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Summary Basis for Regulatory Action

Date:	June 21, 2023
From:	Emmanuel Adu-Gyamfi, PhD Review Committee Chair Division of Gene Therapy 1 Office of Gene Therapy CMC Office of Therapeutic Products
BLA STN:	125781/0
Applicant:	Sarepta Therapeutics, Inc.
Submission Receipt Date:	September 28, 2022
Action Due Date:	May 29, 2023
Proper Name:	delandistrogene moxeparvovec-rokl
Proprietary Name:	ELEVIDYS
Indication:	ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. This indication is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin in skeletal muscle observed in patients treated with ELEVIDYS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Recommended Action:
Certain members of the Review Committee recommend approval of this Biologics License Application (BLA) via the Accelerated Approval pathway, based on the data relevant to their areas of expertise. However, the Clinical, Clinical Pharmacology, and Statistics review teams and supervisors conclude that the data submitted in the BLA in support of Accelerated Approval of ELEVIDYS is not adequate to meet the threshold for approval. Specifically, there is insufficient evidence to support the use of expression of ELEVIDYS micro-dystrophin as a surrogate endpoint that is “reasonably likely to predict clinical benefit” for Accelerated Approval. Therefore, the Review Committee does not recommend approval of the BLA. The Review Committee’s decision was overridden by the Center Director, Dr. Peter Marks. Please refer to Dr. Marks’ memo for additional information.

Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer/Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities Review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Emmanuel Adu-Gyamfi, PhD, CBER/OTP/OGT Lilia Bi, PhD, CBER/OTP/OGT Maureen DeMar, BSN, RN, CBER/OCBQ/DMPQ/ARB Varsha Garnepudi, MS, CBER/OCBQ/DBSQC Simleen Kaur, MSc, CBER/OCBQ/DBSQC Olivia Ou Ma, PhD, CBER/OCBQ/DMPQ/MRB2 Tao Pan, PhD, CBER/OCBQ/DBSQC Sukyoung Sohn, PhD, CBER/OTP/OGT Brian Stultz, MS, CBER/OTP/OGT Andrey Sarafanov, PhD, CBER/OTP/OPPT/DH/HB2
Clinical • Clinical (Product Office) • Postmarketing Safety Pharmacovigilance Review (OBPV/DE) • Bioresearch Monitoring	Mike Singer, MD, PhD, CBER/OTP/OCE Rosa Sherafat-Kazemzadeh, MD, CBER/OTP/OCE Brendan Day, MD, MPH, CBER/OBPV/DPV/PB2 Triet M. Tran, PharmD, CBER/OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB)	Cong Wang, PhD, CBER/OBPV/DB
Pharmacology/Toxicology • Toxicology (Product Office) • Developmental Toxicology (Product Office) • Animal Pharmacology	Theresa Chen, PhD, CBER/OTP/OPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices	Vishnu Sharma, PhD, CDER/OTS/OCP/DPM Atul Bhattaram, PhD, CDER/OTS/OCP/DPM Elin Cho, MS, CBER/OBPV/DB Rong Rong, MD, PhD, CDRH/OPEQ/OHTVII/DIHD/HB Natasha Thorne, PhD, CDRH/OPEQ/OHTVII/DIHD/HB
Advisory Committee Summary	Cellular, Tissue, and Gene Therapies 74th Advisory Committee Meeting, May 12, 2023

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1. Introduction

Sarepta Therapeutics, Inc. (the Applicant) submitted Biologics Licensing Application STN 125781 to seek Accelerated Approval for delandistrogene moxeparvovec-rokl (SRP-9001; proprietary name ELEVIDYS), based on the proposed surrogate endpoint of expression of ELEVIDYS micro-dystrophin at Week 12 following administration of ELEVIDYS.

ELEVIDYS is an adeno-associated virus (AAV) vector-based gene therapy which encodes a novel, engineered protein, ELEVIDYS micro-dystrophin, that contains selected domains of the dystrophin protein present in normal muscle cells. ELEVIDYS is indicated for the treatment of ambulatory patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. The indication is approved under the Accelerated Approval pathway, based on expression of ELEVIDYS micro-dystrophin in skeletal muscle in patients treated with ELEVIDYS in clinical trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial(s).

As summarized in this document, members of the Review Committee recommended Complete Response for ELEVIDYS. Members of the Review Committee do not consider the available data satisfactory to support use of 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 certain subpopulation(s) of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene.

2. Background

Disease Background

DMD is a serious condition with an urgent unmet medical need. DMD results from mutation of the *DMD* (also known as *Dystrophin*) 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 to distal muscles. The lower extremities are affected first, followed by the upper extremities. Isoforms of the dystrophin protein are also normally expressed in cells of the heart and brain. DMD also manifests with dilated cardiomyopathy, as well as cardiac conduction abnormalities. About one-third of affected boys have cognitive and behavioral difficulties, including reduced verbal activity and attention.

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

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. Deflazacort delays loss of motor strength and ambulation, and is the only available therapy to receive FDA approval via the traditional approval pathway.

Four antisense oligonucleotide drugs (eteplirsen [Exondys 51], golodirsen [Vyondys 53], viltolarsen [Viltepso], and casimersen [Amondys 45]) which promote exon skipping have received FDA approval via the Accelerated Approval pathway. In each case, approval was based on the surrogate endpoint of expression of internally-truncated dystrophin protein in a subset of patients with specific *DMD* mutations. The clinical benefit of all four of these drugs remains to be verified.

Product Description

ELEVIDYS consists of a 4.7-kilobase codon-optimized DNA vector genome enclosed within a simian AAV serotype rh74 capsid. Each virion potentially contains a single copy of the vector genome. The vector genome encodes ELEVIDYS micro-dystrophin, a novel, engineered protein consisting of selected domains of the normal, full-length dystrophin protein. The expression cassette contains essential elements to control gene expression, including AAV2 inverted terminal repeats, a chimeric (SV40) intron, and a synthetic polyadenylation signal. The *ELEVIDYS micro-dystrophin* gene is under control of the chimeric MHCK7 (α-myosin heavy chain/creatine kinase 7) promoter, to restrict expression to skeletal and cardiac muscle cells.

Regulatory History

The key regulatory history of ELEVIDYS is outlined in Table 1.

Table 1. Regulatory History

Regulatory Event/Milestone	Date
1. Pre-IND meeting	December 15, 2016
2. IND submission	October 5, 2017
3. Fast Track designation granted	June 3, 2020
4. Orphan Drug designation granted (18-6413)	April 20, 2018
5. BLA 125781/0 submission	September 28, 2022
6. BLA filed	November 25, 2022
7. Mid-Cycle communication	January 24, 2023
8. Late-Cycle meeting	March 13, 2023
9. Advisory Committee meeting	May 12, 2023
10. Action Due Date	May 29, 2023
11. Extended PDUFA Due date	June 22, 2023

Source: FDA
Abbreviations: BLA, Biologics License Application; IND, investigational new drug; N/A, not applicable; PDUFA, Prescription Drug User Fee Act.

3. Chemistry Manufacturing and Controls

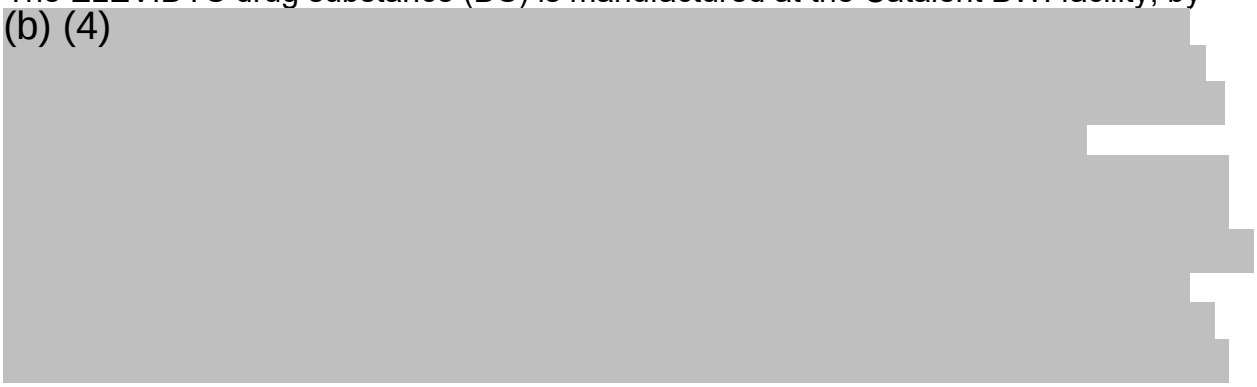
a) Product Quality

The Chemistry, Manufacturing, and Controls (CMC) review team concludes that the manufacturing process and controls for ELEVIDYS are adequate to yield a product with consistent quality attributes, and the CMC review team recommends approval

considering the postmarketing commitment (PMCs) documented under Section 11.c) Recommendation for Postmarketing Activities below.

Manufacturing Summary

The ELEVIDYS drug substance (DS) is manufactured at the Catalent BWI facility, by (b) (4)



The ELEVIDYS drug product (DP) is manufactured at the Catalent BioPark facility. Each DP vial contains an extractable volume of not less than 10 mL, with a nominal concentration of 1.33×10^{13} vg/mL formulated in 7 mM tromethamine/13 mM tromethamine HCl, 200 mM sodium chloride, 1 mM magnesium chloride, 0.001% Poloxamer 188, at (b) (4). The DP manufacturing process includes formulation buffer preparation, (b) (4) sterilizing filtration, aseptic filling, stoppering, and capping. After visual inspection, the vials are packed, stored at (b) (4), and shipped to the labeling and secondary packaging site at the (b) (4) facility. The DP manufacturing process was validated by performing three Process Performance Qualification (PPQ) runs to demonstrate consistency for commercial manufacturing.

Manufacturing Control Strategy

Validation of the DS manufacturing process was conducted by manufacturing (b) (4) PPQ lots in (b) (4) suites at the at the Catalent BWI facility. The upstream and downstream operations for all (b) (4) PPQ DS lots were evaluated to verify that the critical process parameters can be maintained within all pre-established process parameter ranges. The routine microbial in-process testing was below the alert and action levels. Additional studies support that the in-process hold times and microbial testing conducted post-hold met the acceptance criteria.

The manufacturers accept raw materials based on specified quality attributes, including (b) (4). Raw materials derived from animals are appropriately controlled to ensure the absence of microbial contaminants. The DS and DP manufacturing steps are controlled and characterized by a panel of analytical methods that are used for product characterization and release. These include quantitative assays that assess critical quality attributes of the product including: safety, purity, strength (vg/mL), and potency. The potency test measures the ability of ELEVIDYS to successfully transduce a dystrophin-(b) (4) and express ELEVIDYS micro-dystrophin, which is measured via quantitative (b) (4). Collectively, the assays used as part of the overall control strategy for the manufacturing process were found to

be fit-for-purpose. Release and characterization test methods are adequately controlled to assure product safety, purity, and potency.

Stability

The DS is stable for (b) (4) when stored at the long-term storage condition of (b) (4). The DP is stable for 12 months at the storage condition of ≤-60°C. During administration of the DP in the clinic, the DP is thawed and aspirated into an infusion syringe to be infused with a syringe pump. Based on the stability data submitted in the BLA, the thawed DP is stable for up to 24 hours at room temperature (15°C to 25°C) and stable for up to 14 days at 2°C to 8°C.

Comparability

Two manufacturing processes were utilized to generate purified DP to support the clinical program. For early clinical trials (SRP-9001-101 [Study 101] and SRP-9001-102 [Study 102]), the DP was made using manufacturing Process A at Nationwide Children's Hospital (Ohio State University, Columbus, OH). Process A used a (b) (4) -based purification process to achieve a near-complete removal of empty AAV capsids from the final formulated product. For later-stage clinical trials (SRP-9001-103 [Study 103] and the ongoing Phase 3 EMBARK confirmatory trial (SRP-9001-301 [Study 301]), the DP was purified using the to-be-commercialized manufacturing process, referred to as Process B at Catalent Pharma Solutions (Baltimore, MD). Process B utilizes a scaled-up purification method that incorporates chromatography-based methods for separation of the empty capsid residuals from the full capsids. (b) (4) Based on both the Applicant's and FDA's assessment, it was concluded that the Process A and Process B materials are not analytically comparable relative to the levels of empty capsid residuals. The difference in empty capsid residual impurities was found to be significantly different with a statistical probability t-test with p value of p = 0.0002.

b) Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ELEVIDYS DS and DP were found to be adequate for their intended use. The final lot release specification for the DP is shown in Table 2.

Table 2. Drug Product Specification

Attribute	Analytical Procedure	Acceptance Criteria
Appearance Clarity color Visible particles Cap color	(b) (4) Visual inspection	(b) (4) Cap color: Blue
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Identity (vector genome)	(b) (4)	(b) (4)
Identity (vector capsid)	(b) (4)	(b) (4)

Attribute	Analytical Procedure	Acceptance Criteria
Sterility	(b) (4)	No growth
Bacterial endotoxin	(b) (4)	(b) (4)
Capsid purity	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Percent full capsid	(b) (4)	(b) (4)
Particulate matter	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
Vector genome concentration	(b) (4)	(b) (4)
Extractable volume	(b) (4)	(b) (4)

Source: FDA
Abbreviations: AAV, adeno-associated virus; (b) (4)
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c) CBER Lot Release

The lot release protocol template was submitted to the Center for Biologics Evaluation and Research (CBER) for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ELEVIDYS are listed in the table below. The activities performed and inspectional histories are noted in Table 3.

Table 3. Manufacturing Facilities Table for ELEVIDYS

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Catalent Pharma Services Catalent Maryland (BWI) 7555 Harmans Road Harmans, MD 20177, USA DS Manufacturing	3015434301	116950534	PLI	CBER/DMPQ March 2023 VAI
Catalent Pharma Solutions Catalent Maryland (Biopark) 801 West Baltimore Street, Suite 302 Baltimore, MD 21201, USA DP manufacturing	3015558590	618890289	PLI	CBER/DMPQ February 2023 NAI
Sarepta Therapeutics 100 Federal Street Andover, MA 01810 USA DP Release Testing	3012807588	072827382	PLI	ORA/OBPO March 2023 VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4)			Waiver	ORA/OPQO (b) (4)
(b) (4)			Waiver	ORA/OBPO (b) (4)
(b) (4)			Waiver	MRA/(b) (4)

Source: FDA.
Abbreviations: DS, drug substance; DP, drug product; DUNS, Data Universal Numbering System; FEI, FDA Establishment Identifier; (b) (4) MRA, Mutual Recognition Agreement; NAI, no action indicated; OBPO, Office of Biological Products Operations; ORA, Office of Regulatory Affairs; PLI, pre-license Inspection; VAI, voluntary action indicated.

CBER conducted the pre-license inspection (PLI) of the Catalent BWI facility from March 6-10, 2023, and a Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as voluntary action indicated (VAI).

CBER conducted the PLI of the Catalent Biopark facility from February 21-24, 2023, and no Form FDA 483 was issued; the inspection was classified as no action indicated (NAI).

The Office of Regulatory Affairs (ORA) and CBER conducted the Sarepta Therapeutics facility PLI on March 20-24, 2023, and a Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by ORA, and no Form FDA 483 was issued; the inspection was classified as NAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by ORA, and a Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by (b) (4) of (b) (4) and classified as VAI.

e) Container/Closure System

The container closure system consists of a 10 mL cyclic olefin polymer vial (b) (4) closed with a 20-mm rubber stopper (b) (4) and sealed with an aluminum seal and plastic flip-off cap (b) (4)

(b) (4) performed the container closure integrity testing at the (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

f) Environmental Assessment

The Applicant submitted an environmental assessment pursuant to 21 CFR part 25. The Agency determined that approval of ELEVIDYS will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

The pharmacology studies of ELEVIDYS were conducted in rodent models of DMD including *mdx* mice and *Dmd*^{mdx} rats. In pharmacology studies in 4 to 8 week old *mdx* mice (Report Nos. SR-20-001, SR-19-061, SR-20-014, and SR-21-025), single intravenous (IV) administration of ≥1.33×10^{14} vg/kg ELEVIDYS (manufactured by Process A at Nationwide Children Hospital and Process B at ThermoFisher and Catalent) resulted in: i) increased specific force output in the tibialis anterior and diaphragm muscles, ii) reduced dystrophic muscle pathology in skeletal muscles, iii) increased ELEVIDYS micro-dystrophin protein expression in skeletal muscles and heart, with occasional low levels in the liver, and iv) increased β-sarcoglycan staining in the skeletal muscles. Endpoints were evaluated at 12 weeks post-administration in all studies.

In a 6-month pharmacology study (Report No. SR-20-012) in 3 to 4 week old *Dmd*^{mdx} rats, IV administration of 1.33×10^{14} vg/kg ELEVIDYS (manufactured by Process B at Catalent) resulted in i) increased spontaneous activity in an open field assessment, ii) increased heart rate and decreased left ventricle internal diameter during diastole, iii) increased micro-dystrophin protein expression in skeletal muscle and heart, and iv) reduced dystrophic muscle pathology in skeletal muscle and heart. However, administration of ELEVIDYS in older (3-5-month-old) *mdx* rats (Report No. SR-20-013) did not result in any statistically significant improvements in the open field assessment or dystrophic muscle pathology, despite ELEVIDYS micro-dystrophin protein expression in skeletal muscles and heart.

A 6-month good laboratory practice (GLP) toxicology and biodistribution study (Report No. SR-19-050) evaluated single IV administration of 1.33×10^{14} and 4.01×10^{14} vg/kg ELEVIDYS (manufactured by Process B at ThermoFisher) in 6 to 7 weeks old C57BL/6J wild type (WT) and *mdx* mice with interim and terminal sacrifices at 85 and 169 days. No consistent patterns of ELEVIDYS-related adverse findings were observed for body weights, clinical observations, hematology, serum chemistry, or gross and histopathology on a comprehensive list of tissues, and no unscheduled deaths occurred. This study identified a no-adverse-effect-dose-level (NOAEL) of 4.1×10^{14} vg/kg in ELEVIDYS administered to WT and *mdx* mice.

A 12-week GLP toxicology and biodistribution study (Report No. SR-20-066) evaluated single IV administration of 1.33×10^{14} and 4.01×10^{14} vg/kg ELEVIDYS (manufactured by Process B at Catalent) in 7 to 8 weeks old C57BL/6J WT and *mdx* mice. No consistent patterns of ELEVIDYS-related adverse findings for body weights, clinical observations,

hematology, serum chemistry, or gross and histopathology on a comprehensive list of tissues in WT mice, or unscheduled deaths were reported. Similar results were also observed in *mdx* mice with the exception of a 20% increased incidence of possible ELEVIDYS-related exacerbation of hydrocephalus and dilation of ventricles at 4.1×10^{14} vg/kg compared to control mice. This study identified NOAELs of 4.1×10^{14} vg/kg in WT mice and 1.33×10^{14} vg/kg in *mdx* mice.

A 12-week non-GLP study (Report No. SR-21-028) was conducted to further evaluate hydrocephalus and hydrocephalus-related unscheduled deaths in 4 to 8 weeks old *mdx* mice following single IV administration of 4.01×10^{14} vg/kg ELEVIDYS (manufactured by Process B at Catalent). A similar incidence of hydrocephalus and hydrocephalus-related unscheduled deaths was observed in control and 4.01×10^{14} vg/kg ELEVIDYS-injected *mdx* mice; therefore, the occurrence of hydrocephalus was not considered ELEVIDYS-related. Spontaneous hydrocephalus and dilation of ventricles have also been reported in the literature as a background finding in *mdx* mice.

A 3-month GLP toxicology study (Report No. SR-20-015) evaluated single IV administration of ELEVIDYS (manufactured by Process B at Catalent) in neonatal C57BL/6J WT mice administered 1.33×10^{14} and 4.01×10^{14} vg/kg at post-natal day 1. No consistent patterns of ELEVIDYS-related adverse findings for unscheduled deaths, body weights, clinical observations, neurobehavioral tests, femur length, organ weights, or gross and histopathology on a comprehensive list of tissues were observed. This study identified a NOAEL of 4.1×10^{14} vg/kg in ELEVIDYS-administered neonatal WT mice.

Biodistribution of ELEVIDYS was evaluated in two GLP toxicology studies (Report No. SR-19-050 and SR-20-066). Systemic ELEVIDYS distribution was observed, with the highest vector levels in the liver, followed by the adrenal gland, aorta, heart, muscle, and esophagus. The vector was also detected at low levels in other tissues evaluated (e.g., skin, thyroid, trachea, bone, kidney, lung, spleen duodenum, salivary gland, sciatic nerve, jejunum, testes, ileum, stomach, brain, cecum, thymus, pancreas colon, eye, spinal cord, and harderian gland). (b) (4) for detection of AAV-MHCK and the micro-dystrophin transgene was performed with testes samples in two studies (Report No. SR-20-014 and SR-20-015). Of the limited samples evaluated, positive cells were detected at a low frequency.

Animal reproductive and developmental toxicity and carcinogenicity studies were not conducted with ELEVIDYS, which is acceptable based on the patient population and lack of ELEVIDYS-related adverse findings in the toxicology studies.

5. Clinical Pharmacology

The clinical pharmacology evaluation is based on data from three clinical studies, which used ELEVIDYS from two manufacturing processes: Study 101 and Study 102 (Process A product) and Study 103 (Process B/to-be-commercialized product). Both Study 101 and Study 103 are open-label, single-arm studies. Study 102 Part 1 is a randomized, double-blind, placebo-controlled study, while Study 102 Part 2 functionally is an open-label study.

After one-time intravenous (IV) infusion, ELEVIDYS distributed to target tissues, transduced into muscle fibers, and expressed the transgene, ELEVIDYS micro-dystrophin.

Vector Biodistribution and Vector Shedding

Vector Biodistribution

- After IV administration, the ELEVIDYS vector genome copy (VGC) concentration-time profiles in serum showed a bi-phasic disposition characterized by a rapid distribution phase up to 10 days post-dose, followed by a slow and nearly flat terminal elimination phase. The median (min, max) time to reach the first below limit of quantification (BLOQ) followed by 2 consecutive BLOQ samples was 55.3 (20.8, 252.0) days. The median time to achieve the first below limit of quantification [BLOQ] sample followed by 2 consecutive BLOQ samples were 63 days post-dose for serum for Study 103 Cohort 1.

- At Week 12 (90 days for Study 101), ELEVIDYS VGCs were detected in all study subjects. ELEVIDYS muscle tissue exposure (VGC levels) increased with increasing ELEVIDYS dose. High inter-subject variability of VGC levels was observed.

- At the dose 1.33×10^{14} vg/kg, the VGC levels (change from baseline) to Week 12 in muscle tissue biopsy samples were similar for ELEVIDYS manufactured by Process A and ELEVIDYS manufactured by Process B. The mean (standard deviation [SD]) of VGC levels (change from baseline) at Week 12 in muscle tissue biopsy samples were 3.3 (SD: 2.4) VGCs per nucleus and 3.4 (SD: 2.4) VGCs per nucleus from ELEVIDYS Process A (n = 33) product and Process B (n = 20) product, respectively.

- For subjects aged 4 to 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS VGC levels (change from baseline) at Week 12 post-infusion were 3.18 (N=4, SD: 1.54) copies per nucleus in Study 2 Parts 1 and 2 (Process A product) and 2.97 (N=11, SD: 2.15) copies per nucleus in Study 3 Cohort 1 (Process B product).

Vector Shedding

- After administration, ELEVIDYS vector genome was detected in all treated subjects. The median (min, max) time to achieve peak levels were 0.3 (0.2, 13.7) days, 0.3 (0.2, 72.0) days, and 13.1 (0.3, 27.8) days in saliva, urine, and feces, respectively.

- ELEVIDYS vector genome concentrations decreased rapidly. The median time (min, max) to reach the level below the limit of detection was 49.8 (27.8, 169.0) days, 78.2 (26.9, 257.0) days, and 162.0 (76.1, 251.0) days in saliva, urine, and feces, respectively. For Study 103 Cohort 1, the median time to achieve complete elimination as the first below limit of detection (BLOD) sample followed by two consecutive BLOD samples were 49.8 days, 123 days and 162 days post-dose for saliva, urine and feces, respectively.

Pharmacodynamics

After one-time intravenous infusion, ELEVIDYS is expected to be transduced to the target cells and lead to expression of the transgene encoding ELEVIDYS micro-dystrophin. Muscle biopsy samples were collected at baseline and Week 12 post-infusion to evaluate the quantity of expression of the ELEVIDYS transgene (ELEVIDYS micro-dystrophin protein levels, measured by western blot assay), and correct localization of the expressed protein at the sarcolemma membrane by immunofluorescence (IF) staining assay (IF fiber intensity and IF percent ELEVIDYS micro-dystrophin positive fibers [PMDPF; %]).

Amount of ELEVIDYS Micro-dystrophin at Week 12 in Muscle Biopsy Tissue Samples (Western Blot Assay)

The absolute amount of ELEVIDYS micro-dystrophin in muscle biopsy tissue samples were measured by western blot assay, adjusted by muscle content, and expressed as a percent of control (i.e., as a percent of levels of normal, wild-type dystrophin in muscle tissues of healthy individuals without DMD or Becker muscular dystrophy [BMD]). High inter-subject variability was observed in ELEVIDYS micro-dystrophin expression in muscle tissue measured by western blot.

- In Study 102 Part 1, subjects received three different dose levels of ELEVIDYS: 6.29×10^{13} vg/kg (SRP-9001-DL1), 8.94×10^{13} vg/kg (SRP-9001-DL2), and 1.33×10^{14} vg/kg (SRP-9001-DL3, intended dose). ELEVIDYS micro-dystrophin was expressed in a dose-dependent manner. The mean (SD) ELEVIDYS micro-dystrophin levels (percent of control) (change from baseline) at 12 weeks post-infusion were 3.6 (5.7), 28.2 (52.2), and 43.4 (48.6) for subjects receiving SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. ELEVIDYS micro-dystrophin levels were generally maintained to Week 12 of Study 102 Part 2, except for SRP-9001-DL2. In Study 102 Part 2, all subjects who were in the Study 102 Part 1 placebo group received ELEVIDYS at the intended dose (1.33×10^{14} vg/kg). At 12 weeks post-dosing of ELEVIDYS in Part 2, the mean (SD) level of ELEVIDYS micro-dystrophin (percent of control) was 40.8 (32.5), similar to Study 102 Part 1 SRP-9001-DL3.

- In Study 103 Cohort 1, all subjects received ELEVIDYS at the intended dose (1.33×10^{14} vg/kg). The mean (SD) level of ELEVIDYS micro-dystrophin was 54.2 (42.6) at Week 12.

- At the intended dose (1.33×10^{14} vg/kg), the mean (SD) ELEVIDYS micro-dystrophin levels (percent of control) in muscle tissue biopsy samples at Week 12 were 41.3 (35.4) and 54.2 (42.6) for ELEVIDYS Process A (n = 27) product and ELEVIDYS Process B (n = 20) product, respectively. For subjects aged 4 to 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS micro-dystrophin expression levels (change from baseline) at Week 12 following ELEVIDYS infusion were 95.7% (N = 3, SD: 17.9%) in Study 102 Parts 1 and 2 (Process A product) and 51.7% (N = 11, SD: 41.0%) in Study 103 Cohort 1 (Process B product), respectively.

ELEVIDYS Micro-dystrophin Expression at Week 12 in Muscle Biopsy Tissue Samples (Immunofluorescence Staining Assay)

Localization of ELEVIDYS micro-dystrophin at sarcolemma membrane was evaluated by IF staining assay (IF fiber intensity and IF PMDPF [%]). High inter-subject variability was observed for the IF fiber intensity (percent of control) and PMDPF (%) results.

- In Study 102 Part 1, both IF fiber intensity (percent of control) and PMDPF (%) increased with increasing dose of ELEVIDYS. At Week 12, the mean changes from baseline of IF fiber intensity (percent of control) were 7.3 (SD: 7.0), 40.1 (SD: 73.3), and 36.2 (SD: 41.3) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. The mean (SD) increases of PMDPF (%) from baseline were 15.6 (14.8), 30.3 (32.9), and 26.7 (26.0) for SRP-9001-DL1, SRP-9001-DL2, and SRP-9001-DL3, respectively. Both IF fiber intensity (percent of control) and PMDPF (%) continued to increase for all dose levels except SRP-9001-DL2 (8.94×10^{13} vg/kg). Subjects in Study 102 Part 1 placebo group received ELEVIDYS (1.33×10^{14} vg/kg). At 12 weeks post-dosing (Study 102 Part 2, Week 12), the mean (SD) change of ELEVIDYS micro-dystrophin were 74.1 (47.7) and 77.6 (21.9) for IF fiber intensity (percent of control) and PMDPF (%), respectively.

- The mean (SD) changes of ELEVIDYS micro-dystrophin at Week 12 in Study 103 Cohort 1 were 66.5 (64.1) and 48.3 (25.4) for IF fiber intensity (percent of control) and PMDPF (%), respectively.

Correlation Analysis Between ELEVIDYS Micro-dystrophin at Week 12 and Change in NSAA Total Score at Year 1 (Clinical Efficacy Endpoint)

To support the application for Accelerated Approval of ELEVIDYS, the Applicant proposed to use as a surrogate endpoint expression of ELEVIDYS micro-dystrophin protein in muscle biopsy tissue samples at Week 12 following administration of ELEVIDYS. To assess whether the proposed surrogate endpoint is “reasonably likely to predict clinical benefit” to be used for Accelerated Approval, correlation analysis was conducted to evaluate the association between ELEVIDYS micro-dystrophin at Week 12 post-infusion and the clinical outcome, change in the North Star Ambulatory Assessment (NSAA) Total Score at Year 1.

Correlation Analysis Using Study 102 Part 1 Data Only

Based on the limited data available, results of partial Spearman analysis (adjusted for baseline age and NSAA Total Score) using Study 102 Part 1 data only showed no clear association between expression of ELEVIDYS micro-dystrophin and change in NSAA Total Score. Correlation analysis at the age group level also did not suggest clear association between ELEVIDYS micro-dystrophin expression and change in NSAA Total Score, based on limited data. However, improved NSAA Total Score with increased ELEVIDYS micro-dystrophin expression was observed in younger subjects (aged 4-5 years), but not in those aged 6 years and older. Because of the very limited data and exploratory nature of the NSAA assessment, these results in subjects aged 4 to 5 years must be interpreted with caution.

Correlation Analysis Using Pooled Data from Study 102 (Parts 1 & 2) and Study 103

There are concerns regarding correlation analysis using pooled data from Study 102 (Parts 1 and 2) and Study 103 Cohort 1:

- The open-label design may affect change in NSAA Total Score; and

- The open-label design without concurrent control may confound associations between ELEVIDYS micro-dystrophin and change in NSAA Total Score. Results of partial Spearman analysis (adjusted for baseline age and NSAA Total Score) using pooled data suggested ELEVIDYS micro-dystrophin accounts for 11% of the variation in NSAA Total Score change. This result is not sufficiently persuasive to consider expression of ELEVIDYS micro-dystrophin "reasonably likely to predict clinical benefit."

Immunogenicity

- ***Anti-AAVrh75 Antibodies:*** At baseline, all subjects in all three clinical studies had anti-AAV vector rhesus serotype 74 (AAVrh74) total binding antibody titers <1:400, based on an (b) (4) assay. Following administration of ELEVIDYS, elevated anti-AAVrh74 antibody titers were observed in all subjects. Anti-AAVrh74 antibody titers continued to increase over time, reaching peak levels during Week 8 to Week 24, and remained positive during the observation period in all three studies (up to Year 4, Year 2, Week 48, and Week 52 for Study 101, Study 102 Part 1, Study 102 Part 2, and Study 103, respectively). There is no dose-dependent relationship established between ELEVIDYS dose and anti-AAVrh74 antibody response. There is no evident impact observed of anti-AAVrh74 antibodies on muscle transduction or expression of ELEVIDYS micro-dystrophin protein (measured by western blot assay).

- ***Anti-ELEVIDYS Micro-dystrophin Antibodies:*** Anti-ELEVIDYS micro-dystrophin antibodies were assessed in Study 103. Prior to ELEVIDYS infusion, all enrolled subjects were below assay threshold for positivity (<10) for anti-ELEVIDYS micro-dystrophin antibodies. Twenty-one of the 39 subjects developed anti-ELEVIDYS micro-dystrophin antibodies throughout the 52 weeks post-dosing.

- ***Cellular Immune Responses Against AAVrh74 Capsids:*** Cellular immune responses against AAVrh74 were inconsistently observed across all subjects treated with ELEVIDYS. In Study 101, all 4 subjects displayed a positive interferon γ cytokine release after ELEVIDYS infusion. For Study 102 and 103 at Week 4 post-dosing with ELEVIDYS, 4 of 41 subjects (9.8%) and 23 of 39 (59.0%) subjects displayed a positive cellular immune response against AAVrh74, respectively. No evident impact was observed of T-cell mediated cellular response against AAVrh74 capsids on expression of ELEVIDYS micro-dystrophin protein in muscle biopsy samples (assessed at Week 12).

- ***Cellular Immune Responses Against Sarepta's Micro-dystrophin:*** A total of 8 subjects (1 subject in Study 102, and 7 subjects in Study 103) had an elevated cellular immune response greater than threshold at 4 weeks post ELEVIDYS infusion. No evident impact of T-cell mediated cellular response against ELEVIDYS micro-dystrophin was observed on expression of ELEVIDYS micro-dystrophin protein in muscle biopsy samples (assessed at Week 12).

Clinical Pharmacology Conclusion

Available data do not support use of 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 treatment of certain subpopulation(s) of ambulatory patients with DMD with a confirmed mutation in the *DMD* gene.

6. Clinical/Statistical

a) Clinical Program

Proposed Surrogate Endpoint and Clinical Trials

Treatment with SRP-9001 is intended to slow or stabilize progression of DMD, to alter the disease trajectory to a milder, BMD-like phenotype. To qualify for Accelerated Approval, the Applicant proposed 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 of ELEVIDYS.

ELEVIDYS micro-dystrophin is a novel, engineered protein that contains selected domains of the normal, wild-type dystrophin expressed in healthy muscle cells. Consequently, no epidemiologic or pathophysiologic evidence is available regarding the function of ELEVIDYS micro-dystrophin. The protein differs in important ways from both the endogenous shortened forms of dystrophin in patients with BMD, and the internally-truncated dystrophins expressed through exon-skipping drugs. Measurement of levels of ELEVIDYS micro-dystrophin in muscle tissue therefore only provides information 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 DMD.

The BLA submission includes data from three clinical studies: Study 101, Study 102 Part 1 and Part 2, and 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). 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 Part 2, by that point the subjects, caregivers, and evaluators were aware that all subjects had now received ELEVIDYS, 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. Those conditions, however, are not present here: 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; these results constitute the primary basis for the recommendation by the Clinical and Statistical review teams for Complete Response for BLA STN 125781.

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.

The primary efficacy endpoints of Study 102 included change in the quantity of ELEVIDYS micro-dystrophin protein from baseline to Week 12 (Part 1), as measured by western blot; and change in NSAA Total Score from baseline to Week 48 (Part 1).

Study 102 Part 1 enrolled 41 ambulatory male subjects with DMD, aged 4 to 7 years, who either have 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 either of ELEVIDYS (N = 20) or placebo (N = 21). However, the Applicant retrospectively determined that in the ELEVIDYS group, only 8 subjects 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 4 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 (b) (4) 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.

Table 4. Key Demographic Characteristics, Study SRP-9001 (Study 102 Part 1)

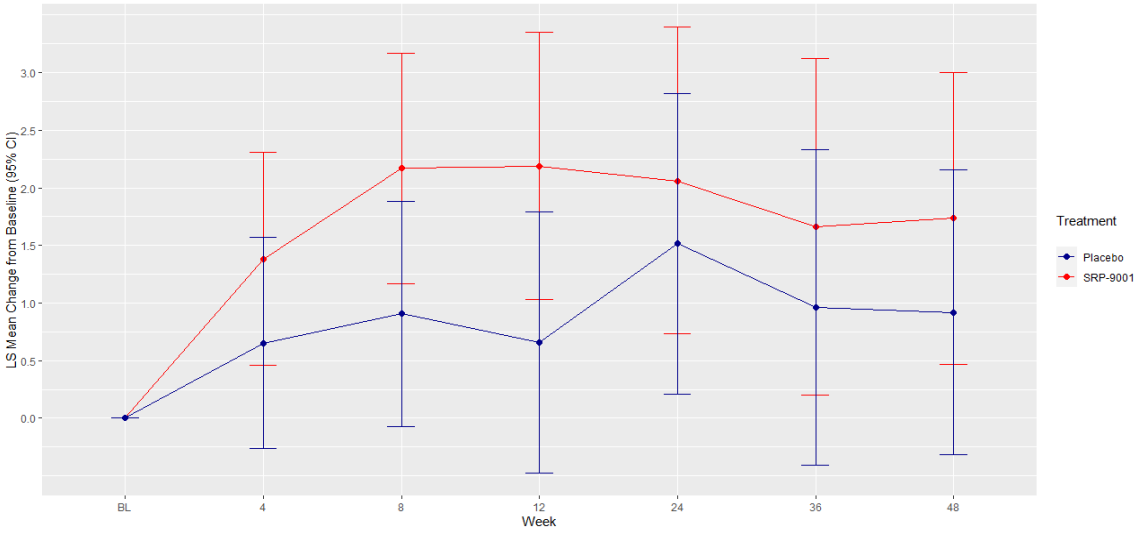
Characteristic	SRP-9001 (n=20)	Placebo (n=21)	Total (N=41)
Age, mean (SD), year	6.3 (1.2)	6.2 (1.1)	6.3 (1.1)
Age, median (min, max), year	6.5 (4.5, 7.9)	6.0 (4.3, 8.0)	6.1 (4.3, 8.0)
Age 4-5 years, n (%)	8 (40%)	8 (38%)	16 (39%)
Age 6-7 years, n (%)	12 (60%)	13 (62%)	25 (61%)
Race, n (%)			
White	13 (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: ELEVIDYS revised USPI.
Abbreviation: NSAA, North Star Ambulatory Assessment; SD, standard deviation; USPI, United States Prescribing Information.

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 ELEVIDYS 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 (Figure 1).

Figure 1. LS Mean Change in NSAA Total Score from Baseline Over Time

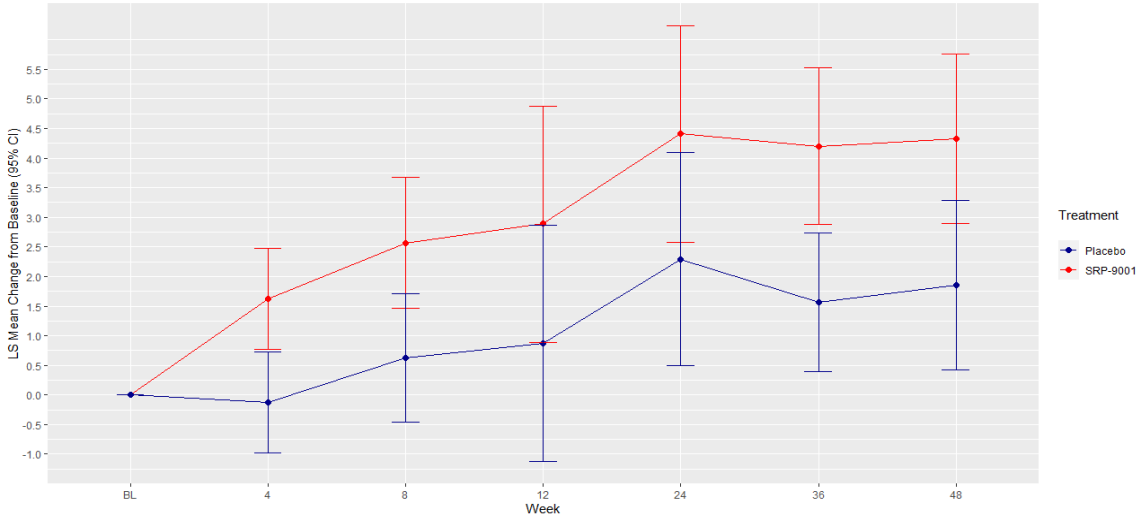


Source: FDA Statistical Reviewer's analysis
Abbreviation: LS, least squares; NSAA, North Star Ambulatory Assessment.

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 (Figure 2). Subjects aged 6 to 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 (Figure 3).

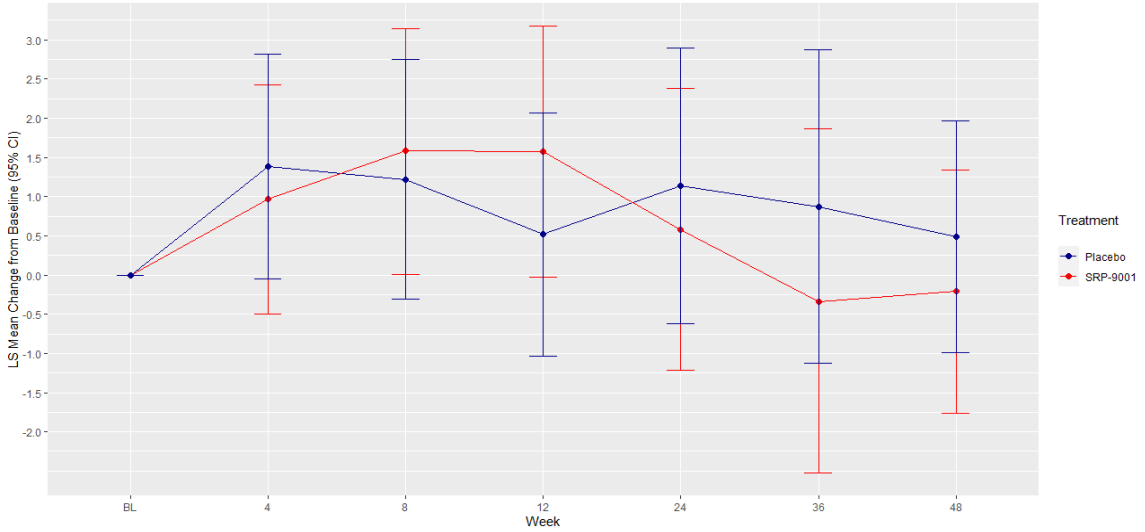
There are several important caveats associated with the exploratory subgroup analysis: it was based on limited sample size; it was not prespecified for hypothesis testing; and no prespecified multiplicity adjustment strategy was employed. Such post hoc subgroup analysis following an overall nonsignificant 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. Data from such exploratory subgroup analyses cannot be used as evidence of effectiveness.

Figure 2. LS Mean Change in NSAA 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.

Figure 3. LS Mean Change in NSAA 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.

As detailed in Section 5 Clinical Pharmacology, expression of ELEVIDYS micro-dystrophin was demonstrated, and increased with increasing dose of ELEVIDYS. However, no clear association was evident overall between expression of ELEVIDYS micro-dystrophin at Week 12 and change in NSAA Total Score at Week 48. Exploratory analysis of the limited data from subjects aged 4 to 5 years (n = 8) suggested improvement in the NSAA Total Score with increased expression of ELEVIDYS micro-dystrophin; no such association was observed in subjects aged 6 to 7 years (n = 11).

The Applicant also performed exploratory analyses comparing change in the NSAA Total Score for subjects treated with ELEVIDYS in the three studies, versus NSAA results for DMD patients from external data sources. The LS mean of the treatment difference in NSAA Total Score from baseline to 1 year was 2.5 points higher in the ELEVIDYS subjects compared to the external controls. However, the same considerations which limit interpretability of open-label studies in this situation also preclude use of external

controls. These results therefore also can only be considered exploratory, and cannot provide evidence of effectiveness to support potential clinical benefit of ELEVIDYS.

Conclusions

Available data do not support use of 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 certain subpopulation(s) of that group. Available data also do not provide clear evidence that ELEVIDYS is likely broadly beneficial for ambulatory patients with DMD. The exploratory nature of the subgroup analyses in the context of a failed well-controlled clinical study, and the limited sample size, also make it challenging to conclude with sufficient confidence 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.

b) Bioresearch Monitoring – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring inspections were conducted at two clinical investigator study sites. One site participated in the conduct of study protocols for Study 102 and Study 103, while the other site participated solely in the conduct of the protocol for Study 103. The inspections did not reveal any issues that impact the data submitted in this original BLA.

c) Pediatrics

The Pediatric Research Equity Act is not applicable to ELEVIDYS for the treatment of patients aged 4-5 years with DMD, because ELEVIDYS received Orphan Drug designation for the treatment of DMD.

The majority of the subjects enrolled in the three clinical studies which were submitted to the BLA were pediatric patients (aged >3 years).

d) Other Special Populations

None.

7. Safety and Pharmacovigilance

Safety

The safety database of ELEVIDYS 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. Prior to 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 total subjects, 45 subjects (Study 101 and Study 102) received ELEVIDYS manufactured by Process A, and 40 subjects received ELEVIDYS manufactured by Process B.

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 with life-threatening immune-mediated myositis has 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 has 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 specific region(s) encoded by the transgene. ELEVIDYS is thus contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.

The following were also observed following ELEVIDYS infusion: acute serious myocarditis; elevation of the cardiac injury marker-I; and acute liver injury (defined as gamma-glutamyl transferase >3 times the upper limit of normal [ULN]); glutamate dehydrogenase >2.5 times ULN; alkaline phosphatase >2 times ULN; or alanine aminotransferase (ALT) >3 times baseline, excluding ALT elevation from degenerating muscle).

The cases of myositis and myocarditis occurred in subjects receiving ELEVIDYS manufactured by Process B.

The safety of re-administration of ELEVIDYS has not been evaluated in humans.

Pharmacovigilance

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for the following:

- Follow-up of spontaneously reported cases with targeted questionnaires, and assessment (based on interval and cumulative data) in periodic safety reports for acute liver injury, immune-mediated myositis, myocarditis (including troponin increased), thrombocytopenia, thrombotic microangiopathy, and rhabdomyolysis.

- Expedited (15-day) reporting (regardless of seriousness or expectedness) to the FDA Adverse Event Reporting System for three years post-licensure for ALI, immune-mediated myositis, myocarditis, and thrombotic microangiopathy.

Completion of the ongoing clinical studies, an extension study for subjects who received ELEVIDYS in the ongoing clinical studies (Study SRP-9001-305), and a voluntary postmarketing sponsor study (Study SRP-9001-401) will provide additional safety and effectiveness follow-up for ELEVIDYS. Study SRP-9001-401 is a planned Phase 4 observational study of safety and efficacy of ELEVIDYS in the postmarketing setting.

For Study SRP-9001-401, 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 227 subjects into each cohort. Duration of follow-up will be a total of 10 years. Proposed milestones are as follows:

- Final protocol submission: July 31, 2023
- Study completion date: December 31, 2037
- Final Study Report completion: June 30, 2038

The proposed pharmacovigilance plan for ELEVIDYS is adequate for the labeled indication. The available data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS), or a postmarketing requirement (PMR) study that is specifically designed to evaluate a particular safety issue as a primary endpoint. There is no agreed-upon postmarketing commitment (PMC) for a safety study for this product.

8. Labeling

The proposed proprietary name, ELEVIDYS, was reviewed by the CBER Advertising and Promotional Labeling Branch (APLB) on December 30, 2022, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on January 12, 2023.

APLB reviewed the prescribing information, and samples of the proposed kit, package, and container labeling presentations on May 5, 2023, and found them acceptable from a promotional and comprehension perspective.

9. 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 ELEVIDYS, 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 ELEVIDYS manufactured by Process B. Members expressed the concern that, if ELEVIDYS 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 ELEVDIYS 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 ELEVDIYS 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 ELEVDIYS 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 ELEVDIYS 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 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 ELEVIDYS 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 from adequate and well-controlled studies, which is lacking in this BLA submission.

10. Other Relevant Regulatory Issues

The submission was granted Priority Review and was granted a Rare Pediatric Disease Priority Review voucher.

11. Recommendations and Benefit/Risk Assessment

a) Recommended Regulatory Action

The Review Committee recommends Complete Response for BLA 125781, because available data do not support use of 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 the treatment of subpopulation(s) 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.

The Review Committee proposes the following comments be conveyed 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 ELEVIDYS.*
>
> *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, based 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 ELEVIDYS.*
>
> *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 ELEVIDYS for the treatment of DMD, including readiness for submission of a BLA.*

b) Benefit/Risk Assessment

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 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 ELEVIDYS micro-dystrophin expression 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 with the placebo group among ambulatory subjects aged 4 to 5 years. But the same exploratory analysis also suggests, among ambulatory subjects aged 6 to 7 years, that there appeared to be no difference between the ELEVIDYS group and the placebo group; moreover, the ELEVIDYS 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. 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 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 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 patients with somewhat poorer functional status. Additionally, the clinical reviewer has safety concerns related to the implications of administering a possibly ineffective gene therapy.

Because ELEVIDYS micro-dystrophin expression is not a suitable surrogate endpoint that is "reasonably likely to predict clinical benefit," the overall potential benefit associated with the Accelerated Approval of ELEVIDYS does not outweigh the known and unknown risks of ELEVIDYS; those risks include serious adverse events observed in the ELEVIDYS clinical studies, and risks more generally present in AAV vector-based gene therapy products as a class.

Additionally, because of 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.

c) Recommendation for Postmarketing Activities

Routine and enhanced pharmacovigilance activities will be conducted for postmarketing safety monitoring of ELEVIDYS, with adverse event reporting as required under 21 CFR 600.80. Ongoing clinical studies, an extension study and a voluntary observational postmarketing sponsor study (Study SRP-9001-401) will provide additional follow-up data regarding safety and effectiveness.

The Review Committee has determined that ELEVIDYS does not require a Postmarketing Requirement safety study or a Risk Evaluation and Mitigation Strategy.

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

Accelerated Approval – Required Studies

1. Completion of 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 compares ELEVIDYS to placebo in 125 ambulatory patients with DMD with a confirmed mutation in the *DMD* gene. The primary endpoint is performance on the NSAA. The 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

2. Sarepta commits to conducting adequate analytical and clinical validation testing to establish an (b) (4) that can be used to identify patients with DMD who may benefit from delandistrogene moxeparvovec-rokl 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 (b) (4) and the clinical trial enrollment assays.

   (b) (4)

   The PMC will be considered fulfilled (b) (4)

The applicant agreed to the following CMC Postmarketing Commitments

3. The Applicant commits to performing (b) (4) "Postmarketing Commitment – Final Study Report" by July 31, 2024
4. The Applicant commits to submitting a final report for the supplemental (b) (4) manufacturing runs for (b) (4) at the Catalent BWI facility as a "Postmarketing Commitment – Final Study Report" by June 30, 2024.
5. The Applicant commits to submitting a final report of the (b) (4) as a "Postmarketing Commitment – Final Study Report" by March 31, 2024.
6. The Applicant commits to revising the system suitability criteria set in the standard operating procedure (SOP) for (b) (4) to reflect the assay variability (percent coefficient of variation; %CV) observed in intermediate precision during assay validation and to submitting the revised SOP. Final Study Report: December 31, 2023
7. The Applicant commits to revising the system suitability in the SOP for the in (b) (4) assay to include a parameter determining (b) (4) and to submitting the revised SOP as a "Postmarketing Study Commitment – Final Study Report" by June 30, 2024.
8. The Applicant commits to reassessing the commercial acceptance criterion for the release testing of potency of SRP-9001 DP after data have been collected on (b) (4) commercial lots and to submitting a "Postmarketing Study Commitment – Final Study Report" by June 30, 2024.
9. The Applicant commits to implement the following CMC change for the ELEVIDYS (b) (4) The CMC change will be submitted as a "Postmarketing Commitment – Final Study Report" by December 31, 2024
10. The Applicant commits to perform (b) (4) The final report will be submitted as a "Postmarketing Study Commitment – Final Study Report" by December 31, 2024