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CENTER DIRECTOR DECISIONAL MEMO

BLA 125781/AMENDMENT 34

Product Name: ELEVIDYS (delandistrogene moxeparvovec-rokl)

Indication: Duchenne Muscular Dystrophy (DMD) in individuals 4 years of age and older

Applicant: Sarepta Therapeutics, Inc.

Author: Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research (CBER), FDA

SUMMARY

This memorandum explains CBER's final decision on Amendment 34, an efficacy supplement to BLA 125781 for ELEVIDYS (delandistrogene moxeparvovec-rokl) from Sarepta Therapeutics, Inc. (Sarepta or the Applicant). ELEVIDYS is an AAVrh74 vector-based gene therapy constructed using the myosin heavy chain kinase 7 (MHCK7) promoter and designed to treat DMD by replacement of the dysfunctional or missing normal dystrophin protein with a shortened dystrophin protein, referred to in this memo as "ELEVIDYS micro-dystrophin."

As described below, the data and information submitted by the Applicant has verified clinical benefit for the indication for which FDA granted accelerated approval in June 2023. The data and information also provide substantial evidence of effectiveness as described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to support traditional approval under section 351(a) of the Public Health Service Act (PHS Act), in ambulatory individuals 4 years of age and older with a confirmed mutation in the *DMD* gene except in those with any deletion in exon 8 and/or exon 9 in the *DMD* gene, in whom its use is contraindicated.[1] In addition, the Applicant has provided substantial evidence of effectiveness of ELEVIDYS in non-ambulatory individuals 4 years of age and older, by demonstrating the drug's ability to elevate micro-dystrophin levels, which is reasonably likely to predict clinical benefit in this population and supports accelerated approval for this population under section 351(a) of the PHS Act pursuant to section 506(c) of the FD&C Act and 21 C.F.R. 601.41. Overall, the demonstrated benefits of ELEVIDYS in the treatment of ambulatory individuals, and the expected benefits of ELEVIDS in the treatment of non-ambulatory individuals, with DMD over 4 years of age who are eligible to receive this therapy in improving key functional endpoints such as the ability to stand, walk, climb stairs, or use their upper extremities outweigh the risks. The benefit to risk considerations are favorable, taking into account the existing uncertainties, such as the ultimate duration of response, which is not yet known, as well as the significant unmet need.

[1] As FDA has noted in several guidance documents, under section 351(a) of the PHS Act, licenses for biological products have been issued only upon a showing that the products are "safe, pure, and potent." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered "substantial evidence" of effectiveness to be necessary to support licensure of a biological product under section 351(a) of the PHS Act. See, e.g., *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, at 4 (May 1998) (available at: https://www.fda.gov/media/71655/download) and *Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products*, at 3 (October 2023) available at: https://www.fda.gov/media/152544/download).

As part of its supplemental application, the Applicant has submitted clinical information from two studies: Study SRP-9001-301 (Study 301), a randomized placebo-controlled trial in individuals ages 4 to 7 years (n=125) designed to confirm the clinical benefit of ELEVIDYS and Study SRP-9001-103 (Study 103), an uncontrolled trial in individuals ages 3 to 18 years of age at screening (n=48) that included treatment of 8 non-ambulatory individuals ages 9 to 20 years during the study. A mixed models for repeated measures (MMRM) approach was used for the evaluation of changes between the two arms of Study 301 for the primary endpoint of North Star Ambulatory Assessment (NSAA) and for the various functional secondary endpoints.

In Study 301, the primary endpoint of change in the NSAA from baseline to Week 52 in ELEVIDYS treated individuals versus those receiving placebo did not reach statistical significance (mean difference of 0.65 points, p = 0.2441). Secondary endpoints that were evaluated in Study 301 (which have also been used individually as the primary endpoints to support prior DMD regulatory approvals), included changes in the time to rise from the floor (TTR) and the four-stair climb (Ascend4).[2] For the two key secondary endpoints reported, there was a -0.64 second (s) (95% confidence interval (CI) - 1.06, -0.23, p=0.0025) change in TTR in the ELEVIDYS treated individuals (n=63) versus placebo (n=61), and there was a -0.42 s (95% CI -0.71, 0.13, p=0.0048) change in the 10 meter walk/run (10MWR test) in the ELEVIDYS treated individuals (n=63) versus placebo (n=61).

Additionally, in the Ascend4 there was a -0.36 s (95% CI -0.71, -0.01, p=0.0412) change in the time to ascend 4 stairs in the ELEVIDYS treated individuals (n=62) versus placebo (n=60). As an exploratory endpoint, the evaluation of change in creatine kinase (CK) between baseline and Week 52, an analysis showed a least-squares mean change of -5138.52 U/L (n=61, 95% CI -6747.47, -3529.57) in the ELEVIDYS group and -794.93 U/L in the placebo group (n=61, 95% CI -2403.70, 813.84) (p=0.0002). Additional supportive clinical and laboratory data and analyses were also submitted for this trial including an analysis of change from baseline velocity for TTR, 10MWR, and Ascend4. The change from baseline to 52 weeks for these values was: TTR 0.4 (1/s) (0.02, 0.07, p=0.0003), 10MWR 0.17 (m/s) (0.07, 0.27, p=0.0008), and for Ascend4 0.16 step/s (95% CI 0.04, 0.28, p=0.0073).

The Center Director Decisional Memo on BLA 125781 of June 21, 2023, explained that Study SRP-9001-102 (Study 102), which constitutes an adequate and well-controlled trial, demonstrated expression of micro-dystrophin at week 12 following administration of ELEVIDYS and, together with other data in the BLA, provided substantial evidence of effectiveness. As part of the supplemental application, information on five ambulatory and non-ambulatory cohorts was provided from Study SRP-9001-103. In this trial, performance of Upper Limb assessment (PUL) data were provided on 6 non-ambulatory patients indicating a change from baseline of -3.8 points on the scale. Data from a non-ambulatory natural history study (n=54) were provided showing a change of -6.3 points from baseline, and it was noted from this small sample that there was a 2.5-point difference in the positive direction. Further supportive data was provided in the original BLA from studies SRP-9001-101 (Study 101), Study 102, and a prior interim analysis of cohort 1 of Study 103.

Our understanding of the mechanism of action of ELEVIDYS and the evidence that ELEVIDYS elevates micro-dystrophin levels, combined with the data in Study 301 demonstrating a correlation between micro-dystrophin levels and clinical benefit in 4 to 7 year old ambulatory individuals (as measured by TTR, 10MWR, and Ascend4), as well as the data in Study 102 showing an association between increased micro-dystrophin levels in 4 to 5 year olds and clinical benefit (measured by NSAA), and data in non-ambulatory

[2] TTR was used as the primary endpoint for the approval of AGAMREE (vamorolone) under new drug application (NDA) 215239, which was approved on October 26, 2023, and Ascend4 was used as the primary endpoint for the approval of DUVYZAT (givinostat hydrochloride) under NDA 217865, which was approved on March 21, 2024.

individuals in Cohort 3 of Study 103, provides substantial evidence that ELEVIDYS elevates dystrophin levels for non-ambulatory individuals and is reasonably likely to predict benefit.

I have read the reviews and recommendations by staff of the Office of Therapeutic Products (OTP) and the Office of Biostatistics and Pharmacovigilance (OBPV) and have discussed with the review team issues surrounding the safety and efficacy information submitted. In addition to the review memoranda, I have reviewed the Applicant's submission and relevant scientific publications. I have also discussed this file with senior staff within CBER and CDER.

To summarize, although I agree with the review team's conclusions regarding product safety and their prior conclusions regarding product quality, I come to a different conclusion regarding the overall interpretation of the data in the efficacy supplement submitted by the Applicant requesting approval of ELEVIDYS for all ambulatory and non-ambulatory individuals. Specifically, although acknowledging that the Applicant's randomized study of ELEVIDYS failed to meet its statistical primary endpoint of improvement versus placebo in the NSAA in ambulatory individuals, I find that the observations regarding the secondary endpoints and exploratory endpoints are compelling and, combined with other data provided in the efficacy supplement and the original BLA, meet the substantial evidence of effectiveness standard as per section 505(d) of the FD&C Act to support traditional approval in the ambulatory population. These endpoints include improvements in time to rise from the floor, 10MWR, Ascend4, and CK levels.

Based on the totality of the evidence, including the data provided from Study 301, I have determined that the Applicant has submitted evidence that verifies the clinical benefit of ELEVIDYS, and has provided substantial evidence of effectiveness to support traditional approval of ELEVIDYS, in ambulatory individuals 4 years of age and older with a confirmed mutation in the *DMD* gene except in those with any deletion in exon 8 and/or exon 9 in the *DMD* gene, in whom its use is contraindicated. An inadequate amount of safety data is available currently to support the use of ELEVIDYS in individuals under 4 years of age.

In addition, clinical data was provided from ambulatory individuals, including that from Study 102 indicating a relationship between micro-dystrophin levels in 4 to 5 year olds with clinical benefit (NSAA), Study 301 establishing a correlation of micro-dystrophin levels in 4 to 7 year olds with clinical benefit (TTR, 10MWR, Ascend4), as well as positive results from cohort 3 of Study 103 on an exploratory clinical endpoint (PUL) in non-ambulatory individuals as well as an effect on micro-dystrophin levels in these individuals. Because the mechanism of action of ELEVIDYS is similar in both situations, these data support the determination that elevating micro-dystrophin levels is reasonably likely to predict clinical benefit in non-ambulatory individuals. This, along with the evidence that ELEVIDYS elevates micro-dystrophin levels, demonstrates substantial evidence of effectiveness to support accelerated approval in non-ambulatory individuals at least 4 years of age with DMD pursuant to section 506(c) of the FD&C Act and 21 CFR 601.41, considering the serious nature of the diseases and the extent of unmet medical need in this group of individuals. A confirmatory randomized, controlled clinical trial in the non-ambulatory population is currently underway.

For all approved indications, the benefit to risk considerations for this product are favorable, taking into consideration the existing uncertainties.

BACKGROUND

Disease background and unmet medical need

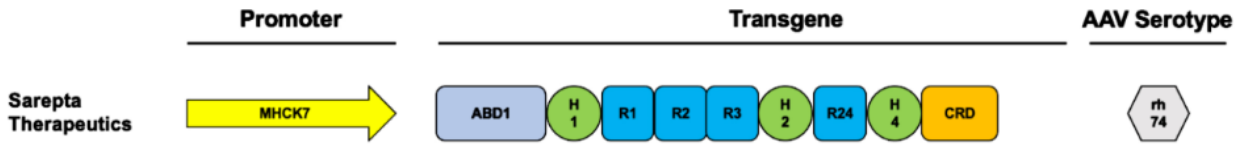
DMD is a severe progressive X-linked recessive disease of muscle caused by a spectrum of mutations in the *DMD* gene encoding dystrophin that are associated with progressive muscle weakness, eventually leading to respiratory failure and death. With best supportive care, adults are wheelchair bound, experience many complications, and even with additional recent advances in supportive care are noted to only have a median life expectancy of 41 years.[3]

Glucocorticoids such as prednisone, deflazacort, and the more recently approved drug vamorolone, were the first drugs found to have some benefit in individuals with DMD, apparently delaying disease progression when given when motor development stops or declines. With the administration of glucocorticoids and best supportive care, individuals with DMD may have improvement of motor function for a few years. However, after peaking at approximately 6 years of age, even on corticosteroids, the muscle function of individuals with DMD ultimately deteriorates due to progressive muscle injury potentially caused by a variety of pathophysiologic mechanisms.[3]

Antisense oligonucleotides (ASOs) have been developed to facilitate exon skipping for specific out-of-frame deletions in the *DMD* gene leading to restoration of dystrophin function. Because of the nature of the genetic mutations, the ASOs can only address a minority of the existing gene mutations, such as a mutation in exon 51 that affects about 14% of individuals with DMD.[4] Additionally, these drugs require repeated administration, and confirmatory clinical trials have yet to be completed for three of the four ASOs available for the treatment of DMD in the United States. A recently completed randomized placebo-controlled clinical trial for one of these products, viltolarsen, failed to reveal a statistically significant change in the time to stand.

Gene therapy has been considered as a potential option to address the treatment of DMD. However, the remarkably large size of the *DMD* gene encoding the dystrophin protein, which serves to link the muscle membrane and cytoskeleton, has precluded consideration of introduction of the entire contiguous coding region of the gene using the current generation of adenoviral-associated virus (AAV) vectors. For this reason, alternative strategies have been taken by several different groups working in this space. These include strategies like Sarepta's ELEVIDYS, which involve trying to introduce shortened length dystrophin molecules (micro-dystrophins) attempting to mimic the situation seen in individuals with milder forms of muscular dystrophy, such as Becker Muscular Dystrophy (see below). ELEVIDYS was granted accelerated approval for the treatment of ambulatory 4- and 5-year-old individuals with DMD based on data previously provided by the Applicant while a randomized trial in ambulatory individuals was ongoing.

ELEVIDYS Micro-dystrophin Gene Therapy Construct



Source: Elangkovan N, Dickson G. Gene Therapy for Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2021;8(s2):S303-S316.

[3] Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. Nat Rev Dis Primers. 2021 Feb 18;7(1):13. doi: 10.1038/s41572-021-00248-3. PMID: 33602943.

[4] Takeda S, Clemens PR, Hoffman EP. Exon-Skipping in Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2021;8(s2):S343-S358. doi: 10.3233/JND-210682. PMID: 34180420; PMCID: PMC8673534.

Summary of Key Clinical Data

ELEVIDYS (delandistrogene moxeparvovec-rokl) is an AAVrh74 vector-based gene therapy constructed using the myosin heavy chain kinase 7 (MHCK7) promoter and designed to treat DMD by replacement of the dysfunctional or missing dystrophin protein with a shortened dystrophin protein about one-third the molecular size of the normal dystrophin protein, called by the Applicant ELEVIDYS micro-dystrophin (hereafter referred to as "micro-dystrophin"). As part of its supplemental application, Sarepta Therapeutics has submitted clinical information from two clinical trials:

1. Study 301, a randomized placebo-controlled trial in individuals ages 4 to 7 (n=125) designed to confirm the clinical benefit of ELEVIDYS as an adequate and well-controlled trial
2. Study 103, an uncontrolled trial in individuals ages 3 to 19 years of age (n=48) updated to include 5 cohorts for which data are available (previously only cohort 1 was submitted)

Other data considered include two studies submitted in the original BLA:

- Study 101, a study in individuals ages 4 to 7 (n=4)
- Study 102, a randomized, double-blind, placebo-controlled crossover trial in individuals ages 4 to 7 (n=41)

Data from Study 301

Study 301 is an ongoing two-part randomized, double-blind, placebo-controlled clinical trial of systemic gene delivery of ELEVIDYS (1.33×10^{14} vg/kg) in 125 male subjects with DMD who were 4 through 7 years of age at randomization. Individuals with certain mutations were excluded, including those between or including exons 1-17, in-frame deletions/duplications, and variants of uncertain significance. Subjects with mutations fully contained within exon 45 (inclusive) were also not eligible since these mutations are associated with a milder DMD phenotype. The primary endpoint of the first part of the study was NSAA total score from baseline to Week 52. Key secondary endpoints included change in TTR from Baseline to Week 52, change in time of 10-meter walk/run (10MWR) from Baseline to Week 52, change in time to ascend 4 steps (Ascend4) from Baseline to Week 52, change in time of 100-meter walk/run (100MWR) from Baseline to Week 52, and change in micro-dystrophin expression by Western blot from Baseline to Week 12. Change in creatine kinase level (CK) was an exploratory endpoint.

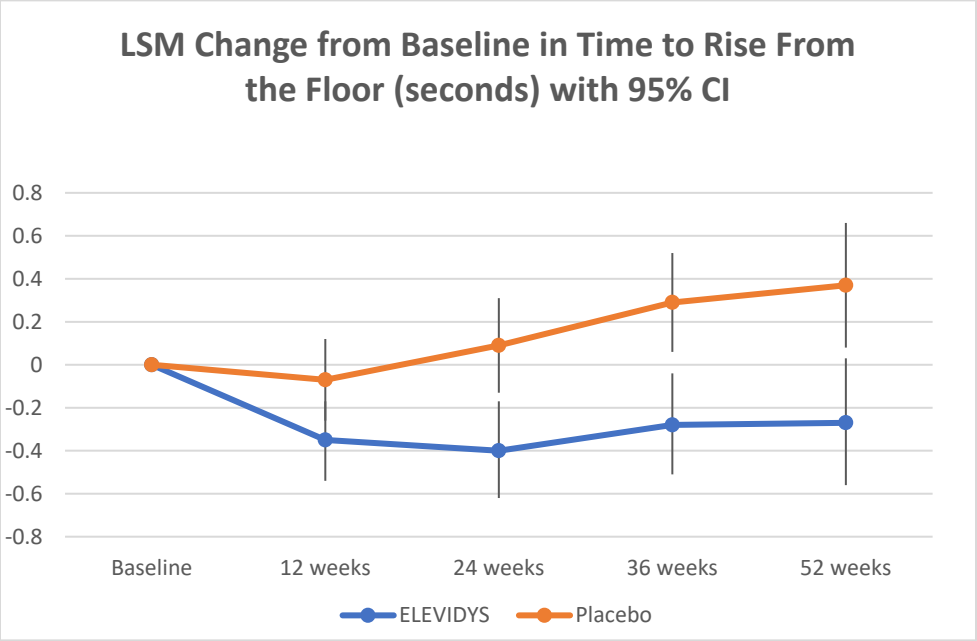
The mean age of enrolled subjects was 6.03 years, and mean weight was 21.83 kg (range: 13.5-41.6 kg); 63 subjects were randomized to receive ELEVIDYS and 62 to placebo. A mixed models for repeated measures (MMRM) approach was used for the evaluation of changes between the two study arms for the primary endpoint of NSAA and the various functional secondary endpoints.

The primary endpoint of change in NSAA from baseline to Week 52 in ELEVIDYS treated individuals versus those receiving placebo did not reach statistical significance (mean difference of 0.65 points, p = 0.2441). Age 4 to 5 years was associated with a greater improvement in NSAA than age 6 to 7 years with a mean difference of 1.32 versus 0.06 points respectively, but this value was not statistically significant (p = 0.0942 in the 4- to 5-year age group).

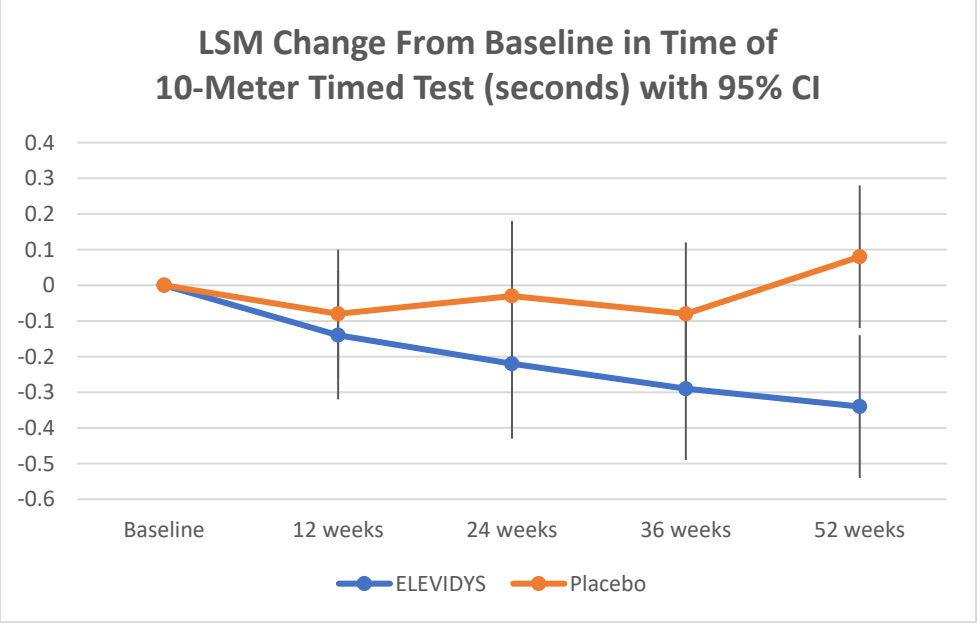
Secondary endpoints that were evaluated in Study 301, two of which have also been used individually as the primary endpoints to support prior DMD regulatory approvals,[5] included changes in the TTR, Ascend4, and the 10MWR timed tests (see figures below). In the analysis performed there was a -0.64 s (95% confidence interval (CI) -1.06, -0.23, p=0.0025) change in TTR in the ELEVIDYS treated individuals (n=63)

[5] See footnote 2, above.

versus placebo (n=61). This difference was present and similar in both the 4- to 5-year age group at -0.50 s (95% CI -0.90, -0.09, p=0.0177) and the 6- to 7-year age group at -0.78 s (95% CI -1.48, -0.08, p=0.0291). A difference was also observed in the 10MWR timed test. There was a -0.42 s (95% CI -0.71, 0.13, p=0.0048) change in the 10MWR test in the ELEVIDYS treated individuals (n=63) versus placebo (n=61). This difference was present and similar in both the 4- to 5-year age group at -0.33 s (95% CI -0.62, -0.03, p=0.0319) and the 6- to 7-year age group at -0.52 s (95% CI -1.01, -0.03, p=0.0363).



Data from Table 5 of Amendment 34 Clinical Overview



Data from Table 6 of Amendment 34 Clinical Overview

Additional secondary endpoints reported by the Applicant included changes in 100-meter walk/run (100MWR), Ascend4, and the stride velocity 95th percentile (SV95C). There was a -3.29 s (95% CI -8.28, 1.70, p=0.1942) change in 100MWR in the ELEVIDYS treated individuals (n=59) versus placebo (n=57). In the Ascend4 by MMRM there was a -0.36 s (95% CI -0.71, -0.01, p=0.0412) change in the time to ascend 4 stairs in the ELEVIDYS treated individuals (n=62) versus placebo (n=60). In the SV95C there was a change of 0.1 m/s (95% CI 0.00, 0.19, p=0.0402) in the ELEVIDYS treated individuals (n=57) versus placebo (n=61).

The Applicant also submitted data for a subpopulation of individuals in Study 301 on micro-dystrophin levels (% control) by Western Blot analysis adjusted by muscle content obtained 12 weeks following treatment with ELEVIDYS (n=17). These levels varied between 0 and 166.88% of control. Exploratory analyses conducted using data provided by the Applicant suggested a moderate correlation between micro-dystrophin levels (% Control) by Western Blot analysis adjusted by muscle content and 10 MWR (R^2=0.3223) and Ascend4 (R^2=0.3447). No clear correlation was seen for TTR, but the changes in this outcome measure were numerically small.

Among several other analyses, the Applicant provided data on MMRM analysis of change from baseline velocity (using the modified intent to treat sample sizes noted above) for TTR, 10MWR, and Ascend4. The change from baseline to 52 weeks for these values was: TTR 0.4 (1/s) (0.02, 0.07, p=0.0003), 10 MWR 0.17 (m/s) (0.07, 0.27, p=0.0008), and for Ascend4 0.16 step/s (95% CI 0.04, 0.28, p=0.0073). Finally, exploratory analyses of several parameters were performed, these included change in creatine kinase level (CK). Between baseline and week 52 the analysis showed a least-squares mean change of -5138.52 U/L (n=61, 95% CI -6747.47, -3529.57) in the ELEVIDYS group and -794.93 U/L in the placebo group (n=61, 95% CI -2403.70, 813.84) (p=0.0002).

Safety data provided on the entire population (n=125) indicate that the most common reported Treatment Related Adverse Events (TEAEs) for the ELEVIDYS group were vomiting, nausea, decreased appetite, and pyrexia. There were 21 Serious Adverse Events (SAEs) in 14 individuals in the ELEVIDYS group (n=63) in and 9 SAEs in 5 individuals on the placebo arm (n=62). No deaths were reported in either group. There was 1 SAE of hepatotoxicity/liver injury reported in the ELEVIDYS treated group, 1 SAE of myocarditis in the ELEVIDYS group, and 1 SAE of left ventricular dysfunction in the placebo group. Increased glutamate dehydrogenase levels within 90 days of dosing were observed in 15 individuals in the ELEVIDYS group and 2 individuals in the placebo group.

Data from Study 103

In addition to the data from Study 301 that was submitted, an updated interim study report was submitted for Study 103 as part of the efficacy supplement. Study 103 explored treating different cohorts of individuals with ELEVIDYS manufactured by the commercial process. The initial BLA submission contained information on Cohort 1 (n=20) from Study 103, and the updated report includes information on Cohorts 2 through 5. These included 7 ambulatory individuals ages 8 through 17 years of age in Cohort 2, 6 non-ambulatory individuals ages 9 through 20 years in cohort 3, 7 ambulatory individuals 3 through 4 years of age in Cohort 4, and 6 ambulatory individuals ages 4 through 8 years of age and 2 non-ambulatory individuals with mutations involving exons 1-17 in Cohort 5.

In the total of 8 non-ambulatory individuals, micro-dystrophin levels were assessed by Western Blot and ranged between barely detectable to over 100% of normal dystrophin levels, which is consistent with the variation in micro-dystrophin levels that were observed in ambulatory individuals. The Applicant also provided exploratory efficacy information in the 6 non-ambulatory individuals in Cohort 3. Performance of Upper Limb assessment (PUL) data were provided indicating a change from baseline of -3.8 points on

the scale. Data from a non-ambulatory natural history study (n=54) were provided showing a change of -6.3 points from baseline, and it was noted from this small sample that there was a 2.5-point difference in the positive direction. In the 6 individuals in Cohort 3 there were 38 TEAEs and no SAEs reported.

Summary

In summary, Study 301 failed to meet its primary endpoint. However, clinically notable changes were noted in the TTR and 10MWR, and in a few other relevant endpoints. An exploratory analysis indicated a moderate correlation between micro-dystrophin levels and 10MWR and Ascend4. Additionally, micro-dystrophin levels and exploratory data were provided for a small number of non-ambulatory individuals from Study 103. No new safety concerns appear to have been identified in the population of ambulatory individuals treated. Safety data in non-ambulatory individuals is limited, given the number of individuals treated to date. An inadequate amount of safety data is available currently to support the use of ELEVIDYS in individuals under 4 years of age.

DISCUSSION

Assessment of the Clinical Data

I have read the reviews and recommendations by staff of OTP and OBPV and have discussed with the review team issues surrounding the safety and efficacy data and information submitted. In addition to the review memoranda, I have reviewed the Applicant's submission and relevant scientific publications. I have also discussed this file with senior staff within CBER. I agree with the review team regarding their evaluation of product safety and their prior conclusions regarding product quality.

However, after carefully reviewing the data submitted by the Applicant, for the reasons outlined in greater detail in the paragraphs below, I find that the Applicant has met the standard for traditional approval in ambulatory individuals at least 4 years of age and accelerated approval in non-ambulatory individuals at least 4 years of age. Specifically, I have concluded that:

- Substantial evidence of effectiveness of clinical benefit has been demonstrated for the original population of ambulatory 4- and 5-year-old individuals with DMD for whom the product previously received accelerated approval, as well as for the larger population of ambulatory individuals with DMD; I therefore determine that the demonstration of effectiveness supports traditional approval in ambulatory individuals at least 4 years of age with DMD.
- Substantial evidence of effectiveness has been demonstrated for non-ambulatory individuals. Based on clinical data submitted regarding the elevation of micro-dystrophin in ambulatory individuals and the relationship between micro-dystrophin levels and clinical outcomes in ambulatory individuals, as well as elevation of micro-dystrophin levels and positive exploratory clinical results in non-ambulatory individuals, and because the mechanism of action of ELEVIDYS is similar in both situations, I conclude that ELEVIDYS has demonstrated an effect on micro-dystrophin levels that is reasonably likely to predict clinical benefit in non-ambulatory individuals. This conclusion supports accelerated approval in non-ambulatory individuals at least 4 years of age with DMD pursuant to section 506(c) of the FD&C Act and 21 CFR 601.41. A confirmatory randomized, controlled clinical trial in the non-ambulatory population is currently underway.
- Across the indicated populations in ambulatory and non-ambulatory individuals, the benefit to risk considerations for this product are favorable, taking into consideration the severe unmet need and existing uncertainties.

Discussion of Study 301

Study 301 failed to meet its primary endpoint. This situation is sometimes encountered in regulatory submissions to FDA. In areas of high unmet medical need, FDA has taken the approach of carefully considering the totality of the evidence to determine whether a product could receive approval.[6] When a study fails to meet its primary endpoint, as is the case for Study 301, consideration of a number of questions may be helpful in determining whether a drug has demonstrated evidence of clinical activity.[7] Key issues that factor into my own determination that Study 301 is an adequate and well-controlled clinical trial that supports a finding of substantial evidence of effectiveness in verifying and demonstrating clinical benefit are noted below.

First, an understanding of the molecular genetics and biology of DMD provides a strong rationale for why delivering micro-dystrophin may be effective in addressing the functional decline that normally occurs in this disease. Based on the observations of minimal or modest functional impairment in certain patients with large deletions in the *DMD* gene (Becker's muscular dystrophy), the Applicant developed and tested their construct in animal models which showed it to be active.

Second, although the primary endpoint of improvement in NSAA versus placebo in Study 301 was not met, the finding of positive changes in multiple relevant secondary endpoints along with supportive information from exploratory analyses, including the moderate correlation of clinical endpoints with micro-dystrophin levels and the reduction in CK levels, indicate that the product can provide clinical benefit to individuals with DMD. Data from Study 102 indicating a potential clinical benefit from the product associated with increased micro-dystrophin levels seen in 4- and 5-year-old individuals are also supportive of this conclusion.

Third, the key secondary outcomes (TTR, 10 MWR and Ascend4) showed improvement in ELEVDYS-treated individuals compared to those treated with placebo. As noted above, TTR and Ascend4 have been used as primary endpoints in trials to support approval of other products for DMD. Though exploratory, a notable reduction was observed in the reduction in CK levels at 52 weeks between the ELEVIDYS and placebo groups once daily corticosteroid dosing in the ELEVIDYS group had returned to baseline and matched the placebo group (mean of 0.6 mg/kg/day in both arms).

Fourth, Duong and colleagues report on the minimal detectable change (MDC) and the minimal clinical important difference (MCID) in annual rate of change of timed function tests in boys with DMD.[8] The values for MDC for 10MWR, TTR, and Ascend4 are -0.138 m/s, -0.026 rise/s, and -0.034 tasks/s, respectively; the corresponding values for MCID are -0.212 m/s, -0.023 rise/s, and -0.035 tasks/s. The values for these annual parameters in Study 301 are -0.17 m/s for 10 MWR, -0.4 (1/s) for TTR, and -0.16 steps/s for Ascend4. For 10 MWR the value is within the MDC, yet modestly lower than the MCID; however, for TTR and Ascend4 the values are both well above the MDC and the MCID.

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[6] Johnston JL, Ross JS, Ramachandran R. US Food and Drug Administration Approval of Drugs Not Meeting Pivotal Trial Primary End Points, 2018-2021. JAMA Intern Med. 2023 Apr 1;183(4):376-380. doi: 10.1001/jamainternmed.2022.6444. Erratum in: JAMA Intern Med. 2023 Apr 1;183(4):394. PMID: 36780148; PMCID: PMC9926353.

[7] See, e.g., Pocock SJ, Stone GW. The Primary Outcome Fails - What Next? N Engl J Med. 2016 Sep 1;375(9):861-70. doi: 10.1056/NEJMra1510064. PMID: 27579636.

[8] Duong T, Canbek J, Birkmeier M, et al. The Minimal Clinical Important Difference (MCID) in Annual Rate of Change of Timed Function Tests in Boys with DMD. J Neuromuscul Dis. 2021;8(6):939-948. doi: 10.3233/JND-210646. PMID: 34151852; PMCID: PMC8673528.

Fifth, although only available from a subpopulation of individuals, the exploratory finding of a moderate correlation of the extent of increase in micro-dystrophin levels with 10 MWR and Ascend4 is also supportive, as is the exploratory analysis of reduction in CK levels at 52 weeks. Although this difference in CK was smaller than initially observed in the trial at 12 weeks, the early increase in corticosteroid administration that was part of the protocol to address the inflammatory response to AAV may have been a confounding factor.

Finally, the effect of ELEVIDYS depends on the delivery of this AAVrh74 vector-based gene therapy to muscle tissue in order for the micro-dystrophin construct can be expressed. Given that a 4-year-old has several kilograms of skeletal muscle (commonly about 10 pounds), it is not all that surprising that only a percentage of total muscle mass might be addressed by this gene therapy, commonly leading to partial, rather than complete correction of the deficits seen in those affected by DMD.[9] It is also not unexpected based on individual differences, that the ultimate effect could vary in different treated individuals. Far from being insignificant, such partial correction may make the difference in critical functional parameters, such as continuation of the ability to climb stairs or walk independently.

In summary, I find that although Study 301 failed to meet its primary endpoint in changing the outcome on the NSAA, it was successful in showing benefit on clinically meaningful endpoints. Those outcomes, along with confirmatory evidence consisting of data from studies 101, 102, and 103 and mechanistic information about the product, provides substantial evidence of effectiveness for traditional approval in ambulatory individuals with DMD at least 4 years of age. Two key secondary endpoints that were used individually for prior regulatory approvals in DMD were positive (TTR and 10MWR) as well as third that is often evaluated in trials, Ascend4, and exploratory data on reduction in CK are supportive. Although it could be argued that the differences in the individuals receiving ELEVIDYS and placebo are relatively small, data in the literature suggest that these differences are clinically meaningful.[10]

Regarding non-ambulatory individuals, based on a totality of the evidence, including the clinical data in ambulatory individuals associated with increased micro-dystrophin levels, combined with the micro-dystrophin levels and preliminary clinical evidence in non-ambulatory individuals, and given that the mechanism of action of ELEVIDYS is similar in both situations, I have determined that increased levels in micro-dystrophin in non-ambulatory individuals are reasonably likely to predict clinical benefit in this population. This conclusion, along with the evidence that ELEVIDYS elevates micro-dystrophin levels, provides substantial evidence of effectiveness to support accelerated approval in non-ambulatory individuals at least 4 years of age with DMD, considering the serious nature of the diseases and the extent of unmet medical need in this group of individuals. These individuals have a serious condition and represent a group with a high unmet medical need for an intervention that could address their further decline in function.

[9] Sidiqi A, Fariha F, Shanta SS, et al. Estimation of Skeletal Muscle Mass in 4-year Old Children Using the D_3-creatinine dilution method. Pediatr Res. 2023; 94(3): 1195-1202. doi: 10.1038/s41390-023-02587-1.

[10] Duong T, Canbek J, Birkmeier M, et al. The Minimal Clinical Important Difference (MCID) in Annual Rate of Change of Timed Function Tests in Boys with DMD. J Neuromuscul Dis. 2021;8(6):939-948. doi: 10.3233/JND-210646. PMID: 34151852; PMCID: PMC8673528.

CONCLUSIONS

Although acknowledging that the Applicant's study conducted to confirm clinical benefit of ELEVIDYS failed to meet its statistical primary endpoint of improvement versus placebo in NSAA, I find that in addition to meeting standards for quality and safety, the available data are compelling, including the positive benefit shown on the secondary endpoints and the exploratory evidence. These indicate clinical benefit compared to placebo that meet the substantial evidence of effectiveness standard as per section 505(d) of the FD&C Act. The totality of the evidence presented supports traditional approval of ELEVIDYS in ambulatory individuals 4 years of age and older with a confirmed mutation in the *DMD* gene except in those with any deletion in exon 8 and/or exon 9 in the *DMD* gene, in whom its use is contraindicated. In non-ambulatory individuals at least 4 years of age, the results obtained with the product in ambulatory individuals and the association of clinical benefit with increased micro-dystrophin levels in the ambulatory population, along with the established effect of the drug to elevate micro-dystrophin levels, support accelerated approval under section 351(a) of the PHS Act pursuant to section 506(c) of the FD&C Act and 21 CFR 601.41. A confirmatory randomized, controlled clinical trial in the non-ambulatory population is currently underway.

Overall, the demonstrated benefits of ELEVIDYS in the treatment of ambulatory individuals, and the expected benefits of ELEVIDYS in non-ambulatory individuals, with DMD over 4 years of age who are eligible to receive this therapy in improving key functional endpoints such as the ability to stand, walk, or climb stairs, outweigh the risks. The benefit to risk considerations are favorable taking into account the existing uncertainties, such as the ultimate duration of response. Although it might be argued that other gene therapy products in development may prove superior to ELEVIDYS in future clinical trials, these products have yet to receive regulatory approval. During this time, the availability of this gene therapy option may help slow or prevent irreversible decline that might otherwise occur in both ambulatory and non-ambulatory individuals, particularly since the latter have few or no alternative treatments available to address their imminent further decline in function over time.