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# BLA Integrated Clinical and Clinical Pharmacology Review Memorandum

| | |
|---|---|
| Application Type | Efficacy Supplement |
| STN | 125781/34 |
| CBER Received Date | December 21, 2023 |
| PDUFA Goal Date | June 21, 2024 |
| Division / Office | DCEGM/OCE |
| Priority Review (Yes/No) | Yes |
| Reviewer Name(s) | Mike Singer, MD, PhD<br><br>Xiaofei Wang, PhD |
| Review Completion Date/Stamped Date | June 18, 2024 |
| Supervisory Concurrence<br>**Branch Chief**<br><br>**Division Director (acting) and Director, Office of Clinical Evaluation**<br><br>**Super Office of Therapeutic Products Director** | <br>Rosa Sherafat-Kazemzadeh, MD<br><br>Lola Fashoyin-Aje, MD, MPH<br><br>Nicole Verdun, MD |
| Applicant | Sarepta Therapeutics, Inc. |
| Established Name | delandistrogene moxeparvovec-rokl |
| Trade Name | ELEVIDYS |
| Pharmacologic Class | Adeno-associated virus (AAV) vector-based gene therapy |
| Formulation(s), including Adjuvants, etc. | Suspension with a nominal concentration of $1.33 \times 10^{13}$ vector genomes (vg) per mL and excipients 200mM sodium chloride, 13mM tromethamine HCl, 7mM tromethamine, 1mM magnesium chloride, 0.001% poloxamer 188 |
| Dosage Form(s) and Route(s) of Administration | Recommended weight-based dose, administered by intravenous infusion:<br>$1.33 \times 10^{14}$ vg per kg of body weight for patients weighing less than 70 kg,<br>$9.31 \times 10^{15}$ vg total fixed dose for patients weighing 70 kg or greater |
| Dosing Regimen | Single dose |
| Proposed Indication(s) and Intended Population(s) | For treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the *DMD* gene |
| Orphan Designated (Yes/No) | Yes |

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## GLOSSARY

| | |
|---|---|
| AAV | adeno-associated virus |
| AAVrh74 | adeno-associated virus serotype rhesus type 74 |
| AE | adverse event |
| BLA | Biologics License Application |
| BMD | Becker muscular dystrophy |
| DMD | Duchenne muscular dystrophy |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |
| LSM | least squares mean |
| MHCK7 | *alpha-myosin heavy chain/creatine kinase 7* promoter |
| mITT | modified intent to treat |
| MWR | Meter Walk/Run test |
| NSAA | North Star Ambulatory Assessment |
| PUL 2.0 | Performance of Upper Arm, version 2.0 |
| SAE | serious adverse event |
| TEAE | treatment-emergent adverse event |
| USPI | United States Prescribing Information |
| vg | vector genome |
| VGC | vector genome copy |

## 1. EXECUTIVE SUMMARY

On December 21, 2023, Sarepta Therapeutics, Inc. (the Applicant) submitted supplemental Biologics License Application (sBLA) 125781/34, seeking approval for ELEVIDYS (delandistrogene moxeparvovec-rokl; also known as SRP-9001) for the following indication and dosage:

**Table 1. ELEVIDYS Indication and Dosage**

| Characteristic | Description |
|---|---|
| Proposed indication: | For the treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the *DMD* gene |
| Proposed dosage: | • $1.33 \times 10^{14}$ vector genomes per kilogram (vg/kg) of body weight for patients weighing less than 70 kg<br>• $9.31 \times 10^{15}$ vg total fixed dose for patients weighing 70 kg or greater |

ELEVIDYS is a non-replicating, recombinant, adeno-associated virus serotype rh74 (AAVrh74)-based vector containing the ELEVIDYS micro-dystrophin (noted hereafter as "micro-dystrophin") transgene under the control of the *MHCK7* promoter. The micro-dystrophin protein expressed by ELEVIDYS is an engineered, shortened (138 kDa) protein containing select domains of the wild type dystrophin (427 kDa) protein produced by healthy muscle cells.

FDA granted accelerated approval to ELEVIDYS on June 22, 2023, 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. Accelerated approval was based on the surrogate endpoint of expression of micro-dystrophin at Week 12 after administration of ELEVIDYS. The recommended dosage, administered via intravenous infusion, is $1.33 \times 10^{14}$ vector genomes (vg) per kg of body weight. At the time of approval of the original BLA, FDA requested and the Applicant agreed to conduct a study to verify and describe the clinical benefit of ELEVIDYS as a postmarketing requirement. Therefore, the requirement for continued approval for this indication was verification and description of clinical benefit in the confirmatory Phase 3 trial, Study SRP-9001-301 Part 1 (Study 301 Part 1).

The supplemental BLA contains results of two studies: Study 301 Part 1 and Study SRP-9001-103 (Study 103). Both studies used ELEVIDYS product manufactured using the commercial process (Process B). In submitting these results, the Applicant intended to: (1) verify the benefit of ELEVIDYS for the approved indication (Study 301 Part 1), and (2) seek expansion of the indication to include (b) (4) patients with DMD.

Study 301 enrolled patients who are ≥4 to <8 years of age, have a confirmed mutation in the *DMD* gene, and are ambulatory. Study 301 enrolled a total of 124 male patients aged 4 to 7 years.

Study 301 Part 1 is randomized, double-blind, and placebo-controlled: 63 patients received ELEVIDYS and 61 received placebo. After completion of Part 1, patients enter Part 2: those who previously received placebo are now treated with ELEVIDYS and vice-versa, in a functionally open-label fashion.

The primary efficacy endpoint for Study 301 Part 1 was the change in the North Star Ambulatory Assessment (NSAA) total score from baseline to Week 52. The key secondary endpoints were: expression of micro-dystrophin at Week 12 after infusion; change in Time to Rise from the floor

from baseline to Week 52; and change in 10-Meter Walk/Run (MWR) time from baseline to Week 52. Other secondary endpoints included change in 100-MWR from baseline to Week 52; and change in Time to Ascend 4 Steps from baseline to Week 52.

Study 301 Part 1 did not meet its primary efficacy endpoint. The least squares mean (LSM) change in the NSAA total score was 2.57 points (95 percent CI: 1.80, 3.34) for the ELEVIDYS group, and 1.92 points (95 percent CI: 1.14, 2.70) for the placebo group. The LSM difference between ELEVIDYS and placebo was 0.65 points (95 percent CI: -0.45, 1.74), which was not statistically significant (p=0.2441).

Study 103 was initiated prior to Study 301, and is an open-label, single-arm study intended to bridge the two product versions, which are not analytically comparable, i.e., to obtain results with ELEVIDYS manufactured using the commercial process (Process B), for comparison to data from earlier studies which were conducted with product manufactured by the laboratory process (Process A). At the time of this review, data from Study 103 were available for 48 male patients with DMD, comprising five cohorts based on age group, ambulatory status, and *DMD* mutations, as shown below:

- Cohort 1: 4 to 7 years, ambulatory (n=20)
- Cohort 2: 8 to 17 years, ambulatory (n=7)
- Cohort 3: Nonambulatory for ≥9 months (n=6)
- Cohort 4: ≥3 to <4 years, ambulatory (n=7)
- Cohort 5a: 4 to <9 years, ambulatory; mutation in DMD exons 1 to 17 (n=6)
- Cohort 5b: Nonambulatory for ≥9 months; mutation in DMD exons 1 to 17 (n=2)

The primary efficacy endpoint for Study 103 evaluated expression of micro-dystrophin protein in muscle tissue at Week 12 after infusion. Exploratory endpoints included the following clinical assessments: NSAA Total Score; Performance of Upper Limb, version 2.0; 100-MWR; Time to Ascend 4 Steps; Time to Rise; and 10-MWR.

Study 103 was the only study submitted to this sBLA that contained data on nonambulatory patients with DMD. Study 103 was not designed to demonstrate clinical efficacy, and the BLA did not contain suitable data to support approval in this population based on a clinical outcome measure.

The safety database of ELEVIDYS consists of 156 male patients with a confirmed mutation in the *DMD* gene who received a single intravenous infusion of ELEVIDYS in four clinical studies of ELEVIDYS to date: two ongoing open-label studies (Study 101 and Study 103), and two studies that included a randomized, double-blind, placebo-controlled period (Study 102 and Study 301). Study 101 and Study 102 used the laboratory (Process A) version of the product; Study 103 and Study 301 used the commercial (Process B) version.

Of note, 144 patients received the recommended dose of $1.33 \times 10^{14}$ vg/kg, and 12 patients (all in Study 102) received lower doses.

To demonstrate the safety of ELEVIDYS for the requested indication, the Applicant provided from Study 103 and Study 301. Analysis of these data did not reveal new safety signals. There were no deaths in either study. No patients with adverse events (AEs) discontinued participation in either study.

No clear difference in occurrence of adverse events was noted for the nonambulatory patients, compared to the ambulatory patients. Data were available, however, for only 8 nonambulatory patients.

The postmarketing experience to date identified a risk of infusion-related reactions, including hypersensitivity reactions and anaphylaxis, which have occurred during ELEVIDYS administration or up to several hours afterwards.

Overall, the most common adverse reactions (incidence ≥5%) include vomiting (65%), nausea (44%), liver injury[1] (40%), pyrexia (29%), and thrombocytopenia (8%).

Several adverse events of special interest have been reported. Two cases of immune-mediated myositis, including one life-threatening case, were observed approximately 1 month after ELEVIDYS infusion. Both cases resolved with sequelae. The patient who experienced life-threatening immune-mediated myositis had a deletion mutation involving exons 3-43 in the *DMD* gene. The other patient 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.

Additionally, acute serious myocarditis and troponin-I elevations, and acute liver injury (ALI)—defined as gamma-glutamyl transferase (GGT) >3 × the upper limit of normal (ULN), glutamate dehydrogenase (GLDH) >2.5 × ULN, alkaline phosphatase >2 × ULN, or alanine aminotransferase (ALT) >3 × baseline excluding ALT elevation from degenerating muscle—have been observed following ELEVIDYS infusion. The myocarditis case resolved with sequelae.

In conclusion, the review team determined that the sBLA does not contain substantial evidence of effectiveness to support the Applicant's request to expand the ELEVIDYS indication. Specifically, the data submitted do not confirm the benefit of ELEVIDYS for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene, as required for continued approval. Moreover, the Applicant provided no satisfactory data to support effectiveness claims for all ages and for non-ambulatory patients.

Although Study 301 Part 1 did not meet its pre-specified primary endpoint, the Applicant conducted analyses of secondary endpoints to support effectiveness claims:

For the clinical key secondary endpoints, the difference in Time to Rise was -0.64 (-1.06, -0.23) seconds, and the difference in 10-MWR was -0.42 (-0.71, -0.13) seconds.

For additional clinical secondary endpoints, the difference in Time to Ascend 4 Steps was -0.36 (-0.71, -0.01) seconds, and the difference for 100-MWR, was -3.29 (-8.28, 1.70) seconds.

The Applicant noted that the point estimate of the difference in each case numerically favors the ELEVIDYS group, and the "nominal" p-values for three of these four endpoints (Time to Rise, 10-MWR, and Time to Ascend 4 Steps) suggest an apparent benefit. The Applicant therefore

1 Includes Aspartate transferase increased, Alanine transaminase increased, Gamma-glutamyl transferase increased, Glutamate dehydrogenase increased, Glutamate dehydrogenase level abnormal, Hepatotoxicity, Hepatic enzyme increased, Hypertransaminasemia, Liver function test increased, Liver injury, Transaminases increased, and Blood bilirubin increased.

made the claim that treatment with ELEVIDYS results in functional benefits that are clinically meaningful and change the trajectory of the disease.

FDA reviewed and confirmed the Applicant's results. However, there are important limitations to concluding from these analyses that ELEVDYS is effective:

In designing Study 301 Part 1, the Applicant did not prespecify further analyses for hypothesis testing, nor did the Applicant include a prespecified multiplicity adjustment strategy. Consequently, we cannot reliably distinguish if these results are due to actual effects of ELEVIDYS, or to chance alone. Although p-values still may be calculated mathematically for these results, such "nominal" (or "raw") p-values are not meaningful as an indication of statistical significance. 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. "Nominal" p-values therefore are not included in this review.

Following evaluation of the totality of the evidence submitted, the clinical reviewer recommends Complete Response for sBLA 125781.34. The basis for this recommendation is as follows:

- The confirmatory study, Study 301 Part 1, failed to demonstrate a statistically significant difference in outcome on the primary efficacy endpoint (change in NSAA Total Score from baseline to Week 52) for patients treated with ELEVIDYS, compared to patients who received placebo.
- Under the circumstances, results from the secondary endpoints cannot support effectiveness of ELEVIDYS. Moreover, the 95 percent CIs for Time to Rise, 10-MWR, and Time to Ascend 4 Steps all contain an upper bound near the zero point (no effect). This observation, while similarly limited in statistical meaning, nevertheless casts further doubt on the Applicant's interpretation. Finally, the small size of the point estimates, even if meaningful, would be of unclear clinical significance.

The videos and testimony provided to the Cellular, Tissue, and Gene Therapies Advisory Committee Meeting (May 12, 2023) attest to the benefit that some patients have obtained from ELEVIDYS. We agree that a sustained benefit is unlikely to result from a placebo effect. Importantly, however, the failure to observe a similar effect in two randomized, double-blind, placebo-controlled clinical trials suggests that any benefit may accrue only to a subset of the DMD population, whose characteristics at present remain unclear.

Micro-dystrophin does not contain all the domains present in the internally truncated dystrophin protein present in the BMD patient described by England, et al.[2] (The coding sequence for that protein exceeds the maximum possible for delivery via an AAV vector.) This difference may at least in part account for the results observed in the ELEVIDYS trials.

Taken together, the totality of the data does not provide substantial evidence of effectiveness of ELEVIDYS for treatment of ambulatory DMD patients of any age. The results argue against traditional approval for ELEVIDYS for ambulatory DMD patients aged 4- to 5-years old, or for broadening of the indication of ELEVIDYS to include (b) (4) DMD patients regardless of age or

2 England, SB, LV Nicholson, MA Johnson, SM Forrest, DR Love, EE Zubrzycka-Gaarn, DE Bulman, JB Harris, and KE Davies, 1990, Very mild muscular dystrophy associated with the deletion of 46% of dystrophin, Nature, 343(6254):180-182.

ambulatory status. As noted above, the clinical reviewer therefore recommends Complete Response for sBLA 125781.34.

### 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Key baseline demographic information is summarized below in Table 2.

**Table 2. Baseline Demographic Information, Study 301, mITT Population**

| Category | ELEVIDYS N=63 | Placebo N=62 | Total N=125 |
|---|---|---|---|
| Age (years) at randomization, n | 63 | 62 | 125 |
| Mean (SD) | 5.98 (1.06) | 6.08 (1.05) | 6.03 (1.05) |
| Median (min, max) | 6.20 (4.07, 7.87) | 6.06 (4.03, 7.99) | 6.10 (4.03, 7.99) |
| Age group at randomization, n (%) | - | - | - |
| 4-5 years old | 30 (47.6%) | 29 (46.8%) | 59 (47.2%) |
| 6-7 years old | 33 (52.4%) | 33 (53.2%) | 66 (52.8%) |
| Sex, n (%) | - | - | - |
| Male | 63 (100.0%) | 62 (100.0%) | 125 (100.0%) |
| Race, n (%) | - | - | - |
| American Indian or Alaska Native | 0 (0%) | 0 (0%) | 0 (0%) |
| Asian | 8 (12.7%) | 11 (17.7%) | 19 (15.2%) |
| Black or African American | 0 (0%) | 2 (3.2%) | 2 (1.6%) |
| Native Hawaiian or other Pacific Islanders | 0 (0%) | 0 (0%) | 0 (0%) |
| White | 49 (77.8%) | 46 (74.2%) | 95 (76.0%) |
| Multiple | 1 (1.6%) | 0 (0%) | 1 (0.8%) |
| Other | 2 (3.2%) | 1 (1.6%) | 3 (2.4%) |
| Not reported | 3 (4.8%) | 2 (3.2%) | 5 (4.0%) |
| Race group, n (%) | - | - | - |
| White | 49 (77.8%) | 46 (74.2%) | 95 (76.0%) |
| Nonwhite | 11 (17.5%) | 14 (22.6%) | 25 (20.0%) |
| Missing | 3 (4.8%) | 2 (3.2%) | 5 (4.0%) |
| Ethnicity, n (%) | - | - | - |
| Hispanic or Latino | 15 (23.8%) | 8 (12.9%) | 23 (18.4%) |
| Not Hispanic or Latino | 47 (74.6%) | 53 (85.5%) | 100 (80.0%) |
| Not reported | 0 (0%) | 1 (1.6%) | 1 (0.8%) |
| Unknown | 1 (1.6%) | 0 (0%) | 1 (0.8%) |

Source: FDA Statistics reviewer
Abbreviations: max = maximum, min = minimum, mITT = modified Intention-to-Treat, N = number of patients in population, n = number of patients in subpopulation, SD = standard deviation

**Table 3. Baseline Demographic Information, Study 103**

| Category | Cohort 1 (N=20) | Cohort 2 (N=7) | Cohort 3 (N=6) | Cohort 4 (N=7) | Cohort 5a (N=6) | Cohort 5b (N=2) | Total (N=48) |
|---|---|---|---|---|---|---|---|
| Age (years) | - | - | - | - | - | - | - |
| Mean (SD) | 5.81 (1.14) | 10.11 (1.51) | 15.26 (4.22) | 3.48 (0.24) | 6.70 (1.43) | 13.43 (1.58) | 7.71 (4.11) |
| Min, max | 4.38, 7.94 | 8.00, 12.05 | 9.86, 20.23 | 3.24, 3.95 | 4.65, 8.61 | 12.31, 14.55 | 3.24, 20.23 |

| Category | Cohort 1 (N=20) | Cohort 2 (N=7) | Cohort 3 (N=6) | Cohort 4 (N=7) | Cohort 5a (N=6) | Cohort 5b (N=2) | Total (N=48) |
|---|---|---|---|---|---|---|---|
| Age category, n (%) | - | - | - | - | - | - | - |
| <4 years | 0 | 0 | 0 | 7 (100.0) | 0 | 0 | 7 (14.6) |
| 4-5 years | 11 (55.0) | 0 | 0 | 0 | 2 (33.3) | 0 | 13 (27.1) |
| 6-7 years | 9 (45.0) | 0 | 0 | 0 | 3 (50.0) | 0 | 12 (25.0) |
| ≥8 years | 0 | 7 (100.0) | 6 (100.0) | 0 | 1 (16.7) | 2 (100.0) | 16 (33.3) |
| Sex, n (%) | - | - | - | - | - | - | - |
| Male | 20 (100.0) | 7 (100.0) | 6 (100.0) | 7 (100.0) | 6 (100.0) | 2 (100.0) | 48 (100.0) |
| Race, n (%) | - | - | - | - | - | - | - |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 1 (5.0) | 1 (14.3) | 0 | 1 (14.3) | 0 | 1 (50.0) | 4 (8.3) |
| Black or African American | 1 (5.0) | 0 | 0 | 0 | 2 (33.3) | 0 | 3 (6.3) |
| Native Hawaiian or Other Pacific Islanders | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White | 15 (75.0) | 5 (71.4) | 6 (100.0) | 6 (85.7) | 4 (66.7) | 1 (50.0) | 37 (77.1) |
| Other | 3 (15.0) | 1 (14.3) | 0 | 0 | 0 | 0 | 4 (8.3) |
| Ethnicity, n (%) | - | - | - | - | - | - | - |
| Hispanic or Latino | 5 (25.0) | 1 (14.3) | 0 | 1 (14.3) | 0 | 0 | 7 (14.6) |
| Not Hispanic or Latino | 15 (75.0) | 6 (85.7) | 6 (100.0) | 6 (85.7) | 6 (100.0) | 2 (100.0) | 41 (85.4) |

Source: Applicant Interim 2 Clinical Study Report SRP-9001-103, pp. 34-35
Abbreviations: max = maximum, min = minimum, N = number of patients in population, n = number of patients in subpopulation, SD = standard deviation

### 1.2 Patient Experience Data

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

**Data Submitted in the Application**

| Check if Submitted | Type of Data | Section Where Discussed, if Applicable |
|---|---|---|
| ☐ | Patient-reported outcome | |
| ☐ | Observer-reported outcome | |
| ☒ | Clinician-reported outcome | 6.1.1, 6.2.1 |
| ☐ | Performance outcome | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |

| Check if Submitted | Type of Data | Section Where Discussed, if Applicable |
|---|---|---|
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| ☐ | **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 | |
| ☐ | Patient-focused drug development meeting | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

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.[3]

3. Wahlgren, L, AK Kroksmark, 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.

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

There is no cure for DMD. The main pharmacologic treatment has been corticosteroids. 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]

Deflazacort is a corticosteroid which received FDA approval in 2017 for the treatment of patients with DMD.[5] Deflazacort is indicated for patients age 2 years and older. 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. Patients 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 percent of patients), golodirsen (Vyondys 53, approved December 12, 2019; ~8 percent of patients), viltolarsen (Viltepso, approved August 12, 2020; ~8 percent of patients), and casimersen (Amondys 45, approved February 25, 2021; ~8 percent of patients).[7,8,9,10] All are antisense oligonucleotides which modify splicing of DMD mRNA to promote translation of shortened forms of the dystrophin protein retaining some function. All four require periodic intravenous administration. Importantly, the clinical benefit of these products has not been confirmed.

ELEVIDYS was granted Accelerated Approval on June 22, 2023. Since then, FDA has granted traditional approval to two additional drugs for treatment of DMD, vamorolone (October 26, 2023) and givinostat (March 21, 2024).

Vamorolone (Agamree) is a novel steroid indicated for treatment of DMD in patients aged 2 years and older.[11] Effectiveness of vamorolone was demonstrated in a multicenter, randomized, double-blind, parallel-group, placebo- and active- controlled 24-week study

4. MedLine Plus, 2021, Duchenne muscular dystrophy, accessed April 4, 2023, https://medlineplus.gov/ency/article/000705.htm.
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, 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, 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, https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0.
11 Santhera Pharmaceuticals, 2023, Prescribing Information: AGAMREE (vamorolone) oral suspension, accessed June 5, 2024, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215239s000lbl.pdf.

involving 121 ambulatory boys aged 4 to less than 7 years old. Two doses of vamorolone were tested: 6 mg/kg/day and 2 mg/kg/day.

The primary endpoint was the change from baseline to Week 24 in Time to Stand velocity for vamorolone 6 mg/kg/day compared to placebo. The key secondary endpoints were change from baseline to Week 24 in Time to Rise velocity for vamorolone 2 mg/kg/day vs. placebo; 6-Minute Walk Test distance for vamorolone 6 mg/kg/day vs. placebo and 2 mg/kg/day vs. placebo) and 10-MWR velocity for vamorolone 6 mg/kg/day vs. placebo and 2 mg/kg/day vs. placebo)

The primary endpoint and key secondary endpoints were met for the vamorolone 6 mg/kg/day treatment group. Results for the vamorolone 2 mg/kg/day group were statistically significant compared to placebo for Time to Rise velocity and 6-Minute Walk Test distance but did not reach statistical significance compared to placebo for 10-MRW velocity.

Givinostat (Duvyzat) is a histone deacetylase inhibitor indicated for treatment of DMD in patients 6 years of age and older. Efficacy was evaluated in a randomized, double-blind, placebo-controlled 18-month Phase 3 study. The primary endpoint was the change from baseline to Month 18 in the Time to Ascend 4 Steps assessment. Patients treated with givinostat demonstrated statistically significant less decline in Time to Ascend 4 Steps compared to patients who received placebo: the mean change from baseline to Month 18 was 1.25 seconds for patients receiving givinostat, compared to 3.03 seconds for patients receiving placebo.

### 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)

On January 11, 2024, the Applicant submitted PBRER #1 covering reporting period September 22, 2023 to November 2, 2023. As of the data lock point for this report, ELEVIDYS had been approved for marketing in the United States, United Arab Emirates, and Qatar, but it had not yet been marketed in the United Arab Emirates or Qatar. Patient exposure was reported as 239 patients treated with ELEVIDYS or placebo in clinical trials and 42 patients treated with ELEVIDYS in the postmarketing setting (all in the United States). The Applicant's Global Safety Database identified five cases of off-label use of ELEVIDYS (all in patients aged 6 years old). No safety-related actions (e.g., labeling changes) had been taken by the manufacturer in the postmarketing setting and no new safety issues were identified in periodic safety reports to date.

On February 14, 2024, an FDA query of the FDA Adverse Event Reporting System (FAERS) database for postmarketing reports for ELEVIDYS returned 31 FAERS reports, including 26 U.S. reports and 5 foreign reports. The majority of reports (n=24; 77.4 percent) were AE reports from a clinical study, whereas only 7 (22.6 percent) reports were spontaneous AE reports. Less than half of the reports (n=14; 45.2 percent) were serious including 13 reports of hospitalization, and 1 classified as “other” serious. There were no reports of death or life-threatening events. The sex for all reports was male and the median age was 7 years old (range 4 to 24 years). The age of patients for spontaneous reports only (excluding AEs from a clinical study) was either 5 or 6 years old.

Review of serious reports (n=14) showed that half of the cases were resolved/recovered at the time of reporting and half were not recovered (or unknown) at time of reporting. The most

notable case among the not recovered cases included a 7-year-old male with exon 8-9 deletion who was enrolled in Study 103 received ELEVIDYS and 29 days later experienced immune-mediated myositis with lasting sequelae (weakness). This case occurred in the clinical trial setting (Patient (b) (6) in Study 103) and ELEVIDYS is now approved with a contraindication for patients with any deletion in exon 8 and/or exon 9 in the DMD gene. Review of the most common Preferred Terms in all reports and serious reports only showed that most reported Preferred Terms are either labeled AEs, closely related to labeled AEs, or nonspecific signs/symptoms with relatively few reports. Review of FAERS reports for ELEVIDYS demonstrates a very limited postmarketing experience, with most reports originating from an interventional study. Review of available FAERS data did not demonstrate a pattern or cluster of reports concerning for a new safety signal. (Note: Spontaneous surveillance systems such as FAERS are patient to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the product.)

After the aforementioned FAERS query, on March 4, 2024, FDA received a serious direct FAERS report regarding a 5-year-old male patient who experienced a life-threatening anaphylactic reaction during ELEVIDYS infusion. Because anaphylactic reaction is a serious, unlabeled AE, this prompted further investigation and action, including sending the Applicant a Newly Identified Safety Issue Notification Letter (BLA 125781/53). In addition, the Applicant submitted an amendment to this efficacy supplement (BLA 125781/34.12), to amend the pharmacovigilance plan and proposed United States Prescribing Information to account for infusion-related reactions, including hypersensitivity and anaphylaxis.

In addition, on May 8, 2024, FDA received four spontaneous FAERS reports of “Device occlusion” submitted by Sarepta Therapeutics. The reports were all nonserious and originated from three unique reporters. Each report described device occlusion during infusion, typically involving the (b) (4) . On May 16, 2024, FDA sent the Applicant an information request inquiring about these cases. On May 24, 2024, the Applicant responded (BLA 125781/65.0) and attributed these occlusion events to use of (b) (4) . The Applicant stated (b) (4) to minimize future occlusion issues.

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

**Table 4. Key Regulatory History of ELEVIDYS**

| 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 patients 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 patients of the proposed studies. |

| Date | Milestone | Background Information |
|---|---|---|
| | | 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) | | - |
| December 20, 2018 | Type B multidisciplinary meeting | FDA stated that expression of micro-dystrophin protein is not currently accepted as a surrogate endpoint considered "reasonably likely to predict clinical benefit" to support Accelerated Approval.<br><br>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) | | - |
| 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 micro-dystrophin at Week 12 after SRP-9001 administration.<br><br>FDA recommended that the Applicant revise the design of Study 103 (the first study to utilize ELEVIDYS 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 101 and Study 102, the Agency is not convinced that a clear correlation exists between expression of micro-dystrophin and clinical benefit. |
| August 6, 2021 | IND placed on Clinical Hold due to SAE – letter issued September 1, 2021 | An SAE was reported of asthenia in a 9-year-old patient in Study 103. He required hospitalization and respiratory support after receiving ELEVIDYS.<br><br>IND placed on Clinical Hold as it did not contain sufficient information required under 21 CFR 312.23 to assess the risks to patients of the proposed studies. |
| October 1, 2021 | Clinical Hold removed – study may proceed | - |

| Date | Milestone | Background Information |
|---|---|---|
| April 29, 2022 | Type C Meeting to discuss possible Accelerated Approval | FDA expressed concerns regarding the ability of expression of micro-dystrophin to predict clinical benefit.<br><br>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 submitted | - |
| May 12, 2023 | Advisory Committee meeting | Eight committee members voted "Yes" and six voted "No" on the voting question: "Do the overall considerations of benefit and risk, taking into account the current uncertainties, support Accelerated Approval of SRP-9001?" |
| June 22, 2023 | Accelerated Approval granted | Postmarketing Requirement of completion of Study 301 Part 1, to "describe and verify clinical benefit of SRP-9001 in ambulatory patients with DMD." The approval letter states that "clinical benefit is evidenced by effects such as improved North Star Ambulatory Assessment (NSAA) Total Score from baseline to Week 52…If this required postmarketing trial fails to verify that clinical benefit is conferred by [ELEVIDYS]…we may withdraw this approval." |
| December 21, 2023 | Supplemental BLA submitted | On February 14, 2024, FDA filed the submission and granted Priority Review |
| January 11, 2024 | 180-Day Accelerated Approval Postmarketing Requirement Progress Report submitted | Applicant reported that Study 301 Part 1 has been completed, and that the final study report for Study 301 Part 1 has been submitted. |
| March 27, 2024 | Infusion-related reactions | In response to a postmarketing case of anaphylaxis associated with administration of ELEVIDYS, FDA sent the Applicant a Newly Identified Safety Issue Notification Letter. The Applicant subsequently submitted an updated Pharmacovigilance Plan and U.S. Prescribing Information to include information on transfusion-related reactions, including hypersensitivity and anaphylaxis. |

Source: FDA
Abbreviations: BLA = Biologics License Application, CFR = Code of Federal Regulations, CMC = chemistry, manufacturing, and controls, DMD = Duchenne muscular dystrophy, FDA = Food and Drug Administration, IND = Investigational New Drug submission, PMR = postmarketing requirement, RMAT = Regenerative Medicine Advanced Therapy, SAE = serious adverse event, sBLA = supplemental Biologics License Application, SRP-9001 = delandistrogene moxeparvovec-rokl, U.S. = United States

## 2.6 Other Relevant Background Information

2.6.1 Special Risks of AAV Vector-Based Gene Therapy Product

Patients receiving a systemically administered 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 gene therapy product. Moreover, the immune response has been found to cross-react 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, potentially beneficial AAV vector-based gene therapy product in the future.

# 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

## 3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate conduct of a complete clinical review.

## 3.2 Compliance With Good Clinical Practices and Submission Integrity

The Applicant stated that the studies were conducted in accordance with the regulations specified in 21 CFR 312 and were compliant with Good Clinical Practice, the International Council for Harmonization E6 Guideline for Good Clinical Practice, Declaration of Helsinki, and applicable local, state, and federal laws to comply with the international ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human patients.

The clinical trials included provisions for informed consent by parents or guardians of all study patients, and for ethical treatment of study patients. Each study was reviewed and approved by the appropriate institutional review boards, as required.

### Bioresearch Monitoring Inspection

Bioresearch Monitoring inspection assignment was issued for one domestic clinical investigator site, which participated in the conduct of Study 301. This site was selected based upon Applicant-reported AEs, protocol deviations, total number of enrolled patients, and previous Bioresearch Monitoring inspection histories. The inspections did not reveal significant problems impacting the data submitted in support of this sBLA (Table 5).

**Table 5. Bioresearch Monitoring Inspections at One Clinical Investigator Site**

| Site ID | Number of Patients Enrolled | Location | Inspection Status |
|---|---|---|---|
| 208 | 9 | Emma Ciafaloni, MD<br>University of Rochester Medical Center<br>601 Elmwood Ave, Room 5-5210, Box 673, Rochester, New York 14642 | No Action Indicated (NAI) |

Source: BLA 125781, FDA Bioresearch Monitoring 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: FDA = Food and Drug Administration, 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 studies**<br>SRP-9001-301<br>SRP-9001-103 |
|---|
| Was a list of clinical investigators provided? X Yes ☐ No |
| Total number of investigators identified: 6 |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 1 |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: X<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in sponsor of covered study: _____<br>Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No<br>Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0<br>Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) |

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

### 4.1 Chemistry, Manufacturing, and Controls

ELEVIDYS is an AAV-based gene therapy designed to deliver the gene encoding micro-dystrophin protein. ELEVIDYS is a nonreplicating rAAVrh74-based vector containing the micro-dystrophin transgene under the control of the chimeric MHCK7 (alpha-myosin heavy chain/creatine kinase 7) promoter. The genome within the ELEVIDYS vector includes no viral genes; consequently, ELEVIDYS is unable to replicate or to revert to a replicating form. micro-dystrophin is an engineered protein composed of selected domains of the normal human

dystrophin protein 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 $1.33 \times 10^{13}$ 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: 200mM sodium chloride, 13mM tromethamine HCl, 7mM tromethamine, 1mM magnesium chloride, and 0.001% poloxamer 188.

No new CMC data was submitted under this sBLA. Please refer to CMC review memo for more information regarding the lot release data and proposed in-use hold time.

### 4.2 Assay Validation

This supplement does not include any new data for assay validation.

### 4.3 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology testing was performed in connection with this sBLA submission.

### 4.4 Clinical Pharmacology

The sBLA contained data and analyses of ELEVIDYS vector biodistribution and transgene expression in muscle biopsies in Study 103 and Study 301 Part 1, and ELEVIDYS vector shedding in Study 103.

#### 4.4.1 Mechanism of Action

ELEVIDYS is a recombinant gene therapy product comprised of a nonreplicating, recombinant, AAVrh74 capsid and a single-strand DNA expression cassette flanked by inverted terminal repeats derived from AAV2. The cassette contains 1) an MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α-myosin heavy chain enhancer; and 2) the DNA transgene encoding the engineered micro-dystrophin protein.

Vector/Capsid: Clinical and nonclinical studies have demonstrated AAVrh74 serotype transduction in skeletal muscle cells. Additionally, in nonclinical studies, AAVrh74 serotype transduction has been demonstrated in cardiac and diaphragm muscle cells.

Promoter: The MHCK7 promoter/enhancer drives transgene expression and has been shown in animal models to drive expression of transgenic micro-dystrophin protein predominantly in skeletal muscle (including diaphragm) and cardiac muscle. In clinical studies, muscle biopsy analyses have confirmed micro-dystrophin expression in skeletal muscle.

Transgene: DMD is caused by mutation of the *DMD* gene resulting in lack of functional dystrophin protein. ELEVIDYS carries a transgene encoding micro-dystrophin protein, which consists of selected domains of the normal dystrophin protein expressed in healthy muscle cells.

Micro-dystrophin has been demonstrated to localize to the sarcolemma.

4.4.2 Human Pharmacodynamics

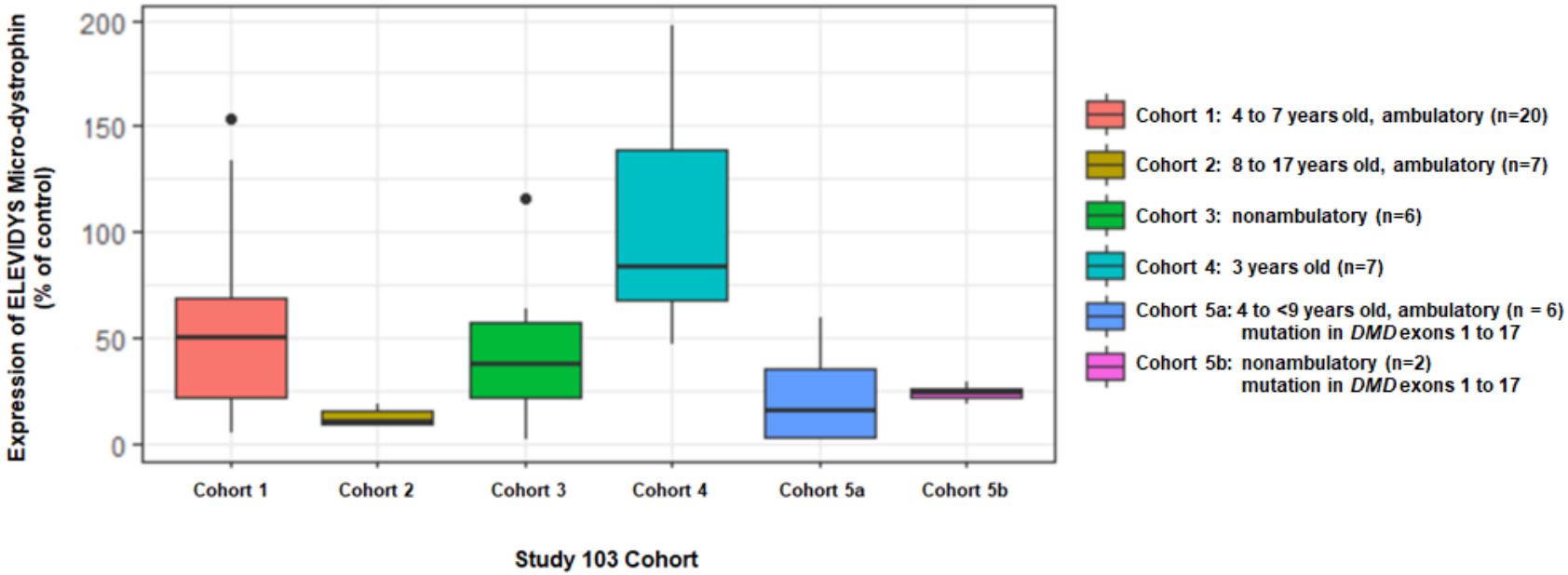
After a one-time intravenous administration ELEVIDYS is expected to be transduced to the target cells and lead to expression of the transgenic protein, micro-dystrophin. Muscle biopsy samples were collected at baseline and Week 12 postinfusion. The quantity of expression of micro-dystrophin (assessed by western blot), correct localization of the protein at the sarcolemma membrane (immunofluorescence fiber intensity, and percent micro-dystrophin positive fibers were evaluated. The results of ELEVIDYS transgene expression in muscle tissue biopsy samples at Week 12 postinfusion are summarized in Table 6, Table 7, and Figure 1.

**Table 6. Expression of Micro-Dystrophin (Change From Baseline, Measured by Western Blot Assay) in Muscle Tissue Biopsy at Week 12 Postinfusion**

| Micro-Dystrophin Change From Baseline[a] | Study 301 Placebo (n=14) | Study 301 ELEVIDYS (n=17) | Study 103 Cohort 1 (n=20) | Study 103 Cohort 2 (n=7) | Study 103 Cohort 3 (n=6) | Study 103 Cohort 4 (n=7) | Study 103 Cohort 5a (n=6) | Study 103 Cohort 5b (n=2) |
|---|---|---|---|---|---|---|---|---|
| Mean (SD) | 0.00 (0.00) | 34.29 (41.04) | 54.21 (42.57) | 11.92 (4.21) | 45.53 (40.59) | 99.64 (51.97) | 22.82 (21.63) | 23.64 (6.93) |
| Median (Q1, Q3) | 0.0 (0.00, 0.00) | 19.11 (7.58, 45.49) | 50.61 (21.53, 68.72) | 10.30 (8.64, 15.54) | 37.27 (17.12, 63.86) | 83.02 (67.16, 138.97) | 18.75 (3.17, 35.43) | 23.64 (18.74, 28.55) |
| Min, Max | 0.00, 0.00 | 0.00, 161.88 | 4.79, 153.92 | 8.13, 18.63 | 1.36, 116.28 | 46.87, 197.25 | 1.93, 58.88 | 18.74, 28.55 |

Source: Reviewer compiled from Applicant's submission
[a] Measured by western blot assay as % of expression of normal dystrophin in control patients.
Abbreviations: Max = maximum, Min = minimum, n = number of patients in the specified group, or the total sample, Q1 = Quartile 1, Q3 = Quartile 3, SD = standard deviation

**Figure 1. Expression of Micro-Dystrophin (Change From Baseline, Measured by Western Blot Assay) in Muscle Biopsy Tissue at Week 12 After Infusion, Study 103**




Source: Clinical Pharmacology reviewer

**Table 7. Micro-Dystrophin Expression in Muscle Biopsy Tissue at Week 12 After Infusion (Change From Baseline, Measured by Immunohistochemistry Assay)**

| Micro-Dystrophin Change From Baseline[a] | Study 301 Placebo (n=14) | Study 301 ELEVIDYS (n=17) | Study 103 Cohort 1 (n=20) | Study 103 Cohort 2 (n=7) | Study 103 Cohort 3 (n=6) | Study 103 Cohort 4 (n=7) | Study 103 Cohort 5a (n=6) | Study 103 Cohort 5b (n=2) |
|---|---|---|---|---|---|---|---|---|
| IF Fiber Intensity (%) | - | - | - | - | - | - | - | - |
| n | 14 | 17 | 20 | 6 | 6 | 7 | 6 | 2 |
| Mean (SD) | 0.26 (0.36) | 20.69 (25.53) | 66.52 (64.06) | 13.23 (8.74) | 34.86 (18.21) | 59.07 (26.91) | 25.00 (38.90) | 25.56 (30.32) |
| Median (Q1, Q3) | 0.14 (0.03, 0.35) | 4.20 (2.84, 35.44) | 54.07 (29.67, 85.13) | 13.73 (6.15, 14.52) | 26.68 (23.20, 40.80) | 54.41 (33.19, 84.12) | 4.98 (1.92, 39.02) | 25.56 (4.12, 47.00) |
| Min, max | 0.00, 1.38 | 0.61, 76.03 | -9.58, 263.55 | 3.03, 28.23 | 22.42, 69.41 | 31.19, 94.58 | 0.46, 98.63 | 4.12, 47.00 |
| IF PDPF | - | - | - | - | - | - | - | - |
| N | 14 | 17 | 20 | 7 | 6 | 7 | 6 | 2 |
| Mean (SD) | 0.74 (0.78) | 32.71 (29.64) | 48.27 (25.37) | 15.85 (8.95) | 28.29 (15.17) | 70.76 (14.95) | 27.52 (28.17) | 34.82 (35.57) |
| Median (Q1, Q3) | 0.44 (0.29, 0.69) | 22.42 (8.53, 65.66) | 53.24 (37.53, 65.85) | 15.91 (12.36, 17.13) | 25.40 (18.80, 44.21) | 68.72 (56.73, 89.36) | 17.08 (12.62, 32.57) | 34.82 (9.67, 59.97) |
| Min, Max | 0.06, 2.63 | 3.86, 86.66 | 1.13, 84.37 | 3.07, 30.75 | 8.76, 47.18 | 53.67, 91.50 | 4.06, 81.68 | 9.67, 59.97 |

Source: Reviewer compiled from Applicant's submission
[a] Measured by western blot assay as % of expression of normal dystrophin in healthy control patients.
Abbreviations: IF = immunofluorescence, Max = maximum, Min = minimum, n = number of patients in the specified group, or the total sample, PDPF = percentage of micro-dystrophin-positive fibers, Q1 = Quartile 1, Q3 = Quartile 3, SD = standard deviation, WB = western blot

4.4.3 Human Pharmacokinetics

**Biodistribution and Vector Shedding of ELEVIDYS**

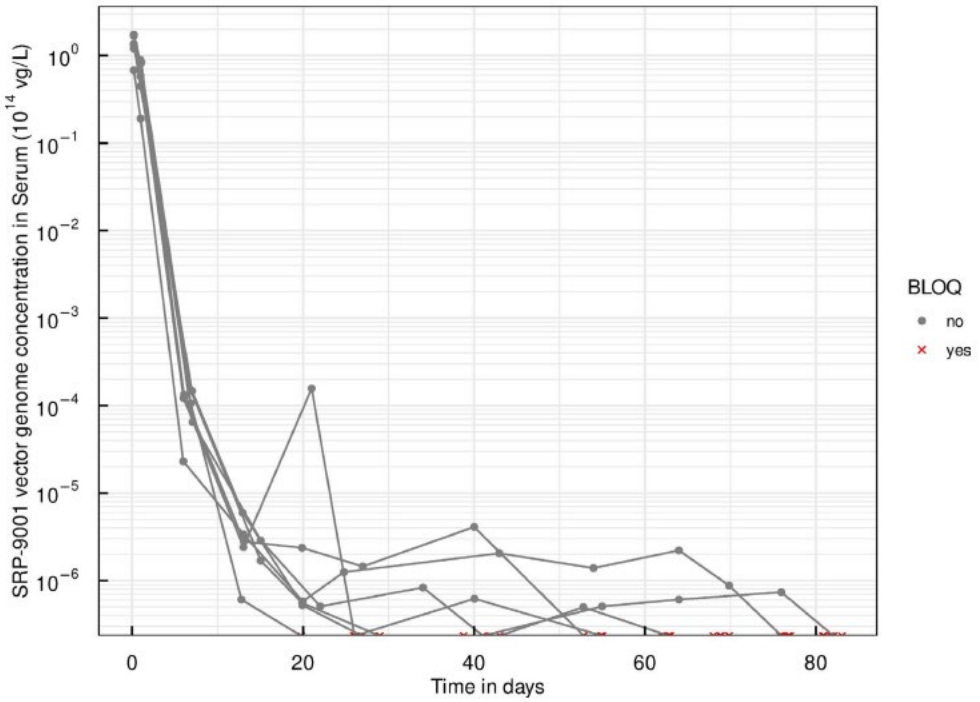
ELEVIDYS Vector Genome in Muscle Tissues

To assess biodistribution (tissue vg exposure) and success of transduction, muscle tissue biopsy samples were collected at baseline and at Week 12 postinfusion, and the levels of ELEVIDYS vector genome copy (VGC) were measured using digital droplet polymerase chain reaction assay and expressed as genome copies per nucleus in Study 103 and Study 301. The results are summarized in Table 8. ELEVIDYS VGC was detected in muscle tissue of all ELEVIDYS-treated patients. High inter-patient variability was observed for VGC levels.

ELEVIDYS Vector Genome in Serum

In the current submission, the Applicant provided ELEVIDYS vg levels in serum for Study 103 Cohort 4 (Figure 2). In Cohort 4, the serum pharmacokinetics profile of ELEVIDYS was similar to that observed in Study 103 Cohort 1, Cohort 2, and Cohort 3 (provided in original BLA submission). After intravenous administration, the ELEVIDYS vector genome concentration-time profiles in serum showed a biphasic disposition characterized by a rapid distribution phase up to 10 days postdose, followed by a slow and nearly flat terminal elimination phase. High inter-patient variability was observed in the terminal elimination phase.

**Figure 2. Individual ELEVIDYS Vector Genome Concentration-Time Profiles in Serum, Study 103 Cohort 4 (N=7)**




Source: Applicant response to FDA information request submitted on 02/02/2024
Abbreviations: BLOQ = below limit of quantification, N = number of subjects in the specified group, or the total sample, SRP-9001 = ELEVIDYS, vg = vector genome

**Table 8. Vector Genome Copies per Nucleus as Measured by ddPCR in Muscle Biopsy Tissue at Week 12 After Infusion**

| Vector Genome Copies per Nucleus | Study 301 Placebo (n=14) | Study 301 ELEVIDYS (n=17) | Study 103 Cohort 1 (n=20) | Study 103 Cohort 2 (n=7) | Study 103 Cohort 3 (n=6) | Study 103 Cohort 4 (n=7) | Study 103 Cohort 5a (n=6) | Study 103 Cohort 5b (n=2) |
|---|---|---|---|---|---|---|---|---|
| n | 14 | 17 | 20 | 7 | 6 | 7 | 6 | 2 |
| Mean (SD) | 0.00 (0.00) | 2.26 (1.55) | 3.44 (2.38) | 1.61 (0.53) | 2.76 (1.08) | 3.00 (1.33) | 2.49 (1.34) | 2.41 (0.07) |
| Median (Q1, Q3) | 0.0 (0.00, 0.00) | 1.77 (1.36, 2.66) | 2.72 (1.88, 4.07) | 1.57 (1.15, 2.06) | 2.79 (1.81, 2.96) | 3.52 (1.93, 4.13) | 2.36 (1.90, 3.51) | 2.41 (2.36, 2.47) |
| Min, max | 0.00, 0.00 | 0.77, 6.92 | 0.74, 9.77 | 0.94, 2.35 | 1.59, 4.62 | 1.11, 4.76 | 0.47, 4.33 | 2.36, 2.47 |

Source: Clinical Pharmacology reviewer, compiled from Applicant's submission
Abbreviations: ddPCR = droplet digital polymerase chain reaction, Max = maximum, Min = minimum, n = number of patients in the specified group, or the total sample, Q1 = Quartile 1, Q3 = Quartile 3, SD = standard deviation

**Vector Shedding**

In Study 103 Cohort 4, ELEVIDYS vector genome concentration versus time results in saliva, urine, and feces (stool) showed biphasic disposition profiles. Vector shedding was measured on the day of administration (Day 1), Day 2, and at Weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 24, 36, 52, 78, and 104 using droplet digital PCR assay for each sample type. The vector shedding results in Cohort 4 were generally consistent with the observations in Cohort 1, Cohort 2, and Cohort 3, presented in the review of the original BLA. High level of variability was also observed. The median time to achieve complete elimination as defined by the first below limit of detection sample followed by two consecutive below limit of detection samples were, 7.3 weeks, 11 weeks, and 24 weeks postdose for saliva, urine, and feces, respectively.

4.4.4 Immunogenicity

**Antibodies to rAAVrh74 and the Micro-Dystrophin Transgene**

Study 103

Patients with pre-existing rAAVrh74 antibody titer exceeding 1:400 were excluded from the study. Across cohorts 1 to 5, a total of 3 of 48 (6%) patients had a screening antibody titer of 1:25; at Day 2, none of the 48 patients had titers that exceeded the lower limit of detection (<1:25). Titers post ELEVIDYS infusion across cohorts 1 to 5 ranged from 1:50 to >1:26,214,400. Maximum titers (>1:26,214,400) were reached 10 to 24 weeks post ELEVIDYS infusion in Cohort 1. Compared to patients who did not have anti-rAAVrh74 antibody titer of 1:25 at screening, the three patients with anti-rAAVrh74 antibody titer of 1:25 at screening had lower mean and median values for ELEVIDYS genome copy numbers and micro-dystrophin levels in muscle biopsy samples at Week 12. The ranges overlapped for both genome copy numbers and micro-dystrophin levels. Due to the small sample size and high inter-patient variability, the impact of anti-rAAVrh74 at screening on ELEVIDYS biodistribution and transgene expression is inclusive.

Across cohorts 1 to 5, micro-dystrophin antibody titers ranged from 1:10 to 1:20,480 post ELEVIDYS infusion. The highest titer observed was 1:20,480 and it occurred at Week 52 in Cohort 1. Due to the limited sampling time points (only one sampling time point post-dosing for muscle biopsy samples), the impact of anti-micro-dystrophin antibodies on ELEVIDYS genome copy numbers and micro-dystrophin levels in muscle biopsy samples cannot be adequately assessed.

Study 301

Patients with AAVrh74 antibody titer exceeding 1:400 were excluded from the study. At baseline, antibody titers to AAVrh74 were <1:400 for all patients. At Week 52, AAVrh74 antibody titer was ≥1:3200 for all patients in the ELEVIDYS group; and <1:400 for 96.8 percent of patients in the placebo group.

At baseline, micro-dystrophin transgene antibody titers of patients were negative for 96.8 percent of patients in the ELEVIDYS group. Post ELEVIDYS infusion, more patients had elevated micro-dystrophin antibody titers from Week 8 to Week 12, which ranged from

negative to 1:1,280. At Week 24, the highest titer was 1:5,120. At Week 52 (Part 1), most of the patients (71.4 percent) had negative antibodies to micro-dystrophin.

**Cellular Immune Response to rAAVrh74 and Micro-dystrophin**

ELISpot Against rAAVrh74

*Study 103*
At baseline, positive results for a T-cell response against rAAVrh74 capsid peptide Pool 3 were observed in patients across cohorts 1 to 5 (12 of 48 patients; 25 percent). Post ELEVIDYS infusion, positive ELISpot results against at least one rAAVrh74 capsid pool was observed in patients across all cohorts. The highest post micro-dystrophin infusion mean spot forming colonies [redacted]value across the cohorts was 62.11 in Pool 3 for Cohort 1 at Week 4. The genome copy numbers and micro-dystrophin levels in muscle biopsy samples at Week 12 post-dosing were similar between patients with positive baseline results and patients with negative baseline results against rAAVrh74. Therefore, there was no observed impact of cellular response against rAAVrh74 at baseline on ELEVIDYS biodistribution and transgene expression value across the cohorts was 62.11 in Pool 3 for Cohort 1 at Week 4.

*Study 301 Part 1*
At baseline, most of the patients (74.6 percent) in the ELEVIDYS group had negative antigen-specific T-cells for AAVrh74 capsid across the three rAAVrh74 capsid peptide pools for both treatment groups with mean (SD) baseline of 6.69 spots/4 × $10^5$ cells plated (12.46 spots/4 × $10^5$ cells plated).

ELISpot Against Micro-dystrophin

*Study 103*
Across Cohorts 1 to 5, at baseline, at least one patient had a positive result for a T-cell response against the three micro-dystrophin peptide pools (6.3 percent of patients against Pools 1 and 2; 2.1 percent of patients against Pool 3). Post ELEVIDYS infusion, positive ELISpot results against at least one micro-dystrophin peptide pool was observed in patients across all cohorts. The highest post ELEVIDYS infusion mean spot forming colonies value across the cohorts was 101.83 in Pool 1 for Cohort 5 at Week 4. Because there was only one sampling time point post-dosing for micro-dystrophin transgene expression, the impact of anti-micro-dystrophin antibodies on ELEVIDYS genome copy numbers and micro-dystrophin levels in muscle biopsy samples cannot be clearly evaluated.

*Study 301 Part 1*
At baseline, most of the patients in the ELEVIDYS group had negative antigen-specific T-cells for micro-dystrophin across the three micro-dystrophin peptide pools with mean (SD) baseline of 3.94 spots/4 × $10^5$ cells plated (4.26 spots/4 × $10^5$ cells plated). Post ELEVIDYS infusion, the number of patients with positive ELISpot results against at least one micro-dystrophin peptide pools increased. The highest value was at Week 52 post ELEVIDYS infusion across pools with a mean (SD) of 36.08 spots/4 × $10^5$ cells plated (149.25 spots/4 × $10^5$ cells plated).

**Reviewer Comment:**
In Study 301, muscle biopsy samples are available for 17 of 63 patients in the ELEVIDYS group; therefore, the impact of immunogenicity on ELEVIDYS distribution and transgene expression is unclear due to the very limited sample size.

The clinical safety of re-administration of ELEVIDYS in the presence of high titers of anti-AAVrh74 total binding antibodies has not been evaluated.

### 4.5 Statistical

Please see Statistics review.

### 4.6 Pharmacovigilance

The Applicant submitted a Pharmacovigilance Plan (Version 7, dated April 3, 2024; BLA 125781/34.12, received April 5, 2024) to monitor safety concerns that could be associated with ELEVIDYS. In this proposed Pharmacovigilance Plan, the Applicant identified infusion-related reactions (including hypersensitivity), acute liver injury, immune-mediated myositis, and thrombocytopenia as important identified risks. Important potential risks include myocarditis and thrombotic microangiopathy. Missing information includes long-term safety; rhabdomyolysis; and oncogenicity due to integration and insertional mutagenesis. Compared to the initially approved Pharmacovigilance Plan (Version 6, dated June 1, 2023; BLA 125781/0.62, received June 2, 2023), the addition of infusion-related reactions (including hypersensitivity) as an important identified risk is the only change in the list of safety concerns. Pharmacovigilance activities associated with safety concerns in the Pharmacovigilance Plan include: signal detection, AE reporting, follow up of cases, targeted questionnaires, monthly review of cases and analysis in aggregate reports, expedited reporting (for acute liver injury, immune-mediated myositis, myocarditis, and thrombotic microangiopathy), follow up from ongoing clinical studies, and a voluntary Phase 4 observational study of safety and efficacy of ELEVIDYS in the postmarketing setting (Study SRP-9001-401).

Should this Efficacy Supplement be approved, OBPV/DPV has the following recommendations for postmarketing safety monitoring of ELEVIDYS.

- Continue routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80.
- Continue enhanced pharmacovigilance for adverse events of special interest (AESIs). Sponsor is required to submit expedited (15-day) reports for acute liver injury, immune-mediated myositis, myocarditis, and thrombotic microangiopathy, regardless of seriousness or expectedness.
- Continue active surveillance with sponsor's voluntary postmarketing observational study (SRP-9001-401).
- The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement (PMR) study. There is no safety-related study as an agreed upon postmarketing commitment (PMC) at this time.

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

### 5.1 Review Strategy

The data constituting the evidence submitted in the BLA supplement derives from two ongoing clinical trials (Study 103 and Study 301 Part 1).

For assessment of efficacy, and in the context of Applicant's proposed indication, the clinical review primarily focused on data from Study 301 Part 1, But also included other data provided in the sBLA that were deemed by the review team to be exploratory for purposes of efficacy, if such data were the basis for the Applicant's claim of effectiveness; such exploratory data were derived from Study 103. For safety, the assessment primarily focused on the safety data from Study 301 Part 1, but also included safety data from Study 103.

Safety of ELEVIDYS was evaluated in the Exposure Analysis Set, consisting of data from 156 male patients with DMD with a confirmed mutation in the *DMD* gene, who received a one-time intravenous infusion of ELEVIDYS in Study 301 Part 1 or Study 103. These patients received the product manufactured according to the commercial process (Process B).

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

(1) Data provided in the sBLA include results from two studies (Table 9) and the relevant modules in the BLA submission.

(2) Publicly available resources, including published reports to for disease background.

(3) Study SRP-9001-102 included in the original BLA review.

### 5.3 Table of Studies/Clinical Trials.

The sBLA includes data from two interventional clinical trials of ELEVIDYS, summarized in Table 9.

**Table 9. Clinical Studies Described in Patients With Duchenne Muscular Dystrophy (DMD) in sBLA 125781.34**

| Study Identifier | Primary Objective | Study Design | Study Endpoint | Study Population | Patients Enrolled |
|---|---|---|---|---|---|
| Study 301 Part 1 | Evaluate effect of ELEVIDYS on change in NSAA Total Score from baseline to Week 52 after infusion | Randomized, double-blinded, placebo-controlled, single dose | Evaluate effect of ELEVIDYS on change in NSAA Total Score from baseline to Week 52 after infusion | Male ambulatory patients ≥4 to <8 years | 125 patients randomized in 1:1 ratio to receive ELEVIDYS (N=63) or placebo (N=62) |
| Study 103 | Evaluate expression of micro-dystrophin, measured by Western blot of biopsied muscle tissue at Week 12 after infusion | Open-label, single-arm, single dose | Evaluate expression of micro-dystrophin, measured by western blot of biopsied muscle tissue at Week 12 after infusion | Male patients; ambulatory patients age ≥3 to <18 years, nonambulatory patients of all ages | 48 patients total:<br>• Cohort 1: 20 ambulatory patients aged ≥4 to <8 years<br>• Cohort 2: 7 ambulatory patients aged ≥8 to <18 years<br>• Cohort 3: 6 nonambulatory patients<br>• Cohort 4: 7 ambulatory patients aged ≥3 to <4 years<br>• Cohort 5: 8 patients total, with *DMD* mutations involving exons 1-17<br>- Cohort 5a: 6 ambulatory patients aged ≥4 to <9 years<br>- Cohort 5b: 2 nonambulatory patients |

Source: FDA reviewer
Abbreviations: DMD = Duchenne muscular dystrophy, N = number of patients in population, NSAA = North Star Ambulatory Assessment

(1) NCT05096221 (Study SRP-9001-301), "A Phase 3, Multinational, Randomized, Double-blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Patients with Duchenne Muscular Dystrophy (EMBARK)," an ongoing, two-part "cross-over" study.
Actual Study Start date: October 27, 2021
Estimated Study Completion Date: November 30, 2024

(2) 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 Patients with Duchenne Muscular Dystrophy (ENDEAVOR)," an ongoing, single-arm "bridging" study.
Actual Study Start date: November 23, 2020
Estimated Study Completion Date: January 31, 2028

### 5.4 Consultations

**Center for Drug Evaluation and Research Pharmacometrics**

A consult request was submitted to CDER/Office of Translational Sciences/Office of Clinical Pharmacology/Division of Pharmacometrics to evaluate the relationship between micro-dystrophin expression levels at Week 12 in muscle biopsy samples, and clinical efficacy endpoints in Study 301 Part 1. Please refer to Sections 6.1 for detailed analysis.

### 5.5 Literature Reviewed (if applicable)

References are indicated in footnotes throughout this document.

## 6. Discussion of Individual Studies/Clinical Trials

### 6.1 Trial #1—SRP-9001-301 (Study 301 Part 1)

Study title: A Phase 3, Multinational, Randomized, Double-blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Patients with Duchenne Muscular Dystrophy (EMBARK)

Clinical Trial Registry Identifier: NCT05096221

#### 6.1.1 Objectives (Primary, Secondary)

The primary objective was to evaluate the effect of ELEVIDYS on physical function, as assessed by change in the NSAA Total Score from baseline to Week 52 after administration.

Secondary objectives were:

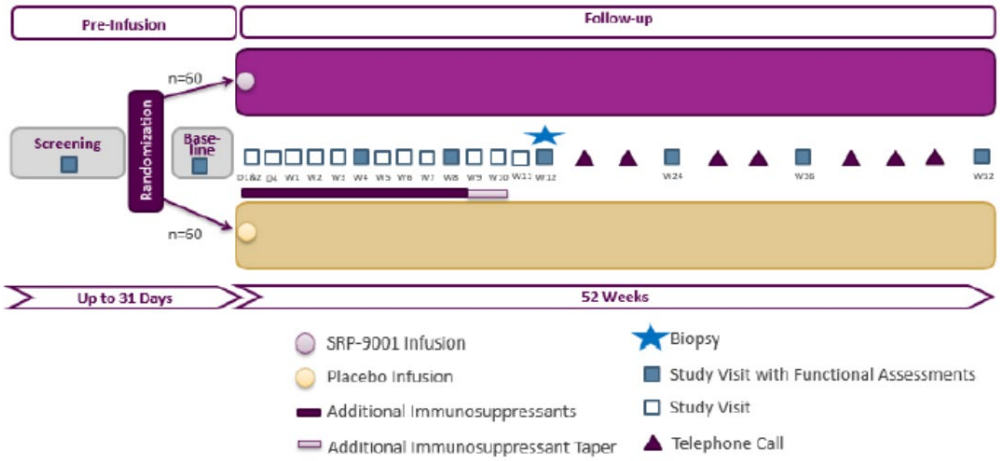
- Evaluate the effect of ELEVIDYS on physical function, assessed by number of skills gained or improved on the NSAA
- Evaluate expression of micro-dystrophin at Week 12, as measured by western blot of biopsied muscle tissue

- Evaluate the effect of ELEVIDYS change from baseline to Week 52 on the following timed function tests:
  - Time to Rise
  - 100-MWR time
  - Time to Ascend 4 Steps
  - 10-MWR time
- Evaluate the effect of ELEVIDYS on change from baseline to Week 52 on the Stride Velocity 95$^{th}$ Centile (SV95C) ambulation assessment, measured via a wearable device
- Evaluate the effect of ELEVIDYS on change from baseline to Week 52 on Mobility and Upper Extremity Function on the PROMIS score, reported by patient or parent/caregiver proxy
- Evaluate the safety of ELEVIDYS, assessed by the following:
  - Incidence of serious SAEs
  - Incidence of treatment-emergent adverse events (TEAE)
  - Incidence of adverse events of special interest
  - Clinically significant changes in vital signs and findings on physical examination
  - Clinically significant changes in safety laboratory assessments, electrocardiogram, and echocardiogram

6.1.2 Design Overview

Study 301 Part 1 was a randomized, double-blind, placebo-controlled trial involving 124 ambulatory male patients aged 4 to 7 years with DMD (Figure 3).

**Figure 3. Schematic Diagram of Design of Study 301 Part 1**




Source: Applicant's Study 301 Interim Study Report, page 20
Abbreviations: n = number of patients in the population, SRP-9001 = delandistrogene moxeparvovec-rokl

**Reviewer Comment:**
Study 301 Part 1 provides the only blinded data in the trial, which is important for interpretation of clinical outcome measures, particularly those that are effort-dependent.

Although patients in Study 301 were randomized and blinding was maintained in Part 2, treatment with ELEVIDYS consists of a single administration, and unlike for true cross-

over studies, no wash-out period is possible for gene therapy trials. Therefore, at the start of Part 2, patients/caregivers and evaluators were aware that all patients have now received ELEVIDYS, making Part 2 effectively an open-label study.

6.1.3 Population

**Key Inclusion Criteria**

- Ambulatory, aged 4 to 7 years,
- Molecular characterization: frameshift (deletion or duplication), premature stop codon, canonical splice site mutation, or other pathogenic variant in the *DMD* gene fully contained between exons 18 to 79 inclusive and expected to result in absence of dystrophin protein
- NSAA Total Score at Screening Visit >16 and <29
- Time to Rise from floor at Screening Visit <5 seconds
- Stable daily dose of oral corticosteroids for at least 12 weeks before Screening Visit; dose and regimen expected to remain constant throughout the study (except for potential modifications to accommodate changes in weight)
- Anti-rAAVrh74 antibody titer ≤1:400 per ELISA

**Key Exclusion Criteria**

- Left ventricular ejection fraction <40 percent on the screening echocardiogram
- Clinical signs and/or symptoms of cardiomyopathy
- Patients with the following *DMD* mutations were not eligible for participation:
  - Mutations between or including exons 1-17
  - In-frame deletions, in-frame duplications, and variants of uncertain significance
  - Mutations fully contained within exon 45 (inclusive)

6.1.4 Study Treatments or Agents Mandated by the Protocol

ELEVIDYS was administered as a one-time, intravenous infusion through a peripheral limb vein. The dose of ELEVIDYS was $1.33 \times 10^{14}$ vg/kg.

Placebo consisted of saline solution (0.9% sodium chloride).

All patients were on a stable dose of corticosteroid, as standard of care treatment for DMD, for at least 12 weeks prior to infusion of ELEVIDYS or placebo. On the day before infusion, patients were started on additional corticosteroid for immunosuppression, prednisone equivalent of 1 mg/kg/day, followed up to a total daily dose of 60 mg/day and continued at this level for at least 60 days, after which patients were tapered from the added steroid and returned to their baseline corticosteroid dose. All patients had baseline titers of anti-AAVrh74 total binding antibodies of <1:400, as determined by an investigational ELISA assay.

6.1.6 Sites and Centers

Study 301 Part 1 was conducted at 42 centers in 9 countries (United States, Belgium, Germany, Hong Kong, Italy, Japan, Spain, Taiwan, and United Kingdom).

## 6.1.7 Surveillance/Monitoring

**Table 10. Schedule of Events, Study 301 Part 1**

| Infusion Period | Pre-Infusion | | Infusion | Post-Infusion | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Scr | B | Infusion | Follow-up Period | | | | | | | | | | | | | | | |
| 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 | W16, 20, 28, 32, 40, 44, 48 | W 24 | W 36 | W52/ ET [a] |
| Visit Window (days) | -31 | NA [b] | NA | NA | ±1 | ±1 | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±14 | ±14 | ±14 |
| Visit Type [c] | C/R[d] | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C |
| Informed consent/assent | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion | X | | X [e] | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | |
| Physical exam [f] | X | X | X | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| Vital signs [g] | X | X | X | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| Height/ulnar length | | X [h] | X | | X | | | X | | | | X | | | | X | | X | X | X |
| Weight | X | X [h] | X [i] | | X | | | X | | | | X | | | | X | | X | X | X |
| NSAA (incl. time to rise from the floor and 10MWR) [j] | X | X [k, l] | | | | | | X | | | | X | | | | X [l] | | X | X | X [k] |
| Timed 4-step test [j] | | X [l] | | | | | | X | | | | X | | | | X [l] | | X | X | X |
| 100MWR [j] | | X [l] | | | | | | X | | | | X | | | | X [l] | | X | X | X |
| ELISA [m] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X |
| ELISpot [m] | | X | | | X | X | | X | | X | | X | | X | | X | | X | | X |
| Hematology [n] | X | | | X | X | X | X | X | | X | | X | | X | | X | | X | X | X |
| Hepatitis B &C Serology, HIV | X | | | | | | | | | | | | | | | | | | | |
| EBV, CMV, parvovirus B19, VZV, HH6, hepatitis A & E | | X | | | | | | | | | | | | | | | | | | |

| Infusion Period | Pre-Infusion | | Infusion | Post-Infusion | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Scr | B | Infusion | Follow-up Period | | | | | | | | | | | | | | | |
| 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 | W16, 20, 28, 32, 40, 44, 48 | W 24 | W 36 | W52/ ET [a] |
| Visit Window (days) | -31 | NA [b] | NA | NA | ±1 | ±1 | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±14 | ±14 | ±14 |
| Visit Type [c] | C/R[d] | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C |
| Electrolytes [o] | | X | | X | | | | | | | | | | | | X | | X | | X |
| Troponin I | | X | | | X | | | X | | | | X | | | | X | | X | X | X |
| Glucose (serum) [p] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| CK [q] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| Liver function [n] | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Renal function [n] | X | | | | X | X | X | X | | | | X | | | | X | | X | X | X |
| hsCRP and complement (CH50, C3, C4, factor B) | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| Vector quantification | | | X [r] | X [s] | X | X | X | X | | X | | X | X | X | X | X | | | | |
| Biomarkers | | X | | | X | | | X | | | | | | | | X | | X | | X |
| *DMD* gene sequence analysis | | X | | | | | | | | | | | | | | | | | | |
| Whole-genome DNA sequence [t] | | X | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X |
| Urinalysis [n] | X | | | X | X | | | X | | | | X | | | | X | | | | |
| Muscle Biopsy [u] | | X | | | | | | | | | | | | | | X | | | | |
| CGI-C | | | | | | | | | | | | | | | | | | X | | X |
| PROMIS [v] | | X | | | | | | X | | | | X | | | | X | | X | X | X |
| Subject/Parent Global Assessment of Overall Severity/Change [v] | | X [w] | | | | | | X | | | | X | | | | X | | X | X | X |

| Infusion Period | Pre-Infusion | | Infusion | Post-Infusion | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Scr | B | Infusion | Follow-up Period | | | | | | | | | | | | | | | |
| 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 | W16, 20, 28, 32, 40, 44, 48 | W 24 | W 36 | W52/ ET [a] |
| Visit Window (days) | -31 | NA [b] | NA | NA | ±1 | ±1 | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±14 | ±14 | ±14 |
| Visit Type [c] | C/R[d] | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C |
| EQ-5D | | X | | | | | | X | | | | X | | | | X | | X | X | X |
| Wearable device [x] | X | | | | | | | | | | | | | | | X | | X | X | X |
| Electrocardiogram [y] | X | | X | | | | | X | | | | | | | | | | | | X |
| Echocardiogram | X | | | | | | | | | | | | | | | | | | | X |
| Cardiac MRI (sub-study) [z] | | X | | | | | | | | | | | | | | | | | | X |
| Musculoskeletal MRI (sub-study) [z] | | X | | | | | | | | | | | | | | | | | | X |
| Study drug infusion [aa] | | | X | | | | | | | | | | | | | | | | | |
| Add-on corticosteroid (1 mg/kg) | | Implement daily add-on **the day prior to the infusion** and for **at least 60 days post-infusion** | | | | | | | | | | | | | | | | | | |
| Add-on corticosteroid tapering | | | | | | | | | | | | | X | X | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | |
| IRT weight input | X | | X | | | | | | | | | | | | | | | | | |
| AE reporting | Ongoing collection beginning at informed consent/ assent | | | | | | | | | | | | | | | | | | | |
| Concomitant medications & procedures | Ongoing collection beginning at informed consent/ assent | | | | | | | | | | | | | | | | | | | |

10MWR = 10-meter walk run; 100MWR = 100-meter walk run test; AE = adverse event; B = Baseline; C = clinic; CGI-C = clinical global impression of change; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; EQ-5D = EuroQol-5D; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; HH6 = human herpesvirus 6; MRI = magnetic resonance imaging; IRT = interactive response technology; NA = not applicable; NSAA = North Star Ambulatory Assessment; PROMIS = Patient-Reported Outcomes Measurement Information System; R = remote; RNA = ribonucleic acid; Scr = screening; T = telephone; VZV = varicella zoster virus; W = week.
NOTE: For this study, a week is 7 days, and each time point is relative to the infusion on Day 1.
a In case of subject withdrawal, Week 52 assessments should be performed at the ET visit.

| Infusion Period | Pre-Infusion | | Infusion | Post-Infusion | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Scr | B | Infusion | Follow-up Period | | | | | | | | | | | | | | | |
| 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 | W16, 20, 28, 32, 40, 44, 48 | W 24 | W 36 | W52/ ET [a] |
| Visit Window (days) | -31 | NA [b] | NA | NA | ±1 | ±1 | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±14 | ±14 | ±14 |
| Visit Type [c] | C/R[d] | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C |

b The Baseline Period will start when eligibility is confirmed and ends on the day prior to the Day 1 infusion.
c Visits indicated as "R" are visits that can be conducted at the clinic or remotely.
d Select screening assessments may be performed remotely. However, the following assessments must be performed in-clinic: NSAA (including time to rise from the floor and timed 10MWR), physical examination, provision of the wearable device, ECG, and ECHO.
e Investigator or designee to confirm no changes to eligibility criteria related to Day 1.
f A full physical examination will be performed at Screening and Week 52/ET and will include: 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 will include general appearance, HEENT, heart, chest, abdomen, and skin.
g 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.
h Baseline weight and height/ulnar length are to be collected on the same day as the 100MWR.
i Weight should be obtained the day prior to study drug infusion.
j 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, then they may be performed within a ± 2-week visit window for Weeks 4 and 8, and a ± 6-week visit window for Weeks 12, 24, 36, and 52.
k Two NSAA scores (including 2 scores for time to rise from the floor and timed 10MWR) will be collected on 2 days at Baseline and Week 52. Note that only 1 score for NSAA (including time to rise from the floor and timed 10MWR) is needed at the ET visit.
l Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
m Antibodies to rAAVrh74 capsid.
n See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
o Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
p Glucose does not require fasting.
q At all visits where CK samples are drawn, parents/caregivers will be asked to limit subject's physical activity level over the 3 days before the scheduled CK assessments.
r Sample to be taken approximately 4 to 6 hours post-infusion.
s Sample to be taken approximately 22 to 26 hours post-infusion.
t 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.
u A muscle biopsy for evaluation of micro-dystrophin expression will be collected from a subset of subjects at Baseline and Week 12. The Baseline biopsy will be of the medial gastrocnemius muscle, preferably on 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 lower extremity. If possible, the biopsy for Week 12 will be of the same muscle group as that used at Baseline on the contralateral side, preferably on the left leg. Every effort should be made to perform the Week 12 biopsy in the specified visit window; however, if the Week 12 biopsy cannot be performed within the window due to events not reasonably foreseen, it may be performed up to 12 weeks after the Week 12 visit. Refer to the Biopsy Surgical and Laboratory Manual.

| Infusion Period | Pre-Infusion | | Infusion | Post-Infusion | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Scr | B | Infusion | Follow-up Period | | | | | | | | | | | | | | | |
| 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 | W16, 20, 28, 32, 40, 44, 48 | W 24 | W 36 | W52/ ET [a] |
| Visit Window (days) | -31 | NA [b] | NA | NA | ±1 | ±1 | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±14 | ±14 | ±14 |
| Visit Type [c] | C/R[d] | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C |

v See Section 10.3.6.1 for specific measures included. The PROMIS measures will be completed by a subset of subjects based on regional availability. Participating subjects will be outlined in the Study Operations Manual.
w Only Subject/Parent Global Assessment of overall Severity will be collected at Baseline.
x Subjects will wear the wearable device daily on both ankles for 3 weeks during the pre-infusion period and for 3 weeks prior to Week 12, 24, 36, and 52/ET visits.
y All ECGs should be performed in triplicate at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
z Only subjects at participating sites will undergo imaging assessments. Refer to the MRI Study Manual for further details.
aa 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

Source: Study 301 Clinical Study Protocol, pp. 18-22
Abbreviations: AE = adverse event, B = Baseline, C = clinic, CGI-C = clinical global impression of change, CK = creatinine kinase, CMV = cytomegalovirus, D = day, DMD = Duchenne muscular dystrophy, DNA = deoxyribonucleic acid, EBV = Epstein-Barr Virus, ECG = electrocardiogram, ECHO = echocardiogram, ELISA = Enzyme-linked immunosorbent assay, ELISpot = Enzyme-linked immunospot, EQ-5D = EuroQol-5D, ET = early termination, HEENT = head, ears, eyes, nose, and throat, HIV = human immunodeficiency virus, hsCRP = high-sensitivity C-reactive protein, HH6 = human herpesvirus 6, IRT = interactive response technology, MRI = magnetic resonance imaging,10MWR =10-meter walk run, 100MWR =100-meter walk run test, NA = not applicable, NSAA = North Star Ambulatory Assessment, PROMIS = Patient-Reported Outcomes Measurement Information System, R = remote, RNA = ribonucleic acid, Scr = screening, T = telephone, VZV = varicella zoster virus, W = week

### 6.1.8 Endpoints and Criteria for Study Success

**Primary Efficacy Endpoint for Study 301 Part 1**

- Change in NSAA Total Score Change from baseline to Week 52

**Secondary Efficacy Endpoints for Study 301 Part 1**

- Number of skills gained or improved on the NSAA
- Quantity of micro-dystrophin protein at Week 12, as measured by western blot
- Change from baseline to Week 52 on Time to Rise
- Change from baseline to Week 52 on 100-MWR time
- Change from baseline to Week 52 on Time to Ascend 4 Steps
- Change from baseline to Week 52 on 10-MWR time
- Change from baseline to Week 52 on the Stride Velocity 95th Centile (SV95C)
- Change from baseline to Week 52 in PROMIS score in Mobility and Upper Extremity
- Incidence of TEAEs
- Incidence of SAE
- Incidence of adverse events of special interest
- Clinically significant changes in vital signs and findings on physical examination
- Clinically significant changes in safety laboratory assessments, electrocardiogram, and echocardiogram

**Primary Outcome Measure: North Star Ambulatory Assessment**

The NSAA is a 17-item rating scale commonly used in clinical studies to measure motor function in ambulatory patients 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; and jumping, hopping, and running. These tasks are performed by the patient in a clinical setting, according to instructions administered by a health care professional.

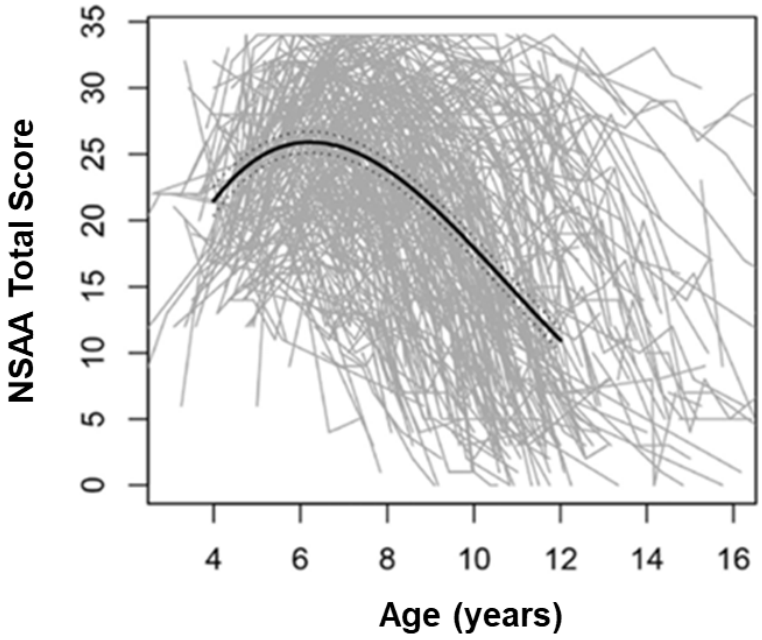
Each item is scored as 0 (unable to achieve independently), 1 (modified method, but not requiring assistance), or 2 (normal). The NSAA Total Score ranges from 0 (unable to perform any activities) to 34 (all activities achieved normally).

Performance on the NSAA can be affected both by the consistency of administration (process-dependence), and by the motivation of the patient and coaching or encouragement by family members, caregivers, or medical staff (effort-dependence).[12] Therefore, in clinical studies employing the NSAA, blinding to treatment assignment is crucial for clear interpretation of results.

Natural history data of 395 patients selected from the North Star Clinical Network database showed heterogeneous disease progression and identified four general trajectories of ambulatory function, measured by the NSAA Total Score over time.[13] Twenty-five percent of the boys were in cluster 1 (NSAA falling to ≤5 at age ~10 years), 35 percent were in cluster 2 (NSAA ≤5 at age ~12 years), 21 percent were in cluster 3 (NSAA ≤5 at age ~14 years), and 19 percent 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). The overall mean trajectory of NSAA Total Score versus age initially increased at a rate of approximately 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 4).

12. Guidance for industry *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment* (February 2018)
13. 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.

**Figure 4. Natural History Data on Trajectories of NSAA Total Score for Individual Patients Over Time**




Source: Modified from 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.
Abbreviation: NSAA = North Star Ambulatory Assessment

**Reviewer Comment:**
Some key context is important for evaluating the NSAA results from the Applicant's clinical trials described in the sBLA (Study 301 Part 1 and Study 103):

- In contrast to objective endpoints such as survival, functional measures such as the NSAA have important limitations. First, they are effort-dependent: performance can be influenced 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. NSAA scores from a clinical study therefore cannot be rigorously compared to scores from external sources such as natural history studies or registries, or even to scores from clinical trials of other drugs for DMD.

- 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 assessed objectively. That was the situation, for example, with onasemnogene abeparvovec-xioi (Zolgensma), the gene therapy which received traditional approval by FDA for the treatment of pediatric patients less than 2 years old with spinal muscular atrophy with bi-allelic mutations in the *survival motor neuron 1* gene. 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 treatment effect of ELEVIDYS is likely to be modest; and as noted above, evaluation of 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 in the sBLA that can provide reliable assessment of NSAA performance are those from Study 301 Part 1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see Statistical review for details.

Patients were randomized in a 1:1 ratio to receive either ELEVIDYS or placebo. Randomization was stratified by age group (≥4 to <6 years or ≥6 to <8 years), and NSAA Total Score (≤22 or >22) at Screening; approximately 50 percent of the patient population was allotted per age group.

**Statistical Hypotheses**

- Primary Efficacy Endpoint: Change in NSAA Total Score from baseline to Week 52

  $H_0$: $\mu_{SRP} = \mu_{placebo}$ versus $H_1$: $\mu_{SRP} \neq \mu_{placebo}$, where $\mu_{SRP}$ and $\mu_{placebo}$ are mean change in NSAA Total Score from baseline to Week 52 in the ELEVIDYS and placebo groups, respectively.

- Key Efficacy Endpoint: Quantity of Micro-dystrophin Protein at Week 12

  $H_0$: $\theta_{SRP} = \theta_{placebo}$ versus $H_1$: $\theta_{SRP} \neq \theta_{placebo}$, where $\theta_{SRP}$ and $\theta_{placebo}$ are mean quantity of micro-dystrophin protein at Week 12

- Key Efficacy Endpoint: Change in Time to Rise from Baseline to Week 52

  $H_0$: $\lambda_{SRP} = \lambda_{placebo}$ versus $H_1$: $\lambda_{SRP} \neq \lambda_{placebo}$, where $\lambda_{SRP}$ and $\lambda_{placebo}$ are mean change in Time to Rise from baseline to Week 52 in the ELEVIDYS and placebo groups, respectively.

- Key Efficacy Endpoint: Change in 10-MWR Time from Baseline to Week 52

  $H_0$: $\lambda_{SRP} = \lambda_{placebo}$ versus $H_1$: $\lambda_{SRP} \neq \lambda_{placebo}$, where $\lambda_{SRP}$ and $\lambda_{placebo}$ are mean change in 10-MWR Time from baseline to Week 52 in the ELEVIDYS and placebo groups, respectively.

**Analysis Method for Primary Endpoint**

A restricted maximum likelihood-based mixed model repeated measures 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 52:

- A mean difference of 2.2 between the ELEVIDYS group and placebo group
- Standard deviation of 3.5 in all patients

- Two-sided alpha level of 0.05 (although only superiority of ELEVIDYS over placebo will be of interest)
- Target power of 90 percent
- 10 percent dropout rate at Week 52

Based on these assumptions, a total of 120 patients (60 patients per study arm) were needed.

The study was not powered for other endpoints.

**Testing**
As per the SAP, the primary endpoint and secondary endpoints will be tested sequentially (with the testing order specified below) to control the overall Type I error at a 2-sided level of 0.05:

- Change in NSAA total score from Baseline to Week 52
- Quantity of micro-dystrophin protein expression at Week 12, as measured by western blot.[14]
- Change in time to rise from the floor from Baseline to Week 52[a]
- Change in time of 10-meter timed test from Baseline to Week 52[a]
- Change in Stride Velocity 95$^{th}$ Centile from Baseline to Week 52
- Change in time of 100-meter timed test from Baseline to Week 52
- Change in time to ascend 4 steps from Baseline to Week 52
- Change in PROMIS Mobility score from Baseline to Week 52
- Change in PROMIS Upper Extremity score from Baseline to Week 52
- Number of skills gained or improved at Week 52, as measured by the NSAA

**Reviewer Comment:**
Study 301 was powered only to test the effect of ELEVIDYS on the primary efficacy endpoint, change in the NSAA Total Score from baseline to Week 52.

Although the study was stratified based on age at baseline (≥4 to <6 years, or ≥6 to <8 years), age subgroup analyses were not prespecified for hypothesis testing, and no prespecified multiplicity adjustment strategy was employed. Similarly, the Applicant did not design the study with prespecified analyses of any secondary endpoints for hypothesis testing, or with a prespecified multiplicity adjustment strategy. Consequently, we cannot reliably distinguish if any of those results are due to actual effects of ELEVIDYS, or to chance alone. Although p values still may be calculated mathematically for those results, such "nominal" (or "raw") p-values are not meaningful as an indication of statistical significance. These "nominal" p-values cannot guide any stakeholders—including patients, family members and caregivers, and prescribers—in making informed decisions about the potential benefit of treatment with ELEVIDYS; "nominal" p-values therefore are not included in this review.

FDA recognizes that DMD treatments with modest effects—when those effects are real—are important and have contributed to greater maintenance of function and increased life span for patients with DMD in the current era. If effective, ELEVIDYS is

14 key secondary efficacy endpoints

expected to have a modest effect: not to cure DMD, but instead to change the disease trajectory from the DMD phenotype to the milder course seen in patients with Becker's muscular dystrophy (BMD). FDA had communicated to the Applicant that without proper statistical pre-specification in Study 301 Part 1, analyses of subgroups or secondary endpoints could only provide hypotheses for further testing, rather than demonstrate or confirm the therapeutic effect of ELEVIDYS.

6.1.10 Study Population and Disposition

Key demographic data are presented in Table 2.

All patients had baseline titers of anti-AAVrh74 total binding antibodies of <1:400, as determined by an investigational enzyme-linked immunosorbent assay.

All patients were receiving a stable dose of corticosteroids as standard of care treatment for DMD, for at least 12 weeks prior to infusion of ELEVIDYS or placebo. The day prior to treatment, the patient'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 clinically indicated.

6.1.10.1 Populations Enrolled/Analyzed

The analysis populations are summarized in Table 11. The primary efficacy analysis and key secondary efficacy analyses were conducted on the modified Intent-to-Treat (mITT) set.

**Table 11. Analysis Populations**

| Population | Description |
|---|---|
| All patients | All screened patients (not including those enrolled under a regional addendum) |
| Intent-to-treat (ITT) | All randomized patients (not including those enrolled under a regional addendum), with treatment group designated according to randomization |
| Modified Intent-to-Treat (mITT) | All randomized patients who received study treatment (not including those enrolled under a regional addendum), with treatment group designated according to randomization; the mITT population was the analysis population for efficacy endpoints |
| Safety | All patients who received study treatment (not including those enrolled under a regional addendum), with treatment group designated according to treatment received |

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

*6.1.10.1.1 Demographics*

The baseline demographics of the patients in Study 103 are summarized in Table 3.

*6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population*

The baseline medical and disease characteristics in the mITT population are summarized in Table 12.

**Table 12. Baseline Medical and Disease Characteristics, mITT Population**

| Characteristic | ELEVIDYS (N=63) | Placebo (N=62) | Total (N=125) |
|---|---|---|---|
| Height (cm) | - | - | - |

| Characteristic | ELEVIDYS (N=63) | Placebo (N=62) | Total (N=125) |
|---|---|---|---|
| Mean (SD) | 108.64 (6.74) | 110.68 (7.44) | 109.65 (7.14) |
| Median (min, max) | 109.00 (93.5, 127.0) | 110.15 (95.2, 127.5) | 109.30 (93.5, 127.5) |
| Weight (kg) | - | - | - |
| Mean (SD) | 21.29 (4.62) | 22.37 (6.42) | 21.83 (5.59) |
| Median (min, max) | 20.20 (13.5, 38.5) | 20.55 (14.1, 41.6) | 20.20 (13.5, 41.6) |
| Body mass index (kg/m$^2$) | - | - | - |
| Mean (SD) | 17.85 (2.20) | 17.89 (3.20) | 17.87 (2.73) |
| Median (min, max) | 17.36 (13.7, 24.9) | 16.56 (13.5, 26.9) | 17.26 (13.5, 26.9) |
| BMI (kg/m$^2$) category | - | - | - |
| <20 | 53 (84.1%) | 52 (83.9%) | 105 (84.0%) |
| ≥20 | 10 (15.9%) | 10 (16.1%) | 20 (16.0%) |
| Years since DMD diagnosis | - | - | - |
| Mean (SD) | 2.62 (1.73) | 2.60 (1.78) | 2.61 (1.75) |
| Median (min, max) | 2.40 (0.0, 6.7) | 2.12 (0.2, 7.6) | 2.27 (0.0, 7.6) |
| Years since corticosteroid treatment started | - | - | - |
| Mean (SD) | 1.07 (0.92) | 0.97 (0.83) | 1.02 (0.88) |
| Median (min, max) | 0.96 (0.23, 6.17) | 0.66 (0.24, 4.01) | 0.77 (0.23, 6.17) |
| Genetic mutation type | - | - | - |
| Large deletion | 45 (71.4%) | 41 (66.1%) | 86 (68.8%) |
| Large duplication | 3 (4.8%) | 3 (4.8%) | 6 (4.8%) |
| Small mutation | 15 (23.8%) | 18 (29.0%) | 33 (26.4%) |
| NSAA total score | - | - | - |
| Mean (SD) | 23.10 (3.75) | 22.82 (3.78) | 22.96 (3.75) |
| Median (Min, Max) | 23.5 (14.0, 32.0) | 22.5 (15.5, 30.0) | 23.0 (14.0, 32.0) |
| 10-meter run/walk time | - | - | - |
| Mean (SD) | 4.82 (0.79) | 4.92 (0.73) | 4.87 (0.76) |
| Median (Min, Max) | 4.60 (3.2, 6.9) | 4.90 (3.7, 7.0) | 4.80 (3.2, 7.0) |
| 100-meter run/walk time, n | 63 | 59 | 122 |
| Mean (SD) | 60.67 (15.55) | 63.00 (17.01) | 61.80 (16.25) |
| Median (min, max) | 58.40 (38.0, 129.2) | 58.10 (38.7, 118.1) | 58.20 (38.0, 129.0) |
| Time to rise from floor | - | - | - |
| Mean (SD) | 3.52 (0.81) | 3.60 (0.68) | 3.56 (0.75) |
| Median (min, max) | 3.35 (1.9, 5.8) | 3.63 (2.3, 5.0) | 3.50 (1.9, 5.8) |
| Time to ascend 4 steps, n | 63 | 61 | 124 |
| Mean (SD) | 3.17 (1.01) | 3.37 (1.09) | 3.27 (1.05) |
| Median (min, max) | 3.00 (1.6, 7.1) | 3.10 (1.5, 7.1) | 3.10 (1.5, 7.1) |
| SV95C, n | 61 | 62 | 123 |
| Mean (SD) | 1.82 (0.30) | 1.77 (0.29) | 1.79 (0.29) |
| Median (min, max) | 1.79 (1.1, 2.5) | 1.79 (1.1, 2.4) | 1.79 (1.1, 2.5) |
| PROMIS score in mobility, n | 60 | 60 | 120 |
| Mean (SD) | 4.29 (0.42) | 4.20 (0.40) | 4.24 (0.41) |
| Median (min, max) | 4.37 (3.0, 5.0) | 4.20 (3.2, 5.0) | 4.33 (3.0, 5.0) |
| PROMIS score in upper extremity, n | 60 | 59 | 119 |
| Mean (SD) | 3.82 (0.94) | 3.60 (0.93) | 3.71 (0.93) |
| Median (min, max) | 4.00 (1.8, 5.0) | 3.75 (1.6, 5.0) | 4.00 (1.6, 5.0) |

Source: FDA statistical review
Abbreviations: BMI = body mass index, DMD = Duchenne muscular dystrophy, Max = maximum, Min = minimum, mITT = modified-Intent to Treat, n = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, NSAA = North Star Ambulatory Assessment, PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation, SV95C = Stride Velocity 95th Centile

**Reviewer Comment:**
Overall, the study was balanced across arms for key demographic and baseline characteristics.

*6.1.10.1.3 Patient Disposition*

A total of 173 patients were screened for the study, of which 42 patients were ineligible.

Of the 131 patients who were randomized, 6 were not dosed. The reasons for discontinuation were infection (two patients), COVID-19 (three patients), and withdrawal due to study schedule (one patient).

6.1.11 Efficacy Analyses

**Primary Efficacy Endpoint**

Change from baseline in the NSAA Total Score was assessed at Week 52 after infusion of ELEVIDYS or placebo.

6.1.11.1 Analyses of Primary Endpoint(s)

The LSM change ± standard error was 2.57±0.39 points for the ELEVIDYS group, and 1.92±0.39 points for the placebo group. The difference was 0.65 points, which was not statistically significant (p value =0.2441).

**Reviewer Comment:**
Because the difference in NSAA Total Score at Week 52 did not demonstrate statistical significance, Study 301 Part 1 failed to verify the benefit of ELEVIDYS.

6.1.11.2 Analyses of Secondary Endpoint(s)

Additional results of interest from Study 301 Part 1 include the following: NSAA results for the 4 to 5-year-old age subgroup and the 6 to 7-year-old age subgroup; and outcomes for the two key secondary clinical endpoints.

The LSM treatment difference in NSAA total score change from baseline to Week 52 was 1.32 (95% CI: (-0.23, 2.87) in the 4-5 age group and 0.06 (95% CI: (-1.52, 1.64) in the 6-7 age group.

Results for the clinical secondary endpoints were as follows:

- Time to Rise (seconds): -0.64 ± 0.21 (95% CI: -1.06, -0.23)
- 10-Meter Walk/Run (seconds): -0.42 ± 0.15 (95% CI: -0.71, -0.13)
- Time to Ascend 4 Steps (seconds): -0.36 ± 0.18 (95% CI: -0.71, -0.01)
- 100-Meter Walk/Run (seconds): -3.29 ± 2.52 (95% CI: -8.28, 1.70)

**Reviewer Comment:**
Although the key secondary endpoints of Time to Rise and 10-MWR appear to show a numerical improvement for the ELEVIDYS arm compared to placebo, these analyses were not prespecified for hypothesis testing, and no multiplicity adjustment for Type 1 error control was applied; consequently, the results of these analyses cannot be attributed to an actual treatment effect, and therefore are considered exploratory.

For the NSAA Total Score for the 6- to 7-year-old age subgroup, the point estimate of LSM treatment difference was 0.06 (-1.52, 1.64) points, a similar result to that obtained for this subgroup in Study 102 Part 1 [-0.70 (-3.02, 1.62) points]. The Applicant attributed the outcome in Study 102 Part 1 to a substantial imbalance in baseline functional status, favoring the placebo patients, in this age subgroup. No such imbalance was present in Study 301 Part 1, which may call into question both that proposed explanation, as well as support for an indication for older patients. However, such conclusions cannot be reached definitively from these data, for the reasons noted earlier.

Regarding the secondary clinical efficacy endpoints, the Applicant has pointed out that in all four cases the point estimates numerically favor the ELEVIDYS group, and that the "nominal" p values support three of these four results (Time to Rise, 10- MWR, and Time to Ascend 4 Steps). However, because the primary efficacy analysis was not statistically significant, the results for secondary endpoints are subject to inflated type 1 error rates.

We have several considerations regarding these results:

- We note again that "nominal" p-values cannot support a conclusion of benefit.
- The 95 percent confidence intervals for Time to Rise, 10-MWR, and Time to Ascend 4 Steps all contain an upper bound near the zero point, indicating no effect. This observation, while similarly limited in statistical meaning, nevertheless casts further doubt on the claim of benefit.
- The small size of the point estimates would be of unclear clinical significance.

6.1.11.3 Additional Analysis

Study 102 Part 1 is the A only other randomized, double-blind, placebo-controlled study for which data are available. Both studies failed to demonstrate statistical significance on the primary efficacy endpoint, change from baseline in the NSAA.

**Table 13. Efficacy Analysis Results in Comparing Study 301 Part 1 and Study 102 Part 1, Overall and by Age Groups, mITT Population**

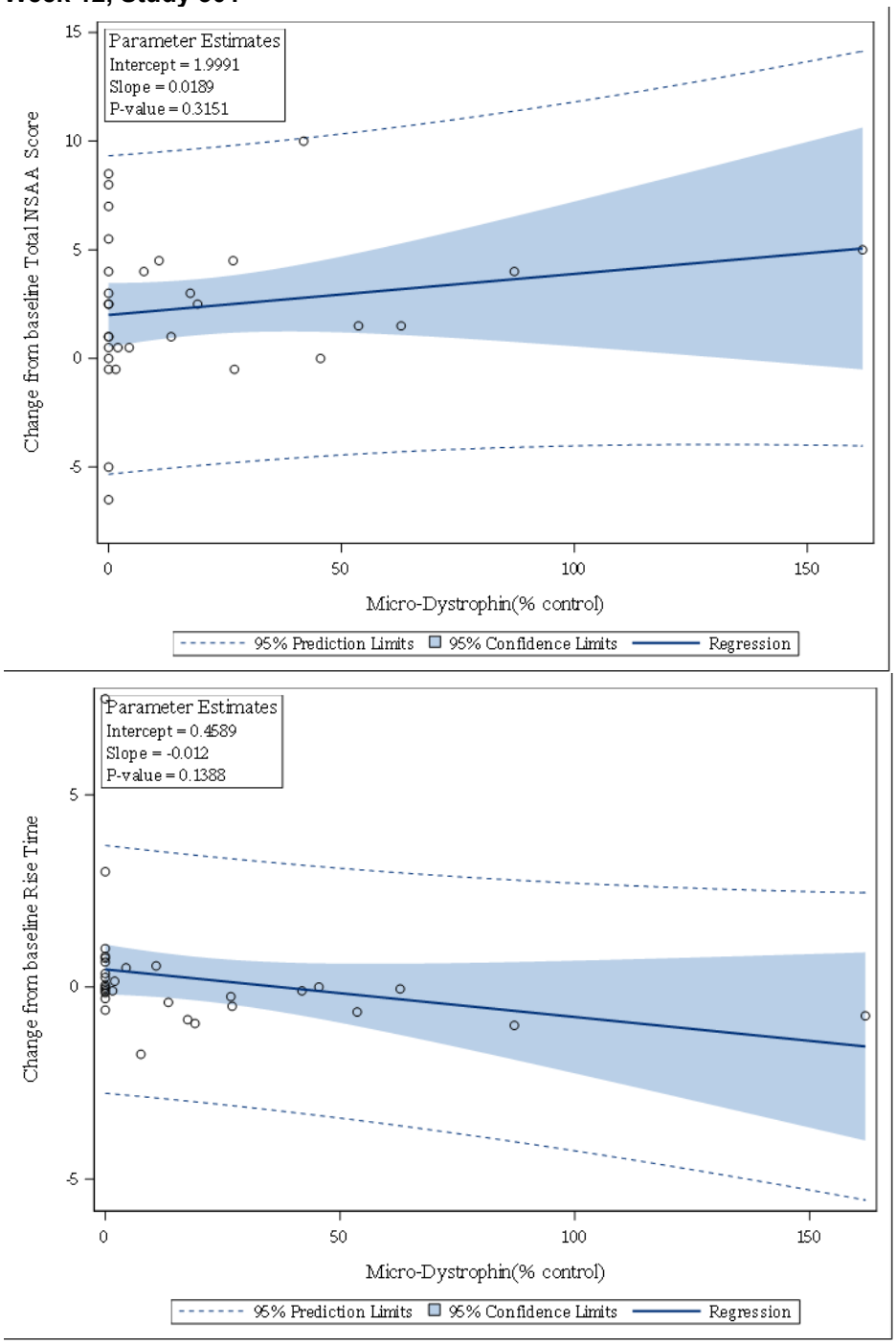
| Endpoint | Difference in LSM (95% CI) at Week 52 in Study 301 | Difference in LSM (95% CI) at Week 48 in Study 102 |
|---|---|---|
| Primary endpoint: NSAA total score | - | - |
| Overall | 0.65 (-0.45, 1.74) | 0.82 (-1.03, 2.67) |
| Key secondary endpoint: Time to rise (seconds) | - | - |
| Overall | -0.64 (-1.06, -0.23) | -0.50 (-1.22, 0.23) |
| 4-5 years old | -0.50 (-0.90, -0.09) | -0.30 (-1.32, 0.72) |
| 6-7 years old | -0.78 (-1.48, -0.08) | -0.56 (-1.59, 0.47) |
| Key secondary endpoint: 10-MWR timed test (seconds) | - | - |
| Overall | -0.42 (-0.71, -0.13) | 0.49 (-0.08, 1.06) |
| 4-5 years old | -0.33 (-0.62, -0.03) | 0.16 (-0.69, 1.02) |
| 6-7 years old | -0.52 (-1.01, -0.03) | 0.76 (-0.01, 1.54) |
| NSAA total score for age subgroups | | |
| 4-5 years old | 1.32 (-0.23, 2.87) | 2.47 (0.52, 4.43) |
| 6-7 years old | 0.06 (-1.52, 1.64) | -0.70 (-3.02, 1.62) |

Source: FDA Statistical Reviewer
Abbreviations: CI = confidence interval, LSM = least square mean; mITT = modified intent-to-treat, MWR = Meter Walk/Run test, NSAA = North Star Ambulatory Assessment, SE = standard error

#### 6.1.11.4 Analysis of Micro-Dystrophin Expression at Week 12 and Clinical Outcomes

The analysis of micro-dystrophin data shows the presence of a trend of changes in clinical endpoints (NSAA total score and Time to Rise from floor) with increasing levels of micro-dystrophin (Figure 5). Of note, the data was obtained from only 25% of patients enrolled in Study 301 Part 1 (n=17 for ELEVIDYS group and n=14 for placebo group).

**Figure 5. Change From Baseline NSAA at Week 52 Vs. Micro-Dystrophin Levels at Week 12, Study 301**




Source: Pharmacometrics Consult Reviewer's Analysis. Please see section 5.4.

**Reviewer Comment:**
Considering that micro-dystrophin expression levels were available in only 25% of patients randomized in Study 301 Part 1, the analysis results may not truly represent the

relationship between micro-dystrophin and the clinical efficacy endpoint in the entire study population. Therefore, results should be interpreted with caution.

6.1.11.5 Dropouts and/or Discontinuations

Please see 6.1.10.1.3, Patient Disposition.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety evaluable population in Study 301 Part 1 comprised 125 patients: 63 patients who received ELEVIDYS, and 62 patients who received placebo. Patients were followed for a mean of 54.78 weeks. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 26.0.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 5.0 was used for grading of the AEs. Events not listed in the CTCAE were assessed according to the following scale:

- Grade 1: Mild, asymptomatic, or mild symptoms, clinical or diagnostic observations only, intervention not indicated
- Grade 2: Moderate, minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care ADL
- Grade 4: With life-threatening consequences, urgent intervention indicated
- Grade 5: Death related to AE

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that emerged during treatment having been absent pretreatment or worsens relative to the pretreatment state. The rates of any TEAEs and SAES and treatment-related TEAEs and SAEs that occurred in ELEVIDYS arm were compared with the placebo arms.

A serious adverse event (SAE) was defined as any AE that resulted in any of the following:

- Death
- Life-threatening event
- Required or prolonged inpatient hospitalization:
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event

6.1.12.2 Overview of Adverse Events

As of the data cutoff (September 13, 2023), 19 patients experienced 30 SAEs in Study 301 Part 1: 14 (22.2 percent) patients in the ELEVIDYS group reported 21 SAEs, and 5 (8.1 percent) patients in the placebo group reported 9 SAEs.

The most common SAEs (occurring in ≥2 percent of patients) for both treatment and placebo groups were COVID-19 infection (3.2 percent in the ELEVIDYS group and 1.6 percent in the placebo group) and vomiting (3.2 percent in the ELEVIDYS group and 1.6 percent in the placebo group).

Of the 30 SAEs, 10 were considered treatment-related SAEs. The 10 treatment-related SAEs occurred in 7 patients (11.1%), all of whom were in the ELEVIDYS group. These SAEs were myocarditis, rhabdomyolysis, hepatotoxicity, liver injury, elevated gamma-glutamyltransferase, elevated hepatic enzyme, elevated transaminases, nausea, vomiting, and pyrexia.

A total of 119 patients experienced at least 1 AE: 62 patients (52.1 percent) in the ELEVIDYS group, and 57 patients (47.9 percent) in the placebo group.

Overall, patients reported 1166 TEAEs: 664 (56.9 percent) in the ELEVIDYS group, and 502 (43 percent) in the placebo group.

Of the TEAEs, 278 (23.8 percent) were considered treatment-related TEAEs. Patients in the ELEVIDYS group reported 235 (84.5 percent) of the treatment-related TEAEs, and patients in the placebo group reported 43 (15.5 percent).

**Table 14. Adverse Events, Study 301 Part 1, Safety Population**

| Category | ELEVIDYS (N=63) n (%) | Placebo (N=62) n (%) | Total (N=125) n (%) |
|---|---|---|---|
| Number of AEs | 674 | 514 | 1188 |
| Number of TEAEs | 664 | 502 | 1166 |
| Number of SAEs | 21 | 9 | 30 |
| Number of treatment-related TEAEs | 235 | 43 | 278 |
| Number of treatment-related SAEs | 10 | 0 | 10 |
| Patients with any AE | 62 (98.4) | 57 (91.9) | 119 (95.2) |
| Patients with any TEAE | 62 (98.4) | 57 (91.9) | 119 (95.2) |
| Patients with any SAE | 14 (22.2) | 5 (8.1) | 19 (15.2) |
| Patients with any treatment-related TEAE | 48 (76.2) | 17 (27.4) | 65 (52.0) |
| Patients with any treatment-related SAE | 7 (11.1) | 0 | 7 (5.6) |
| Patients with any AE leading to study discontinuation | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 |

Source: SRP-9001-301 Clinical Study Report, Table 14.3.1
Abbreviations: AE = adverse event, n = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, SAE = serious adverse event, TEAE = treatment-emergent adverse event

**Reviewer Comment:**
The larger number of SAEs in the ELEVIDYS group compared to the placebo group is an important consideration regarding the benefit-risk profile of ELEVIDYS.

6.1.12.3 Deaths

No deaths were reported in Study 301 Part 1.

### 6.1.12.4 Nonfatal Serious Adverse Events

**Table 15. Treatment-Related Serious Adverse Events of Patients by System Organ Class and Preferred Term, Study 301 Part 1, Safety Population**

| System Organ Class<br>Preferred Term | ELEVIDYS (N=63)<br>n (%) | Placebo (N=62)<br>n (%) | Total (N=125)<br>n (%) |
|---|---|---|---|
| Any treatment-related SAE | 7 (11.1) | 0 | 7 (5.6) |
| Cardiac disorders | 1 (1.6) | 0 | 1 (0.8) |
| Myocarditis | 1 (1.6) | 0 | 1 (0.8) |
| Gastrointestinal disorders | 1 (1.6) | 0 | 1 (0.8) |
| Nausea | 1 (1.6) | 0 | 1 (0.8) |
| Vomiting | 1 (1.6) | 0 | 1 (0.8) |
| General disorders and administration site conditions | 1 (1.6) | 0 | 1 (0.8) |
| Pyrexia | 1 (1.6) | 0 | 1 (0.8) |
| Hepatobiliary disorders | 2 (3.2) | 0 | 2 (1.6) |
| Hepatotoxicity | 1 (1.6) | 0 | 1 (0.8) |
| Liver injury[a] | 1 (1.6) | 0 | 1 (0.8) |
| Investigations | 3 (4.8) | 0 | 3 (2.4) |
| Gamma-glutamyltransferase increased | 1 (1.6) | 0 | 1 (0.8) |
| Hepatic enzyme increased | 1 (1.6) | 0 | 1 (0.8) |
| Transaminases increased | 1 (1.6) | 0 | 1 (0.8) |
| Musculoskeletal and connective tissue disorders | 1 (1.6) | 0 | 1 (0.8) |
| Rhabdomyolysis | 1 (1.6) | 0 | 1 (0.8) |

Source: FDA
[a]Acute liver injury in a 16-year-old patient who was an alpha-1 antitrypsin carrier.
Abbreviations: n = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, SAE = serious adverse event

### 6.1.12.6 Clinical Test Results

**Table 16. Clinically Significant Abnormalities in Laboratory Parameters for ≥10% of Patients, Study 301 Part 1, Safety Population**

| Parameter | CTCAE Grade or Other Criteria | ELEVIDYS (N=63)<br>n (%) | Placebo (N=62)<br>n (%) | Total (N=125)<br>n (%) |
|---|---|---|---|---|
| Patients with any potentially clinically significant abnormalities | - | 63 (100.0) | 62 (100.0) | 125 (100.0) |
| ALT | Grade 1: >1.5 – 3×baseline if baseline is abnormal (or > ULN – 3×ULN if baseline is normal) | 17 (27.0) | 15 (24.2) | 32 (25.6) |
| ALT | Grade 2: >3 – 5×baseline if baseline is abnormal (or >3.0 – 5.0×ULN if baseline is normal) | 7 (11.1) | 0 | 7 (5.6) |
| ALT | Grade 3: >5 – 20×baseline if baseline is abnormal (or >5 – 20×ULN if baseline is normal) | 2 (3.2) | 0 | 2 (1.6) |
| ALT | Grade 4: >20×baseline if baseline is abnormal (or | 0 | 0 | 0 |

| Parameter | CTCAE Grade or Other Criteria | ELEVIDYS (N=63) n (%) | Placebo (N=62) n (%) | Total (N=125) n (%) |
|---|---|---|---|---|
| | >20×ULN if baseline is normal) | | | |
| AST | Grade 1: >1.5 – 3×baseline if baseline is abnormal (or > ULN – 3×ULN if baseline is normal) | 38 (60.3) | 40 (64.5) | 78 (62.4) |
| sAST | Grade 2: >3 – 5 baseline if baseline is abnormal (or >3 – 5×ULN if baseline is normal) | 13 (20.6) | 1 (1.6) | 14 (11.2) |
| AST | Grade 3: >5 – 20×baseline if baseline is abnormal (or >5 – 20×ULN if baseline is normal) | 4 (6.3) | 0 | 4 (3.2) |
| AST | Grade 4: >20×baseline if baseline is abnormal (or >20×ULN if baseline is normal) | 0 | 0 | 0 |
| GGT | Grade 1: >1 – 2.5×ULN if baseline is normal (or >2 – 2.5×baseline if baseline is abnormal) | 18 (28.6) | 4 (6.5) | 22 (17.6) |
| GGT | Grade 2: >2.5 – 5×ULN if baseline is normal (or >2.5 – 5×baseline if baseline is abnormal) | 9 (14.3) | 0 | 9 (7.2) |
| GGT | Grade 3: >5 – 20×ULN if baseline is normal (or >5 – 20×baseline if baseline is abnormal) | 9 (14.3) | 0 | 9 (7.2) |
| GGT | Grade 4: >20×ULN if baseline is normal (or >20×baseline if baseline is abnormal) | 2 (3.2) | 0 | 2 (1.6) |
| Platelets | Grade 1: <LLN – $75\times10^9$ | 21 (33.3) | 10 (16.1) | 31 (24.8) |
| Platelets | Grade 2: $<75\times10^9$ – $50\times10^9$ | 0 | 0 | 0 |
| Platelets | Grade 3: $<50\times10^9$ – $25\times10^9$ | 2 (3.2) | 0 | 2 (1.6) |
| Platelets | Grade 4: $<25\times10^9$ | 0 | 0 | 0 |
| Bilirubin | Grade 1: >1 – 1.5×ULN if baseline is normal (or >1 – 1.5×baseline if baseline is abnormal) | 4 (6.3) | 0 | 4 (3.2) |
| Bilirubin | Grade 2: >1.5-3×ULN if baseline is normal (or >1.5 – 3×baseline if baseline is abnormal) | 1 (1.6) | 0 | 1 (0.8) |
| Bilirubin | Grade 3: >3 – 10×ULN if baseline is normal (or >3.0 – 10×baseline if baseline is abnormal) | 0 | 0 | 0 |

| Parameter | CTCAE Grade or Other Criteria | ELEVIDYS (N=63) n (%) | Placebo (N=62) n (%) | Total (N=125) n (%) |
|---|---|---|---|---|
| Bilirubin | Grade 4: >10×ULN if baseline is normal (or >10×baseline if baseline is abnormal) | 0 | 0 | 0 |
| Creatine kinase | Grade 1: >1 – 2.5×ULN | 2 (3.2) | 0 | 2 (1.6) |
| Creatine kinase | Grade 2: >2.5 – 5×ULN | 4 (6.3) | 1 (1.6) | 5 (4.0) |
| Creatine kinase | Grade 3: >5 – 10×ULN | 19 (30.2) | 3 (4.8) | 22 (17.6) |
| Creatine kinase | Grade 4: >10×ULN | 63 (100.0) | 62 (100.0) | 125 (100.0) |
| Hemoglobin | Grade 1:<1×≥10 g/dL | 2 (3.2) | 6 (9.7) | 8 (6.4) |
| Hemoglobin | Grade 2: <10 g/dL and ≥8 g/dL | 1 (1.6) | 1 (1.6) | 2 (1.6) |
| Hemoglobin | Grade 3: <8 g/dL | 0 | 0 | 0 |
| ALP | Decrease from baseline: ≤15% | 58 (92.1) | 59 (95.2) | 117 (93.6) |
| ALP | Decrease from baseline: >15% and ≤45% | 61 (96.8) | 56 (90.3) | 117 (93.6) |
| ALP | Decrease from baseline: >45% | 6 (9.5) | 5 (8.1) | 11 (8.8) |
| LDH | >2.0×baseline | 0 | 3 (4.8) | 3 (2.4) |
| Complement 3 | ≥0.75 and <1×LLN | 19 (30.2) | 8 (12.9) | 27 (21.6) |
| Complement 3 | <0.75×LLN within and after 2 weeks of infusion | 0 | 0 | 0 |
| Complement 4 | ≥0.75 and <1×LLN | 33 (52.4) | 13 (21.0) | 46 (36.8) |
| Complement 4 | <0.75×LLN within and after 2 weeks of infusion | 29 (46.0) | 3 (4.8) | 32 (25.6) |

Source: Table 32, SRP-9001-301 Clinical Study Report
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal

6.1.12.7 Dropouts and/or Discontinuations

There were no withdrawals due to AE. Discontinuation is not applicable, as the treatment is a one-time infusion.

6.1.13 Study Summary and Conclusions

The most common TEAEs (those occurring in ≥20 percent of patients) for both treatment groups were vomiting, nausea, pyrexia, COVID-19 infection, cough, and upper respiratory tract infection.

The observed common TEAEs are expected since all patients were receiving long-term corticosteroid treatment as standard of care for DMD.

The 10 treatment-related SAEs were myocarditis, rhabdomyolysis, liver insults of varying severity, nausea, vomiting, and pyrexia.

Overall, there were no new safety signals detected during Study 301 and ELEVIDYS safety profile remains unchanged.

### 6.2 Trial #2—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 Patients with Duchenne Muscular Dystrophy (ENDEAVOR).

NCT04626674

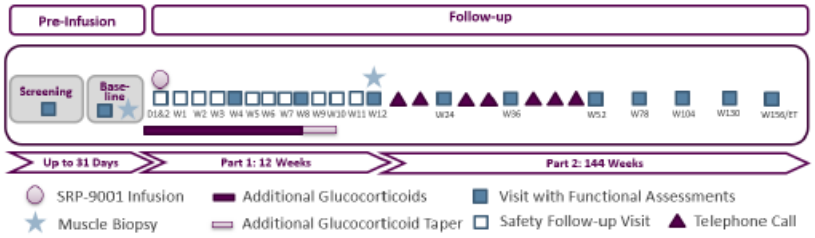
6.2.1 Objectives (Primary, Secondary, etc)

Study 103 was the first of the Applicant's clinical studies to use ELEVIDYS manufactured by the commercial process (Process B). Study 103 was intended as a "bridging" study between the initial manufacturing process A and the commercial process B, to compare expression of micro-dystrophin, and other clinical pharmacologic properties, as well as safety, in patients receiving the commercial product, rather than the laboratory product (Process A) used in earlier studies.

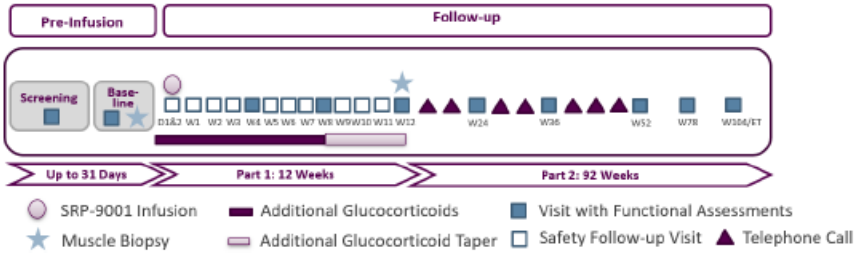
6.2.2 Design Overview

**Figure 6. Schematic Diagram of Design of Study 103 Cohorts**

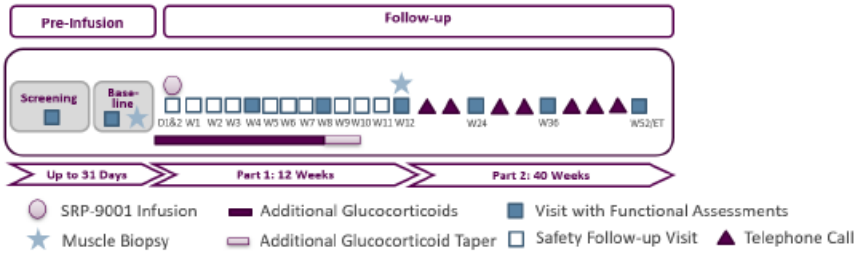
*Cohorts 1 to 3*




*Cohort 4*




*Cohort 5*




Source: Study SRP-9001-103 Clinical Study Protocol version 8 (May 31, 2023), pp. 23-39
Abbreviations: D = day, ET = early termination, W = week

Study 103 is a multicenter Phase 1b single-arm, open-label, single-dose clinical trial. Study 103 currently comprises five (of a planned seven) cohorts, based on age, ambulatory status, and DMD mutations (with Cohort 5 further subdivided into Cohort 5a and Cohort 5b). At the time of the data cutoff, the study involved 48 male patients:

Data from the following cohorts was included in the supplemental BLA submission:

- Cohort 1: 4 to 7 years old, ambulatory (n=20)
- Cohort 2: 8 to 17 years old, ambulatory (n=7)
- Cohort 3: nonambulatory (n=6)
- Cohort 4: 3 years old (n=7)
- Cohort 5a: 4 to <9 years old, ambulatory; mutation in *DMD* exons 1 to 17 (n=6)
- Cohort 5b: nonambulatory, mutation in *DMD* exons 1 to 17 (n=2)

The following cohorts are planned:

- Cohort 6: Approximately 6 ambulatory patients, age ≥2 to <3 years old at screening
- Cohort 7: Approximately 6 nonambulatory patients with moderate to severe pulmonary impairment; mutations fully contained between exons 18 to 79, inclusive

The duration of each patient's participation in Study 103 is expected to be approximately 160 weeks for Cohorts 1 to 3, 108 weeks for Cohorts 4 and 6, 56 weeks for Cohort 5, and 82 weeks for Cohort 7.

After completion of Study 103, patients will be invited to enroll in an extension study for at least 5 years after ELEVIDYS infusion, to assess long-term safety and efficacy.

**Reviewer Comment:**
Safety data from Cohorts 1 to 5 of Study 103 are included in the overall consideration of product safety. However, the only clinical outcome data in the BLA for nonambulatory patients is generated from 6 patients enrolled in Cohort 4 and 2 patients enrolled in Cohort 5b.

Data from Cohort 6 and Cohort 7 are not included in the supplemental BLA submission; no efficacy or safety data were available for Cohort 6 or Cohort 7 at the time of the data cutoff (September 13, 2023).

6.2.3 Population

The key eligibility criteria for each cohort are summarized in Table 17:

**Table 17. Key Eligibility Criteria, Study 103, Cohorts 1-7**

| Cohort | Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|---|
| Cohort 1 | • Age ≥4 to <8 years old at Screening<br>• Ambulatory<br>• NSAA Total Score >17 and ≤26 at Screening<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• Patients with *DMD* mutation between or including exons 1 to 17 not eligible |
| Cohort 2 | • Age ≥8 to <18 years old at Screening<br>• Ambulatory<br>• NSAA Total Score ≥15 and ≤26 at Screening<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• FVC <50% of predicted value and/or requirement for nocturnal ventilatory support at Screening<br>• Patients with *DMD* mutation between or including exons 1 to 17 not eligible |

| Cohort | Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|---|
| Cohort 3 | • Nonambulatory for ≥9 months[a]<br>• NSAA walk score =0<br>• Unable to perform 10-MWR at Screening<br>• PUL 2.0 entry item score ≥2<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• FVC <50% of predicted value and/or requirement for nocturnal ventilatory support at Screening<br>• Patients with *DMD* mutation between or including exons 1 to 17 not eligible |
| Cohort 4 | • Age ≥3 to <4 years old at Screening<br>• Ambulatory<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• Patients with *DMD* mutation between or including exons 1 to 17 not eligible |
| Cohort 5a | • Age ≥4 to <9 years old at Screening<br>• Ambulatory<br>• Time to Rise from floor ≤7 seconds at Screening<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation partially or fully contained between exons 1 to 17 expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• Patients with *DMD* deletions fully including exons 9 to 13 are not eligible |
| Cohort 5b | • Nonambulatory for ≥9 months[a]<br>• NSAA walk score =0<br>• Unable to perform 10-MWR at Screening<br>• PUL 2.0 entry item score ≥2<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation partially or fully contained between exons 1 to 17 expected to cause absence of dystrophin protein | • LVEF <40% on Screening echocardiogram, or clinical signs and/or symptoms of cardiomyopathy<br>• FVC <50% of predicted value and/or requirement for nocturnal ventilatory support at Screening<br>• Patients with *DMD* deletions fully including exons 9 to 13 are not eligible |
| Cohort 6 | • Age ≥2 to <3 years old at Screening<br>• Ambulatory<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • Patients with *DMD* mutation between or including exons 1 to 17 not eligible |

| Cohort | Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|---|
| Cohort 7 | • Nonambulatory for ≥9 months[a]<br>• NSAA walk score =0<br>• Unable to perform 10-MWR at Screening<br>• Stable FVC <40% of predicted and/or requirement for nocturnal ventilatory support at Screening<br>• rAAVrh74 antibody titer ≤1:400<br>• *DMD* mutation fully contained between exons 18 to 79 (inclusive) expected to cause absence of dystrophin protein | • Patients with *DMD* mutation between or including exons 1 to 17 not eligible |

Source: Modified from FDA Statistical Review
[a] Onset of loss of ambulation is defined as patient- or caregiver-reported age of continuous wheelchair use, approximated to nearest month.
Abbreviations: DMD = Duchenne muscular dystrophy, FVC = forced vital capacity, LVEF = left ventricular ejection fraction, MWR = Meter Walk/Run test, NSAA = North Star Ambulatory Assessment, PUL = Performance of Upper Limb (version 2.0) assessment

**Table 18. Treatment Exposure, Full Analysis Set, All Available Data**

| Statistics | Cohort 1 (N=20) | Cohort 2 (N=7) | Cohort 3 (N=6) | Cohort 4 (N=7) | Cohort 5 (N=8) | Total (N=48) |
|---|---|---|---|---|---|---|
| Dose ($\times 10^{14}$ vg/kg) [a] | | | | | | |
| n | 20 | 7 | 6 | 7 | 8 | 48 |
| Mean (SD) | 1.45 (0.12) | 1.31 (0.14) | 1.25 (0.06) | 1.24 (0.05) | 1.75 (0.26) | 1.42 (0.22) |
| Median | 1.42 | 1.30 | 1.25 | 1.24 | 1.84 | 1.36 |
| Q1, Q3 | 1.38, 1.58 | 1.20, 1.32 | 1.20, 1.30 | 1.20, 1.24 | 1.70, 1.88 | 1.24, 1.59 |
| Min, Max | 1.27, 1.63 | 1.20, 1.61 | 1.18, 1.30 | 1.19, 1.35 | 1.16, 2.00 | 1.16, 2.00 |
| Number of Years following SRP-9001 Treatment | | | | | | |
| n | 20 | 7 | 6 | 7 | 8 | 48 |
| Mean (SD) | 2.47 (0.14) | 1.98 (0.15) | 2.05 (0.03) | 1.46 (0.10) | 0.54 (0.18) | 1.88 (0.71) |
| Median | 2.55 | 2.01 | 2.04 | 1.47 | 0.54 | 2.06 |
| Q1, Q3 | 2.32, 2.59 | 2.00, 2.06 | 2.02, 2.06 | 1.39, 1.51 | 0.44, 0.70 | 1.47, 2.37 |
| Min, Max | 2.26, 2.67 | 1.65, 2.11 | 2.01, 2.11 | 1.30, 1.62 | 0.21, 0.73 | 0.21, 2.67 |
| Number of Subjects in Time Category following SRP-9001 Treatment | | | | | | |
| < 12 Weeks (n) | 0 | 0 | 0 | 0 | 1 | 1 |
| 12 Weeks to < 24 Weeks (n) | 0 | 0 | 0 | 0 | 1 | 1 |
| 24 Weeks to < 1 Year (n) | 0 | 0 | 0 | 0 | 6 | 6 |
| 1 Year to < 2 Years (n) | 0 | 2 | 0 | 7 | 0 | 9 |
| ≥ 2 Years (n) | 20 | 5 | 6 | 0 | 0 | 31 |

Source: Study SRP-9001-103 Interim 2 Clinical Study Report, page 60
Abbreviations: Max = maximum, Min = minimum, n (%) = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, Q1 = Quartile 1, Q3 = Quartile 3, SD = standard deviation, SRP-9001 = delandistrogene moxeparvovec-rokl (ELEVIDYS), vg = vector genome

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

ELEVIDYS was administered as a single intravenous infusion through a peripheral vein.

Dosing was stratified by weight: patients who weighed <70 kg on study Day 1 received a dose of $1.33 \times 10^{14}$ vg/kg, and patients weighing ≥70 kg on study Day 1 received a total fixed dose of $9.31 \times 10^{15}$ vg, the equivalent of the dose of $1.33 \times 10^{14}$ vg/kg administered for a 70 kg patient.

6.2.5 Directions for Use

A topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) could be applied to the skin prior to insertion of the intravenous catheter for infusion of ELEVIDYS, in accordance with site and patient preference.

Patients were closely monitored for at least 6 hours following completion of ELEVIDYS infusion.

6.2.6 Sites and Centers

Study 103 is taking place at five centers, all in the United States.

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. In addition, a study-specific Safety Review Committee was formed to review safety data and to determine whether dosing may be allowed to proceed after the first two sentinel patients in Cohorts 1 to 4.

The Study 103 visit schedules are shown in Figure 7.

**Figure 7. Schedule of Events, Study 103 Cohorts**

*Cohort 1 Schedule of Events*

| 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/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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | 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 | | X | | X | | X | | X | X | X | X | X | X | X |
| Vital signs [e] | X | X | X | 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 |
| Weight [f] | 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[h] | X[i] | | | | | | X | | | | X | | | | X[i] | | 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 |
| 100MWR [g] | X | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| ELISA [j] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| ELISpot [j] | | X | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| Hematology [k] | 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 [l] | | X | | X | | | | | | | | | | | | X | | X | | X | | X | | X |
| Troponin I | | X | | | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Glucose [m] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| CK [n] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| Liver function [k] | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| Renal function [k] | 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 |
| Vector quantification | | | X[o] | X[p] | 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/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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |
| Biomarkers | | X | | | X | | | X | | | | | | | | X | | X | | X | | | | X |
| *DMD* gene sequence analysis | | X | | | | | | | | | | | | | | | | | | | | | | |
| Whole-genome DNA sequence [q] | | X | | | | | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X | | X | | X |
| Blood sample for immune epitope mapping [r] | | | | | | | | A single sample taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| HLA typing [s] | | | | | | | | A single sample may be taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| Urinalysis [k] | X | | | X | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Muscle Biopsy [t] | | X | | | | | | | | | | | | | | X | | | | | | | | |
| ECG [u] | X | | X | | | | | X | | | | | | | | | | | | X | | X | | X |
| ECHO | X | | | | | | | | | | | | | | | | | | | X | | X | | X |
| Vector shedding samples (saliva/urine/stool) [v] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | | |
| Study drug infusion [w] | | | X | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid | | | Implement daily add-on **the day prior to** the infusion and **for at least 60 days post-infusion** | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid 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 | | | | | | | | | | | | | | | | | | | | | | | |

10MWR = 10-meter walk run; 100MWR = 100-meter walk run test; AE = adverse event; B = Baseline; C = clinic; CH50 = total complement; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HIV = human immunodeficiency virus; HLA = human leucocyte antigen; hsCRP = high-sensitivity C-reactive protein; HH6 = human herpesvirus 6; N/A = not applicable; NSAA = North Star Ambulatory Assessment; PE = physical examination; Scr = Screening; R = remote; rAAVrh74 = recombinant adeno-associated virus rhesus type 74; RNA = ribonucleic acid; T = telephone; VZV = varicella zoster virus; W = week.

a In case of subject withdrawal, Week 156 assessments should be performed at the ET visit.

b Visits indicated as "R" are visits that can be conducted at the clinic or remotely. Visits indicated as "C" have to be conducted at the clinic.

c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening before subject is dosed.

d A full physical examination will be performed at Screening ,Week 52, and Week 156/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 measure at the timepoints indicated in Section 10.4.3.

| 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/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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |

f Weight taken on Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day 1 should be used to calculate total volume of study drug administered, as 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, then they may be performed within a ± 2-week visit window for Weeks 4 and 8, and a ± 6-week visit window for Weeks 12, 24, 36, and 52. Prior to age 4, the NSAA and timed function tests (time to rise from floor, 10MWR, 100MWR, timed 4-step tests) should be attempted but it is not a protocol deviation if they are not felt to be valid by the clinical evaluator.
h Refer to Section 8.1 (inclusion criteria) and Section 8.2 (exclusion criteria) for subjects in Cohort 1 eligibility criteria at Screening.
i Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
j Antibodies to rAAVrh74 capsid and micro-dystrophin transgene (ELISA) and cellular immune responses to rAAVrh74 and micro-dystrophin transgene (ELISpot).
k See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
l Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
m Glucose does not require fasting.
n 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 assessments.
o Sample to be taken approximately 4 to 6 hours post-infusion.
p Sample to be taken approximately 22 to 26 hours post-infusion.
q 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.
r If it is not feasible to complete this requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details.
s If saliva is not available or cannot be collected due to the subject's age or undefined reason, blood may be drawn for HLA haplotyping, as long as it does not exceed the allowable total blood volume collection for that age group
t A muscle biopsy for evaluation of micro-dystrophin expression will be collected. For Cohorts 1, the Baseline biopsy will be of the medial gastrocnemius muscle, preferably on 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 lower extremity. If possible, the biopsy for Week 12 will be of the same muscle group as that used at Baseline on the contralateral side. Refer to the Surgical and Laboratory Biopsy Manual.
u All ECGs should be performed in triplicate at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
v Subjects will have samples collected at all study visits indicated (clinic and remote) unless the Sponsor 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 the infusion. Further details will be outlined in the Vector Shedding Manual.
w 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

*Cohort 2 Schedule of Events*

| 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/ 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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | 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 | | X | | X | | X | | X | X | X | X | X | X | X |
| Vital signs [e] | X | X | X | 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 |
| Weight [f] | 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[h] | X[i] | | | | | | X | | | | X | | | | X[i] | | 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 |
| 100MWR [g] | X | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| PUL (Version 2.0)[g] | X | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| PFTs (FVC, PEF)[g] | X[h] | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| ELISA [j] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| ELISpot [j] | | X | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| Hematology [k] | 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 [l] | | X | | X | | | | | | | | | | | | X | | X | | X | | X | | X |
| Troponin I | | X | | | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Glucose [m] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| CK [n] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| Liver function [k] | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| Renal function [k] | X | | | | 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/ 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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |
| 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 |
| Vector quantification | | | X[o] | X[p] | 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 [q] | | X | | | | | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X | | X | | X |
| Blood sample for immune epitope mapping [r] | | | | | | | | A single sample taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| HLA typing [s] | | | | | | | | A single sample may be taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| Urinalysis [k] | X | | | X | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Muscle Biopsy [t] | | X | | | | | | | | | | | | | | X | | | | | | | | |
| ECG [u] | X | | X | | | | | X | | | | | | | | | | | | X | | X | | X |
| ECHO [v] | X | | | | | | | | | | | | | | | | | | | X | | X | | X |
| Cardiac MRI (sub-study) | | X | | | | | | | | | | | | | | | | | | X | | X | | X |
| Musculoskeletal MRI (sub-study) | | 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 | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid | | | Implement daily add-on **the day prior to** the infusion and for **at least 60 days post-infusion** | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid Tapering | | | | | | | | | | | | | X | X | | | | | | | | | | |
| Drug Shipment Request Form | | X | | | | | | | | | | | | | | | | | | | | | | |
| Adverse Event Reporting | Ongoing collection beginning at informed consent/ assent | | | | | | | | | | | | | | | | | | | | | | | |

| 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/ 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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |
| Concomitant Medications and Procedures | Ongoing collection beginning at informed consent/ assent | | | | | | | | | | | | | | | | | | | | | | | |

10MWR = 10-meter walk run; 100MWR = 100-meter walk run test; AE = adverse event; B = Baseline; C = clinic; CH50 = total complement; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; 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; HH6 = human herpesvirus 6; MRI = magnetic resonance imaging; N/A = not applicable; NSAA = North Star Ambulatory Assessment; PE = physical examination; PEF = peak expiratory flow; PFT = pulmonary function test; PUL = Performance of the Upper Limb; Scr = Screening; R = remote; rAAVrh74 = recombinant adeno-associated virus rhesus type 74; RNA = ribonucleic acid; T = telephone; VZV = varicella zoster virus; W = week.

a In case of subject withdrawal, Week 156 assessments should be performed at the ET visit.
b Visits indicated as "R" are visits that can be conducted at the clinic or remotely. Visits indicated as "C" have to be conducted at the clinic.
c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening before subject is dosed.
d A full physical examination will be performed at Screening ,Week 52, and Week 156/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 measure at the timepoints indicated in Section 10.4.3.
f Weight taken on Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day 1 should be used to calculate total volume of study drug administered, as 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, then they may be performed within a ± 2-week visit window for Weeks 4 and 8, and a ± 6-week visit window for Weeks 12, 24, 36, and 52. Prior to age 4, the NSAA and timed function tests (time to rise from floor, 10MWR, 100MWR, timed 4-step tests) should be attempted but it is not a protocol deviation if they are not felt to be valid by the clinical evaluator.
h Refer to Section 8.1 (inclusion criteria) and Section 8.2 (exclusion criteria) for subjects in Cohort 2 eligibility criteria at Screening.
i Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
j Antibodies to rAAVrh74 capsid and micro-dystrophin transgene (ELISA) and cellular immune responses to rAAVrh74 and micro-dystrophin transgene (ELISpot).
k See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
l Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
m Glucose does not require fasting.
n 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 assessments.
o Sample to be taken approximately 4 to 6 hours post-infusion.
p Sample to be taken approximately 22 to 26 hours post-infusion.
q 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.
r If it is not feasible to complete this requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details.
s If saliva is not available or cannot be collected due to the subject's age or undefined reason, blood may be drawn for HLA haplotyping, as long as it does not exceed the allowable total blood volume collection for that age group
t A muscle biopsy for evaluation of micro-dystrophin expression will be collected. For Cohorts 2, the Baseline biopsy will be of the biceps muscle, preferably on the right arm. If the biceps 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 on the contralateral side. Refer to the Surgical and Laboratory Biopsy Manual.

| 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/ 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 | +/-21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |

u All ECGs should be performed in triplicate at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
v For time points after Screening, subjects undergoing cardiac MRI assessments do not also need to have an ECHO performed at time points when a cardiac MRI is performed.
w Subjects will have samples collected at all study visits indicated (clinic and remote) unless the Sponsor 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 the 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

*Cohort 3 Schedule of Events*

| 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/ 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 | +/- 21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | 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 | | X | | X | | X | | X | X | X | X | X | X | X |
| Vital signs [e] | X | X | X | 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 |
| Weight [f] | X | X | X | | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| PUL (Version 2.0)[g] | X[h] | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| PFTs (FVC, PEF)[g] | X[h] | X[i] | | | | | | X | | | | X | | | | X[i] | | X | X | X | X | X | X | X |
| ELISA [j] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| ELISpot [j] | | X | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X | | X |
| Hematology [k] | 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 [l] | | X | | X | | | | | | | | | | | | X | | X | | X | | X | | X |
| Troponin I | | X | | | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Glucose [m] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| CK [n] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| Liver function [k] | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| Renal function [k] | 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 |
| Vector quantification | | | X[o] | X[p] | X | X | X | X | | X | | X | X | X | X | X | | X | X | X | | | | |
| Biomarkers | | 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/ 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 | +/- 21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |
| *DMD* gene sequence analysis | | X | | | | | | | | | | | | | | | | | | | | | | |
| Whole-genome DNA sequence [q] | | X | | | | | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X | | X | | X |
| Blood sample for immune epitope mapping [r] | | | | | | | | A single sample taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| HLA typing [s] | | | | | | | | A single sample may be taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| Urinalysis [k] | X | | | X | X | | | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| Muscle Biopsy [t] | | X | | | | | | | | | | | | | | X | | | | | | | | |
| ECG [u] | X | | X | | | | | X | | | | | | | | | | | | X | | X | | X |
| ECHO [v] | X | | | | | | | | | | | | | | | | | | | X | | X | | X |
| Cardiac MRI (sub-study) | | X | | | | | | | | | | | | | | | | | | X | | X | | X |
| Musculoskeletal MRI (sub-study) | | 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 | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid | | | Implement daily add-on **the day prior to** the infusion and for **at least 60 days post-infusion** | | | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid 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 | | | | | | | | | | | | | | | | | | | | | | | |

AE = adverse event; B = Baseline; C = clinic; CH50 = total complement; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; 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; HH6 = human herpesvirus 6; MRI = magnetic resonance imaging; N/A = not applicable; PE = physical examination; PEF = peak expiratory flow; PFT = pulmonary function test; PUL = Performance of the Upper Limb; Scr = Screening; R = remote; rAAVrh74 = recombinant adeno-associated virus rhesus type 74; RNA = ribonucleic acid; T = telephone; VZV = varicella zoster virus; W = week.

| 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/ 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 | +/- 21 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C | C | C |

a In case of subject withdrawal, Week 156 assessments should be performed at the ET visit.
b Visits indicated as "R" are visits that can be conducted at the clinic or remotely. Visits indicated as "C" have to be conducted at the clinic.
c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening before subject is dosed.
d A full physical examination will be performed at Screening ,Week 52, and Week 156/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 measure at the timepoints indicated in Section 10.4.3.
f Weight taken on Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day 1 should be used to calculate total volume of study drug administered, as 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, then they may be performed within a ± 2-week visit window for Weeks 4 and 8, and a ± 6-week visit window for Weeks 12, 24, 36, and 52.
h Refer to Section 8.1 (inclusion criteria) and Section 8.2 (exclusion criteria) for subjects in Cohort 3 eligibility criteria at Screening.
i Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
j Antibodies to rAAVrh74 capsid and micro-dystrophin transgene (ELISA) and cellular immune responses to rAAVrh74 and micro-dystrophin transgene (ELISpot).
k See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
l Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
m Glucose does not require fasting.
n 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 assessments.
o Sample to be taken approximately 4 to 6 hours post-infusion.
p Sample to be taken approximately 22 to 26 hours post-infusion.
q 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.
r If it is not feasible to complete this requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details.
s If saliva is not available or cannot be collected due to the subject's age or undefined reason, blood may be drawn for HLA haplotyping, as long as it does not exceed the allowable total blood volume collection for that age group
t A muscle biopsy for evaluation of micro-dystrophin expression will be collected. For Cohort 3, the Baseline biopsy will be of the biceps muscle, preferably on the right arm. If the biceps 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 on the contralateral side. Refer to the Surgical and Laboratory Biopsy Manual.
u All ECGs should be performed in triplicate at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
v For time points after Screening, subjects undergoing cardiac MRI assessments do not also need to have an ECHO performed at time points when a cardiac MRI is performed.
w Subjects will have samples collected at all study visits indicated (clinic and remote) unless the Sponsor 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 the 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

*Cohort 4 Schedule of Events*

| 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/ 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 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C |
| Informed consent/assent | X | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion [c] | X | | X[b] | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | | | |
| Physical Exam [d] | X | 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 | | X | | X | | X | | X | X | X | X | X |
| Height/ulnar length | X | X | | | | | | X | | | | X | | | | X | | X | X | X | X | X |
| Weight [f] | X | X | X | | X | | | X | | | | X | | | | X | | X | X | X | X | X |
| NSAA (including time to rise from the floor and 10MWR) [g] | X | X[h] | | | | | | X | | | | X | | | | X[h] | | X | X | X | X | X |
| Timed 4-step test [g] | | X[h] | | | | | | X | | | | X | | | | X[h] | | X | X | X | X | X |
| 100MWR [g] | X | X[h] | | | | | | X | | | | X | | | | X[h] | | X | X | X | X | X |
| ELISA [i] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X |
| ELISpot [i] | | X | | X | X | X | | X | | | | X | | X | | X | | X | | X | | X |
| Hematology [j] | 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 [k] | | X | | X | | | | | | | | | | | | X | | X | | X | | X |
| Troponin I | | X | | | X | | | X | | | | X | | | | X | | X | X | X | X | X |
| Glucose [l] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X |
| CK [m] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | X | X |
| Liver function [j] | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X |
| Renal function [j] | 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 |

| 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/ 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 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C |
| Vector quantification | | | X[n] | X[o] | 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 [p] | | X | | | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X | | X |
| Blood sample for immune epitope mapping [q] | | | | A single sample taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | | | |
| HLA typing [r] | | | | A single sample may be taken in Part 1 or Part 2, see Investigator Lab Manual for details. | | | | | | | | | | | | | | | | | | |
| Urinalysis [j] | X | | | X | X | | | X | | | | X | | | | X | | X | X | X | X | X |
| Muscle Biopsy [s] | | X | | | | | | | | | | | | | | X | | | | | | |
| ECG [t] | X | | X | | | | | X | | | | | | | | | | | | X | | X |
| ECHO | X | | | | | | | | | | | | | | | | | | | X | | X |
| Vector shedding samples (saliva/urine/stool) [u] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X |
| Study drug infusion [v] | | | X | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid | | | Implement daily add-**1 week prior to the infusion** and for **at least 60 days post-infusion** | | | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid Tapering | | | | | | | | | | | | | X | X | 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 | | | | | | | | | | | | | | | | | | | | | |

10MWR = 10-meter walk run; 100MWR = 100-meter walk run test; AE = adverse event; B = Baseline; C = clinic; CH50 = total complement; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HIV = human immunodeficiency virus; HLA = human leucocyte antigen; hsCRP = high-sensitivity C-reactive protein; HH6 = human herpesvirus 6; N/A = not applicable; NSAA = North Star Ambulatory Assessment; PE = physical examination;Scr = Screening; R = remote; rAAVrh74 = recombinant adeno-associated virus rhesus type 74; RNA = ribonucleic acid; Scr = Screening; T = telephone; VZV = varicella zoster virus; W = week.
a In case of subject withdrawal, Week 104 assessments should be performed at the ET visit.

| 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/ 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 |
| Visit type [b] | C | C | C | C | C | R | R | C | R | R | R | C | R | R | R | C | T | C | C | C | C | C |

b Visits indicated as "R" are visits that can be conducted at the clinic or remotely. Visits indicated as "C" have to be conducted at the clinic.
c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening before subject is dosed.
D A full physical examination will be performed at Screening ,Week 52, and Week 104/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 measure at the timepoints indicated in Section 10.4.3.
f Weight taken on Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day 1 should be used to calculate total volume of study drug administered, as 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, then they may be performed within a ± 2-week visit window for Weeks 4 and 8, and a ± 6-week visit window for Weeks 12, 24, 36, and 52. Prior to age 4, the NSAA and timed function tests (time to rise from floor, 10MWR, 100MWR, timed 4-step tests) should be attempted but it is not a protocol deviation if they are not felt to be valid by the clinical evaluator.
h Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
i Antibodies to rAAVrh74 capsid and micro-dystrophin transgene (ELISA) and cellular immune responses to rAAVrh74 and micro-dystrophin transgene (ELISpot).
j See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
k Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
l Glucose does not require fasting.
m 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 assessments.
n Sample to be taken approximately 4 to 6 hours post-infusion.
o Sample to be taken approximately 22 to 26 hours post-infusion.
p 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.
q If it is not feasible to complete this requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details.
r If saliva is not available or cannot be collected due to the subject's age or undefined reason, blood may be drawn for HLA haplotyping, as long as it does not exceed the allowable total blood volume collection for that age group
s A muscle biopsy for evaluation of micro-dystrophin expression will be collected. For Cohort 4, the Baseline biopsy will be of the medial gastrocnemius muscle, preferably on 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 lower extremity. If possible, the biopsy for Week 12 will be of the same muscle group as that used at Baseline 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 (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
u Subjects will have samples collected at all study visits indicated (clinic and remote) unless the Sponsor 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 the infusion. Further details will be outlined in the Vector Shedding Manual.
v 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

*Cohort 5 Schedule of Events*

| 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/ 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 | |
| Visit type [b] | C | C | C | C | C | R | R | C | C | C | R | C | R | R | R | C | T | 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 | X | | X | | X | | X | | X | X | X | |
| Vital signs [e] | 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 | |
| Weight [f] | X | X | X | | X | | | X | | | | X | | | | X | | X | X | X | |
| NSAA (including time to rise from the floor and 10MWR) [g] | X[h] | X[i] | | | | | | X | | | | X | | | | X[l] | | X | X | X | |
| Timed 4-step test [g] | | X[l] | | | | | | X | | | | X | | | | X[l] | | X | X | X | |
| 100MWR [g] | X | X[l] | | | | | | X | | | | X | | | | X[l] | | X | X | X | |
| PUL (Version 2.0)[g] | X[h] | X[l] | | | | | | X | | | | X | | | | X[l] | | X | X | X | |
| PFTs (FVC, PEF)[g] | X[h] | X[l] | | | | | | X | | | | X | | | | X[l] | | X | X | X | |
| ELISA [j] | X | | | X | X | X | | X | | | | X | | X | | X | | X | | X | |
| ELISpot [j] | | X | | X | | X | | X | X | X | | X | | X | | X | | X | | X | |
| Hematology [k] | 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 [l] | | X | | X | | | | | | | | | | | | X | | X | | X | |
| Troponin I | | X | | | X | | | X | X | X | | X | | | | X | | X | X | X | |
| Glucose [m] | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X | |
| CK [n] | X | | | X | X | X | | X | X | X | | X | | X | | X | | X | X | X | |
| Liver function k | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | |
| Renal function k | 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/ 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 |
| Visit type [b] | C | C | C | C | C | R | R | C | C | C | R | C | R | R | R | C | T | C | C | C |
| hsCRP and complement (CH50, C3, C4, and factor B) | X | | | X | X | X | | X | | X | | X | | X | | X | | X | X | X |
| Vector quantification | | | X[o] | X[p] | X | X | X | X | | X | | X | X | X | X | X | | X | X | X |
| Biomarkers | | X | | | X | | | X | | | | | | | | X | | X | | X |
| *DMD* gene sequence analysis | | X | | | | | | | | | | | | | | | | | | |
| Whole-genome DNA sequence [q] | | X | | | | | | | | | | | | | | | | | | |
| RNA sequence | | X | | | | | | X | | | | X | | | | X | | X | X | X |
| Blood sample for immune epitope mapping [r] | | | | A single sample taken in Part 1 or Part 2, see Investigator Laboratory Manual for details. | | | | | | | | | | | | | | | | |
| HLA typing [s] | | | | X | | | | | | | | | | | | | | | | |
| Urinalysis [k] | X | | | X | X | | | X | | | | X | | | | X | | X | X | X |
| Muscle Biopsy [t] | | X | | | | | | | | | | | | | | X | | | | |
| ECG [u] | X | | X | | | | | X | | | | | | | | | | | | X |
| ECHO [v] | X | | | | | | | | | | | | | | | | | | | X |
| Cardiac MRI (sub-study) | | X | | | | | | | | | | | | | | | | | | X |
| Musculoskeletal MRI (sub-study) | | X | | | | | | | | | | | | | | | | | | X |
| Study drug infusion [w] | | | X | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid | | | Implement daily add-on **the day prior to** the infusion and **for at least 60 days post-infusion** | | | | | | | | | | | | | | | | | |
| Add-on glucocorticoid 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 | | | | | | | | | | | | | | | | | | | |

| 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/ 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 |
| Visit type [b] | C | C | C | C | C | R | R | C | C | C | R | C | R | R | R | C | T | C | C | C |

10MWR = 10-meter walk run; 100MWR = 100-meter walk run test; AE = adverse event; B = Baseline; C = clinic; CH50 = total complement; CK = creatine kinase; CMV = cytomegalovirus; D = day; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = electrocardiogram; ECHO = echocardiogram; ELISA = Enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked immunospot; 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; HH6 = human herpesvirus 6; MRI = magnetic resonance imaging; N/A = not applicable; NSAA = North Star Ambulatory Assessment; PE = physical examination; PEF = peak expiratory flow; PFT = pulmonary function test; PUL = Performance of the Upper Limb; Scr = Screening; R = remote; rAAVrh74 = recombinant adeno-associated virus rhesus type 74; RFF = rise from the floor ; RNA = ribonucleic acid; Scr = Screening; T = telephone; VZV = varicella zoster virus; W = week.

a In case of subject withdrawal, Week 52 assessments should be performed at the ET visit.
b Visits indicated as "R" are visits that can be conducted at the clinic or remotely. Visits indicated as "C" have to be conducted at the clinic.
c Investigator or designee to confirm no changes to eligibility criteria since eligibility criteria assessment for screening before subject is dosed.
d A full physical examination will be performed at Screening and Week 52/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 measure at the timepoints indicated in Section 10.4.3.
f Weight taken on Screening visit should be used to complete Drug Shipment Request Form. Weight taken on Day 1 should be used to calculate total volume of study drug administered, as 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, then they may be performed within a ± 2-week visit window for Weeks 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 Cohort 5a only. Prior to age 4, the NSAA and timed function tests (time to rise from floor, 10MWR, 100MWR, timed 4-step tests) should be attempted but it is not a protocol deviation if they are not felt to be valid by the clinical evaluator. PUL (Version 2.0 and PFTs (FVC, PEF) assessments apply to Cohort 5b only.
h Refer to Section 8.1 (inclusion criteria) and Section 8.2 (exclusion criteria) for subjects in Cohort 5 eligibility criteria at Screening.
i Baseline and Week 12 functional assessments must be performed prior to the biopsy procedure.
j Antibodies to rAAVrh74 capsid and micro-dystrophin transgene (ELISA) and cellular immune responses to rAAVrh74 and micro-dystrophin transgene (ELISpot).
k See Section 10.4.6.1 for a list of specific analytes. Note that at Week 12, samples will be collected before the biopsy.
l Specific analytes include sodium, chloride, potassium, and carbon dioxide. At Week 12, samples will be collected before the biopsy.
m Glucose does not require fasting.
n 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 assessments.
o Sample to be taken approximately 4 to 6 hours post-infusion.
p Sample to be taken approximately 22 to 26 hours post-infusion.
q 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.
r . If it is not feasible to complete this requirement in Part 1, this sampling should be completed in Part 2. See Laboratory Manual for further details. For Cohort 5 only: sample to be taken at Week 11.
s If saliva is not available or cannot be collected due to the subject's age or undefined reason, blood may be drawn for HLA haplotyping, as long as it does not exceed the allowable total blood volume collection for that age group
t A muscle biopsy for evaluation of micro-dystrophin expression will be collected. For Cohort 5a, the Baseline biopsy will be of the medial gastrocnemius muscle, preferably on 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 lower extremity. For Cohort 5b, the Baseline biopsy will be of the biceps muscle, preferably on the right arm. If the biceps 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 on the contralateral side. Refer to the Surgical and Laboratory Biopsy Manual.

| 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/ ET[x] |
| 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 |
| Visit type [y] | C | C | C | C | C | R | R | C | C | C | R | C | R | R | R | C | T | C | C | C |

u All ECGs should be performed in triplicate at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). On Day 1 only, triplicate ECGs will be taken both before and following the end of the infusion.
v For time points after Screening, subjects undergoing cardiac MRI assessments do not also need to have an ECHO performed at time points when a cardiac MRI is performed.
w 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 (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied prior to infusions per site and subject preference.

Source: Study SRP-9001-103 Clinical Study Protocol version 8 (May 31, 2023), pp. 23-39
Abbreviations: AE = adverse event, B = Baseline, C = clinic, CH50 = total complement, CK = creatinine kinase, CMV = cytomegalovirus, D = day, DMD = Duchenne muscular dystrophy, DNA = deoxyribonucleic acid, EBV = Epstein-Barr Virus, ECG = electrocardiogram, ECHO = echocardiogram, ELISA = Enzyme-linked immunosorbent assay, ELISpot = Enzyme-linked immunospot, ET = early termination, FVC = forced vital capacity, HEENT = head, ears, eyes, nose, and throat, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, hsCRP = high-sensitivity C-reactive protein, HH6 = human herpesvirus 6, MRI = magnetic resonance imaging, 10MWR =10-meter walk run test, 100MWR =100-meter walk run test, 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, rAAVrh74 = recombinant adeno-associated virus rhesus type 74, R = remote, RNA = ribonucleic acid, Scr = screening, T = telephone, VZV = varicella zoster virus, W = week

### 6.2.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint for Study 103 is expression of micro-dystrophin, measured by western blot of biopsied muscle tissue, at Week 12 after infusion of ELEVIDYS.

The secondary efficacy endpoints are:

- Evaluation of vector shedding
- Expression of micro-dystrophin, measured by immunofluorescence analysis of fiber intensity and by percent micro-dystrophin-positive muscle fibers
- Immunogenicity of ELEVIDYS, as measured by detection of antibodies to the rAAVrh74 capsid
- Safety of ELEVIDYS

**Reviewer Comment:**
As noted above, Study 103 was the first of the Applicant's studies to use ELEVIDYS manufactured using the commercial process. FDA recommended that the Applicant perform the study in a randomized, double-blind, concurrent-control manner, so that it could serve as a true bridging study to enable comparison of clinical outcomes, as well as expression of micro-dystrophin across products manufactured using the two processes. The Applicant opted instead to conduct Study 103 as an open-label study.

Exploratory endpoints included evaluation of functional outcome measures, such as the NSAA and the PUL (version 2.0), in selected cohorts at designated times. The open-label design, however, precludes rigorous assessment of these clinical outcome measures.

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis of the primary endpoint was descriptive.

Based on experience and comparability data, the Applicant determined that a sample size of up to approximately 58 patients (at least 6 in each cohort) would be adequate to

describe expression of micro-dystrophin and vector shedding in patients treated with product manufactured by the commercial process (Process B).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The Analysis Population consisted of the Full Analysis Set (all patients who enrolled in the study and received ELEVIDYS).

6.2.11 Efficacy Analyses

The following clinical efficacy assessments are discussed below for Study 103:

- NSAA
- PUL 2.0
- 100-MWR time
- Time to Ascend 4 Steps
- Time to Rise
- 10-MWR time

The tested populations were in the following cohorts:
- Cohort 1: 4 to 7 years old, ambulatory (n=20)
- Cohort 2: 8 to 17 years old, ambulatory (n=7)
- Cohort 3: nonambulatory (n=6)
- Cohort 4: 3 years old (n=7)

**Reviewer Comment:**
These clinical outcome measures are all effort-dependent, making the results, including the magnitude of change, challenging to interpret in the absence of blinding and a concurrent control. Disease heterogeneity further complicates interpretation of the results.

6.2.11.1 North Star Ambulatory Assessment

The Applicant evaluated change in the NSAA Total Score from baseline for patients in Cohort 1, Cohort 2, and Cohort 4 (Table 19). The baseline NSAA Total Score for patients in these cohorts ranged from 11 to 26 (out of the maximum possible score of 34 points).

**Table 19. North Star Ambulatory Assessment: Change in Total Score From Baseline to Week 52 and Week 104**

| Time Point | Cohort 1 [4-7 Years Old, Ambulatory] Mean Δ ± SD (n=20) | Cohort 2 [8-17 Years Old, Ambulatory] Mean Δ ± SD (n=7) | Cohort 4 [≥3 to <4 Years Old, Ambulatory] Mean Δ ± SD (n=7) |
|---|---|---|---|
| Week 52 | 4.0±3.5 | -0.1±6.6 | 6.0±1.8 |
| Week 104 | 3.6±4.3 | -2.7±7.2[a] | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 11, pp. 47-48)
[a] Results are for six patients; results for Week 104 visit for one patient had not been scored.
Abbreviations: n = number of patients in the specified group, or the total sample, SD = standard deviation

Patients in Cohort 1 demonstrated a mean improvement from baseline at Week 52 (4.0±3.5 points), which was essentially maintained at Week 104 (3.6±4.3 points).

Patients in Cohort 2 showed a mean decline from baseline at Week 52, with further decline at Week 104.

Patients in Cohort 4 showed a mean improvement from baseline at Week 52. Week 104 data were not available for Cohort 4 due to insufficient follow up. Of note, no patient in Cohort 4 was able to complete all NSAA items at both baseline and at Week 52.

**Reviewer Comment:**
As discussed above, the NSAA is an effort-dependent outcome measure. Results from open-label studies are therefore inherently challenging to interpret. The small sample size in each cohort further limits interpretation of these results.

We note that patients in Cohort 1 and Cohort 4 are in the age range in which improvement on the NSAA is expected to occur with standard of care treatment alone. Since the Applicant did not include a concurrent control(s) in Study 103, we cannot determine whether the improvement noted in Cohort 1 and Cohort 4 can be attributed to the product.

Similarly, without a concurrent control, we cannot clearly ascertain whether the decline observed in Cohort 2 indicates lack of effect of the product, or whether the patients would have experienced an even greater decline on standard of care treatment alone.

6.2.11.2 Performance of Upper Limb, Version 2.0

PUL 2.0 is a clinician-reported outcome measure used to evaluate motor function in the upper limbs in patients with DMD.

PUL 2.0 begins with an entry item, to broadly characterize the patient's starting functional level. The entry item is scored from 0 (no useful function of hands) to 6 (able to abduct both arms simultaneously, with elbows maintained in full extension until the elbows reach the ears). The entry item score is not included in the PUL 2.0 Total Score. Instead, the entry item score determines which of the 22 functional tasks are tested.

The tasks are designed to reflect various activities of daily living. Performance on each item is graded as 0 (unable to complete), 1 (completes independently but with modifications), or 2 (completes without compensatory modifications). The total score ranges from 0 to 42, with a higher score indicating greater function.

The 22 tasks are subdivided into 3 domains: shoulder level (6 items, maximum score 12), elbow level (9 items, maximum score 17) and distal level (7 items, maximum score 13) dimension. Each domain can be scored separately, with the three results then added to obtain the total score.

**Table 20. Change in PUL 2.0 Total Score: Baseline to Week 52 and Week 104, Study 103**

| Time Point | Cohort 2 [8-17 Years Old, Ambulatory] ΔPUL Mean ± SD (n=7) | Cohort 3 [Nonambulatory for ≥9 Months] ΔPUL Mean ± SD (n=6) | Cohort 5b [Nonambulatory for ≥9 Months] ΔPUL Mean ± SD (n=2) |
|---|---|---|---|
| Week 52 | -0.3±2.1 | -1.5±0.8 | 3.0±1.4 |
| Week 104 | -2.3±4.3 | -3.8±2.7 | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 16, pp. 55-56)
Abbreviations: n = number of patients in the specified group, or the total sample, PUL = Performance of Upper Arm, SD = standard deviation

**Reviewer Comment:**
The clinical significance of these results is challenging to interpret in the absence of concurrent controls.

The PUL 2.0 also is both effort-dependent and process-dependent. Due to the former, outcomes from open-label studies are highly susceptible to bias. The latter prevents rigorous comparison to scores from external sources such as natural history studies or registries, or even to scores from clinical trials of other drugs for DMD.

Further complicating interpretation is the likelihood, supported by data from the Applicant's randomized, double-blind, placebo-controlled studies, that any treatment effect of ELEVIDYS is likely to be modest.

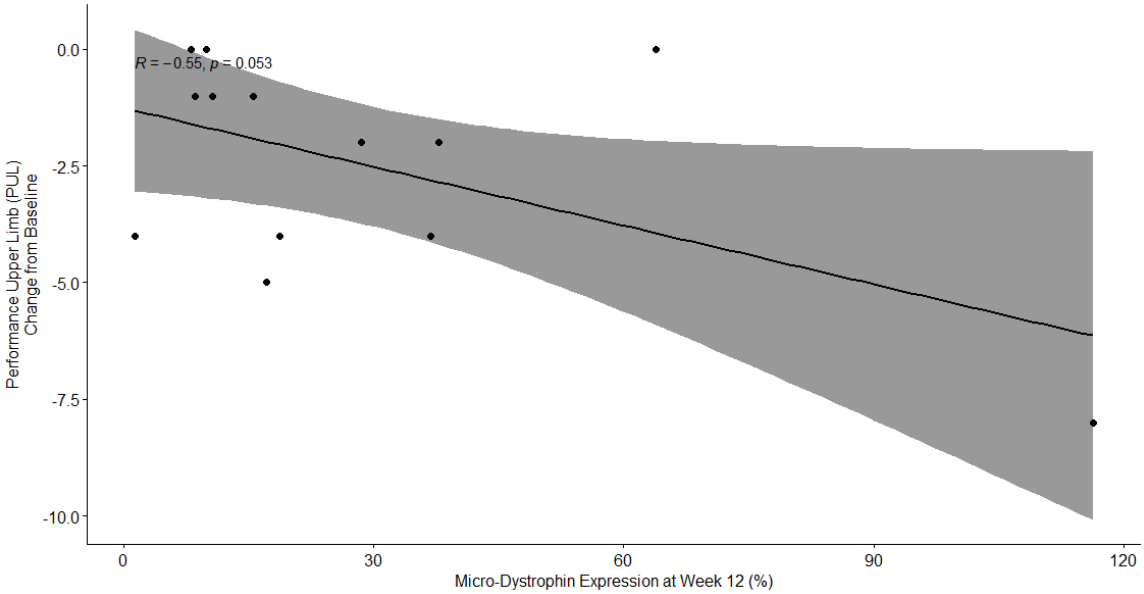
Heterogeneity in PUL 2.0 outcomes adds another complicating element. Changes in PUL Total Score occur over time and are associated with age and functional status. Coratti, et al.[15] reported that younger ambulatory patients demonstrate multiple gains in ability. Older ambulatory patients typically show the lowest loss rates, primarily in the shoulder domain. The highest loss rate was observed in the shoulder domain in patients transitioning from ambulatory to nonambulatory status (6-Minute Walk Test distance of <250 meters), and in the elbow and distal domains of nonambulatory patients.

Pane and colleagues[16] report that although loss of function is progressive, the rate of loss differs across the three domains, and is nonlinear. To enable clear interpretation of score changes, multiple factors should be considered, including genotype and, the following factors, as appropriate for the individual patient: the extent of the patient's ambulatory ability (based on 6-Minute Walk Test distance); whether that patient has entered the transition period from ambulatory to nonambulatory status; the time since loss of ambulation for patients unable to ambulate.

15 Coratti, G, M Pane, C Brogna, A D'Amico, E Pegoraro, L Bello, VA Sansone, E Albamonte, E Ferraroli, ES Mazzone, L Fanelli, S Messina, M Sframeli, M Catteruccia, G Cicala, A Capasso, M Ricci, S Frosini, G De Luca, E Rolle, R De Sanctis, N Forcina, G Norcia, L Passamano, M Scutifero, A Gardani, A Pini, G Monaco, MG D'Angelo, D Leone, R Zanin, GL Vita, C Panicucci, C Bruno, T Mongini, F Ricci, A Berardinelli, R Battini, R Masson, G Baranello, C Dosi, E Bertini, V Nigro, L Politano, and E Mercuri, 2024, Gain and loss of upper limb abilities in Duchenne muscular dystrophy patients: A 24-month study, Neuromuscul Disord, 34:75-82.
16 Pane, M, G Coratti, C Brogna, F Bovis, A D'Amico, E Pegoraro, L Bello, V Sansone, E Albamonte, E Ferraroli, ES Mazzone, L Fanelli, S Messina, M Catteruccia, G Cicala, M Ricci, S Frosini, G De Luca, E Rolle, R De Sanctis, N Forcina, G Norcia, L Passamano, A Gardani, A Pini, G Monaco, MG D'Angelo, A Capasso, D Leone, R Zanin, GL Vita, C Panicucci, C Bruno, T Mongini, F Ricci, A Berardinelli, R Battini, R Masson, G Baranello, C Dosi, E Bertini, L Politano, and E Mercuri, 2023, Longitudinal Analysis of PUL 2.0 Domains in Ambulant and Non-Ambulant Duchenne Muscular Dystrophy Patients: How do they Change in Relation to Functional Ability?, J Neuromuscul Dis, 10(4):567-574.

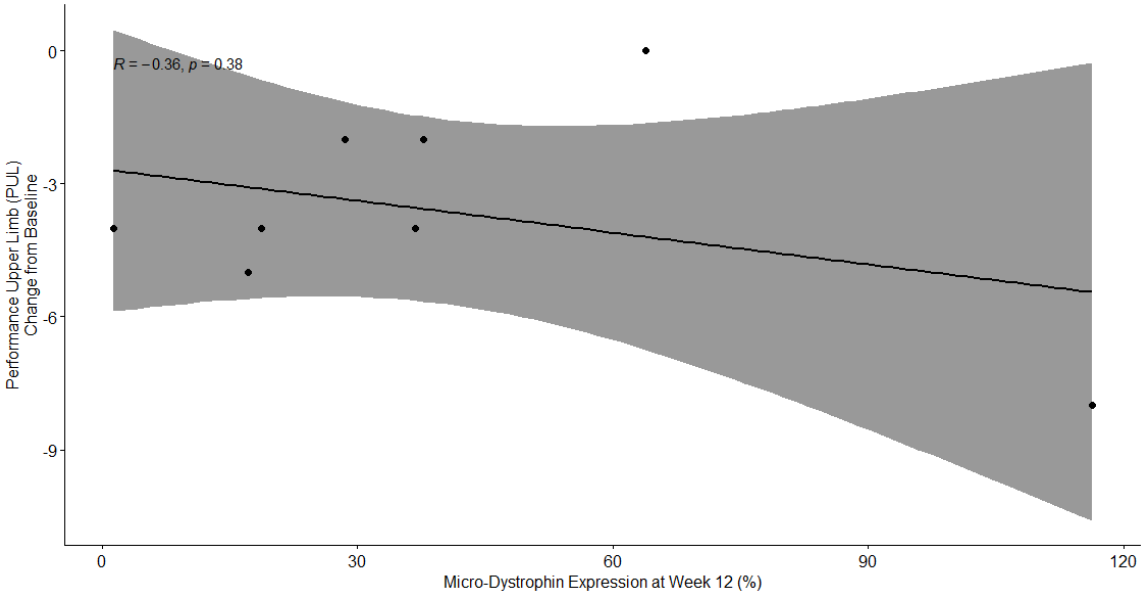
The Applicant's PUL 2.0 results also do not support use of expression of micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit." FDA analysis (Figure 8) did not show a statistically significant relationship (p=0.25) between expression of micro-dystrophin and scores on PUL 2.0 for the overall group of nonambulatory patients of any age (Cohort 3 and Cohort 5b) and older patients who are still ambulatory (Cohort 2). Similarly, no statistically significant association (p=0.68) was present (Figure 9) for the nonambulatory patients (Cohort 3 and Cohort 5b). However, although in both cases the slope of the regression line is negative, we cannot conclude that increased expression of micro-dystrophin results in patients with lower PUL 2.0 scores; the limited available data, particularly for patients producing higher levels of micro-dystrophin, do not permit a reliable assessment of such a relationship.

**Figure 8. Association Between Level of Micro-Dystrophin (Measured by Western Blot) and Scores on PUL 2.0, Combined Group of Nonambulatory Patients of Any Age (Cohort 3 and Cohort 5b) and Older Ambulatory Patients (Cohort 2),Study 103**




Source: FDA Clinical Pharmacology reviewer
The slope of the regression line R = -0.55 (p=0.053). The Spearman correlation coefficient is -0.34 (p=0.25).
Abbreviation: PUL 2.0 = Performance of Upper Limb (version 2.0)

**Figure 9. Association Between Level of Micro-Dystrophin (Measured by Western Blot) and Scores on PUL 2.0, All Nonambulatory Patients (Cohort 3 and Cohort 5b), Study 103**




Source: FDA Clinical Pharmacology reviewer
Abbreviation: PUL 2.0, Performance of Upper Limb (version 2.0)

6.2.11.3 100-Meter Walk/Run Time

The Applicant evaluated change in the 100-MWR Time for patients in Cohort 1, Cohort 2, and Cohort 4 (Table 21). The baseline time for patients in these cohorts was <148 seconds.

**Table 21. 100-Meter Walk/Run Time: Change From Baseline to Week 52 and Week 104, Study 103**

| Time Point | Cohort 1 [4-7 Years Old, Ambulatory] Mean Δ ± SD (n=20) | Cohort 2 [8-17 Years Old, Ambulatory] Mean Δ ± SD (n=7) | Cohort 4 [≥3 to <4 Years Old, Ambulatory] Mean Δ ± SD (n=2)[a] |
|---|---|---|---|
| Week 52 | -8.02±9.21 | 12.17±14.60 | -25.95±16.48 |
| Week 104 | -3.22±17.31 | 21.42±20.42 | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 12, pp. 49-50)
[a] Although Cohort 4 comprises 7 patients; nonmissing values were available for only 2 patients both at baseline and Week 52. For the remaining patients, baseline results were not valid (1 patient) or not completed (1 patient) due to patient behavior; Week 52 results were not valid (2 patients) or not performed (1 patient) due to patient behavior.
Abbreviations: n = number of patients in the specified group, or the total sample, SD = standard deviation

Patients in Cohort 1 demonstrated a mean improvement from baseline at Week 52, which diminished by Week 104.

Patients in Cohort 2 showed a mean decline from baseline at Week 52, with further decline at Week 104.

For Cohort 4, data were available for only two patients both at baseline and Week 52. Week 104 data were not available for Cohort 4.

**Reviewer Comment:**
The 100-MWR is effort-dependent, making results challenging to interpret in the absence of blinding and a concurrent control.

It is not clear whether the initial improvement seen in Cohort 1 at Week 52 (-8.02±9.21), followed by diminished improvement at Week 104 (-3.22±17.31), represents a modest effect which declines over time, or simply random fluctuation, particularly considering the wide standard deviation in both cases.

Without a concurrent control, we cannot clearly determine whether the decline observed in Cohort 2 both at Week 52 and Week 104 indicates lack of effect of the product for these patients, or whether the patients would have experienced an even greater decline on standard of care treatment alone.

It is difficult to reach any conclusions for Cohort 4 since data could be obtained from only two patients both at baseline and Week 52.

6.2.11.4 Time to Ascend 4 Steps

The Applicant evaluated change in the Time to Ascend 4 Steps for patients in Cohort 1, Cohort 2, and Cohort 4 (Table 22). The baseline time for patients in these cohorts was <10.5 seconds.

**Table 22. Time to Ascend 4 Steps: Change From Baseline to Week 52 and Week 104, Study 103**

| Time Point | Cohort 1 [4-7 Years Old, Ambulatory] Mean Δ ± SD (n=20) | Cohort 2 [8-17 Years Old, Ambulatory] Mean Δ ± SD (n=7) | Cohort 4 [≥3 to <4 Years Old, Ambulatory] Mean Δ ± SD (n=7) |
|---|---|---|---|
| Week 52 | -0.79±0.88 | 0.69±1.27 | -2.26±1.32 |
| Week 104 | -0.15±1.38 | 1.52±1.64 | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 13, pp. 50-51)
Abbreviations: n = number of patients in the specified group, or the total sample, SD = standard deviation

Patients in Cohort 1 demonstrated a mean improvement from baseline at Week 52 (-0.79±0.88), which diminished at Week 104 (-0.15±1.38).

Patients in Cohort 2 showed a mean decline from baseline at Week 52, with further decline at Week 104.

Patients in Cohort 4 showed a mean improvement from baseline at Week 52. Week 104 data were not available.

**Reviewer Comment:**
The Time to Ascend 4 Steps assessment is effort-dependent, making results challenging to interpret without blinding and a concurrent control.

It is not clear whether the initial improvement seen in Cohort 1 at Week 52, followed by diminished improvement at Week 104, represents a modest effect which declines over

time, or simply random fluctuation. The extent of potential improvement was within the standard deviation at both time points.

Without a concurrent control, we cannot clearly determine whether the decline observed in Cohort 2 both at Week 52 and Week 104 indicates lack of effect of the product for these patients, or whether the patients would have experienced an even greater decline with standard of care treatment.

6.2.11.5 Time to Rise

The Applicant evaluated change in the Time to Rise for patients in Cohort 1, Cohort 2, and Cohort 4 (Table 23). The baseline time for patients in these cohorts was <10.5 seconds.

**Table 23. Time to Rise: Change From Baseline to Week 52 and Week 104, Study 103**

| Time Point | Cohort 1 [4-7 Years Old, Ambulatory] Mean Δ ± SD (n=20) | Cohort 2 [8-17 Years Old, Ambulatory] Mean Δ ± SD (n=6) | Cohort 4 [≥3 to <4 Years Old, Ambulatory] Mean Δ ± SD (n=6) |
|---|---|---|---|
| Week 52 | -0.48±1.47 | 0.35±1.33 | -0.95±1.23 |
| Week 104 | 4.09±3.44[a] | 6.95±5.07[b] | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 16, pp. 52-53)
[a] Data for 19 patients.
[b] Data for 4 patients.
Abbreviations: n = number of patients in the specified group, or the total sample, SD = standard deviation

Patients in Cohort 1 demonstrated a small mean improvement from baseline to Week 52 (-0.48±1.47), followed by a substantial decline at Week 104 (4.09±3.44).

Patients in Cohort 2 showed a small mean decline from baseline at Week 52, with a substantial further decline at Week 104.

Patients in Cohort 4 showed a mean improvement from baseline at Week 52, within the range of the standard deviation. Week 104 data were not available.

**Reviewer Comment**
The Time to Rise is effort-dependent, making results challenging to interpret without blinding and a concurrent control.

It is not clear if the initial small improvement seen in Cohort 1 at Week 52, followed by decline from baseline at Week 104, represents a small, non-durable treatment effect which declines over time. The extent of improvement at Week 52 was within the standard deviation.

Without a concurrent control, we cannot clearly determine whether the decline observed in Cohort 2 both at Week 52 and Week 104 is due to lack of effect of the product, or whether these patients would have experienced an even greater decline with standard of care treatment.

### 6.2.11.6 10-Meter Walk/Run Time

The Applicant evaluated change in the 10-MWR Time for patients in Cohort 1, Cohort 2, and Cohort 4 (Table 24). The baseline time for patients in these cohorts was <9.4 seconds.

**Table 24. 10-Meter Walk/Run Time: Change From Baseline to Week 52 and Week 104, Study 103**

| Time Point | Cohort 1 [4-7 Years Old, Ambulatory] Mean Δ ± SD (n=20) | Cohort 2 [8-17 Years Old, Ambulatory] Mean Δ ± SD (n=7) | Cohort 4 [≥3 to <4 Years Old, Ambulatory] Mean Δ ± SD (n=7) |
|---|---|---|---|
| Week 52 | -0.77±0.84 | 0.97±1.08 | -1.60±1.20[a] |
| Week 104 | -0.11±1.42 | 2.27±1.95[b] | - |

Source: Modified from Applicant (Study SRP-9001-103 Interim 2 Clinical Study Report, Table 15, pp. 53-54)
[a] Data for 6 patients.
[b] Data for 6 patients.
Abbreviations: n = number of patients in the specified group, or the total sample, SD = standard deviation

Patients in Cohort 1 demonstrated a small mean improvement from baseline to Week 52, followed by a decline at Week 104.

Patients in Cohort 2 showed a small mean decline from baseline at Week 52, with a further decline at Week 104.

Patients in Cohort 4 showed a mean improvement from baseline at Week 52. Week 104 data were not available.

**Reviewer Comment**
The 10-MWR is effort-dependent; results are challenging to interpret without blinding and a concurrent control. Moreover, variability is quite high in all cohorts and at all time points.

It is not clear if the initial small improvement seen in Cohort 1 at Week 52, followed by diminished improvement from baseline at Week 104, represents a modest effect which declines over time. The results may constitute a spurious finding, due to the high variability (standard deviation) relative to the mean.

Without a concurrent control, we cannot clearly determine whether the decline observed in Cohort 2 both at Week 52 and Week 104 is due to lack of effect of the product, or whether these patients would have experienced an even greater decline with standard of care treatment.

6.2.11.1 Analyses of Primary Endpoint(s)

- A mean increase in expression of micro-dystrophin (assessed by western blot, adjusted by muscle content) from baseline to Week 12 was observed in Cohorts 1 to 5; the mean increase was statistically significant for all five cohorts ($p<0.05$).
- A mean increase in expression of micro-dystrophin (assessed by intensity of immunofluorescent staining of muscle fibers, as a percent of control) from baseline to

Week 12 was observed in Cohorts 1 to 5; the mean increase was statistically significant for all 5 cohorts ($p<0.05$).

- A mean increase in expression of micro-dystrophin (assessed by percent of muscle fibers demonstrating immunofluorescent-positive staining for micro-dystrophin) from baseline to Week 12 was observed in Cohorts 1 to 5; the mean increase was statistically significant for all five cohorts ($p<0.05$).
- A mean increase in ELEVIDYS vector genome copies per nucleus (measured by digital droplet polymerase chain reaction assay) from baseline to Week 12 was observed in Cohorts 1 to 5, demonstrating biodistribution and successful transduction. The mean increases were statistically significant for Cohorts 1 to 5 ($p<0.05$).

**Reviewer Comment**
The observation of expression of micro-dystrophin in muscle biopsy tissue at Week 12 is consistent with earlier findings in Study 102 Part 1. The clinical meaningfulness, however, remains unclear. Please see reviewer comment in Section 6.2.11.2 on the analysis of association of micro-dystrophin expression and functional outcomes.

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population for Study 103 consists of 48 patients who received ELEVIDYS. TEAEs include all adverse events that first occurred or increased in severity since the study treatment of ELEVIDYS in the Primary Analysis Set.

**Table 25. Adverse Events, Study 103, Full Analysis Set**

| | Cohort 1 (N=20) n (%) | Cohort 2 (N=7) n (%) | Cohort 3 (N=6) n (%) | Cohort 4 (N=7) n (%) | Cohort 5 (N=8) n (%) | Total (N=48) n (%) |
|---|---|---|---|---|---|---|
| Number of AEs | 223 | 91 | 38 | 119 | 79 | 550 |
| Number of TEAEs | 219 | 86 | 38 | 109 | 75 | 527 |
| Mild | 188 | 67 | 33 | 61 | 67 | 416 |
| Moderate | 27 | 16 | 5 | 48 | 7 | 103 |
| Severe | 4 | 3 | 0 | 0 | 1 | 8 |
| Number of SAEs | 2 | 3 | 0 | 0 | 1 | 6 |
| Number of treatment-related TEAEs | 106 | 27 | 12 | 21 | 39 | 205 |
| Mild | 90 | 16 | 11 | 15 | 31 | 163 |
| Moderate | 12 | 8 | 1 | 6 | 7 | 34 |
| Severe | 4 | 3 | 0 | 0 | 1 | 8 |
| Number of treatment-related SAEs | 2 | 3 | 0 | 0 | 1 | 6 |
| Subjects with any AEs | 20 (100.0) | 7 (100.0) | 6 (100.0) | 7 (100.0) | 8 (100.0) | 48 (100.0) |
| Subjects with any TEAEs | 20 (100.0) | 7 (100.0) | 6 (100.0) | 7 (100.0) | 8 (100.0) | 48 (100.0) |
| Subjects with any SAEs | 2 (10.0) | 2 (28.6) | 0 | 0 | 1 (12.5) | 5 (10.4) |
| Subjects with any treatment-related TEAEs | 18 (90.0) | 5 (71.4) | 5 (83.3) | 6 (85.7) | 8 (100.0) | 42 (87.5) |
| Subjects with any treatment-related SAEs | 2 (10.0) | 2 (28.6) | 0 | 0 | 1 (12.5) | 5 (10.4) |
| Subjects with any AEs leading to study discontinuation | 0 | 0 | 0 | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 |

Source: SRP-9001-103 Clinical Study Report, Table 14.3.1.1
Abbreviations: AE = adverse event, n = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, SAE = serious adverse event; TEAE = treatment-emergent adverse event

### 6.2.12.2 Overview of Adverse Events

Table 25 summarizes adverse events reported in Study 103. Overall, 87.5% of patients experienced treatment-related TEAEs; treatment-related SAEs occurred in 10.4% of patients. No patients discontinued from the study due to AE.

**Table 26. Treatment-Related TEAEs and Treatment-Related SAEs, Study 103 Cohort 2, Cohort 4, and Cohort 5, and Study 301 Part 1 ELEVIDYS Treatment Group**

| Parameter | Study 103 Cohort 2 (n=7) | Study 103 Cohort 3 (n=6) | Study 103 Cohort 5 (n=8) | Study 103 Overall (n=48) | Study 301 Part 1 ELEVIDYS (n=63) |
|---|---|---|---|---|---|
| Age, mean (SD) years | 10.11 (1.51) | 3.48 (0.24) | 8.38 (3.26) | 7.71 (4.11) | 5.98 (1.06) |
| Patients with any treatment-related TEAEs | 5 (71.4) | 6 (85.7) | 8 (100) | 42 (87.5) | 48 (76.2) |
| Patients with any treatment-related SAEs | 2 (28.6) | 0 | 1 (12.5) | 5 (10.4) | 7 (11.1) |

Source: FDA
Abbreviations: n = number of patients in the specified group, or the total sample, SAE = serious adverse event, SD = standard deviation, TEAE = treatment-emergent adverse event

**Reviewer Comment**
In Study 301 Part 1, the rate of treatment-related TEAEs (76.2%) and treatment-related SAEs (11.1%) in patients who received ELEVIDYS were comparable with those reported in Study 103 (Table 14).

Table 26 compares the frequency of treatment-related TEAEs and treatment-related SAEs between the three cohorts in Study 103 which enrolled older and/or non-ambulatory patients (who typically are higher weight, and therefore received higher total doses of ELEVIDYS), the overall Study 103 population, and the ELEVIDYS arm of Study 301 Part 1. Although 100% of patients in Cohort 5 (mean age 8.38±3.26 years) experienced treatment-related TEAEs, only 1 patient (12.5%) had a treatment-related SAE. The frequency was similar for Study 103 and Study 301 Part 1.

6.2.12.3 Deaths

No deaths were reported.

6.2.12.4 Nonfatal Serious Adverse Events

**Table 27. Nonfatal Serious Adverse Events, Safety Population, Study 103**

| Preferred Term | Severity/Relatedness | Outcome |
|---|---|---|
| Hypertransaminasaemia | Severe/Yes | Resolved |
| Vomiting | Severe/Yes | Resolved |
| Immune-mediated myositis | Life-threatening or permanently disabling/Yes | Resolved with Sequelae |
| Vomiting | Severe/Yes | Resolved |
| Myocarditis | Severe/Yes | Resolved with Sequelae |
| Immune-mediated myositis | Severe/Yes | Resolved with Sequelae |

Source: SRP-9001-103 Clinical Study Report, Table 24

## 6.2.12.5 Adverse Events of Special Interest

**Table 28. Adverse Events of Special Interest, Study 103, Full Analysis Set: Patients With Elevations in Hepatic Laboratory Tests (Hepatoxicity) and Platelet Count (Thrombocytopenia)**

| Category | Cohort 1 (N=20) n (%) | Cohort 2 (N=7) n (%) | Cohort 3 (N=6) n (%) | Cohort 4 (N=7) n (%) | Cohort 5 (N=8) n (%) | Total (N=48) n (%) |
|---|---|---|---|---|---|---|
| Subjects meeting any GGT/GLDH criteria below | 5 ( 25.0) | 1 ( 14.3) | 0 | 1 ( 14.3) | 1 ( 12.5) | 8 ( 16.7) |
| GGT or GLDH > 8 x ULN | 5 ( 25.0) | 1 ( 14.3) | 0 | 1 ( 14.3) | 1 ( 12.5) | 8 ( 16.7) |
| GGT or GLDH > 5 x ULN and persists for >= 2 weeks and not included in the row above | 0 | 0 | 0 | 0 | 0 | 0 |
| GGT or GLDH > 3 x ULN and either total bilirubin >2 x ULN or international normalized ratio > 1.5 and not included in two rows above | 0 | 0 | 0 | 0 | 0 | 0 |
| GGT or GLDH > 3 x ULN and the new appearance [1] and not included in three rows above | 0 | 0 | 0 | 0 | 0 | 0 |
| Platelet count < 75,000/mm3 | 1 ( 5.0) | 1 ( 14.3) | 0 | 0 | 0 | 2 ( 4.2) |
| Troponin I > 3 × ULN or 3 × Baseline for subjects with elevated Baseline values | 6 ( 30.0) | 1 ( 14.3) | 0 | 1 ( 14.3) | 2 ( 25.0) | 10 ( 20.8) |

Source: Table 14.3.2.4.1, SRP-9001-103 Clinical Study Report
[1] GGT or GLDH >3×ULN and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5 percent) potentially related to hepatic inflammation. Patients satisfying the condition in rows above are not included here.
Abbreviations: AESI = adverse event of special interest, GGT = gamma-glutamyl transferase, GLDH = glutamate dehydrogenase, n (%) = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, ULN = upper limit of normal

6.2.12.6 Clinical Test Results

**Table 29. Patients With Potentially Clinically Significant Abnormalities in Selected Laboratory Parameters by Grade, Study 103, Full Analysis Set**

| Parameter | CTCAE Grade (Maximum Grade at Any Time After Baseline) | Cohort 1 (N=20) n (%) | Cohort 2 (N=20) n (%) | Cohort 3 (N=20) n (%) | Cohort 4 (N=20) n (%) | Cohort 5 (N=20) n (%) | Total (N=48) n (%) |
|---|---|---|---|---|---|---|---|
| Patients with any potentially clinically significant abnormalities | - | 17 (85.0) | 7 (100.0) | 5 (83.3) | 6 (85.7) | 7 (87.5) | 42 (87.5) |
| ALT | Grade 1: 1.5 – 3.0×baseline (or > ULN – 3.0×ULN if baseline normal) | 3 (15.0) | 2 (28.6) | 2 (33.3) | 1 (14.3) | 2 (25.0) | 10 (20.8) |
| ALT | Grade 2: >3.0 – 5.0×baseline (or >3.0 – 5.0×ULN if baseline normal) | 2 (10.0) | 1 (14.3) | 1 (16.7) | 2 (28.6) | 0 | 6 (12.5) |
| ALT | Grade 3: >5.0 – 20.0×baseline (or >5.0 – 20.0×ULN if baseline normal) | 0 | 0 | 0 | 0 | 0 | 0 |
| ALT | Grade 4: >20.0×baseline (or >20.0×ULN if baseline normal) | 0 | 0 | 0 | 0 | 0 | 0 |
| AST | Grade 1: 1.5 – 3.0×baseline (or > ULN – 3.0×ULN if baseline normal) | 10 (50.0) | 5 (71.4) | 4 (66.7) | 3 (42.9) | 3 (37.5) | 25 (52.1) |
| AST | Grade 2: >3.0 – 5.0×baseline (or >3.0 – 5.0×ULN if baseline normal) | 3 (15.0) | 1 (14.3) | 0 | 1 (14.3) | 0 | 5 (10.4) |
| AST | Grade 3: >5.0 – 20.0×baseline (or >5.0 – 20.0× ULN if baseline normal) | 0 | 0 | 0 | 0 | 0 | 0 |
| AST | Grade 4: >20.0×baseline (or >20.0×ULN if baseline normal) | 0 | 0 | 0 | 0 | 0 | 0 |

| Parameter | CTCAE Grade (Maximum Grade at Any Time After Baseline) | Cohort 1 (N=20) n (%) | Cohort 2 (N=20) n (%) | Cohort 3 (N=20) n (%) | Cohort 4 (N=20) n (%) | Cohort 5 (N=20) n (%) | Total (N=48) n (%) |
|---|---|---|---|---|---|---|---|
| GGT | Grade 1: > ULN – 2.5×ULN (or >2.0 – 2.5×baseline if baseline abnormal) | 3 (15.0) | 3 (42.9) | 2 (33.3) | 0 | 4 (50.0) | 12 (25.0) |
| GGT | Grade 2: >2.5× – 5.0×ULN (or >2.5 – 5.0×baseline if baseline abnormal) | 0 | 0 | 0 | 1 (14.3) | 1 (12.5) | 2 (4.2) |
| GGT | Grade 3: >5.0 – 20.0×ULN (or >5.0 – 20.0×baseline if baseline abnormal) | 4 (20.0) | 1 (14.3) | 0 | 1 (14.3) | 0 | 6 (12.5) |
| GGT | Grade 4: >20.0×ULN (or >20.0×baseline if baseline abnormal) | 0 | 0 | 0 | 0 | 0 | 0 |
| Platelets | Grade 1: <LLN – $75\times10^9$ | 7 (35.0) | 4 (57.1) | 3 (50.0) | 4 (57.1) | 6 (75.0) | 24 (50.0) |
| Platelets | Grade 2: $<75\times10^9$-$50\times10^9$ | 1 (5.0) | 1 (14.3) | 0 | 0 | 0 | 2 (4.2) |
| Platelets | Grade 3: $<50\times10^9$ – $25\times10^9$ | 0 | 0 | 0 | 0 | 0 | 0 |
| Platelets | Grade 4: $<25\times10^9$ | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Table 25, SRP-9001-103 Clinical Study Report
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, GGT = gamma-glutamyl transferase, LLN = lower limit of normal, n (%) = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, ULN = upper limit of normal

6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts due to an AE. Discontinuation is not applicable, as the treatment is a one-time infusion.

6.2.13 Study Summary and Conclusions

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated overview of efficacy was not conducted, because efficacy data from the two studies could not be reliably compared: Study 301 Part 1 was randomized, double-blind, and placebo-controlled, whereas Study 103 was open-label and thus highly susceptible to bias.

8. INTEGRATED OVERVIEW OF SAFETY

## 8.1 Safety Assessment Methods

The integrated overview of safety is based on pooled data from the four studies included in the BLA submission (Exposure Analysis Set): two ongoing open-label studies (Study 101 and Study 103), and two studies that included a randomized, double-blind, placebo-controlled period (Study 102 and Study 301). Study 101 and Study 102 used the laboratory (Process A) version of the product; Study 103 and Study 301 used the commercial (Process B) version.

## 8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database of ELEVIDYS consists of 156 male patients with a confirmed mutation in the *DMD* gene who received a single intravenous infusion of ELEVIDYS in the four clinical studies of ELEVIDYS to date.

At the time of administration, patients in the ELEVIDYS treatment group had a mean age of 6.7 years (range 3 to 20) and mean weight of 24.6 kg (range 12.5 to 80.1). Of note, 144 patients received the recommended dose of $1.33 \times 10^{14}$ vg/kg, and 12 patients (all in Study 102 Part 1) received lower doses.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 156 patients were included in the Exposure Analysis Set for the pooled analysis.

The Applicant submitted a pooled analysis of safety in the Clinical Overview (Module 2.5) for the supplemental BLA submission. The Applicant's analysis includes the following:

- Adverse events by age group (<8 years vs. ≥8 years) from Study 301 Part 1 and Study 103 (Section 4.5.2)
- Pooled adverse events from Study 101, Study 102, Study 103 (Cohorts 1-5) and Study 301 Part 1 (Section 3.1.6)

**Reviewer Comment:**
No new safety issues were apparent in the pooled analyses.

No difference in safety profile was observed for patients 8 years of age and older, compared to younger patients. Most patients were younger than 8 years old (95 patients aged <8 years vs. 16 patients aged ≥8 years; age range 3 to 20 years); the limited safety data limits meaningful assessment in older age group.

8.2.3 Categorization of Adverse Events

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

The Safety Population included all patients who received ELEVIDYS.

A TEAE is 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 is defined as a TEAE that the study investigator considers related to the study drug.

Per 21 CFR 201.57(c)(7), an adverse reaction is "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." Correspondingly, the adverse reactions described here are treatment-related treatment-emergent adverse events.

The most common adverse reactions (incidence ≥5%) across all studies are summarized in Table 30.

Adverse reactions were typically seen within the first 2 weeks after dosing (nausea, vomiting, thrombocytopenia, pyrexia), or within the first 2 months after dosing (immune-mediated myositis, liver injury). Vomiting may occur as early as on the day of the infusion.

**Table 30. Adverse Reactions (Incidence ≥5%) Following Treatment With ELEVIDYS in Clinical Studies**

| **Adverse Reactions** | **ELEVIDYS (N=156) %** |
|---|---|
| Vomiting | 65 |
| Nausea | 43 |
| Liver injury[a] | 40 |
| Pyrexia | 28 |
| Thrombocytopenia[b c] | 8 |

Source: Applicant's Clinical Overview, Table 17
[a] Includes: AST increased, ALT increased, GGT increased, GLDH increased, GLDH level abnormal, Hepatotoxicity, Hepatic enzyme increased, Hypertransaminasaemia, Liver function test increased, Liver injury, Transaminases increased, Blood bilirubin increased.
[b] Includes: Thrombocytopenia, Platelet count decreased.
[c] Transient, mild, asymptomatic decrease in platelet counts.
Abbreviation: N = number of patients in the specified group, or the total sample

Table 31 below presents the most frequent adverse reactions from Study 301 Part 1.

**Table 31. Adverse Reactions Occurring in ELEVIDYS-Treated Patients and at Least Twice More Frequently Than With Placebo, Study 301 Part 1**

| Adverse Reactions | ELEVIDYS (N=63) % | Placebo (N=62) % |
|---|---|---|
| Vomiting | 64 | 19 |
| Nausea | 40 | 13 |
| Liver injury[a] | 41 | 8 |
| Pyrexia | 32 | 24 |
| Thrombocytopenia[b,c] | 3 | 0 |

Source: Applicant's Clinical Overview, Table 16
[a] Includes: AST increased, ALT increased, GGT increased, GLDH increased, GLDH level abnormal, Hepatotoxicity, Hepatic enzyme increased, Hypertransaminasaemia, Liver function test increased, Liver injury, Transaminases increased.
[b] Includes: platelet count decreased, thrombocytopenia.
[c] Transient, mild, asymptomatic decrease in platelet counts.
Abbreviation: N = number of patients in the specified group, or the total sample

The following adverse reactions have been identified during postapproval use of ELEVIDYS: infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during or up to several hours following ELEVIDYS administration.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

A total of 45 patients (from Study 101 and Study 102) received ELEVIDYS manufactured by Process A. Process A ELEVIDYS has a (b) (4) compared to Process B ELEVIDYS; the two products are not analytically comparable.

All patients in Study 301 Part 1 and Study 103 received ELEVIDYS manufactured by the commercial process (Process B).

### 8.4 Safety Results

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

Overall in Study 301 Part 1 and Study 103, 24 patients experienced a total of 36 SAEs.

Treatment-related SAEs included: GGT increased (n=1), hepatic enzyme increased (n=1), transaminases increased (n=2), hepatotoxicity (n=1), liver injury (n=1), myocarditis (n=2), immune-mediated myositis (n=2), nausea (n=1), vomiting (n=3), pyrexia (n=1), and rhabdomyolysis (n=1).

**Reviewer Comment:**
All SAEs are reported as resolved. The 2 cases of immune-mediated myositis and one case of myocarditis resolved with sequelae. The remaining treatment-related SAEs resolved without sequelae.

Aside from rhabdomyolysis, all SAEs that were considered treatment-related by the investigator represent labeled adverse events.

8.4.3 Study Dropouts/Discontinuations

No patient experienced an adverse event that led to study discontinuation.

8.4.4 Common Adverse Events

**Table 32.Treatment-Emergent Adverse Events (≥5%) by System Organ Class and Preferred/Grouped Term, Study 103 and Study 301 Part 1, Safety Population**

| System Organ Class<br>Preferred/Grouped Term | Study 103 ELEVIDYS (N=48) n (%) | Study 301 ELEVIDYS (N=63) n (%) | Study 301 Placebo (N=62) n (%) | Total (N=173) n (%) |
|---|---|---|---|---|
| Any TEAE | 48 (100) | 62 (98.4) | 57 (91.9) | 167 (96.5) |
| Blood and lymphatic system disorders | 6 (12.5) | 1 (1.6) | 3 (4.8) | 10 (5.8) |
| Thrombocytopenia | 5 (10.4) | 1 (1.6) | 0 | 6 (3.5) |
| Cardiac disorders | 1 (2.1) | 4 (6.3) | 2 (3.2) | 7 (4.0) |
| Ear and labyrinth disorders | 3 (6.3) | 4 (6.3) | 0 | 7 (4.0) |
| Endocrine disorders | 3 (6.3) | 4 (6.3) | 4 (6.5) | 11 (6.4) |
| Cushingoid | 2 (4.2) | 4 (6.3) | 4 (6.5) | 10 (5.8) |
| Eye disorders | 2 (4.2) | 1 (1.6) | 4 (6.5) | 7 (4.0) |
| Gastrointestinal disorders | 41 (85.4) | 50 (79.4) | 33 (53.2) | 124 (71.7) |
| Abdominal pain | 1 (2.1) | 5 (7.9) | 7 (11.3) | 13 (7.5) |
| Abdominal pain upper | 11 (22.9) | 10 (15.9) | 9 (14.5) | 30 (17.3) |
| Constipation | 10 (20.8) | 5 (7.9) | 5 (8.1) | 20 (11.6) |
| Diarrhoea | 6 (12.5) | 6 (9.5) | 13 (21.0) | 25 (14.5) |
| Nausea | 23 (47.9) | 25 (39.7) | 8 (12.9) | 56 (32.4) |
| Vomiting | 28 (58.3) | 40 (63.5) | 12 (19.4) | 80 (46.2) |
| General disorders and administration site conditions | 21 (43.8) | 31 (49.2) | 23 (37.1) | 75 (43.4) |
| Fatigue | 7 (14.6) | 9 (14.3) | 6 (9.7) | 22 (12.7) |
| Pyrexia | 9 (18.8) | 20 (31.7) | 15 (24.2) | 44 (25.4) |
| Vessel puncture site bruise | 3 (6.3) | 0 | 0 | 3 (1.7) |
| Hepatobiliary disorders | 3 (6.3) | 6 (9.5) | 0 | 9 (5.2) |
| Immune system disorders | 3 (6.3) | 3 (4.8) | 2 (3.2) | 8 (4.6) |
| Infections and infestations | 33 (68.8) | 48 (76.2) | 43 (69.4) | 124 (71.7) |
| Conjunctivitis | 2 (4.2) | 2 (3.2) | 4 (6.5) | 8 (4.6) |
| COVID-19 | 13 (27.1) | 17 (27.0) | 9 (14.5) | 39 (22.5) |
| Ear infection | 4 (8.3) | 6 (9.5) | 6 (9.7) | 16 (9.2) |
| Enterobiasis | 0 | 5 (7.9) | 0 | 5 (2.9) |
| Gastroenteritis viral | 4 (8.3) | 4 (6.3) | 1 (1.6) | 9 (5.2) |
| Influenza | 8 (16.7) | 9 (14.3) | 4 (6.5) | 21 (12.1) |
| Nasopharyngitis | 6 (12.5) | 9 (14.3) | 12 (19.4) | 27 (15.6) |
| Upper respiratory tract infection | 11 (22.9) | 12 (19.0) | 17 (27.4) | 40 (23.1) |
| Viral infection | 6 (12.5) | 5 (7.9) | 5 (8.1) | 16 (9.2) |
| Viral upper respiratory tract infection | 3 (6.3) | 3 (4.8) | 0 | 6 (3.5) |

| System Organ Class<br>Preferred/Grouped Term | Study 103 ELEVIDYS (N=48) n (%) | Study 301 ELEVIDYS (N=63) n (%) | Study 301 Placebo (N=62) n (%) | Total (N=173) n (%) |
|---|---|---|---|---|
| Injury, poisoning and procedural complications | 19 (39.6) | 18 (28.6) | 25 (40.3) | 62 (35.8) |
| Arthropod bite | 3 (6.3) | 1 (1.6) | 2 (3.2) | 6 (3.5) |
| Contusion | 6 (12.5) | 7 (11.1) | 9 (14.5) | 22 (12.7) |
| Fall | 4 (8.3) | 5 (7.9) | 7 (11.3) | 16 (9.2) |
| Procedural pain | 3 (6.3) | 1 (1.6) | 0 | 4 (2.3) |
| Skin abrasion | 0 | 1 (1.6) | 4 (6.5) | 5 (2.9) |
| Investigations | 30 (62.5) | 30 (47.6) | 17 (27.4) | 77 (44.5) |
| Alanine aminotransferase increased | 5 (10.4) | 3 (4.8) | 1 (1.6) | 9 (5.2) |
| Aspartate aminotransferase increased | 5 (10.4) | 3 (4.8) | 2 (3.2) | 10 (5.8) |
| Blood creatine phosphokinase increased | 4 (8.3) | 1 (1.6) | 4 (6.5) | 9 (5.2) |
| Gamma-glutamyltransferase increased | 6 (12.5) | 5 (7.9) | 0 | 11 (6.4) |
| Glutamate dehydrogenase level abnormal[a] | 15 (31.3) | 18 (28.6) | 2 (3.2) | 35 (20.2) |
| Liver function test increased[b] | 7 (14.6) | 3 (4.8) | 2 (3.2) | 12 (6.9) |
| Troponin I abnormal[c] | 10 (20.8) | 2 (3.2) | 2 (3.2) | 14 (8.1) |
| Metabolism and nutrition disorders | 18 (37.5) | 20 (31.7) | 7 (11.3) | 45 (26.0) |
| Decreased appetite | 15 (31.3) | 20 (31.7) | 3 (4.8) | 38 (22.0) |
| Musculoskeletal and connective tissue disorders | 16 (33.3) | 17 (27.0) | 21 (33.9) | 54 (31.2) |
| Arthralgia | 1 (2.1) | 6 (9.5) | 3 (4.8) | 10 (5.8) |
| Back pain | 3 (6.3) | 4 (6.3) | 4 (6.5) | 11 (6.4) |
| Muscle spasms | 2 (4.2) | 2 (3.2) | 4 (6.5) | 8 (4.6) |
| Myalgia | 2 (4.2) | 4 (6.3) | 1 (1.6) | 7 (4.0) |
| Pain in extremity | 8 (16.7) | 7 (11.1) | 12 (19.4) | 27 (15.6) |
| Rhabdomyolysis | 1 (2.1) | 2 (3.2) | 4 (6.5) | 7 (4.0) |
| Neoplasms benign, malignant, and unspecified (incl cysts and polyps) | 0 | 0 | 3 (4.8) | 3 (1.7) |
| Nervous system disorders | 13 (27.1) | 13 (20.6) | 10 (16.1) | 36 (20.8) |
| Headache | 10 (20.8) | 7 (11.1) | 8 (12.9) | 25 (14.5) |
| Product issues | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Psychiatric disorders | 13 (27.1) | 19 (30.2) | 14 (22.6) | 46 (26.6) |
| Aggression | 1 (2.1) | 1 (1.6) | 4 (6.5) | 6 (3.5) |
| Insomnia | 4 (8.3) | 0 | 3 (4.8) | 7 (4.0) |
| Irritability | 3 (6.3) | 9 (14.3) | 4 (6.5) | 16 (9.2) |
| Renal and urinary disorders | 6 (12.5) | 6 (9.5) | 10 (16.1) | 22 (12.7) |
| Respiratory, thoracic, and mediastinal disorders | 18 (37.5) | 18 (28.6) | 28 (45.2) | 64 (37.0) |
| Cough | 9 (18.8) | 12 (19.0) | 18 (29.0) | 39 (22.5) |
| Nasal congestion | 1 (2.1) | 1 (1.6) | 7 (11.3) | 9 (5.2) |
| Oropharyngeal pain | 1 (2.1) | 0 | 4 (6.5) | 5 (2.9) |
| Rhinorrhoea | 7 (14.6) | 5 (7.9) | 7 (11.3) | 19 (11.0) |
| Sinus congestion | 3 (6.3) | 0 | 2 (3.2) | 5 (2.9) |
| Skin and subcutaneous tissue disorders | 10 (20.8) | 17 (27.0) | 17 (27.4) | 44 (25.4) |
| Rash | 3 (6.3) | 6 (9.5) | 3 (4.8) | 12 (6.9) |
| Surgical and medical procedures | 1 (2.1) | 0 | 0 | 1 (0.6) |

| System Organ Class<br>Preferred/Grouped Term | Study 103 ELEVIDYS (N=48) n (%) | Study 301 ELEVIDYS (N=63) n (%) | Study 301 Placebo (N=62) n (%) | Total (N=173) n (%) |
|---|---|---|---|---|
| Vascular disorders | 4 (8.3) | 2 (3.2) | 2 (3.2) | 8 (4.6) |
| Flushing | 3 (6.3) | 0 | 0 | 3 (1.7) |

Source: FDA
[a] Includes 'glutamate dehydrogenase level abnormal' and 'glutamate dehydrogenase increased.'
[b] Includes 'liver function test increased', 'hepatic enzyme increased', and 'transaminases increased.'
[c] Includes 'troponin I abnormal' and 'troponin increased.'
Abbreviations: COVID-19 = Coronavirus Disease 2019, n (%) = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, TEAE = treatment-emergent adverse event

In Study 301 Part 1, the most common AEs (Table 29) among both treatment groups (≥20% of total patients) were vomiting (63.5% in ELEVIDYS group vs. 19.4% in placebo group), nausea (39.7% vs. 12.9%), pyrexia (31.7% vs. 24.2%), COVID-19 (27% vs. 14.5%), cough (19% vs. 29%) and upper respiratory tract infection (19% vs. 27.4%).

The most common treatment-related AEs among both treatment groups (≥10% of total patients) in Study 301 Part 1 were vomiting (54% ELEVIDYS vs. 0% placebo), nausea (31.7% vs. 8.1%), decreased appetite (27% vs. 1.6%), and glutamate dehydrogenase increased (23.8% vs. 3.2%).

In Study 103, the most common TEAEs (Table 29) across all patients (>30%) were vomiting (58.3%), nausea (47.9%), decreased appetite (31.3%), and glutamate dehydrogenase increased (31.3%). These TEAEs were also the most common TEAEs considered by the investigator to be related to treatment.

**Reviewer Comment:**
The most commonly reported adverse events in Study 301 Part 1 and Study 103 were either AEs included on the ELEVIDYS product label, AEs closely related to the dose on the product label or involved coincident viral infections.

8.4.5 Clinical Test Results

Please see discussion in Section 8.4.8.

8.4.6 Systemic Adverse Events

Please see discussion in Section 8.4.8.

8.4.8 Adverse Events of Special Interest

The following were considered Adverse Events of Special Interest (AESIs): Acute liver injury, immune-mediated myositis, thrombocytopenia, myocarditis, thrombotic microangiopathy, rhabdomyolysis, and oncogenicity (Table 30).

**Acute Liver Injury**

In Study 301 Part 1, acute liver injury (ALI) events were more common in the ELEVIDYS group (n=26 patients; 41.3%) than the placebo group (n=5 patients; 8.1%). Most cases were mild in severity and occurred within 90 days after infusion. Five patients in the

ELEVIDYS group received intravenous steroids to manage ALI, compared to no patients in the placebo group. No liver dysfunction or liver failure was reported.

In Study 103, a total of 22 (45.8%) patients met search criteria for hepatotoxicity TEAEs. Most AEs were of mild or moderate intensity; however, 3 AEs were severe, including one SAE (hypertransaminasemia). No patients demonstrated clinically important liver dysfunction, and all cases resolved spontaneously or with corticosteroid treatment.

**Immune-Mediated Myositis**

In Study 301 Part 1, the frequency of immune-mediated myositis (according to TEAEs retrieved by the search criteria) was comparable between the ELEVIDYS group (n=4 patients; 6.3%) and the placebo group (n=4 patients; 6.5%). However, treatment-related immune-mediated myositis occurred more often in the ELEVIDYS group (n=3) than the placebo group (n=1). All cases were mild or moderate in severity and most TEAEs occurred more than 90 days after infusion. None of the patients in the dataset underwent biopsy or experienced severe weakness, and therefore did not meet the case definition for probable or possible immune-mediated myositis.

In Study 103, two (4.2%) patients experienced treatment-related SAEs of immune-mediated myositis. Both cases occurred about 1 month after ELEVIDYS infusion. Both patients (Patient (b) (6) and Patient (b) (6) ) had a deletion mutation involving exon 8 and/or exon 9 in the DMD gene. (These mutations currently are listed in the ELEVIDYS USPI as contraindications to treatment.) Both patients experienced severe muscle weakness, dyspnea, dysphagia, and hypophonia. Both patients were hospitalized and received immunomodulatory treatment; both demonstrated some improvement in muscle strength, but neither returned to baseline.

**Thrombocytopenia**

In Study 301, two patients in the ELEVIDYS group experienced AEs of diminished platelet count (<75,000/$mm^3$), although in both cases the samples were reported to show clotting or clumping.

In Study 103, a total of 6 (12.5%) patients reported at least one TEAE of thrombocytopenia. All cases occurred during Week 1, with recovery or a trend towards recovery by Week 2. All were of mild or moderate severity and resolved.

**Myocarditis**

In Study 301 Part 1, 2 patients (2 patients in each treatment group) experience TEAEs with Preferred Terms of myocarditis and/or troponin increased. Three of these patients experienced mild troponin increase more than 130 days ELEVIDYS infusion; the findings were assessed by the investigator as not related. The fourth patient (Patient (b) (6) , in the ELEVIDYS group) experienced an SAE of myocarditis and severe troponin increased within 2 weeks of administration of ELEVIDYS. Although the report did not meet Brighton Collaboration criteria for myocarditis per the Applicant's assessment, an independent cardiology expert assessed the case as probably related.

On May 3, 2024, FDA received a late-breaking FAERS report (FAERS ID #23815109) of an asymptomatic 7-year-old male patient in Study 301 who had received either

ELEVIDYS or placebo and was found to have elevated troponin during Week 24 routine blood testing. An echocardiogram showed “focal hypokinesis suggestive for Grade 3 focal myocarditis.” He was hospitalized and treated with immunoglobulin therapy; the event was ongoing at the time of reporting.

In Study 103, a total of 10 (20.8%) patients met search criteria for myocarditis (which includes Preferred Terms for troponin increased). Eight (16.7%) patients experienced troponin I increased. All cases of troponin I increased were mild; 6 cases resolved without sequelae, and 2 cases resolved with sequelae (ongoing troponin fluctuation, attributed to underlying disease). One patient (Patient (b) (6) ) experienced an SAE of myocarditis and a TEAE of cardiomyopathy. He had pre-existing cardiomyopathy and recovered but required addition of two new cardiac medications.

### Thrombotic Microangiopathy

No cases of thrombotic microangiopathy were reported after administration of ELEVIDYS, in either Study 301 Part 1 or Study 103.

### Rhabdomyolysis

In Study 301, TEAEs retrieved for rhabdomyolysis were more common among patients in the placebo group (n=14 patients; 22.6%) than in the ELEVIDYS group (n=10 patients; 15.9%). The study investigator assessed one patient in each group as having treatment-related rhabdomyolysis. Under the case definition, no cases met criteria for the “probable” category; 3 AEs in 2 patients met criteria for the “possible” category; and the remaining AEs fit criteria for the “unlikely” category. Neither patient in the “possible” category experienced renal impairment.

In Study 103, a total of 4 (8.3%) patients experienced TEAEs related to rhabdomyolysis: chromaturia (n=1), rhabdomyolysis (n=1), or myalgia (n=2). All cases were mild or moderate in severity and were considered related to treatment.

### Oncogenicity

No malignancies were reported in either Study 301 Part 1 or Study 103.

**Table 33. Adverse Events of Special Interest, by System Organ Class and Preferred/Grouped Term, Study 103 and Study 301 Part 1, Safety Population**

| System Organ Class<br>Preferred/Grouped Term | Study 103 ELEVIDYS (N=48) n (%) | Study 301 ELEVIDYS (N=63) n (%) | Study 301 Placebo (N=62) n (%) | Total (N=173) n (%) |
|---|---|---|---|---|
| Any AESI | 47 (97.9) | 54 (85.7) | 45 (72.6) | 146 (84.4) |
| Blood and lymphatic system disorders | 5 (10.4) | 1 (1.6) | 0 | 6 (3.5) |
| Thrombocytopenia | 5 (10.4) | 1 (1.6) | 0 | 6 (3.5) |
| Cardiac disorders | 1 (2.1) | 4 (6.3) | 2 (3.2) | 7 (4.0) |
| Bradycardia | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Cardiomyopathy | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Left ventricular dysfunction | 1 (2.1) | 0 | 1 (1.6) | 2 (1.2) |
| Myocarditis | 1 (2.1) | 1 (1.6) | 0 | 2 (1.2) |
| Sinus tachycardia | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Tachycardia | 0 | 2 (3.2) | 0 | 2 (1.2) |

| System Organ Class<br>Preferred/Grouped Term | Study 103<br>ELEVIDYS<br>(N=48)<br>n (%) | Study 301<br>ELEVIDYS<br>(N=63)<br>n (%) | Study 301<br>Placebo<br>(N=62)<br>n (%) | Total<br>(N=173)<br>n (%) |
|---|---|---|---|---|
| Gastrointestinal disorders | 39 (81.3) | 46 (73.0) | 33 (53.2) | 118 (68.2) |
| Abdominal discomfort | 0 | 2 (3.2) | 2 (3.2) | 4 (2.3) |
| Abdominal distension | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Abdominal pain | 1 (2.1) | 5 (7.9) | 7 (11.3) | 13 (7.5) |
| Abdominal pain upper | 11 (22.9) | 10 (15.9) | 9 (14.5) | 30 (17.3) |
| Diarrhoea | 6 (12.5) | 6 (9.5) | 13 (21.0) | 25 (14.5) |
| Epigastric discomfort | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Nausea | 23 (47.9) | 25 (39.7) | 8 (12.9) | 56 (32.4) |
| Rectal haemorrhage | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Retroperitoneal haematoma | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Vomiting | 28 (58.3) | 40 (63.5) | 12 (19.4) | 80 (46.2) |
| Hepatobiliary disorders | 3 (6.3) | 6 (9.5) | 0 | 9 (5.2) |
| Hepatobiliary disease | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Hepatotoxicity | 1 (2.1) | 3 (4.8) | 0 | 4 (2.3) |
| Hypertransaminasaemia | 2 (4.2) | 1 (1.6) | 0 | 3 (1.7) |
| Liver injury | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Immune system disorders | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Immune-mediated adverse reaction | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Investigations | 27 (56.3) | 28 (44.4) | 14 (22.6) | 69 (39.9) |
| Activated partial thromboplastin time prolonged | 0 | 0 | 2 (3.2) | 2 (1.2) |
| Alanine aminotransferase increased | 5 (10.4) | 3 (4.8) | 1 (1.6) | 9 (5.2) |
| Aspartate aminotransferase increased | 5 (10.4) | 3 (4.8) | 2 (3.2) | 10 (5.8) |
| Blood creatine phosphokinase increased | 4 (8.3) | 1 (1.6) | 4 (6.5) | 9 (5.2) |
| Blood glucose increased | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Cardiac murmur | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Coagulation test abnormal | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Complement factor C4 decreased | 1 (2.1) | 2 (3.2) | 0 | 3 (1.7) |
| Gamma-glutamyltransferase increased | 6 (12.5) | 5 (7.9) | 0 | 11 (6.4) |
| Glutamate dehydrogenase level abnormal[a] | 15 (31.3) | 18 (28.6) | 2 (3.2) | 35 (20.2) |
| Haemoglobin urine present | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Liver function test increased[b] | 7 (14.6) | 3 (4.8) | 2 (3.2) | 12 (6.9) |
| Platelet count decreased | 1 (2.1) | 1 (1.6) | 0 | 2 (1.2) |
| Protein urine present | 1 (2.1) | 2 (3.2) | 1 (1.6) | 4 (2.3) |
| Pulmonary function test decreased | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Total complement activity decreased | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Total complement activity increased | 0 | 2 (3.2) | 0 | 2 (1.2) |
| Troponin I abnormal[c] | 10 (20.8) | 3 (4.8) | 2 (3.2) | 15 (8.7) |
| White blood cell count increased | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |

| System Organ Class<br>Preferred/Grouped Term | Study 103<br>ELEVIDYS<br>(N=48)<br>n (%) | Study 301<br>ELEVIDYS<br>(N=63)<br>n (%) | Study 301<br>Placebo<br>(N=62)<br>n (%) | Total<br>(N=173)<br>n (%) |
|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | 16 (33.3) | 18 (28.6) | 22 (35.5) | 56 (32.4) |
| Arthralgia | 1 (2.1) | 6 (9.5) | 3 (4.8) | 10 (5.8) |
| Back pain | 3 (6.3) | 4 (6.3) | 4 (6.5) | 11 (6.4) |
| Coccydynia | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Groin pain | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Hand deformity | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Immune-mediated myositis | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Muscle spasms | 2 (4.2) | 2 (3.2) | 4 (6.5) | 8 (4.6) |
| Muscular weakness | 1 (2.1) | 0 | 3 (4.8) | 4 (2.3) |
| Musculoskeletal pain | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Myalgia | 2 (4.2) | 4 (6.3) | 1 (1.6) | 7 (4.0) |
| Myositis | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Neck pain | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Osteopenia | 2 (4.2) | 0 | 0 | 2 (1.2) |
| Osteoporosis | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Pain in extremity | 8 (16.7) | 8 (12.7) | 12 (19.4) | 28 (16.2) |
| Rhabdomyolysis | 1 (2.1) | 2 (3.2) | 4 (6.5) | 7 (4.0) |
| Scoliosis | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Synovial cyst | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Synovitis | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Nervous system disorders | 10 (20.8) | 9 (14.3) | 8 (12.9) | 27 (15.6) |
| Cerebral haematoma | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Haemorrhage intracranial | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Headache | 10 (20.8) | 8 (12.7) | 8 (12.9) | 26 (15.0) |
| Psychiatric disorders | 14 (29.2) | 20 (31.7) | 15 (24.2) | 49 (28.3) |
| Adjustment disorder with anxiety | 2 (4.2) | 0 | 0 | 2 (1.2) |
| Affect lability | 1 (2.1) | 1 (1.6) | 0 | 2 (1.2) |
| Aggression | 1 (2.1) | 2 (3.2) | 4 (6.5) | 7 (4.0) |
| Agitation | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Anger | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Anxiety | 2 (4.2) | 0 | 3 (4.8) | 5 (2.9) |
| Attention deficit hyperactivity disorder | 1 (2.1) | 3 (4.8) | 1 (1.6) | 5 (2.9) |
| Behaviour disorder | 0 | 2 (3.2) | 2 (3.2) | 4 (2.3) |
| Compulsions | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Depression | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Dysphemia | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Enuresis | 1 (2.1) | 0 | 1 (1.6) | 2 (1.2) |
| Insomnia | 5 (10.4) | 0 | 3 (4.8) | 8 (4.6) |
| Irritability | 5 (10.4) | 9 (14.3) | 4 (6.5) | 18 (10.4) |
| Mental disorder | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Obsessive-compulsive disorder | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Oppositional defiant disorder | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Personality change | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Poor quality sleep | 2 (4.2) | 0 | 0 | 2 (1.2) |
| Sleep disorder | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Tic | 1 (2.1) | 0 | 0 | 1 (0.6) |

| System Organ Class<br>Preferred/Grouped Term | Study 103<br>ELEVIDYS<br>(N=48)<br>n (%) | Study 301<br>ELEVIDYS<br>(N=63)<br>n (%) | Study 301<br>Placebo<br>(N=62)<br>n (%) | Total<br>(N=173)<br>n (%) |
|---|---|---|---|---|
| Renal and urinary disorders | 6 (12.5) | 6 (9.5) | 10 (16.1) | 22 (12.7) |
| Acute kidney injury | 0 | 0 | 1 (1.6) | 1 (0.6) |
| Chromaturia | 1 (2.1) | 1 (1.6) | 3 (4.8) | 5 (2.9) |
| Dysuria | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Glycosuria | 1 (2.1) | 0 | 1 (1.6) | 2 (1.2) |
| Haematuria | 1 (2.1) | 1 (1.6) | 4 (6.5) | 6 (3.5) |
| Haemoglobinuria | 2 (4.2) | 0 | 0 | 2 (1.2) |
| Myoglobinuria | 0 | 1 (1.6) | 1 (1.6) | 2 (1.2) |
| Pollakiuria | 1 (2.1) | 0 | 1 (1.6) | 2 (1.2) |
| Proteinuria | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Urinary incontinence | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Urinary tract pain | 1 (2.1) | 0 | 0 | 1 (0.6) |
| Urine abnormality | 0 | 1 (1.6) | 0 | 1 (0.6) |
| Urine odour abnormal | 0 | 1 (1.6) | 0 | 1 (0.6) |

Source: FDA
[a] Includes 'glutamate dehydrogenase level abnormal' and 'glutamate dehydrogenase increased.'
[b] Includes 'liver function test increased,' 'hepatic enzyme increased," and 'transaminases increased.'
[c] Includes 'troponin I abnormal' and 'troponin increased.'
Abbreviations: AESI = adverse event of special interest, n (%) = number of patients with the specified characteristic, N = number of patients in the specified group, or the total sample, SRP-9001 = delandistrogene moxeparvovec-rokl

## 8.5 Additional Safety Evaluations

### 8.5.1 Dose Dependency for Adverse Events

The recommended ELEVIDYS dose for individuals weighing 10 kg to 70 kg is $1.33 \times 10^{14}$ vg per kg of body weight. Individuals weighing ≥70 kg are administered a fixed dose of $9.31 \times 10^{15}$ vg, corresponding to the dose for a 70 kg patient.

Only 2 patients, both in Study 103, received a dose greater than $9.31 \times 10^{15}$ vg. Both patients were nonambulatory:

- Patient (b) (6) (15 years old; body weight 80.1 kg) in Study 103 Cohort 3 received a total dose of $9.43 \times 10^{15}$ vg
- Patient (b) (6) (14.6 years old; body weight 59 kg) in Study 103 Cohort 5b received a total dose of $9.86 \times 10^{15}$ vg

No dose dependency was evident for serious adverse events.

### 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, patients 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 patients with higher titers of anti-AAVrh74 total binding antibodies (>1:400) have not been evaluated.

Please see Section 4.4.4 Immunogenicity.

8.5.9 Person-to-Person Transmission, Shedding

Please see Section 4.4.3 Pharmacokinetics regarding vector shedding studies.

### 8.6 Safety Conclusions

Clinical safety findings from Study 301 Part 1 and Study 103 are largely consistent with the known safety profile for ELEVIDYS.

During postapproval use of ELEVIDYS, the adverse reactions of infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during or up to several hours following ELEVIDYS administration. The US Prescribing Information will be updated to include these adverse reactions.

## 9. Additional Clinical Issues

In considering the categories below, please note that DMD is largely a disease affecting male patients in childhood to young adulthood. Some of the situations below could theoretically result from vector shedding resulting in transmission to other populations.

### 9.1 Special Populations

ELEVIDYS is contraindicated in patients with any deletion that fully includes exons 9-13 in the *DMD* gene.

The safety and efficacy of ELEVIDYS in patients with renal impairment has not been studied.

The safety and efficacy of ELEVIDYS in patients with preexisting hepatic impairment or laboratory signs of liver injury have not been studied.

9.1.1 Human Reproduction and 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 percent to 4 percent, and 15 percent to 20 percent, 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 patients 3 years of age and older. However, the clinical efficacy of ELEVIDYS has not been confirmed, nor has the safety of ELEVIDYS been established in pediatric patients 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

Following evaluation of the totality of the evidence submitted, the clinical reviewer recommends Complete Response for sBLA 125781. The basis for this recommendation is:

- The confirmatory study, Study 301 Part 1 failed to demonstrate a statistically significant difference in outcome on the primary efficacy endpoint (change in NSAA Total Score from baseline to Week 52) for patients treated with ELEVIDYS, compared to patients who received placebo.
- In designing Study 301, the Applicant did not prespecify further analyses for statistical hypothesis testing, nor did the Applicant include a prespecified multiplicity adjustment strategy. Therefore, we cannot reliably determine if any of the age subgroup, secondary endpoint, or exploratory outcomes—whether they favor the product or placebo—are related to effects of ELEVIDYS or are merely the result of chance alone.

With the awareness that we cannot reliably establish the likelihood that the subgroup and secondary outcomes for Study 301 are due to chance alone, we then considered what information we could obtain from those results.

For the NSAA Total Score for the 6- to 7-year-old age subgroup, the result was similar to that for this subgroup in Study 102 Part 1. The Applicant attributed the poor outcome in Study 102 Part 1 to a substantial imbalance in baseline functional status, favoring the placebo patients, in this age subgroup. No such imbalance was present in Study 301 Part 1, which may call into question both that proposed explanation, as well as the efficacy of the product for older patients. However, such conclusions cannot be reached definitively from these data, for the aforementioned reasons.

Regarding the secondary clinical efficacy endpoints, the Applicant has pointed out that in all four cases the point estimates numerically favor the ELEVIDYS group, and that the

"nominal" p-values for three of these four endpoints (Time to Rise, 10-MWR, and Time to Ascend 4 Steps) support an apparent benefit.

As detailed above, we note that "nominal" p-values cannot support a conclusion of benefit (or harm). In addition, the 95 percent CIs for Time to Rise, 10-MWR, and Time to Ascend 4 Steps all contain an upper bound near the zero point (no effect). This observation, while similarly limited in statistical meaning, nevertheless casts further doubt on the Applicant's interpretation. Finally, the small size of the point estimates would be of unclear clinical significance.

The videos and testimony provided to the Cellular, Tissue, and Gene Therapies Advisory Committee Meeting (May 12, 2023) attest to the benefit that some patients have obtained from ELEVIDYS. We agree that a sustained benefit is unlikely to result from a placebo effect. Importantly, however, the failure to observe a similar effect in two randomized, double-blind, placebo-controlled clinical trials suggests that any benefit may accrue only to a subset of the DMD population, whose characteristics at present remain unclear and would require further investigation.

Taken together, the totality of the data does not provide substantial evidence of effectiveness of ELEVIDYS for treatment of ambulatory DMD patients of any age. The results argue against traditional approval for ELEVIDYS for ambulatory DMD patients aged 4- to 5-years old, or for broadening of the indication of ELEVIDYS to include (b) (4) DMD patients, regardless of age or ambulatory status.

The clinical reviewer therefore recommends Complete Response for sBLA 125781.34 because the data have not confirmed the clinical benefit of ELEVIDYS.

# 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

## 11.1 Risk-Benefit Considerations

Risk-benefit considerations are described in Table 34.

**Table 34. Risk-Benefit Considerations**

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • DMD is an X-linked recessive genetic disorder caused by mutations in the *Dystrophin* (*DMD*) 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.<br>• 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. | • 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. |
| Unmet Medical Need | • 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.<br>• When ELEVIDYS was granted Accelerated Approval on June 22, 2023, only one drug for treatment of DMD had been approved by FDA via the traditional approval pathway: deflazacort (Emflaza), a corticosteroid which delays loss of motor strength and loss of ambulation and is indicated for patients 2 years of age and older. Four exon-skipping antisense oligonucleotide drugs (eteplirsen, golodirsen, viltolarsen, and casimersen) had received approval via the FDA Accelerated Approval pathway, based on the surrogate endpoint of expression of internally truncated dystrophin protein, each for a subset of patients with specific DMD mutations. The clinical benefit of all four of these drugs remains to be verified.<br>• After ELEVIDYS received Accelerated Approval, FDA has since granted traditional approval to two additional drugs for treatment of DMD: vamorolone (Agamree), a novel steroid indicated for treatment of DMD in patients aged 2 years and older; and givinostat (Duvyzat), a histone deacetylase inhibitor indicated for treatment of DMD in patients 6 years of age and older. | • Although standard of care, corticosteroids have many associated adverse effects.<br>• The therapeutic landscape for DMD has recently improved, with availability of vamorolone (Agamree) and givinostat (Duvyzat).<br>• A substantial unmet need remains for better therapies for DMD. |

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Clinical Benefit | • The Supplemental BLA submission includes data from two studies: Study 301 Part 1 and Study 103. Confirmation of clinical benefit of ELEVIDYS as a condition of the Accelerated Approval rests on the outcome of Study 301 Part 1, the only randomized, double-blind, and placebo-controlled Phase 3 study for which data are available.<br>• Study 301 Part 1 failed to demonstrate a statistically significant difference in outcome on the primary efficacy endpoint, change in the North Star Ambulatory Assessment from baseline to Week 52, for patients treated with ELEVIDYS compared to patients who received placebo.<br>• Study 103 was the first of the Applicant's clinical studies to use ELEVIDYS manufactured by the commercial process, and was intended as a "bridging" study to compare effects obtained with the commercial (Process B) product to those obtained with the laboratory (Process A) product. | • The NSAA is effort-dependent and process-dependent. Consequently, NSAA results from open-label studies are difficult to interpret, and comparison of clinical study results to results from external sources are not suitably reliable.<br>• The open-label design of Study 103 precludes a full bridging comparison, since efficacy cannot be reliably compared to results from earlier studies which used the laboratory product.<br>• The data from Study 301 Part 1 do not verify and confirm the benefit of ELEVIDYS in the 4 to 5 year-old age group.<br>• The data from Study 103 do not support broadening of the indication to include other age groups or nonambulatory patients with DMD. |

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk | • The safety database of ELEVIDYS consists of 156 male patients with a confirmed mutation in the *DMD* gene who received a single intravenous infusion of ELEVIDYS in four clinical studies of ELEVIDYS to date, including one completed open-label study (SRP 101), one ongoing open-label study (Study 103), and two studies that included a randomized, double-blind, placebo-controlled period (Study 102 and Study 301). There were no deaths.<br>• The most common adverse reactions (incidence ≥5%) include vomiting (65%), nausea (44%), liver injury (40%), pyrexia (29%), and thrombocytopenia (8%).<br>• Adverse events of special interest were: hepatotoxicity, cardiotoxicity (including myocarditis and elevated troponin-I levels), and life-threatening immune-mediated myositis.<br>• Two cases of immune-mediated myositis, including one life-threatening case, were observed about 1 month after ELEVIDYS infusion.<br>• Acute serious myocarditis and troponin-I elevations, and ALI—defined as GGT >3×ULN, GLDH >2.5×ULN, alkaline phosphatase >2×ULN, or ALT >3×baseline excluding ALT elevation from degenerating muscle—have been observed following ELEVIDYS infusion.<br>• Infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during or up to several hours following ELEVIDYS administration. | • The safety database for patients exposed to ELEVIDYS is acceptable for this serious disease with a major unmet medical need.<br>• Because of 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. |
| 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, ALI = acute liver injury, ALT = alanine aminotransferase, BLA = biologics license application, DMD = Duchenne muscular dystrophy, FDA = Food and Drug Administration, GGT = gamma-glutamyl transferase, GLDH = glutamate dehydrogenase, NSAA = North Star Ambulatory Assessment, ULN = upper limit of normal

### 11.2 Risk-Benefit Summary and Assessment

Data submitted to the sBLA do not establish substantial evidence of benefit in patients with DMD.

Although the risks of ELEVIDYS appear similar to those of other AAV vector-based gene therapies, the lack of confirmed benefit results in an unfavorable overall benefit-risk 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 studies to support traditional approval.

### 11.4 Recommendations on Regulatory Actions

Based on analysis by the review team of the clinical data in the sBLA submission, the clinical reviewer concludes that data from the confirmatory Study SRP-9001-301 Part 1 does not verify the benefit of ELEVIDYS in the 4-5-year-old age group, and that data from Study 103 do not provide substantial evidence of effectiveness to support expansion of the approved indication to (b) (4) DMD patients. Therefore, the clinical reviewer recommends Complete Response for sBLA 125781.34.

**Reviewer Comment:**
The CBER Center Director, Dr. Peter Marks, is approving the sBLA by overriding the review team's recommendation; please refer to the Center Director memo which has not been reviewed by the review team, for details on the basis for approval. At the direction of Center Director, the product Prescribing information has been revised to reflect the following indication.

The following indication will be approved in individuals at least 4 years of age:

- For the treatment of Duchenne muscular dystrophy (DMD) in patients who are ambulatory and have a confirmed mutation in the *DMD* gene.
- For the treatment of DMD in patients who are non-ambulatory and have a confirmed mutation in the *DMD* gene.

  The DMD indication in non-ambulatory patients is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

### 11.5 Labeling Review and Recommendations

Substantial changes to sections 1, 5, 6, 12 and 14 of the Prescribing Information were made 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.

### 11.6 Recommendations on Postmarketing Actions

The following postmarketing study was discussed and agreed upon by FDA and the Applicant to verify and describe the clinical benefit of ELEVIDYS in patients with DMD:

> **Accelerated Approval Required Studies**
>
> Conduct and submit the results of a randomized, controlled trial to verify and confirm the clinical benefit of delandistrogene moxeparvovec-rokl in patients with Duchenne muscular dystrophy who are non-ambulatory and have a confirmed mutation in the *DMD* gene. The trial should evaluate the effects of delandistrogene moxeparvovec-rokl on an endpoint that assesses clinical benefit.

The projected Trial Completion date is May 30, 2027. The final study report will be submitted as a “Postmarketing Requirement” – Final Study Report” by November 30, 2027.