Change in North Star Ambulatory Assessment Total Score From Baseline to Week 48, by Subgroup



Source: FDA Statistical Reviewer's analysis
Abbreviation: NSAA, North Star Ambulatory Assessment.

Reviewer Assessment:

For all three dose levels of ELEVIDYS administered during Study 102 Part 1, the 95% confidence intervals of the LS mean treatment difference in NSAA Total Score at Week 48 include zero, indicating no effect; subjects receiving the intended dose demonstrated the poorest outcome. Due to the small sample sizes at each dose level, however, it is not possible to draw any strong conclusions from this analysis, which also can only be considered exploratory.

6.2.11.4 Dropouts and/or Discontinuations

Among the total of 43 randomized subjects of the Intent-to-Treat population, 2 subjects (one each from the ELEVIDYS group and the placebo group) discontinued participation in the study before dosing, due to withdrawal of consent.

All 41 treated subjects completed Study 102 Part 1.

Two subjects who received ELEVIDYS in Study 102 Part 1 were not administered placebo in Study 102 Part 2 due to TEAEs (irritability and femur fracture).

6.2.11.5 Exploratory Analyses

In Study 102 Part 2, subjects in the Part 1 placebo group received ELEVIDYS and demonstrated a mean increase of 1.3 points (SD 2.7) in NSAA Total Score from their Part 2 baseline to Week 48.

For subjects who received ELEVIDYS in Part 1, the mean change in NSAA Total Score change from their Part 2 baseline to Week 48 was 0.1 points (SD 6.6). However, exploratory analysis of that group by age range shows that at Week 48 of Part 2, the mean NSAA Total Score for those in the 4 to 5 years subgroup increased from their Part 2 baseline by 0.4 points (SD 2.4), while the mean NSAA Total Score for the 6 to 7 years subgroup declined by 4.3 (SD 5.1) from their Part 2 baseline.

Reviewer Comment:

Due to the open-label, uncontrolled design of Study 102 Part 2, these clinical outcome data are susceptible to bias and. Their clinical meaningfulness is uncertain.

E6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population for Study 102 consists of 41 subjects who received the product. In Part 1, 20 subjects were treated with ELEVIDYS and 21 subjects were treated with placebo. In Part 2, the 21 subjects who received placebo in Part 1 were treated with ELEVIDYS and 18 subjects who had received ELEVIDYS in Part 1 were administered placebo. Two subjects who had received ELEVIDYS in Part 1 were not treated in Part 2.

TEAEs include all adverse events that first occurred or increased in severity since the study treatment of ELEVIDYS or placebo in the Primary Analysis Set.

6.2.12.2 Overview of Adverse Events

Table 20 summarizes treatment-related adverse events reported in Study 102 Part 1. Overall, 85% of subjects in the ELEVIDYS group, versus 38% of subjects in the placebo group, experienced at least one TEAE.

Table 20. Treatment-related Adverse Events in Study 102 Part 1

System Organ Class Preferred Term	ELEVIDYS N = 20 n (%)	Placebo N = 21 n (%)	All Subjects N = 41 n (%)
Any treatment-related AE	17 (85.0)	8 (38.1)	25 (61.0)
Blood and lymphatic system disorders	1 (5.0)	0 (0.0)	1 (2.4)
Thrombocytosis	1 (5.0)	0 (0.0)	1 (2.4)
Gastrointestinal disorders	16 (80.0)	6 (28.6)	22 (53.7)
Abdominal discomfort	0 (0.0)	1 (4.8)	1 (2.4)
Abdominal pain	3 (15.0)	0 (0.0)	3 (7.3)
Abdominal pain upper	3 (15.0)	1 (4.8)	4 (9.8)
Gastroesophageal reflux disease	1 (5.0)	0 (0.0)	1 (2.4)
Nausea	6 (30.0)	2 (9.5)	8 (19.5)
Vomiting	12 (60.0)	4 (19.0)	16 (39.0)
General disorders and administration site conditions	1 (5.0)	0 (0.0)	1 (2.4)
Pyrexia	1 (5.0)	0 (0.0)	1 (2.4)

System Organ Class Preferred Term	ELEVIDYS N = 20 n (%)	Placebo N = 21 n (%)	All Subjects N = 41 n (%)
Hepatobiliary disorders	1 (5.0)	0 (0.0)	1 (2.4)
Hepatomegaly	1 (5.0)	0 (0.0)	1 (2.4)
Liver injury	1 (5.0)	0 (0.0)	1 (2.4)
Investigations	6 (30.0)	0 (0.0)	6 (14.6)
Alanine aminotransferase increased	1 (5.0)	0 (0.0)	1 (2.4)
Aspartate aminotransferase increased	1 (5.0)	0 (0.0)	1 (2.4)
Blood bilirubin increased	2 (10.0)	0 (0.0)	2 (4.9)
Gamma-glutamyl transferase increased	5 (25.0)	0 (0.0)	5 (12.2)
Liver function test increased	1 (5.0)	0 (0.0)	1 (2.4)
Transaminases increased	1 (5.0)	0 (0.0)	1 (2.4)
Urobilinogen urine increased	1 (5.0)	0 (0.0)	1 (2.4)
Metabolism and nutrition disorders	6 (30.0)	0 (0.0)	6 (14.6)
Decreased appetite	6 (30.0)	0 (0.0)	6 (14.6)
Musculoskeletal and connective tissue disorders	3 (15.0)	2 (9.5)	5 (12.2)
Pain in extremity	1 (5.0)	1 (4.8)	2 (4.9)
Rhabdomyolysis	2 (10.0)	1 (4.8)	3 (7.3)

Source: FDA

Abbreviation: AE, adverse event.

Table 21 provides the proportion of subjects who reported at least one treatment-related TEAE in Study Part 1 of the Study 102. Overall, vomiting was the most frequent treatment-related TEAE across all groups. Subjects in the ELEVIDYS group reported more treatment-related TEAEs than did subjects in the placebo group. There was no clinically meaningful difference in subjects who reported treatment-related TEAEs across ELEVIDYS groups treated at different dose levels.

Table 21. Treatment-related Treatment-Emergent Adverse Event by Preferred Term, Study 102 Part 1

Preferred Term	SRP-9001^a 6.29 × 10¹³ vg/kg (N=6) % (n)	SRP-9001^a 8.94 × 10¹³ vg/kg (N=6) % (n)	SRP-9001 Intended Dose 1.33 × 10¹⁴ vg/kg (N=8) % (n)	Total (N=20) % (n)	Placebo (N=21) % (n)	Total (N=41) % (n)
Subjects with any treatment-related TEAE	83.3 (5)	83.3 (5)	87.5 (7)	85.0 (17)	42.9 (9)	63.4 (26)
Abdominal discomfort	0	0	0	0	4.8 (1)	2.4 (1)
Abdominal pain	0	0	37.5 (3)	15.0 (3)	0	7.3 (3)
Abdominal pain upper	0	33.3 (2)	12.5 (1)	15.0 (3)	4.8 (1)	9.8 (4)
Alanine aminotransferase increased	0	0	12.5 (1)	5.0 (1)	0	2.4 (1)
Aspartate aminotransferase increased	0	0	12.5 (1)	5.0 (1)	0	2.4 (1)
Blood bilirubin increased	16.7 (1)	0	12.5 (1)	10.0 (2)	0	4.9 (2)
Decreased appetite	16.7 (1)	33.3 (2)	37.5 (3)	30.0 (6)	0	14.6 (6)

Preferred Term	SRP-9001 ^a 6.29 × 10 ¹³ vg/kg (N=6) % (n)	SRP-9001 ^a 8.94 × 10 ¹³ vg/kg (N=6) % (n)	SRP-9001 Intended Dose 1.33 × 10 ¹⁴ vg/kg (N=8) % (n)	Total (N=20) % (n)	Placebo (N=21) % (n)	Total (N=41) % (n)
Gamma-glutamyl transferase increased	16.7 (1)	16.7 (1)	37.5 (3)	25.0 (5)	0	12.2 (5)
Gastroesophageal reflux disease	0	16.7 (1)	0	5.0 (1)	0	2.4 (1)
Hepatomegaly	0	16.7 (1)	0	5.0 (1)	0	2.4 (1)
Liver function test increased	0	16.7 (1)	0	5.0 (1)	0	2.4 (1)
Liver injury	0	16.7 (1)	0	5.0 (1)	0	2.4 (1)
Nausea	33.3 (2)	16.7 (1)	37.5 (3)	30.0 (6)	9.5 (2)	19.5 (8)
Pain in extremity	33.3 (2)	0	0	10.0 (2)	4.8 (1)	7.3 (3)
Proteinuria	0	0	0	0	4.8 (1)	2.4 (1)
Pyrexia	0	0	12.5 (1)	5.0 (1)	0	2.4 (1)
Rhabdomyolysis	16.7 (1)	16.7 (1)	0	10.0 (2)	4.8 (1)	7.3 (3)
Thrombocytosis	0	0	12.5 (1)	5.0 (1)	0	2.4 (1)
Transaminases increased	0	0	12.5 (1)	5.0 (1)	0	2.4 (1)
Urobilinogen urine increased	16.7 (1)	0	0	5.0 (1)	0	2.4 (1)
Vomiting	83.3 (5)	33.3 (2)	62.5 (5)	60.0 (12)	19.0 (4)	39.0 (16)

Source: Adapted from BLA 125781, Study102 Part 2 Clinical Study Report, Table 30

^a In the SRP-9001 group (N = 20), the intended dose was 1.33 × 10¹⁴ vg/kg, with 12 patients receiving a dose lower than the intended dose (6 subjects received 6.29 × 10¹³ vg/kg, and 6 subjects received 8.94 × 10¹³ vg/kg).

Abbreviation: TEAE, treatment-emergent adverse event.

6.2.12.6 Clinical Test Results

Elevation in AST, ALT, GGT, and decrease in platelets (< 150 × 10⁹/L, or < 200 × 10⁹/L with a decrease of at least 100 × 10⁹/L) were much more frequent in the ELEVIDYS group than in the placebo group (Table 22).

Table 22. Proportion of Subjects With Potentially Clinically Significant Abnormalities in Laboratory Parameters, Study 102 Part 1

Parameter	Abnormal Criteria	ELEVIDYS (N = 20) % (n)	Placebo (N = 21) % (n)	Total (N = 41) % (n)
Chemistry	-	-	-	-
Subjects with any potentially clinically significant abnormalities	—	100.0 (20)	95.2 (20)	97.6 (40)
BUN (mmol/L)	>1.5 × baseline and >ULN	5.0 (1)	4.8 (1)	4.9 (2)
Creatinine (mcmol/L)	>ULN	5.0 (1)	0	2.4 (1)
Potassium (mmol/L)	>5.5 mmol/L or <3 mmol/L	5.0 (1)	0	2.4 (1)
AST [SGOT] (U/L)	≥2 × baseline value	70.0 (14)	33.3 (7)	51.2 (21)
ALT [SGPT] (U/L)	≥2 × baseline value	30.0 (6)	0	14.6 (6)
Gamma-glutamyl transferase (U/L)	>3 × baseline or >ULN	35.0 (7)	0	17.1 (7)
Alkaline phosphatase (U/L)	>1.5 × ULN	0	0	0
Albumin (g/L)	<LLN or >ULN	0	4.8 (1)	2.4 (1)
Total bilirubin (mcmol/L)	>1.5 × ULN	10.0 (2)	0	4.9 (2)
Lactate dehydrogenase (U/L)	≥2 × baseline value	25.0 (5)	14.3 (3)	19.5 (8)
Creatine phosphokinase (U/L)	≥2 × baseline value	40.0 (8)	38.1 (8)	39.0 (16)
Cystatin C (mg/L)	>ULN	5.0 (1)	0	2.4 (1)
GLDH (U/L)	>ULN	0	4.8 (1)	2.4 (1)
Total protein (g/dL)	>ULN	20.0 (4)	4.8 (1)	12.2 (5)
Amylase (U/L)	>ULN	5.0 (1)	0	2.4 (1)
C-reactive protein (mg/L)	>ULN	20.0 (4)	9.5 (2)	14.6 (6)
Complement Total (CAE Units)	>ULN	95.0 (19)	52.4 (11)	73.2 (30)
C3 (mg/dL)	>ULN	0	0	0
C4 (mg/dL)	>ULN	30.0 (6)	14.3 (3)	22.0 (9)
Factor B (mg/dL)	>ULN	45.0 (9)	42.9 (9)	43.9 (18)

Parameter	Abnormal Criteria	ELEVIDYS (N = 20) % (n)	Placebo (N = 21) % (n)	Total (N = 41) % (n)
Hematology	-	-	-	-
Subjects with any potentially clinically significant abnormalities	—	95.0 (19)	52.4 (11)	73.2 (30)
Hematocrit (proportion of 1)	<LLN	15.0 (3)	4.8 (1)	9.8 (4)
Hemoglobin (g/L)	<LLN	25.0 (5)	4.8 (1)	14.6 (6)
Red blood cell count (trillion/L)	<LLN	15.0 (3)	0	7.3 (3)
White blood cell count (10 ⁹ /L)	>1.5 × ULN or < LLN	40.0 (8)	19.0 (4)	29.3 (12)
Platelet count (10 ⁹ /L)	<150 or <200 with a decrease of at least 100	70.0 (14)	4.8 (1)	36.6 (15)
Basophils (abs) (10 ⁹ /L)	>ULN or <LLN	0	9.5 (2)	4.9 (2)
Eosinophils (abs) (10 ⁹ /L)	>1.5 × ULN or <LLN	10.0 (2)	14.3 (3)	12.2 (5)
Lymphocytes (abs) (10 ⁹ /L)	<LLN	10.0 (2)	14.3 (3)	12.2 (5)
Monocytes (abs) (10 ⁹ /L)	<LLN	5.0 (1)	4.8 (1)	4.9 (2)
Neutrophils (abs) (10 ⁹ /L)	>1.5 × ULN or <0.000001	5.0 (1)	23.8 (5)	14.6 (6)
Urinalysis	-	-	-	-
Subjects with any potentially clinically significant abnormalities	—	-	0	0
Protein in urine	>1+	-	0	0

Source: Adapted from BLA 125781, Study 102 Clinical Study Report, Table P2.14.3.4.3.1

Abbreviations: abs, absolute count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; abs, absolute; BUN, blood urea nitrogen; GLDH, glutamate dehydrogenase; LLN, lower limit of normal; SGOT, serum glutamic-oxaloacetic transaminase; ULN, upper limit of normal

6.3 Trial #3: SRP-9001-103 (Study 103)

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

National Clinical Trial Registry: NCT04626674

- Assess vector shedding
- Evaluate the immunogenicity of ELEVIDYS, as assessed by detection of antibodies to rAAVrh74
- Evaluate the safety of ELEVIDYS
- Evaluate expression of ELEVIDYS micro-dystrophin (measured by immunofluorescence) at Week 12

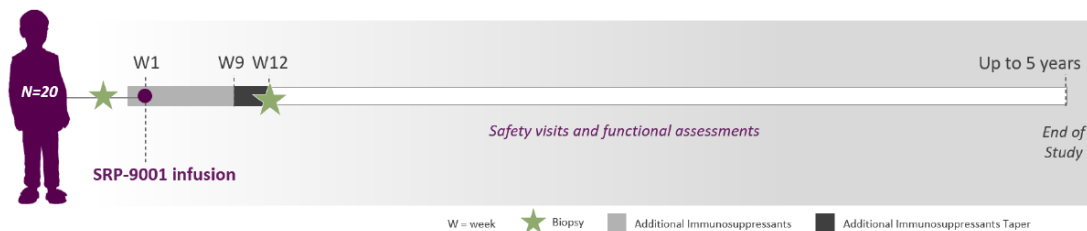
One of the exploratory objectives was to evaluate the effect of ELEVIDYS on NSAA Total Score in ambulatory subjects with DMD.

6.3.2 Design Overview

Study 103 is an ongoing, two-part, open-label, single-arm, single-dose study with planned four cohorts, enrolled based on the subjects' age and ambulation status.

Study 103 consists of 4 periods: an up to approximately 3-week screening period, an approximately 1-week baseline period, a 1-day infusion period, and a 260-week follow-up period (Figure 15).

Figure 15. Schematic Diagram of Study 103 Design



Source: Applicant's Briefing Document for the Cellular, Tissue and Gene Therapies Advisory Committee.

6.3.3 Population

Key Inclusion Criteria

- Cohorts 1, 2, 4: ability to ambulate; Cohort 3: non-ambulatory
- Age:
 - Cohort 1: ≥ 4 to < 8 years
 - Cohort 2: ≥ 8 to < 18 years, inclusive
 - Cohort 3: no age restriction
 - Cohort 4: ≥ 3 to < 4 years
- Molecular characterization:
 - Cohorts 1 and 3 (all subjects): Definitive diagnosis of DMD
 - Cohorts 2 (1 subject) and 4 (all subjects): Frameshift mutation (deletion or duplication), premature stop codon, canonical splice site mutation, or other pathogenic variant between exons 18 to 79 (inclusive)
- Anti-rAAVrh74 antibody titer $\leq 1:400$ per ELISA assay
- Serum creatine kinase level > 1000 U/L
- 100-meter walk/run test
 - Cohorts 1 and 2: $< 95^{\text{th}}$ percentile predicted time
- NSAA score:
 - Cohort 1: NSAA Total Score > 17 and ≤ 26
 - Cohort 2: NSAA Total Score ≥ 15 and ≤ 26
 - Cohort 3: NSAA walk score of 0, inability to perform 10-meter walk/run test, and Performance of the Upper Limb entry item score ≥ 2

- Corticosteroid dose:
 - For Cohorts 1, 2, and 3: Stable weekly dose equivalent of oral corticosteroids for at least 12 weeks prior to screening, with the dose expected to remain constant throughout the first year of the study (except for potential modifications to accommodate changes in weight)
 - For Cohort 4: subjects who do not yet require use of chronic corticosteroids for treatment of DMD in the opinion of the investigator, and are not receiving corticosteroids at the time of screening.

Key Exclusion Criteria

- Left ventricular ejection fraction <40% on the screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy
- Treatment with any of the following therapies, according to the time frames specified:
 - Within 12 weeks of Day 1: use of human growth factor
 - Within 6 months of Day 1: any investigational medication
 - Cohort 1 and 4: any treatment designed to increase dystrophin expression (e.g., ataluren [Translarna], eteplirsen, golodirsen, or viltolarsen). NOTE: Subjects in Cohort 2 and 3 on these treatments are expected to stop prior to Day 1.
 - Treatments designed to increase dystrophin expression may be resumed and/or started after Week 72
 - Receipt of a live-virus vaccine within 4 weeks, or of an inactivated-virus vaccine within 2 weeks, of the Day 1 visit, or expected to undergo vaccination during the first 3 months after Day 1
- Abnormal laboratory values considered clinically significant:
 - GGT >2 × upper limit of normal
 - Total bilirubin > ULN
 - White blood cell count >18,500/ mcL
 - Platelets ≤ 150,000/mcL

6.3.4 Study Treatments or Agents Mandated by the Protocol

All subjects received ELEVIDYS. Subjects who weighed <70 kg on Day 1 received a dose of 1.33×10^{14} vg/kg; subjects who weighed ≥70 kg on Day 1 received a dose of 9.31×10^{15} vg/kg (equivalent to a dose of 1.33×10^{14} vg/kg for a 70 kg subject).

Reviewer Comments:

Subjects in Study 103 received ELEVIDYS manufactured by Process B (the to-be-marketed ELEVIDYS product). Although intended as a bridging study to enable comparison of ELEVIDYS manufactured by Process B to that produced via Process A, Study 103 had an open-label, single-arm design. Study 103 was the only study that evaluated Process B ELEVIDYS.

Subjects in Cohorts 1, 2, and 3 received at least 1 mg/kg of a glucocorticoid (prednisone/prednisolone) daily, in addition to their baseline stable oral corticosteroid dose, for at least 60 days after ELEVIDYS infusion; the 1 mg/kg/day added steroid dosing will be followed by up to a total daily dose of 60 mg/day (except for added steroids in the event of relevant GGT increases and/or other clinically significant

abnormalities of liver function). Subjects in Cohort 4 who are not on oral corticosteroids for DMD at screening will start prednisone/prednisolone at 1.5 mg/kg/day 1 week prior to ELEVIDYS infusion; corticosteroid treatment will continue for at least 60 days after ELEVIDYS infusion.

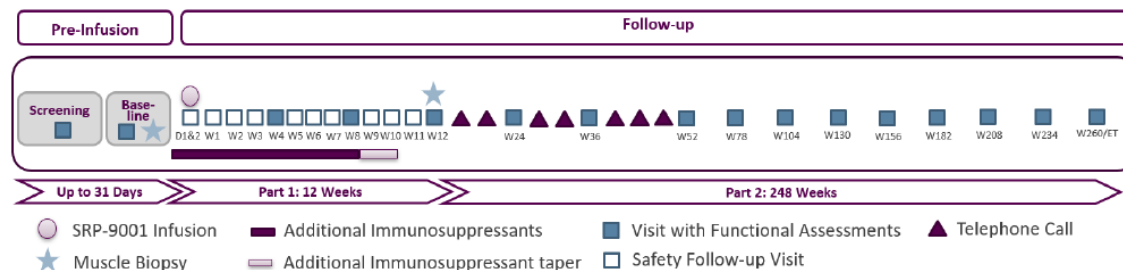
6.3.6 Sites and Centers

- Stanford University, Palo Alto, CA
- University of California, Davis, Sacramento, CA
- Washington University in St. Louis, St. Louis, MO
- Nationwide Children's Hospital, Columbus, OH
- Children's Hospital of The King's Daughters, Norfolk, VA

6.3.7 Surveillance/Monitoring

Figure 16 provides a schematic diagram of Study 103 visits. Table 25 lists the schedule of events.

Figure 16. Visits for Study 103



Source: BLA125781, Study 103 Protocol.

Table 25. Schedule of Events for Study 103

Infusion period	Pre-Infusion		Infusion	Post-Infusion																											
Trial period	Scr	B	Infusion	Follow-Up Period: Part 1														Follow-Up Period: Part 2													
Visit name	Scr	B	D1	D2	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 16, 20, 28, 32, 40, 44, 48	W 24	W 36	W 52	W 78	W 104	W 130	W 156	W 182	W 208	W 234	W 260/ET			
Visit window (days)	(-31)	N/A	N/A	N/A	+/- 1	+/- 1	+/- 1	+/- 3	+/-3	+/-3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 7	+/-7	+/- 14	+/- 14	+/- 14	+/- 21	+/- 21	+/- 21	+/- 22	+/- 21	+/- 21	+/- 21	+/- 21			
Visit type ^b	C	C	C	C	C	R	R	C	R,C ^{aa}	R,C ^{aa}	R	C	R	R	R	C	T	C	C	C	C	C	C	C	C	C	C	C			
Informed consent/assent	X																														
Inclusion/exclusion ^c	X		X ^c																												
Medical history	X																														
Physical Exam ^d	X	X	X	X	X	X		X	X ^{aa}	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X			
Vital signs ^e	X	X	X	X	X	X		X	X ^{aa}	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X			
Height/ulnar length	X	X						X				X				X		X	X	X	X	X	X	X	X	X	X	X			
Weight ^f	X	X	X		X			X				X				X		X	X	X	X	X	X	X	X	X	X	X			
NSAA (including time to rise from the floor and 10MWR) ^g	X ^b	X ⁱ						X				X				X ⁱ		X	X	X	X	X	X	X	X	X	X	X			
Timed 4-step test ^g		X ⁱ						X				X				X ⁱ		X	X	X	X	X	X	X	X	X	X	X			
100MWR ^g	X	X ⁱ						X				X				X ⁱ		X	X	X	X	X	X	X	X	X	X	X			
PUL (Version 2.0) ^g	X ⁱ	X ⁱ						X				X				X ⁱ		X	X	X	X	X	X	X	X	X	X	X			
PFTs (FVC, PEF) ^g	X	X ⁱ						X				X				X ⁱ		X	X	X	X	X	X	X	X	X	X	X			
ELISA ^k	X			X	X	X		X				X		X		X		X		X		X		X		X		X			
ELISpot ^k		X		X	X ²	X		X	X ^{aa}	X ^{aa}		X		X		X		X		X		X		X		X		X			
Hematology ^l	X			X	X	X	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X			
Hepatitis B and C Serology, HIV	X																														
EBV, CMV, parvovirus B19, VZV, HH6, hepatitis A & E		X																													
Electrolytes ^m		X		X												X		X		X		X		X		X		X			
Troponin I		X			X			X	X ^{aa}	X ^{aa}		X				X		X	X	X	X	X	X	X	X	X	X	X			

Infusion period	Pre-Infusion		Infusion	Post-Infusion																															
Trial period	Scr	B	Infusion	Follow-Up Period: Part 1														Follow-Up Period: Part 2																	
Visit name	Scr	B	D1	D2	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 16, 20, 28, 32, 40, 44, 48	W 24	W 36	W 52	W 78	W 104	W 130	W 156	W 182	W 208	W 234	W 260/ET ^a							
Visit window (days)	(-31)	N/A	N/A	N/A	+/- 1	+/- 1	+/- 1	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 7	+/- 7	+/- 14	+/- 14	+/- 14	+/- 21	+/- 21	+/- 21	+/- 22	+/- 21	+/- 21	+/- 21	+/- 21							
Visit type ^b	C	C	C	C	C	R	R	C	R,C ^{aa}	R,C ^{aa}	R	C	R	R	R	C	T	C	C	C	C	C	C	C	C	C	C	C							
Glucose ^a	X			X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X							
CK ^o	X			X	X	X		X	X ^{aa}	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X							
Liver function ¹	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X							
Renal function ¹	X				X	X	X	X				X				X		X	X	X	X	X	X	X	X	X	X	X							
hsCRP and complement (CH50, C3, C4, and factor B)	X			X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X							
Vector quantification			X ^p	X ^q	X	X	X	X		X		X	X	X	X	X		X	X	X															
Biomarkers		X			X			X								X		X		X								X							
DMD gene sequence analysis		X																																	
Whole-genome DNA sequence ^r		X																																	
RNA sequence		X						X				X				X		X	X	X		X		X		X		X							
Blood sample for immune epitope mapping ^y									A single sample of 10 mL taken in Part 1 or Part 2, see Investigator Laboratory Manual for details.																										
HLA typing				X																															
Urinalysis ¹	X			X	X			X				X				X		X	X	X	X	X	X	X	X	X	X	X							
Muscle Biopsy ⁵		X														X																			
ECG ^t	X		X					X												X		X		X		X		X							
ECHO ^u	X																			X		X		X		X		X							
Cardiac MRI (sub-study) ^v		X																		X		X		X		X		X							
Musculoskeletal MRI (sub-study) ^v		X																		X		X		X		X		X							
Vector shedding samples (saliva/urine/stool) ^w		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X													
Study drug infusion ^x			X																																

Infusion period	Pre-Infusion		Infusion	Post-Infusion																								
Trial period	Scr	B	Infusion	Follow-Up Period: Part 1												Follow-Up Period: Part 2												
Visit name	Scr	B	D1	D2	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 16, 20, 28, 32, 40, 44, 48	W 24	W 36	W 52	W 78	W 104	W 130	W 156	W 182	W 208	W 234	W 260 ET ^a
Visit window (days)	(-31)	N/A	N/A	N/A	+/- 1	+/- 1	+/- 1	+/- 3	+/-3	+/-3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 7	+/-7	+/- 14	+/- 14	+/- 14	+/- 21	+/- 21	+/- 21	+/- 22	+/- 21	+/- 21	+/- 21	+/- 21
Visit type ^b	C	C	C	C	C	R	R	C	R,C ^{aa}	R,C ^{aa}	R	C	R	R	R	C	T	C	C	C	C	C	C	C	C	C	C	C
Add-on corticosteroid			Implement daily add-on <u>the day prior to the infusion</u> for Cohorts 1, 2, 3, <u>1 week prior for Cohort 4, and for at least 60 days post-infusion</u>																									
Add-on corticosteroid Tapering													X	X														
Drug Shipment Request Form		X																										
Adverse Event Reporting	Ongoing collection beginning at informed consent/ assent																											
Concomitant Medications and Procedures	Ongoing collection beginning at informed consent/ assent																											

Source: BLA125781, Study 103 Protocol

^a In case of subject withdrawal, Week 260 assessment should be performed at the early termination (ET) visit.

^b Visits indicated as "R" can be conducted at the clinic or remotely. Visits indicated "C" must be conducted at the clinic.

^c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening.

^d A full physical examination will be performed at Screening, Week 52, and Week 260/ET and includes general appearance, HEENT, heart, chest (respiratory), abdomen (gastrointestinal), skin, lymph nodes, extremities, and the musculoskeletal and neurological systems. A brief physical examination will be performed at all other visits indicated and includes general appearance; HEENT; heart chest; abdomen; and skin.

^e Vital signs to be collected include blood pressure, heart rate, respiratory rate, and temperature (oral, tympanic, or axillary). On Day 1, vital signs will be measured at the time points indicated in Section 10.4.3

^f Weight taken at Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day should be used to calculate total volume of study drug administration, outlined in the Pharmacy Manual and Dose Administration Manual.

^g Every effort should be made to perform functional assessments in the specified visit window; however, if the assessments cannot be performed within the window due to events not reasonably foreseen, the assessments may be performed within a ± 2 -week visit window for Week 4 and 8, and a ± 6 -week visit window for Weeks 12, 24, 36, and 52. NSAA (including time to rise from the floor and 10MWR), timed 4-step test, and 100MWR assessments apply to Cohorts 1, 2, and 4 only. Prior to age 4 years, the NSAA and timed function tests (time to rise from floor, 10 MWR, 100 MWR, timed 4-step test) should be attempted, but it is not a protocol deviation if they are not considered to be valid by the clinical evaluator. PUL (Version 2.0) and PFT (FVC, PEF) assessments apply to Cohorts 2, 3, and 5b only. Subjects in Cohorts 2, 3, and 5b must have an FVC $\geq 50\%$ of predicted at screening.

^h Subjects in Cohort 1 must have an NSAA Total Score > 17 and ≤ 26 , subjects in Cohort 2 must have an NSAA Total Score ≥ 15 and ≤ 26 , and subjects in Cohort 5a must have a REF ≤ 7 seconds at the Screening visit.

ⁱ Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.

^j Subjects in Cohort 3 and 5b must have a PUL score ≥ 2 at Screening.

^k Antibodies to rAAVrh74 capsid and ELEVIDYS micro-dystrophin (ELISA) and cellular immune response to rAAVrh74 and ELEVIDYS micro-dystrophin (ELISpot).

^l See Section 10.4.6.1 for a list of specific analytes. Notes that at Week 12, samples will be collected before the biopsy.

^m Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.

ⁿ Fasting is not required for glucose test.

^o At all visits where CK samples are drawn, parents/guardians/subjects will be asked to limit subject's physical activity level over the 3 days before the scheduled CK test.

^p Sample to be taken approximately 4 to 6 hours post-infusion.

^q Sample to be taken approximately 22 to 26 hours post-infusion.

^r Blood sample for whole-genome sequencing is optional, based upon local regulations and Institutional Review Board/Ethics Committee approval. An additional informed consent/assent form must be signed prior to collection of samples.

^s A muscle biopsy for evaluation of expression of ELEVIDYS micro-dystrophin will be obtained. For Cohorts 1, 4, and 5a, the baseline biopsy will be of medial gastrocnemius muscle, preferably from the right leg. If the medial gastrocnemius muscle is not viable, prior approval from the Sponsor is required for using an alternate muscle of the upper extremity. If possible, the biopsy for Week 12 will be of the same muscle group as that used at baseline, but on the contralateral side. Refer to the Surgical and Laboratory Biopsy Manual.

^t All ECGs should be performed in triplicate at a consistent time of day throughout the study, and before any invasive procedures (e.g., blood draws, study drug infusion, or biopsy). On Day 1 only, the triplicate ECGs will be taken both before and after the infusion.

^u For time points after Screening, subjects undergoing cardiac MRI assessment do not also need to undergo echocardiogram at the time points when the cardiac MRI is performed.

^v Only subjects in Cohorts 2, 3, and 5 at participating sites in respective sub-studies will undergo imaging assessment.

^w Vector shedding assessments will be performed in subjects in Cohorts 1 to 4 only. Subjects will have samples collected at all study visits indicated (clinic and remote) unless the Applicant deems that a sample type may stop being collected, as described in the Vector Shedding Manual. The samples collected will include saliva, urine, and stool, and will be stored until analysis. For samples that will be obtained on Day 1, the samples will be collected ≥ 6 hours following completion of infusion. Further details will be outlined in the Vector Shedding Manual.

^x Study treatment will be administered by intravenous infusion (approximately 1-2 hours). Subjects are to be closely monitored for at least 6 hours following completion of the infusion. A topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) may be applied prior to infusion, per study site and subject preference.

^y A total of 10 mL of blood is required. If it is not feasible to complete the requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details. For Cohort 5 only, samples to be taken at Week 11.

^z For Cohorts 1 and 4 only

^{aa} For Cohort 5 only.

Abbreviations: 10MWR, 10 meter walk run test; 100MWR, 100-meter walk run test; AE, adverse event; B, baseline; C, clinic; CK, creatine kinase; CMV cytomegalovirus; D, day; DMD, Duchenne muscular dystrophy; EBV, Epstein-Barr Virus; ECG, electrocardiogram; ELISA, Enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunospot assay; ET, early termination; FVC, forced vital capacity; HEENT, head, ears, eyes, nose, and throat; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; hsCRP, high-sensitivity C-reactive protein; HHV6, human herpesvirus 6; NA, not applicable; NSAA, North Star Ambulatory Assessment; PE, physical examination; PEF, peak expiratory flow; PFT, pulmonary function test; PUL, Performance of the Upper Limb test; Scr, Screening; R, remote; T, telephone; VZV, varicella zoster virus; W, week.

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoint

Change in quantity of ELEVIDYS micro-dystrophin protein from baseline to Week 12 (Part 1) as measured by Western blot

Secondary Endpoints

- Vector shedding in urine, saliva, and stool following ELEVIDYS infusion until 3 consecutive results below level of detection
- Antibody titers to rAAVrh74
- Safety, including incidence of TEAEs, adverse events of special interest, and SAEs
- Change in quantity of ELEVIDYS micro-dystrophin protein from Baseline to Week 12, as measured by immunofluorescence (fiber intensity and percent ELEVIDYS micro-dystrophin positive fibers)

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis of the primary endpoint in this study was descriptive.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The Full Analysis Set, including all subjects who received ELEVIDYS, was used as the analysis population for Study 103.

6.3.10.1.1 Demographics

Key demographic information is shown in Table 26 below.

Table 26. Key Demographic Characteristics, Study 103

Demographics	Cohort 1 (N = 20)	Cohort 2 (N = 7)	Cohort 3 (N = 6)	Cohort 4 (N = 7)
Age (years)				
Mean (SD)	5.81 (1.14)	10.11 (1.51)	15.26 (4.22)	3.48 (0.24)
Min, max	4.38, 7.94	8.00, 12.05	9.86, 20.23	3.24, 3.95
4 to 5 years, n (%)	11 (55.0)	0	0	0
6 to 7 years, n (%)	9 (45.0)	0	0	0
Race, n (%)				
White	15 (75.0)	5 (71.4)	6 (100.0)	6 (85.7)
Non-white	5 (25.0)	2 (28.6)	0	1 (14.3)
Weight, kg				
Mean (SD)	21.15 (4.23)	37.06 (7.64)	59.93 (15.17)	15.16 (1.60)
Min, max	15.2, 33.1	28.0, 50.5	36.1, 80.1	12.5, 16.5

Source: BLA 125781 Sarepta CTGTAC Briefing Document.

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

All subjects were on a stable dose of corticosteroids for at least 12 weeks prior to ELEVIDYS infusion and throughout the first year of the study, and had baseline titer of anti-AAVrh74 total binding antibodies <1:40, as determined by an investigational ELISA.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean (SD) baseline NSAA Total Score was 22.1 (range, 18-26) and 20.7 (range, 17-26) for Cohorts 1 and 2, respectively. Mean score on the Performance of the Upper Limb test at baseline was 38.9 (range, 33-42) and 22.2 (range, 18-31) for Cohorts 2 and 3, respectively.

6.3.10.1.3 Subject Disposition

A total of 39 subjects (Cohort 1: 20 subjects; Cohort 2: 7 subjects; Cohort 3: 6 subjects; and Cohort 4: 6 subjects) were enrolled, dosed, and included in the Full Analysis Set population. All subjects were treated with the intended dose of Process ELEVIDYS (1.33×10^{14} vg/kg); 34 of 39 subjects completed Part 1 of the study as of the cutoff date for this Summary of Clinical Efficacy.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Among the 20 ambulatory subjects with DMD who received the intended dose of Process B ELEVIDYS in Study 103 Cohort 1, the mean (SD) level of ELEVIDYS micro-dystrophin was 54.2% (42.6) at Week 12.

Reviewer Comment:

Study 103 is intended as a “bridging” study to show that treatment with ELEVIDYS manufactured by Process B results in expression of ELEVIDYS micro-dystrophin at a level comparable to treatment with Process A ELEVIDYS. Per Clinical Pharmacology Reviewer assessment, the level of ELEVIDYS micro-dystrophin, measured by Western blot, following treatment with Process B ELEVIDYS was slightly higher than that following treatment with Process A ELEVIDYS. The mean (SD) and median (min, max) levels of ELEVIDYS micro-dystrophin (percent of control) in muscle biopsy tissue samples from Process A ELEVIDYS (n = 27) were 41.3% (35.4) and 39.7% (0.0, 116.3), respectively. The mean (SD) and median (min, max) level of ELEVIDYS micro-dystrophin (percent of control) in muscle biopsy tissue samples following treatment with Process B ELEVIDYS (n = 20) were 54.2% (42.6) and 50.6% (4.8, 153.9), respectively.

6.3.11.3 Subpopulation Analyses

Subpopulation analyses were not conducted, due to the small sample size in each cohort.

6.3.11.4 Dropouts and/or Discontinuations

No subject was discontinued from the study.

6.3.11.5 Exploratory Analyses

In Cohort 1 at Week 52 following ELEVIDYS infusion, the mean change from baseline in NSAA Total Score was 4.0 points (SD 3.5).

Reviewer Comment:

Due to the open-label, uncontrolled design of Study 103, NSAA scores must be interpreted with caution.

6.3.12 Safety Analyses

6.3.12.1 Methods

The safety population consists of 78 subjects, for whom data was reported for up to Week 52 for Cohort 1, and up to the clinical cutoff date (April 6, 2022) for Cohorts 2 through 4.

6.3.12.2 Overview of Adverse Events

Table 27 summarizes the treatment-related adverse events observed in Study 103. Overall, the frequency and type of treatment-related adverse events experienced by subjects in Study 103 were similar to the treatment-related adverse events observed in Studies 101 and 102.

Table 27. Treatment-related Adverse Events, Study 103

System Organ Class Preferred Term	ELEVIDYS N = 40 n (%)
Any treatment-related AE	33 (82.5)
Blood and lymphatic system disorders	6 (15.0)
Thrombocytopenia	5 (12.5)
Thrombocytosis	1 (2.5)
Cardiac disorders	1 (2.5)
Cardiomyopathy	1 (2.5)
Left ventricular dysfunction	1 (2.5)
Myocarditis	1 (2.5)
Gastrointestinal disorders	27 (67.5)
Abdominal pain upper	4 (10.0)
Constipation	5 (12.5)
Diarrhea	2 (5.0)
Nausea	15 (37.5)
Vomiting	19 (47.5)
General disorders and administration site conditions	6 (15.0)
Fatigue	4 (10.0)
Malaise	1 (2.5)
Pyrexia	2 (5.0)
Hepatobiliary disorders	2 (5.0)
Hepatotoxicity	1 (2.5)
Hypertransaminasaemia	1 (2.5)
Investigations	17 (42.5)
Alanine aminotransferase increased	3 (7.5)
Aspartate aminotransferase increased	4 (10.0)
Blood creatine phosphokinase increased	3 (7.5)
Blood lactate dehydrogenase increased	2 (5.0)
Complement factor c4 decreased	1 (2.5)
Gamma-glutamyl transferase increased	4 (10.0)
Glutamate dehydrogenase increased	13 (32.5)
Hepatic enzyme increased	3 (7.5)
Liver function test increased	1 (2.5)
Transaminases increased	3 (7.5)
Troponin increased	1 (2.5)

System Organ Class Preferred Term	ELEVIDYS N = 40 n (%)
Metabolism and nutrition disorders	13 (32.5)
Decreased appetite	13 (32.5)
Hyperlipidemia	1 (2.5)
Musculoskeletal and connective tissue disorders	3 (7.5)
Back pain	1 (2.5)
Immune-mediated myositis	1 (2.5)
Myalgia	1 (2.5)
Rhabdomyolysis	1 (2.5)
Nervous system disorders	6 (15.0)
Headache	3 (7.5)
Lethargy	2 (5.0)
Poor quality sleep	1 (2.5)
Renal and urinary disorders	3 (7.5)
Chromaturia	1 (2.5)
Hemoglobinuria	2 (5.0)
Proteinuria	1 (2.5)
Skin and subcutaneous tissue disorders	2 (5.0)
Hyperhidrosis	1 (2.5)
Pruritus	1 (2.5)

Source: FDA

Abbreviation: AE, adverse event.

6.3.12.3 Deaths

There were no deaths reported in this study.

6.3.12.4 Nonfatal Serious Adverse Events

SAEs in the Table 28 below were all related to the treatment.

Table 28. Treatment-related SAEs, Study SRP-9001-103

System Organ Class Preferred Term	SRP-9001 N =40 n (%)
Any SAE	4 (10.0)
Cardiac disorders	1 (2.5)
Myocarditis	1 (2.5)
Gastrointestinal disorders	2 (5.0)
Vomiting	2 (5.0)
Hepatobiliary disorders	1 (2.5)
Hypertransaminasaemia	1 (2.5)
Musculoskeletal and connective tissue disorders	1 (2.5)
Immune-mediated myositis	1 (2.5)

Source: FDA

Abbreviation: SAE, serious adverse event.

6.3.12.5 Adverse Events of Special Interest

Please see Section 8 Integrated Summary of Safety.

6.3.12.6 Clinical Test Results

Table 29. Proportion of Subjects with Potentially Clinically Significant Abnormalities in Laboratory Parameters, Study 103

Parameter	PCS Abnormal Criteria	Cohort 1 (N = 20) % (n)	Cohort 2 (N = 7) % (n)	Cohort 3 (N = 6) % (n)	Cohort 4 (N = 6) % (n)	Total (N=39) % (n)
Subjects with any potentially clinically significant abnormalities	—	100.0 (20)	100.0 (7)	100.0 (6)	100.0 (6)	100.0 (39)
Albumin (g/L)	<LLN or >ULN	0	14.3 (1)	0	0	2.6 (1)
Alkaline phosphatase (U/L)	>1.5 × ULN	0	0	0	0	0
Alanine aminotransferase (U/L)	≥2 × baseline value	15.0 (3)	28.6 (2)	16.7 (1)	50.0 (3)	23.1 (9)
Amylase (U/L)	>ULN	15.0 (3)	28.6 (2)	0	0	12.8 (5)
Aspartate aminotransferase (U/L)	≥2 × baseline value	40.0 (8)	42.9 (3)	33.3 (2)	50. (3)	41.0 (16)
Bilirubin (mg/dL)	>1.5 × ULN	5.0 (1)	0	0	0	2.6 (1)
Blood urea nitrogen (mmol/L)	>1.5 × baseline and >ULN	0	0	16.7 (1)	0	2.6 (1)
Complement C3 (mg/dL)	<LLN	35. (7)	42.9 (3)	16.7 (1)	66.7 (4)	38.5 (15)
Complement C4 (mg/dL)	<LLN	75.0 (15)	85.7 (6)	33.3 (2)	100.0 (6)	74.4 (29)
Complement B (mg/dL)	<LLN	5.0 (1)	0	0	0	2.6 (1)
Complement CH50 (U/mL)	<LLN	0	0	0	0	0
Creatine kinase (U/L)	≥2 × baseline value	10.0 (2)	0	0	16.7 (1)	7.7 (3)
Creatinine (umol/L)	>ULN	0	0	0	0	0
C reactive protein (mg/L)	>ULN	0	28.6 (2)	16.7 (1)	0	7.7 (3)
Cystatin C (mg/L)	>ULN	0	0	16.7 (1)	0	2.6 (1)
Gamma-glutamyl transferase (U/L)	>3 × baseline or >ULN	35.0 (7)	57.1 (4)	33.3 (2)	50.0 (3)	41.0 (16)

Source: Adapted from BLA 125781, Study 103 Clinical Study Report
Cutoff Date: 2022-04-06, so there were only 39 subjects in Study 103
Abbreviations: LLN, lower limit of normal; PCS, potentially clinically significant; ULN, upper limit of normal.

6.3.12.7 Dropouts and/or Discontinuations

As the study treatment involves a single infusion, discontinuation from treatment was not applicable for this study. No discontinuations occurred due to adverse events.

6.3.13 Study Summary and Conclusions

The level of ELEVIDYS micro-dystrophin expression (measured by Western blot) following treatment with Process B ELEVIDYS was slightly higher than that following treatment with Process A ELEVIDYS.

The safety profile of Process B ELEVIDYS appears acceptable. However, myositis and myocarditis were only observed with Process B ELEVIDYS.

Elevated troponin-I was observed in 4 subjects in Study 103 (troponin-I was not assessed in the studies using Process A ELEVIDYS). Although none of these events was associated with clinical complications or acute changes on cardiac imaging changes, the long-term effects of this heart muscle injury on the underlying cardiomyopathy in patients with DMD are not known.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

The clinical reviewer does not recommend an integrated overview of efficacy (i.e., an analysis using pooled data from all subjects treated with intravenous infusion of ELEVIDYS), for the following reasons:

- Study 101 and Study 102 used Process A ELEVIDYS. Study 103 used Process B ELEVIDYS. Process A ELEVIDYS and Process B ELEVIDYS are not analytically comparable.
- NSAA and other clinical outcome measures are effort-dependent. It is challenging to evaluate combined clinical outcome data from open-label, uncontrolled studies (Study 101, Study 102 Part 2, and Study 103) and from a randomized, double-blind, placebo-controlled study (Study 102 Part 1).

The Applicant compared data study subjects to data from external control patients, for functional endpoints. The comparative analyses included both study-level and integrated analysis, based on ELEVIDYS-treated subjects from Studies 101, 102, and 103. In this review memo, only the integrated-level analysis is presented; the analysis of only study-level data does not add important information to affect the conclusions.

External Control Data Sources:

- Cooperative International Neuromuscular Research Group Duchenne Natural History Study
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) study
- Eli Lilly and Company study of tadalafil for DMD (H6D-MC-LVJJ)

All external control sources contain 3 functional assessments which overlap with the variables collected in Studies 101, 102, and 103: NSAA Total Score, 10MWR, and timed rise from the floor.

7.1.4 Analysis of Primary Endpoint(s)

Primary Analysis Set

The Integrated Summary of Efficacy Target Dose 1.33×10^{14} vg/kg) 1-year analysis set included 4 subjects in Study 101, 29 subjects in Study 102, and 20 subjects in Cohort 1 of Study 103, for a total of 53 subjects.

Primary Endpoint

Functional endpoint: change in NSAA Total Score from baseline to 1 year.

Statistical Method

The primary external control analysis was conducted using a propensity score weighting method. Propensity scores were estimated through a logistic regression model, in which the dependent variable is the probability of receiving ELEVIDYS, and model covariates include the baseline age group (aged 4-5 years versus 6-7 years versus 8 years), 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 ELEVIDYS -treated subjects were given a weight of 1, and external control subjects were weighed by propensity score divided by the quantity (1 minus propensity score).

A weighted linear regression model was then fitted on the weighted data to assess the treatment effect of ELEVIDYS, 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% confidence intervals, were presented.

Reviewer Comments:

It is important to note that the comparison to external controls has the following major flaws:

- The disease course of DMD is highly heterogeneous in this age range, increasing the likelihood of noncomparable patients across data sources.
- The effect of ELEVIDYS treatment is unlikely to be more than moderate, and thus the analysis will not provide results persuasive enough to overcome potential biases in nonconcurrent analysis.
- It is difficult to determine with confidence that the external control populations are similar to the study population with regard to all key baseline characteristics, including unobserved baseline characteristics.
- Outcome measures (e.g., NSAA Total Score) are process-dependent, so data generated from different studies are not directly comparable.
- The validity of the propensity score weighting method depends on critical and unverifiable assumptions, including 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 ELEVIDYS treatment.

Due to these limitations/weaknesses, comparison of ELEVIDYS data to those from external controls can only be considered exploratory.

7.1.11 Efficacy Conclusions

According to the Applicant, among a total of 765 patients from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study, Finding the Optimum Regimen for Duchenne Muscular Dystrophy study, and Eli Lilly and Company dataset, 131 patients met all the applied entry criteria considered consistent with the characteristics of subjects enrolled in the ELEVIDYS studies and were followed for outcomes for at least 1 year. Of the 53 subjects in the Applicant's Integrated Summary of Efficacy Target Dose 1-year dataset, 52 subjects were included in the primary analysis; one subject did not undergo the Week 48 assessment in Study 102 Part 2 due to recovery from Achilles tendon surgery.

The LS mean of treatment difference in NSAA Total Score from baseline to Year 1 between the two groups was 2.5 [95% CI: 1.6, 3.5], suggesting improved functional outcomes for subjects treated with ELEVIDYS compared to the external controls.

Of note, the only reliable data, which are from Study 102 Part 1 (the randomized, double-blind, and placebo-controlled trial), demonstrated no statistically significant difference in change in NSAA Total Score at Week 48 between subjects who received ELEVIDYS compared to those who received placebo, despite confirmed expression of ELEVIDYS micro-dystrophin at Week 12 in the ELEVIDYS-treated subjects. Based on the results of partial Spearman analysis at the individual subject level, there is no clear association between expression of ELEVIDYS micro-dystrophin at Week 12 (determined by Western blot) and NSAA Total Score. Data from Study 102 Part 1 may suggest a potential benefit of treatment with ELEVIDYS in the 4 to 5 year age group, but potentially no benefit in the 6 to 7 year age group.

Available data do not support expression of ELEVIDYS micro-dystrophin as a surrogate endpoint that is "reasonably likely to predict clinical benefit" for Accelerated Approval. Available data do not provide clear evidence that ELEVIDYS is likely beneficial for ambulatory patients with DMD. It is challenging to conclude with reasonable confidence from the data provided by the Applicant either that ELEVIDYS is likely effective for younger patients, or that it is likely ineffective for older patients or for patients with somewhat poorer functional status.

Reviewer Comment:

To provide additional context for the comparison of ELEVIDYS-treated subjects to external controls, the FDA statistical reviewer performed an analogous propensity score-adjusted analysis comparing placebo subjects from Study 102 Part 1 to the external controls. In this analysis, the LS mean of treatment difference in NSAA Total Score from baseline to Year 1 between the two groups was 0.7 [95% CI: -0.3, 1.6], indicating potentially improved functional outcomes also for the placebo subjects compared to the external controls. This analysis is susceptible to all the limitations of the Applicant's analysis, and serves only to provide evidence of the lack of comparability of the ELEVIDYS study population to the external control population. This result reinforces the exploratory nature, and the limited interpretability, of the Applicant's comparison to external control.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated overview of safety is based on pooled data from the three studies included in the BLA submission (Exposure Analysis Set).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The Exposure Analysis Set included 85 male subjects with DMD with a confirmed mutation in the *DMD* gene in the three ongoing clinical studies (Study 101, Study 102, and Study 103). All subjects were exposed to a one-time intravenous infusion of ELEVIDYS. The mean age was 7.12 years (range, 3.24 to 20.23 years)

Forty-five subjects in Study 101 and Study 102 received ELEVIDYS manufactured by Process A, and the 40 subjects in Study 103 received ELEVIDYS manufactured by Process B.

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

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

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

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 30 provides baseline characteristics and demographic information for all subjects in the Exposure Analysis Set.

Table 30. Demographic Information for Safety Population, Exposure Analysis Set

Characteristic	Process A Lower Dose N = 12 n (%)	Process A Target Dose N = 33 n (%)	Process B N = 40 n (%)	All Subjects N = 85 n (%)
Sex, n (%)	-	-	-	-
Male	12 (100.0)	33 (100.0)	40 (100.0)	85 (100.0)
Female	0	0	0	0
Age, years	-	-	-	-
Mean (SD)	6.0 (1.2)	6.9 (1.3)	7.6 (4.3)	7.1 (3.1)
Median (min, max)	5.7 (4.5, 7.8)	7.1 (4.0, 8.9)	6.2 (3.2, 20.2)	6.6 (3.2, 20.2)

Characteristic	Process A Lower Dose N = 12 n (%)	Process A Target Dose N = 33 n (%)	Process B N = 40 n (%)	All Subjects N = 85 n (%)
Age groups (years), n (%)	-	-	-	-
Non-ambulatory	0	0	6 (15.0)	6 (7.1)
<4 years old, ambulatory	0	0	7 (17.5)	7 (8.2)
4-5 years old, ambulatory	6 (0.5)	7 (21.2)	11 (27.5)	24 (28.2)
6-7 years old, ambulatory	6 (0.5)	20 (60.6)	9 (22.5)	35 (41.2)
≥8 years old, ambulatory	0	6 (18.2)	7 (17.5)	13 (15.3)
The Race, n (%)	-	-	-	-
White	8 (66.7)	25 (75.8)	32 (80.0)	65 (76.5)
Non-white	4 (33.3)	8 (24.2)	8 (20.0)	20 (23.5)
Baseline BMI group, kg/m ² , n (%)	-	-	-	-
<20	11 (91.7)	24 (72.7)	28 (70.0)	63 (74.1)
≥20	1 (8.3)	9 (27.3)	12 (30.0)	22 (25.9)

Source: FDA

Abbreviations: BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.

Table 31 compares the severity of adverse events observed with Process A ELEVIDYS and Process B ELEVIDYS. Overall, the rate of occurrence of SAEs was similar between Process A ELEVIDYS at the intended dose (9.1%) and Process B ELEVIDYS (10%). The percentage of subjects with TEAEs was similar between subjects who received the intended dose of Process A ELEVIDYS (91%) and Process B ELEVIDYS (83%).

Table 31. Adverse Events for Safety Population, Exposure Analysis Set

Event	Process A Lower Dose N = 12 n (%)	Process A Intended Dose N = 33 n (%)	Process B N = 40 n (%)	All Subjects N = 85 n (%)
Any AE	12 (100.0)	33 (100.0)	38 (95.0)	83 (97.6)
Mild	12 (100.0)	33 (100.0)	37 (92.5)	82 (96.5)
Moderate	12 (100.0)	31 (93.9)	19 (47.5)	62 (72.9)
Severe	4 (33.3)	4 (12.1)	5 (12.5)	13 (15.3)
Any SAE	4 (33.3)	3 (9.1)	4 (10.0)	11 (12.9)
SAEs requiring hospitalization	3 (25.0)	3 (9.1)	4 (10.0)	10 (11.8)

Source: FDA

Abbreviation: AE, adverse event; SAE, serious adverse event.

Corticosteroid use was summarized for three periods in the Exposure Analysis Set: 1) 12 weeks before Day -1; 2) Day -1 to Day 60; and 3) Day 61 to data cutoff dates. The length of use in days and average dose per day were summarized for each of the three periods. In general, the duration of use of corticosteroids was comparable between the groups across the first 2 periods; for the last period, subjects treated with Process A ELEVIDYS have taken part in their studies longer than have subjects treated with Process B ELEVIDYS, so duration of use obviously is longer. The average dose of corticosteroids was comparable between the groups.

8.2.3 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities.

The Safety Population included all subjects who received ELEVIDYS.

A TEAE will be defined as an adverse event that emerges during the treatment and follow-up period (having been absent prior to treatment), or worsens relative to the pre-treatment state. A drug-related TEAE will be defined as a TEAE that the study investigator considers related to the study drug.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Among the Exposure Analysis Set of 85 subjects, 45 subjects received Process A ELEVIDYS and 40 received Process B ELEVIDYS. Process A ELEVIDYS has a lower percentage of empty-capsid impurities compared to Process B ELEVIDYS. The pooled data therefore may not represent the safety of the to-be-marketed Process B ELEVIDYS.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred during any of the studies.

8.4.2 Nonfatal Serious Adverse Events

Twelve subjects had a total of 14 SAEs (2 subjects had 2 SAEs each). For 8 (66.7%) of the 12 subjects, the SAEs were considered related to ELEVIDYS. Twelve of the 14 SAEs resolved, while 2 SAEs recovered/resolved with sequelae (residual weakness in the case of immune-mediated myositis; additional long-term cardiac medication in the myocarditis case).

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

Table 32 summarizes SAEs in the Exposure Analysis Set.

Table 32. Serious Adverse Events by Subject, Exposure Analysis Set

Treatment Sequence	Actual dose of SRP-9001 (vg/kg)	Subject #	Age at Screening (years) ^a	System Organ Class/Preferred Term (Verbatim Term)	Start Date (Day) ^b / End Date (Day) ^b	Severity/ Relatedness	Outcome
Study SRP-9001-101 (Process A material) – No serious adverse events occurred during this study.							
Study SRP-9001-102 (Process A material) – Part 1							
SRP-9001 - Not Treated ^c	6.27E13	(b) (6)	7.79	Musculoskeletal and connective tissue disorders/Rhabdomyolysis (Rhabdomyolysis)	(b) (6)	Severe/ Yes	Recovered/Resolved
SRP-9001 - Placebo	8.98E13		4.96	Hepatobiliary disorders/Liver injury (Acute liver injury)		Severe/ Yes	Recovered/Resolved
				Musculoskeletal and connective tissue disorders/Rhabdomyolysis (Rhabdomyolysis)		Severe/ Yes	Recovered/Resolved
SRP-9001 - Placebo	1.34E14		7.85	Hepatobiliary disorders /Hypertransaminasaemia (Transaminitis [elevated LFT])		Severe/ Yes	Recovered/Resolved
Study SRP-9001-102 (Process A material) – Part 2							
Placebo - SRP-9001	1.33E14	(b) (6)	6	Injury, poisoning and procedural complications/femur fracture (Mid-shaft right femur fracture)	(b) (6)	Severe/ No	Not recovered/not resolved
Placebo - SRP -9001	1.33E14		8.82	Infections and infestations/ Appendicitis (Appendicitis)		Severe/ No	Recovered/Resolved
SRP -9001 - Placebo	8.95E13		7.18	Injury, poisoning and procedural		Severe/ No	Recovered/Resolved

Treatment Sequence	Actual dose of SRP-9001 (vg/kg)	Subject #	Age at Screening (years) ^a	System Organ Class/Preferred Term (Verbatim Term)	Start Date (Day) ^b / End Date (Day) ^b	Severity/ Relatedness	Outcome
				complications/Femur fracture (Closed torus fractur of L femur)			
<i>Study SRP-9001-101 (Process A material) – No serious adverse events occurred during this study.</i>							
SRP -9001 - Not Treated ^c	8.94E13	(b) (6)	6.08	Injury, poisoning and procedural complications/Femur fracture (Closed nondisplaced subtrochanteric fracture of left femur)	(b) (6)	Severe/ No	Recovered/Resolved
<i>Study SRP-9001-103 (Process B material)</i>							
SRP-9001 (Cohort 1)	1.33E14	(b) (6)	7.14	Hepatobiliary disorders /Hypertransaminasaemia (Transaminitis)		Severe/ Yes	Recovered/Resolved
SRP-9001 (Cohort 1)	1.33E14	(b) (6)	7.85	Gastrointestinal disorders/Vomiting (Vomiting secondary to AAV transfer)		Severe/ Yes	Recovered/Resolved
SRP-9001 (Cohort 2)	1.33E14	(b) (6)	8.95	Musculoskeletal and connective tissue disorders/Immune-mediated myositis (Muscle weakness secondary to immune-mediated adverse reaction)		Severe/ Yes	Recovered/Resolved with sequelae
SRP-9001 (Cohort 2)	1.33E14	(b) (6)	11.75	Gastrointestinal disorders/Vomiting (Vomiting)		Severe/ Yes	Recovered/Resolved
				Cardiac disorders/Myocarditis (Myocarditis)		Severe/ Yes	Recovered/Resolved with sequelae

Source: BLA 125781 Updated Table 13, 120-Day Safety Update; Applicant's Response to Clinical information request, March 28, 2023.

Note: Treatment-emergent adverse events include all adverse events that occurred or increased in severity since receipt of the study treatment.

Note: Adverse events are coded using Medical Dictionary for Regulatory Affairs, Version 24.1.

Note: Screening age = (date of informed consent – date of birth + 1)/365.25; for Study 102 Part 2, age at ELEVIDYS infusion is used.

Note: Day = Start date – First Dose date + 1. If Start date First Dose date, day = Start date - First Dose date.

Note: Subjects (b) (6) were treated with ELEVIDYS in Study 102 Part 1 and did not receive treatment in Study Part 2 due to adverse events but remained in the study for follow-up: Subjects (b) (6) had a nonserious TEAE of irritability that was considered steroid-related, and Subject (b) (6) had an SAE of femur fracture that required surgery and significant recovery time, hence, the subject returned to his home country.

Abbreviations: AAV, adeno-associated virus; L, left, LFT, liver function test, SAE, serious adverse event; TEAE, treatment-emergent adverse event.

8.4.3 Study Dropouts/Discontinuations

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

8.4.4 Common Adverse Events

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

Table 33. Treatment-related Treatment-Emergent Adverse Events in the Pooled Safety Population, Exposure Analysis Set

System Organ Class/Preferred Term	Process A			All Subjects N = 85 n (%)
	Process A N = 12 n (%)	Target Dose N = 33 n (%)	Process B N = 40 n (%)	
Any TEAE	10 (83.3)	30 (90.9)	33 (82.5)	73 (85.9)
Blood and lymphatic system disorders	0 (0.0)	6 (18.2)	6 (15.0)	12 (14.1)
Thrombocytopenia	0 (0.0)	5 (15.2)	5 (12.5)	10 (11.8)
Thrombocytosis	0 (0.0)	1 (3.0)	1 (2.5)	2 (2.4)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Cardiomyopathy	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Left ventricular dysfunction	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Myocarditis	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Gastrointestinal disorders	10 (83.3)	28 (84.8)	27 (67.5)	65 (76.5)
Abdominal pain	0 (0.0)	4 (12.1)	0 (0.0)	4 (4.7)
Abdominal pain upper	2 (16.7)	9 (27.3)	4 (10.0)	15 (17.6)
Constipation	0 (0.0)	1 (3.0)	5 (12.5)	6 (7.1)
Diarrhea	0 (0.0)	0 (0.0)	2 (5.0)	2 (2.4)
Gastroesophageal reflux disease	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.2)
Nausea	3 (25.0)	14 (42.4)	15 (37.5)	32 (37.6)
Vomiting	7 (58.3)	24 (72.7)	19 (47.5)	50 (58.8)
General disorders and administration site conditions	0 (0.0)	7 (21.2)	6 (15.0)	13 (15.3)
Asthenia	0 (0.0)	2 (6.1)	0 (0.0)	2 (2.4)
Fatigue	0 (0.0)	3 (9.1)	4 (10.0)	7 (8.2)
Malaise	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Pyrexia	0 (0.0)	5 (15.2)	2 (5.0)	7 (8.2)
Hepatobiliary disorders	1 (8.3)	3 (9.1)	2 (5.0)	6 (7.1)
Hepatomegaly	1 (8.3)	1 (3.0)	0 (0.0)	2 (2.4)
Hepatotoxicity	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Hypertransaminasaemia	0 (0.0)	1 (3.0)	1 (2.5)	2 (2.4)
Liver injury	1 (8.3)	1 (3.0)	0 (0.0)	2 (2.4)

System Organ Class/Preferred Term	Process A	Process A Target Dose	Process B	All Subjects
	N = 12 n (%)	N = 33 n (%)	N = 40 n (%)	N = 85 n (%)
Investigations	3 (25.0)	17 (51.5)	17 (42.5)	37 (43.5)
Alanine aminotransferase increased	0 (0.0)	2 (6.1)	3 (7.5)	5 (5.9)
Aspartate aminotransferase increased	0 (0.0)	2 (6.1)	4 (10.0)	6 (7.1)
Blood bilirubin increased	1 (8.3)	3 (9.1)	0 (0.0)	4 (4.7)
Blood creatine phosphokinase increased	0 (0.0)	1 (3.0)	3 (7.5)	4 (4.7)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	2 (5.0)	2 (2.4)
Complement factor c4 decreased	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Gamma-glutamyl transferase increased	2 (16.7)	9 (27.3)	4 (10.0)	15 (17.6)
Glutamate dehydrogenase increased	0 (0.0)	3 (9.1)	13 (32.5)	16 (18.8)
Hepatic enzyme increased	0 (0.0)	4 (12.1)	3 (7.5)	7 (8.2)
Liver function test increased	1 (8.3)	0 (0.0)	1 (2.5)	2 (2.4)
Transaminases increased	0 (0.0)	0 (0.0)	3 (7.5)	3 (3.5)
Troponin increased	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Urobilinogen urine increased	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.2)
Weight decreased	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.2)
White blood cell count decreased	0 (0.0)	2 (6.1)	0 (0.0)	2 (2.4)
Metabolism and nutrition disorders	3 (25.0)	20 (60.6)	13 (32.5)	36 (42.4)
Decreased appetite	3 (25.0)	20 (60.6)	13 (32.5)	36 (42.4)
Hyperlipidemia	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Musculoskeletal and connective tissue disorders	3 (25.0)	3 (9.1)	3 (7.5)	9 (10.6)
Arthralgia	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.2)
Back pain	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Immune-mediated myositis	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Myalgia	0 (0.0)	2 (6.1)	1 (2.5)	3 (3.5)
Pain in extremity	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.2)
Rhabdomyolysis	2 (16.7)	0 (0.0)	1 (2.5)	3 (3.5)
Nervous system disorders	0 (0.0)	3 (9.1)	6 (15.0)	9 (10.6)
Headache	0 (0.0)	1 (3.0)	3 (7.5)	4 (4.7)
Lethargy	0 (0.0)	2 (6.1)	2 (5.0)	4 (4.7)
Poor quality sleep	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Psychiatric disorders	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.2)
Generalized anxiety disorder	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.2)
Renal and urinary disorders	1 (8.3)	2 (6.1)	3 (7.5)	6 (7.1)
Chromaturia	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Glycosuria	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.2)
Hematuria	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.2)
Hemoglobinuria	0 (0.0)	0 (0.0)	2 (5.0)	2 (2.4)
Ketonuria	1 (8.3)	1 (3.0)	0 (0.0)	2 (2.4)
Proteinuria	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)

System Organ Class/Preferred Term	Process A	Process A Target Dose	Process B	All Subjects
	N = 12 n (%)	N = 33 n (%)	N = 40 n (%)	N = 85 n (%)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	2 (5.0)	2 (2.4)
Hyperhidrosis	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)
Pruritus	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.2)

Source: FDA

Abbreviation: TEAE, treatment-emergent adverse event.

8.4.5 Clinical Test Results

Please see discussion in Section 8.4.7.

8.4.6 Systemic Adverse Events

Please see discussion in Section 8.4.7.

8.4.7 Adverse Events of Special Interest

Acute Serious Liver Injury

In ambulatory patients with DMD, high aminotransferase levels (ALT and AST up to $\sim 22 \times$ ULN) originating from degenerating muscle are often observed.²⁸

Both acute liver injury and acute serious liver injury have been reported in clinical trials of ELEVIDYS. ALI is defined as GGT $>3 \times$ ULN, GLDH $>2.5 \times$ ULN, alkaline phosphatase $>2 \times$ ULN, or ALT $>3 \times$ baseline excluding ALT elevation from degenerating muscle in subjects with DMD. Acute serious liver injury is defined as an adverse event satisfying the definition for ALI and the seriousness criteria of death, life-threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, or important medical event.

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

Although the percentage of subjects treated with Process B ELEVIDYS who experienced ALI based on elevated GLDH is higher than that in subjects treated with Process A ELEVIDYS, in earlier studies (Study 101 and Study 102 Part 1, which utilized Process A ELEVIDYS), GLDH was not measured. GLDH was monitored in Study 102 Part 2 and Study 103 because GLDH may be a more sensitive indicator of ALI.²⁹ However, when utilizing GGT-based criteria, the number of ALI events for subjects treated with Process B ELEVIDYS (18%) is comparable to that observed in subjects treated with Process A ELEVIDYS (16%) (Table 34).

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

²⁸. McMillan HJ, Gregas M, Darras BT, et al. Serum transaminase levels in boys with Duchenne and Becker muscular dystrophy. *Pediatrics*. 2011 Jan;127(1):e132-6.

²⁹. Harrill, AH, J Roach, I Fier, JS Eaddy, CL Kurtz, DJ Antoine, DM Spencer, TK Kishimoto, DS Pisetsky, BK Park, and PB Watkins, 2012, The effects of heparins on the liver: application of mechanistic serum biomarkers in a randomized study in healthy volunteers, *Clin Pharmacol Ther*, 92(2):214-220.

Table 34. Occurrence of Acute Liver Injury, Studies 101, 102, and 103

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

Source: FDA

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

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

Immune-Mediated Myositis (IMM)

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

Reviewer Comment:

On June 13, 2023, the Applicant reported a second case of immune-mediated myositis that occurred in a 7-year-old subject with a deletion mutation involving exons 8 and 9 in the *DMD* gene. The diagnosis of Grade 3 immune-mediated myositis was made 26 days after treatment with ELEVIDYS, when the subject presented with generalized weakness in the setting of a concurrent streptococcal pharyngitis and rhino-enterovirus infection. He also had elevation of troponin-I to 0.593 ug/L (baseline, 0.195 mcg/L; reference range, 0.000-0.058 mcg/L) without symptoms of cardiac involvement. His echocardiogram showed normal cardiac function; electrocardiogram showed sinus arrhythmia. He was treated with pulse corticosteroids and intravenous immunoglobulin, and was discharged on Day 35.

The subject was enrolled in Study 103 Cohort 5, a new cohort enrolling subjects with mutations in exons 1 through 17 in the *DMD* gene. Of note, this subject is not part of the 85-subject Exposure Analysis Set, and this case of immune-mediated myositis is not included in the tables describing incidence of myositis.

The Applicant states, “This immune reaction may be due to a T-cell based response from lack of self-tolerance to a specific region encoded by the transgene corresponding to exons 1-17 of the *DMD* gene” and “epitope mapping available for the first case of [immune-mediated myositis] indicated that peptides from exons 8 and 9 are key antigenic epitopes of the N-terminal dystrophin region. This is consistent with results from four additional cases of immune-mediated myositis from other sponsors conducting AAV gene therapy studies of shortened dystrophin, in which epitope mapping

demonstrated reactivity to peptides located somewhere in the exon range of 8-11.³⁰ These epitope mapping results are in line with the observation that exons 8 and 9 demonstrate immunoreactivity. As noted previously, the T-cell immune reaction appears to be localized to exons 8 and 9; no immune response has been observed in exon 10.” Because of the two cases of immune-mediated myositis, “ELEVIDYS is contraindicated in patients with any deletion in exons 8 and/or 9 in the *DMD* gene.”

The reviewer considers the Applicant’s explanation, and the proposed contraindication, to be appropriate.

Myocarditis and Elevated Troponin-I

(b) (6)

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

The other subject in the ongoing, double-blind Study 301 Part 1 presented with high fever, vomiting, and seizure-like episode within 24 hours after receiving study treatment (either ELEVIDYS or placebo), and his troponin-I increased to 2,724.64 pcg/mL (reference ≤ 45.00 pcg/mL). He was admitted to the Pediatric Intensive Care Unit due to hypotension, and received corticosteroids, antibiotics, and intravenous fluids. Troponin-I levels peaked at 6,283.38 pcg/mL and total CK level was 42,567 U/L (reference range, <15 to 87 U/L) on Day 2 after study treatment. Electrocardiogram and echocardiogram were unchanged from baseline, and the subject was discharged home on Day 3 after study treatment. Myocarditis was diagnosed based on the clinical presentation, and resolved without clinical sequelae.

In Study 103, four subjects experienced elevations in troponin-I above the upper limit of normal (> 0.058 mcg/L), but no clinical complications were observed.

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

Myocarditis and elevated troponin-I have been observed only in subjects receiving ELEVIDYS manufactured via Process B. Testing for troponin-I was not in place for Study 101 and Study 102, in which Process A ELEVIDYS was used.

Thrombocytopenia

Decreases from baseline in platelet count were observed in 5 subjects in Study 102 and 5 subjects in Study 103, occurring between 7 to 16 days after ELEVIDYS infusion.

³⁰ Bonnemann CG, Dystrophin Immunity after Gene Therapy for Duchenne’s Muscular Dystrophy, 2023, NEJM 388:2294-2296

Platelet counts fell to as low as 51,000 /mm³, but clinical complications were not observed.

Concern Regarding Cross-Reactivity with Other AAV-Based Gene Therapy Products

AAV capsids are immunogenic and induce anti-AAV antibodies and T-cell responses. Antibodies to AAV capsids may block transduction and thereby inhibit transgene expression in target cells. Moreover, binding of antibodies to Fc receptors of various immune cells, such as macrophages, can potentiate an inflammatory response by stimulating production of inflammatory cytokines such as interferons, or by increasing vector-specific immune responses. These antibodies may also activate the complement cascade, and induce thrombotic microangiopathy.

Antibodies against one AAV serotype can cross-react with capsids of other AAV serotypes.³¹ Because of these concerns regarding potential cross-reactivity with other AAV-based gene therapy products, patients who receive ELEVIDYS and for whom it is ineffective likely will not be eligible to receive a future effective AAV vector-based gene therapy.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Table 35 provides a comparison of the occurrence of treatment-related adverse events for the three dose levels of Study 102. Overall, the occurrence of treatment-related adverse events occurred at a similar frequency for the three dose levels (83.3% for Dose Levels 1 and 2, versus 93.1% for the Target Dose Level).

Reviewer Comment:

Although due to the limited sample size, it is challenging to identify a clear dose-dependent correlation with any specific TEAEs. The frequency of the following bolded TEAEs appears to have been at least 5% higher in the Target Dose Group compared to the lower-dose groups.

Table 35. Treatment-related Adverse Events by Dose Level, Study 102 Part 1 and Part 2

System Organ Class Preferred Term	ELEVIDYS Dose Level 1 N = 6 n (%)	ELEVIDYS Dose Level 2 N = 6 n (%)	ELEVIDYS Target Dose N = 29 n (%)	All Subjects N = 41 n (%)
Any treatment-related AE	5(83.3)	5 (83.3)	27 (93.1)	37 (90.2)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	6 (20.7)	6 (14.6)
Thrombocytopenia	0 (0.0)	0 (0.0)	5 (17.2)	5 (12.2)
Thrombocytosis	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)

³¹. American Society of Gene + Cell Therapy and FDA, 2023, Immune Responses to AAV Vectors, accessed, April 4, 2023, <https://asgct.org/asgct-events/january-2023/immune-responses-to-aav-vectors>.

System Organ Class Preferred Term	ELEVIDYS Dose Level 1 N = 6 n (%)	ELEVIDYS Dose Level 2 N = 6 n (%)	ELEVIDYS Target Dose N = 29 n (%)	All Subjects N = 41 n (%)
Gastrointestinal disorders	5 (83.3)	5 (83.3)	25 (86.2)	35 (85.4)
Abdominal pain	0 (0.0)	0 (0.0)	4 (13.8)	4 (9.8)
Abdominal pain upper	0 (0.0)	2 (33.3)	9 (31.0)	11 (26.8)
Constipation	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Gastroesophageal reflux disease	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.4)
Nausea	2 (33.3)	1 (16.7)	13 (44.8)	16 (39.0)
Vomiting	5 (83.3)	2 (33.3)	21 (72.4)	28 (68.3)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	6 (20.7)	6 (14.6)
Asthenia	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Fatigue	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Pyrexia	0 (0.0)	0 (0.0)	5 (17.2)	5 (12.2)
Hepatobiliary disorders	0 (0.0)	1 (16.7)	3 (10.3)	4 (9.8)
Hepatomegaly	0 (0.0)	1 (16.7)	1 (3.4)	2 (4.9)
Hypertransaminasaemia	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Liver injury	0 (0.0)	1 (16.7)	1 (3.4)	2 (4.9)
Investigations	2 (33.3)	1 (16.7)	14 (48.3)	17 (41.5)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Blood bilirubin increased	1 (16.7)	0 (0.0)	3 (10.3)	4 (9.8)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Gamma-glutamyl transferase increased	1 (16.7)	1 (16.7)	9 (31.0)	11 (26.8)
Glutamate dehydrogenase increased	0 (0.0)	0 (0.0)	3 (10.3)	3 (7.3)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Liver function test increased	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.4)
Urobilinogen urine increased	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.4)
Weight decreased	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
White blood cell count decreased	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Metabolism and nutrition disorders	1 (16.7)	2 (33.3)	18 (62.1)	21 (51.2)
Decreased appetite	1 (16.7)	2 (33.3)	18 (62.1)	21 (51.2)
Musculoskeletal and connective tissue disorders	2 (33.3)	1 (16.7)	3 (10.3)	6 (14.6)
Arthralgia	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Myalgia	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Pain in extremity	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.4)
Rhabdomyolysis	1 (16.7)	1 (16.7)	0 (0.0)	2 (4.9)
Nervous system disorders	0 (0.0)	0 (0.0)	3 (10.3)	3 (7.3)
Headache	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Lethargy	0 (0.0)	0 (0.0)	2 (6.9)	2 (4.9)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Generalized anxiety disorder	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)

System Organ Class Preferred Term	ELEVIDYS Dose Level 1 N = 6 n (%)	ELEVIDYS Dose Level 2 N = 6 n (%)	ELEVIDYS Target Dose N = 29 n (%)	All Subjects N = 41 n (%)
Renal and urinary disorders	0 (0.0)	1 (16.7)	2 (6.9)	3 (7.3)
Glycosuria	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.4)
Hematuria	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.4)
Ketonuria	0 (0.0)	1 (16.7)	1 (3.4)	2 (4.9)

Source: FDA

Note: TEAEs that are bolded occurred at a frequency of at least 5% more in the target dose group when compared with the lower dose groups.

Abbreviation: AE, adverse event; TEAE, treatment-emergent adverse event.

8.5.2 Time Dependency for Adverse Events

In the Exposure Analysis Set, 79 (94.0%) subjects who experienced a TEAE reported their first event within the first two weeks after ELEVIDYS administration.

Vomiting occurred ≤2 weeks after ELEVIDYS administration for 48 (56.5%) subjects.

Hepatotoxicity events were experienced within 60 days (typically not before 2 weeks after infusion), with the 4-week time frame the most common window in which subjects to experience a hepatotoxicity event (e.g., elevated GLDH) deemed representative of ALI. The same temporal pattern applies to the gastrointestinal events of nausea/vomiting and ALI.

Table 36. Treatment-Emergent Adverse Events by Preferred Term, Reaction Time of First Occurrence, Exposure Analysis Set

Reaction Time of First Occurrence	Process A (N = 45)	Process A Target Dose (N = 33)	Process B (N = 40)	Target Dose (N = 73)	All Subjects (N = 85)
Number of TEAEs					
0-2 weeks	41	34	44	63	68
>2 weeks–60 days	47	34	30	48	57
>60 days–90 days	14	14	16	22	23
>90 days–6 months	25	13	20	25	35
>6 months–1 year	37	25	15	29	40
>1 year	45	32	1	27	38
Subjects with any TEAE					
0-2 weeks, n (%)	44 (97.8)	32 (97.0)	35 (87.5)	67 (91.8)	79 (92.9)
>2 weeks–60 days, n (%)	0	0	0	0	0
>60 days–90 days, n (%)	1 (2.2)	1 (3.0)	1 (2.5)	2 (2.7)	2 (2.4)
>90 days–6 months, n (%)	0	0	0	0	0
>6 months–1 year, n (%)	0	0	1 (2.5)	1 (1.4)	1 (1.2)
>1 year, n (%)	0	0	0	0	0

Source: BLA 125781 ISS Day 120Table 2.2.3.1

Note: A subject is counted only once for multiple events within each Preferred Term.

Note: TEAEs include all adverse events that first occurred or increased in severity since the study treatment with ELEVIDYS in the Exposure Analysis Set.

Note: Reaction Timing of First Occurrence = First Occurrence event date in Exposure Analysis Set – ELEVIDYS Infusion Date + 1

Note: N = number of subjects in the Exposure Analysis Set; n = number of subjects within a specific category.

Percentages calculated as $100 \times (n/N)$

Abbreviation: TEAE, treatment-emergent adverse event.

8.5.3 Product-Demographic Interactions

No clear evidence is discernable to indicate increased product-demographic interactions related to treatment with ELEVIDYS.

8.5.6 Human Carcinogenicity

No studies have been performed to evaluate the effects of ELEVIDYS on carcinogenesis, mutagenesis, or impairment of fertility; based on characteristics of the product and preclinical data, such studies were not warranted.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

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

In ELEVIDYS clinical studies, subjects were required to have baseline anti-AAVrh74 total binding antibodies of <1:400, measured using an investigational total binding-antibody ELISA. The safety and efficacy of ELEVIDYS in subjects with higher titers of anti-AAVrh74 total binding antibodies (\geq 1:400) have not been evaluated.

Across Studies 101, 102, and 103 (evaluating a total of 84 subjects), elevated titers of anti-AAVrh74 total binding antibodies were observed in all subjects following the one-time infusion of ELEVIDYS. Titers of anti-AAVrh74 total binding antibody reached at least 1:409,600 in every subject, with the highest observed titers exceeding 1:26,214,400 in certain subjects. The safety of re-administration of ELEVIDYS in the presence of high titers of anti-AAVrh74 total binding antibodies has not been evaluated in humans.

8.5.9 Person-to-Person Transmission, Shedding

Please see Section 4.4.4 Pharmacokinetics regarding vector shedding.

8.6 Safety Conclusions

Serious adverse events, including myocarditis and immune-mediated myositis, related to Process B ELEVIDYS were observed.

The most frequent adverse reactions (incidence \geq 5%) observed in the studies include vomiting (61%), nausea (40%), liver function test increased (37%), pyrexia (24%), and thrombocytopenia (12%). No subjects discontinued study participation due to adverse reactions. There were no deaths.

High titers of anti-AAVrh74 antibodies were observed following infusion of ELEVIDYS in all subjects. Due to potential safety and efficacy concerns, high titers of anti-AAVrh74 antibodies are expected to preclude the possibility of re-administration of ELEVIDYS. In addition, cross-reactivity to AAV vectors of other serotypes may occur, which for patients

for whom ELEVIDYS is ineffective likely would preclude future administration of a future effective AAV vector-based gene therapy.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Pregnancy Data

In the general population of the United States, the estimated background risks of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

9.1.2 Use During Lactation

There is no information available on the presence of ELEVIDYS in human milk; effects on the breastfed infant; or effects on milk production.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

The clinical studies included pediatric subjects 3 years of age and older. However, the clinical efficacy of ELEVIDYS has not been established, nor has the safety of ELEVIDYS been established in pediatric subjects younger than 3 years of age.

9.1.4 Immunocompromised Patients

The safety and efficacy of ELEVIDYS in immunocompromised patients with DMD have not been studied.

9.1.5 Geriatric Use

The safety and efficacy of ELEVIDYS in geriatric patients with DMD have not been studied.

10. CONCLUSIONS

To support Accelerated Approval, a surrogate endpoint must be “reasonably likely to predict clinical benefit.” Determination of whether a candidate surrogate endpoint is “reasonably likely to predict clinical benefit” is a matter of judgment, dependent on biological plausibility; empirical evidence (which may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data); and sufficient supportive clinical data.

Since ELEVIDYS micro-dystrophin is a novel protein that does not occur in nature, epidemiologic data are not available, and the effect of ELEVIDYS micro-dystrophin on the pathophysiology of DMD is not known.

The only randomized, double-blinded, placebo-controlled study for which data are available, Study 102 Part 1, did not meet its primary functional efficacy endpoint of change in NSAA Total Score from baseline to Week 48, despite confirmed expression of ELEVIDYS micro-dystrophin in study subjects.

Exploratory analysis of data from Study 102 Part 1 may suggest potential benefit of treatment with ELEVIDYS in the 4 to 5-year-old age group; but potentially no benefit in the 6 to 7-year-old age group. However, an important caveat is that these analyses were not prespecified for hypothesis testing and no prespecified multiplicity adjustment strategy was employed. Such post hoc subgroup tests following an overall nonsignificant test in the population as a whole can only be considered hypothesis-generating.

Study 101 and Study 103 were single-arm, open-label studies, so assessment of the clinical outcome, change in NSAA Total Score from baseline to Week 52, is not reliable, because the NSAA is an effort-driven outcome measure susceptible to expectation bias in the setting of an unblinded, single-arm trial.

Available clinical data do not indicate a persuasive association between expression of ELEVIDYS micro-dystrophin and clinical benefit in ambulatory patients with DMD. Thus, there is insufficient evidence that expression of ELEVIDYS micro-dystrophin may serve as a surrogate endpoint “reasonably likely to predict clinical benefit” or Accelerated Approval of ELEVIDYS.

The safety database included 85 subjects from the three clinical studies describe in the BLA submission. The major risks associated with ELEVIDYS infusion include acute serious liver injury, myocarditis, immune-mediated myositis, and immunogenicity.

High titers of anti-AAVrh74 antibodies after treatment with ELEVIDYS are expected to preclude the possibility of re-administration, due to potential safety and efficacy concerns. In addition, cross-reactivity to AAV vectors of other serotypes may occur, which likely would preclude treatment of patients for whom ELEVIDYS is ineffective with a future, effective AAV vector-based gene therapy.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations are described in Table 37.

Table 37. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • DMD is a X-linked recessive genetic disorder caused by mutations in the <i>Dystrophin</i> (<i>DMD</i>) gene, resulting in the absence or near-absence of functional dystrophin protein. Lack of dystrophin leads to degeneration of muscle fibers, followed by inflammation and subsequent replacement of muscle by fibrotic and adipose tissue. • Loss of muscle strength is progressive and occurs proximally to distally, first in the lower extremities and then in the upper extremities. Patients typically require a wheelchair by adolescence. Death occurs around age 30, generally due to respiratory insufficiency and cardiomyopathy. 	<p>DMD is a serious and ultimately fatal disease. Muscle strength progressively worsens, leading to loss of ambulation by adolescence, followed by decline in respiratory and cardiac function, resulting in death typically in the fourth decade.</p>
Unmet Medical Need	<ul style="list-style-type: none"> • The main pharmacologic treatment for DMD is corticosteroids (usually deflazacort or prednisone). In addition, symptomatic treatment includes physical therapy, surgery to correct progressive scoliosis, medications for cardiac function, assisted ventilation, and tracheostomy. • Deflazacort is FDA-approved for patients with DMD ≥2 years of age. Deflazacort treatment has been shown to improve muscle strength and have fewer adverse effects compared to prednisone. • Four exon-skipping drugs (eteplirsen, golodirsen, viltolarsen, and casimersen) have received FDA approval via the Accelerated Approval pathway to treat a minority of patients with DMD with amenable mutations in the <i>DMD</i> gene. The clinical benefit of these drugs remains unknown, since none of the confirmatory clinical studies have been completed. 	<ul style="list-style-type: none"> • There is a substantial unmet need for better therapies for DMD. • Although standard of care, corticosteroids have many associated adverse effects.
Clinical Benefit	<ul style="list-style-type: none"> • The BLA submission includes data from Study 101, Study 102 (Part 1 and Part 2), and Study 103. All three studies enrolled subjects aged 4-7 years, a time during which patients with DMD generally show improvement on the NSAA with standard of care corticosteroid treatment alone. Study 101 and Study 102 used Process A ELEVIDYS . Study 103 used Process B ELEVIDYS . • Study 101 was a first-in-human, open-label, single-arm, study involving four subjects. The 4-year follow-up results are consistent with natural history data for DMD. • Study 102 Part 1 was the only randomized, double-blind, and placebo-controlled study for which data are available. A statistically significant greater increase in expression of ELEVIDYS micro-dystrophin (measured by Western blot) from baseline to Week 12 was observed in the ELEVIDYS group compared to the placebo group; however, no statistically significant difference was present between the two groups in change in the NSAA Total Score from baseline to Week 48. 	<ul style="list-style-type: none"> • The NSAA is effort-dependent and process-dependent. Consequently, NSAA results from open-label studies are difficult to interpret, and comparison to results from external sources are not suitably reliable. • Comparison to external controls is interpretable under circumstances in which the disease is homogeneous, the treatment has a large effect, and the clinical endpoint can be objectively assessed. Those conditions were not present here: progression of DMD is heterogeneous; improvement on the NSAA occurs with standard of care treatment alone; and any effect of ELEVIDYS is likely to be moderate. Therefore, without randomized, double-blind, placebo-controlled

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> At the start of Study Part 2, the subjects, caregivers, and evaluators knew that by that point, all subjects had received ELEVIDYS, so Part 2 essentially was open-label. Study 103 was an open-label, single-arm, “bridging” study to assess safety, as well as expression of ELEVIDYS micro-dystrophin, following treatment with Process B ELEVIDYS. ELEVIDYS manufactured by Process B contains a higher percentage of empty-capsid impurities, and therefore is not analytically comparable to ELEVIDYS manufactured by Process A. Expression of ELEVIDYS micro-dystrophin at Week 12 was demonstrated. 	<p>studies, it is challenging to clearly determine the effect of ELEVIDYS.</p> <ul style="list-style-type: none"> There is no substantial evidence of effectiveness from adequate and well-controlled studies to support traditional approval of ELEVIDYS. There is substantial evidence of expression of ELEVIDYS micro-dystrophin after ELEVIDYS infusion; however, available data do not support the conclusion that this biomarker is “reasonably likely to predict clinical benefit” for use as a surrogate endpoint for Accelerated Approval.
Risk	<ul style="list-style-type: none"> The safety database included 85 subjects. The most common adverse reactions were vomiting (61%), nausea (40%), acute liver injury (37%), pyrexia (24%), and thrombocytopenia (12%). Adverse events of special interest were: hepatotoxicity, cardiotoxicity (including myocarditis and elevated troponin-I levels), and life-threatening immune-mediated myositis. Hepatotoxicity was observed at a similar frequency in subjects who received Process A ELEVIDYS and Process B ELEVIDYS. Myocarditis and myositis were observed only in subjects who received Process B ELEVIDYS. 	<ul style="list-style-type: none"> The safety database for patients exposed to ELEVIDYS is small but sufficient to assess frequent adverse events, and is acceptable for this serious disease with a major unmet medical need. Because of cross-reactivity against capsids of other AAV serotypes, subjects who receive ELEVIDYS and for whom it is ineffective likely will not be able to receive any future effective AAV-based gene therapy.
Risk Management	Safety risks have not been identified that would require risk management beyond enhanced and standard pharmacovigilance.	The proposed pharmacovigilance plan is acceptable.

Source: FDA

Abbreviations: AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; FDA, Food and Drug Administration; NSAA, North Star Ambulatory Assessment..

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA do not establish a substantial likelihood of benefit in ambulatory patients with DMD.

Although the risks of ELEVIDYS appear similar to those of other AAV vector-based gene therapies, the lack of demonstrable possible benefit results in an unfavorable overall risk-benefit profile. In addition, because of possible cross-reactivity against capsids of other AAV serotypes, patients who receive ELEVIDYS and for whom it is ineffective likely will not be able to receive any future effective AAV-based gene therapy.

11.3 Discussion of Regulatory Options

The Applicant has not provided substantial evidence of effectiveness from adequate and well-controlled trials to support traditional approval.

The Applicant has provided substantial evidence that ELEVIDYS infusion leads to expression of ELEVIDYS micro-dystrophin, the candidate surrogate endpoint for Accelerated Approval. However, to support Accelerated Approval, the surrogate endpoint must be “reasonably likely to predict clinical benefit.” Determination of whether a candidate surrogate endpoint is “reasonably likely to predict clinical benefit” is a matter of judgment, dependent on biological plausibility; empirical evidence (which may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data); and sufficient supportive clinical data.

Since ELEVIDYS micro-dystrophin is a novel protein that does not occur in nature, epidemiologic data are not available, and the effect of ELEVIDYS micro-dystrophin expression on the pathophysiology of DMD is not known. The data in the BLA submission do not demonstrate a persuasive correlation between expression of ELEVIDYS micro-dystrophin and clinical benefit. Thus, there is insufficient evidence that ELEVIDYS micro-dystrophin expression is “reasonably likely to predict clinical benefit.” Expression of ELEVIDYS micro-dystrophin expression is a suitable surrogate endpoint to support Accelerated Approval of ELEVIDYS for the treatment of ambulatory patients with DMD due to mutation in the *DMD* gene.

Available data from exploratory analysis suggests improved NSAA Total Score with increased expression of ELEVIDYS micro-dystrophin in subjects aged 4 to 5 years; however, data are limited (n = 8 subjects), and no clear association was observed in subjects aged 6 to 7 years.

Exploratory subgroup analysis suggests that the ELEVIDYS group may have had a better NSAA outcomes compared to the placebo group among ambulatory subjects aged 4 to 5 years. Exploratory analysis also suggests, among ambulatory subjects aged 6 to 7 years, no difference between the ELEVIDYS group and the placebo group; moreover, the ELEVIDYS group showed no improvement from baseline. However, these exploratory subgroup analyses following an overall nonsignificant test in the population as a whole can only be considered hypothesis-generating. Therefore, these data are insufficient to support expression of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval of ELEVIDYS for even a limited patient population, such as ambulatory pediatric patients aged 4 through 5 years old with DMD due to mutation in the *DMD* gene.

Available data do not provide clear evidence that ELEVIDYS is likely beneficial for ambulatory patients with DMD. It is challenging to conclude with reasonable confidence from the data provided by the Applicant either that ELEVIDYS is likely effective for younger patients, or that it is likely ineffective for older patients or for patients with somewhat poorer functional status. The clinical reviewer also has significant safety concerns related to the possibility of administering an ineffective gene therapy.

11.4 Recommendations on Regulatory Actions

According to analysis of the clinical data in the BLA submission by the clinical reviewer and statistical reviewer, and considering the assessment in the Clinical Pharmacology Review, the clinical reviewer concludes that there is insufficient evidence to support expression of ELEVIDYS micro-dystrophin as a surrogate endpoint “reasonably likely to predict clinical benefit” for Accelerated Approval of ELEVIDYS for the treatment of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene, or for the treatment of a limited subpopulation of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene. Based on available data, the overall potential benefit associated with Accelerated Approval does not outweigh the known and unknown risks associated with ELEVIDYS. Therefore, the clinical reviewer recommends Complete Response for BLA 125781.

11.5 Labeling Review and Recommendations

The review team made substantial changes to each section of the Prescribing Information, based on available clinical study data and on FDA guidance on product labeling. The clinical reviewer and the CBER Advertising and Promotional Labeling Branch consider the revised Prescribing Information to be acceptable.

The overall content of the Prescribing Information suitably conveys known information regarding safety and efficacy results shown in clinical studies of ELEVIDYS.

Reviewer Comment:

This BLA submission will be approved by CBER leadership via the Accelerated Approval pathway, for a narrow patient population. The review team therefore worked with the Applicant on the Prescribing Information.

11.6 Recommendations on Postmarketing Actions

The following postmarketing studies have been discussed and mutually agreed upon by FDA and the Applicant for this submission:

ACCELERATED APPROVAL REQUIRED STUDIES

Complete Study SRP-9001-301 Part 1, an ongoing, randomized, double-blinded clinical trial intended to describe and verify clinical benefit of ELEVIDYS in ambulatory patients with DMD. The study evaluates the primary endpoint of change in NSAA Total Score and compares treatment with ELEVIDYS versus placebo in 125 ambulatory subjects with DMD with confirmed mutation in the *DMD* gene. Trial Completion date is September 30, 2023. The final study report will be submitted as a “Postmarketing Requirement – Final Study Report” by January 31, 2024.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

The Applicant commits to conducting adequate analytical and clinical validation testing to establish an (b) (4) [REDACTED], in order to identify patients with DMD who may benefit from ELEVIDYS therapy. The results of the validation study are intended to inform product labeling. The clinical validation should be supported by a clinical bridging study comparing the in (b) (4) [REDACTED] and the clinical trial enrollment assays. (b) (4) [REDACTED]. The final study report will be submitted as a "Postmarketing Commitment – Final Study Report" by January 30, 2025.

Reviewer Comment:

This BLA submission will be approved by CBER leadership via the Accelerated Approval pathway for a narrow patient population. The review team therefore worked with the Applicant both on postmarketing requirement and postmarketing commitment studies.

The Applicant also clarified that after Accelerated Approval and prior to the availability of an FDA-authorized test to determine titers of anti-AAVrh74 total binding antibodies, the Applicant plans to use a laboratory-developed test (LDT) to determine antibody serostatus prior to administration of ELEVIDYS. This LDT is the same test procedure as the LDT (b) (4) [REDACTED] used in the confirmatory study, (b) (4) [REDACTED].

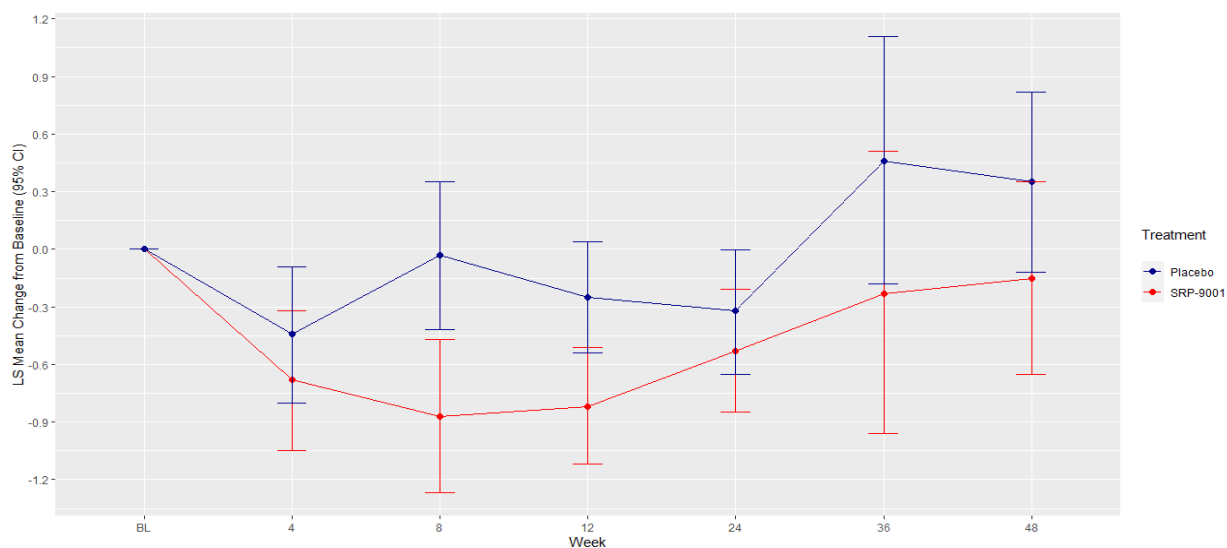
This LDT has been developed by (b) (4) [REDACTED], owned by (b) (4) [REDACTED]. The AAVrh74 total binding antibody LDT will be used to determine eligibility for all patients prescribed ELEVIDYS for DMD, and will be conducted at a single laboratory (b) (4) [REDACTED] in the United States.

The Applicant will train health care providers (HCPs) on the AAVrh74 total binding antibody LDT ordering process immediately after Accelerated Approval of ELEVIDYS. The HCP will either request or conduct a specimen draw for each potential patient, and the collected serum sample will be shipped to (b) (4) [REDACTED]. Only an HCP-ordered sample will be accepted by (b) (4) [REDACTED] will provide the patient's test result to the requesting HCP.

APPENDIX 2. EXPLORATORY ASSESSMENTS OF SECONDARY FUNCTIONAL ENDPOINTS IN STUDY 102 PART 1

Please note that for each secondary endpoint, a negative change from baseline corresponds to improvement (i.e., less time required to complete the task).

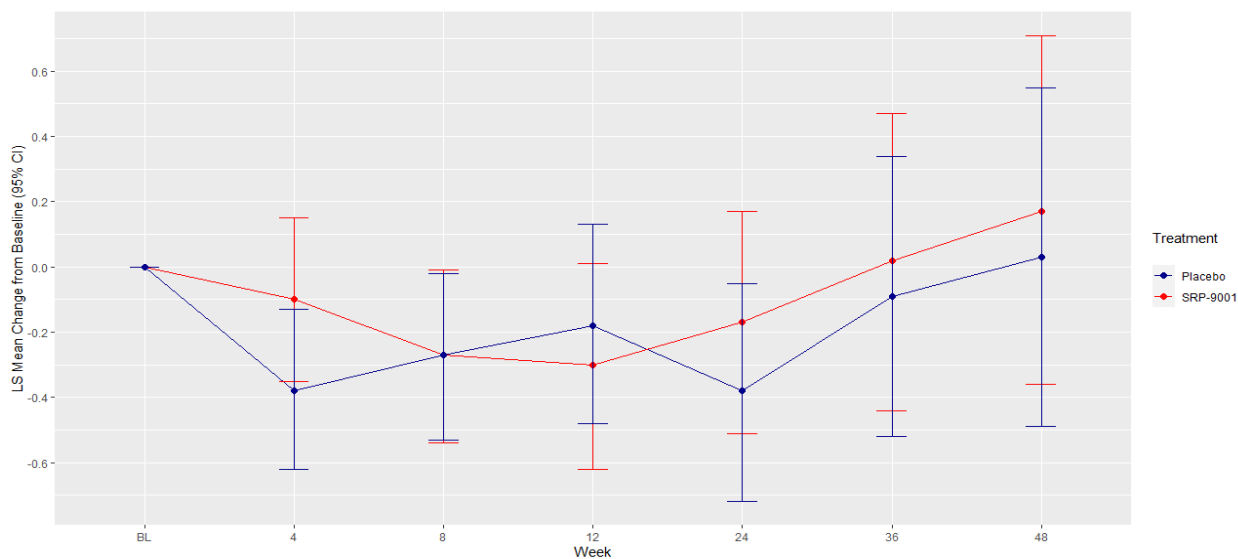
Figure 17. Change in Time to Rise from the Floor From Baseline to Week 48



Source: FDA

Abbreviations: LS, least squares; CI, confidence interval.

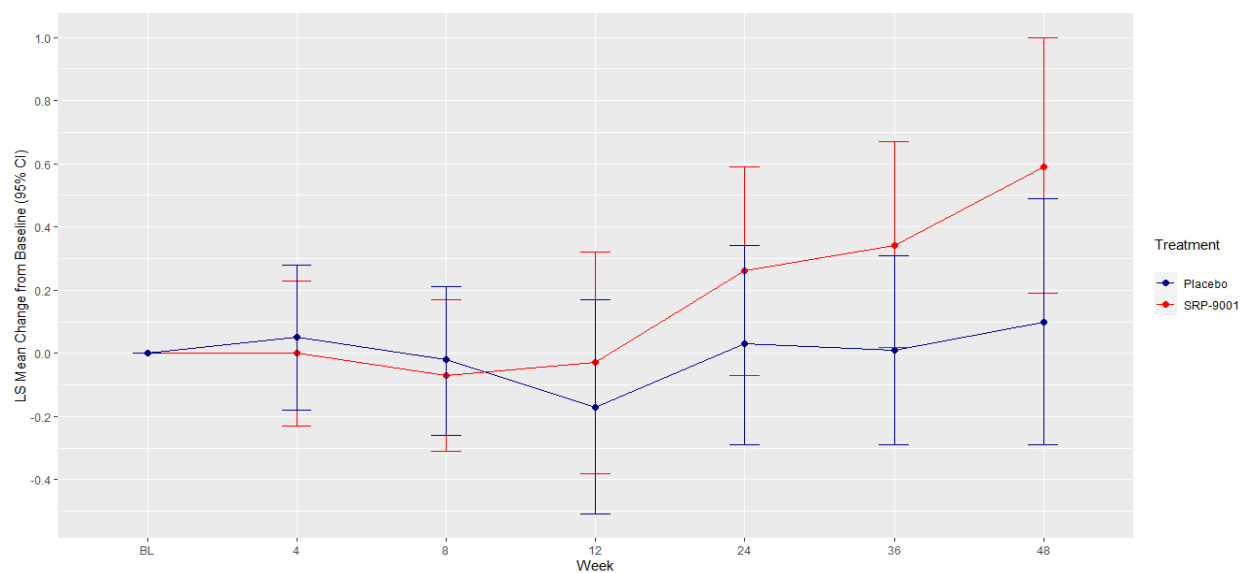
Figure 18. Change in Time to Ascend 4 Steps From Baseline to Week 48



Source: FDA

Abbreviations: LS, least squares; CI, confidence interval.

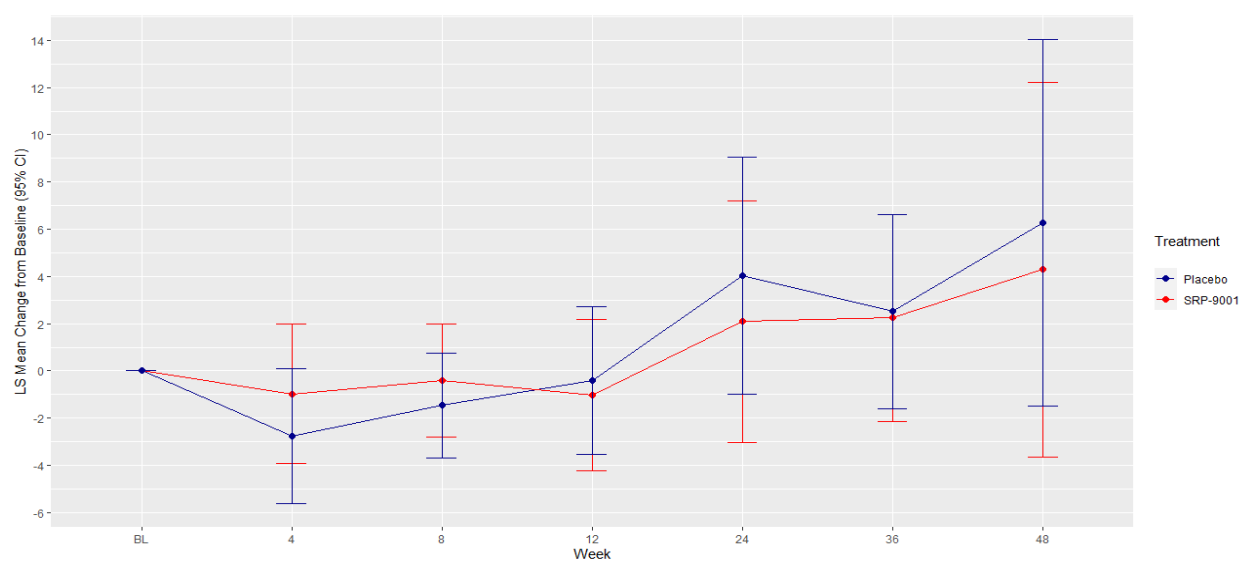
Figure 19. Change in Time of 10-Meter Timed Test From Baseline to Week 48



Source: FDA

Abbreviations: LS, least squares; CI, confidence interval.

Figure 20. Change in Time of 100-Meter Timed Test From Baseline to Week 48



Source: FDA

Abbreviations: LS, least squares; CI, confidence interval.