U.S. FOOD & DRUG ADMINISTRATION

June 20, 2024

Kenneth D. Eichenbaum, MD, MSE,
Assistant Professor
(b) (6)

Sent via email to: (b) (6)

Re: Citizen Petition (Docket Number: FDA-2024-P-2730)

Dear Dr. Eichenbaum:

This letter responds to the Citizen Petition dated June 2, 2024 (Petition) that you (Petitioner) submitted to the Food and Drug Administration (FDA, the Agency, we) regarding the Biologics License Application (BLA) for ELEVIDYS (delandistrogene moxeparvovec-rokl).

In the Petition, Petitioner requests that FDA (1) Refuse to approve an expanded indication for ELEVIDYS; and (2) Re-evaluate the benefit-risk profile for ELEVIDYS.[1]

This letter responds to the Petition in full. We have reviewed the petition and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR § 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition. Today, we are approving an expanded indication for ELEVIDYS.

I. BACKGROUND

A. ELEVIDYS

ELEVIDYS is an AAVrh74 vector-based gene therapy designed to treat Duchenne Muscular Dystrophy (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.[2]

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

[1] Petition at 1.
[2] Center Director Decisional Memo, at 2, https://www.fda.gov/media/169707/download?attachment (2023 Center Director Decisional Memo).

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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]

On June 22, 2023, FDA granted approval under the accelerated approval statutory provisions and regulations for ELEVIDYS to Sarepta Therapeutics, Inc (Sarepta) for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.[4]

The accelerated approval of ELEVIDYS was based, in part, on Study 102 "a randomized, double-blind, placebo-controlled crossover trial in individuals ages 4 to 7 (n=41) using a version of the product not intended for commercialization (Process A SRP9001)."[5]

As a condition of approval, Sarepta was required to "[c]omplete Study SRP-9001-301 Part 1, an ongoing, randomized, double-blinded clinical trial intended to describe and verify clinical benefit of [ELEVIDYS] in ambulatory patients with [DMD]. The trial evaluates the primary endpoint of North Star Ambulatory Assessment (NSAA) and compares [ELEVIDYS] to placebo in 125 ambulatory patients with DMD with confirmed mutation in the *DMD* gene."[6] Sarepta referred to Study SRP-9001-301 Part 1 as the EMBARK study.[7]

In December 2023, Sarepta submitted a supplement to expand the indication of ELEVIDYS to include all ambulatory and non-ambulatory individuals with DMD with a confirmed mutation in the *DMD* gene. In support of the expanded indication, and to satisfy Sarepta's postmarketing requirement, Sarepta submitted the results of the EMBARK study. The supplement also included clinical information from Study 103, an uncontrolled trial in individuals 3 to 19 years of age, that included treatment of 8 non-ambulatory individuals.

On June 20, 2024, FDA approved Sarepta's supplement. As part of this approval action, FDA granted traditional approval for ELEVIDYS in ambulatory individuals 4 years of age and older with DMD with a confirmed mutation in the *DMD* gene and accelerated approval for ELEVIDYS in non-ambulatory individuals 4 years of age and older with DMD with a confirmed mutation in the *DMD* gene.

B. Statutory and Regulatory Background

FDA approval of a BLA submitted under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262(a)) is based on a showing that the product is "safe, pure, and potent," a demonstration that the facility in which the product is manufactured,

[3] 2023 Center Director Decisional Memo, at 1-2.
[4] ELEVIDYS Approval Letter, https://www.fda.gov/media/169715/download?attachment.
[5] Center Director Decisional Memo, at 2, https://www.fda.gov/media/169707/download?attachment.
[6] ELEVIDYS Approval Letter, https://www.fda.gov/media/169715/download?attachment.
[7] See https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-us-fda-acceptance-efficacy.

processed, packed, or held meets applicable standards, and the applicant's consent to inspection of the manufacturing facility.[8] Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). As FDA has noted in several guidance documents, 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.[9]

i. Substantial Evidence of Effectiveness

Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires an applicant to provide "substantial evidence" to establish a drug's effectiveness of effectiveness. The statute defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." FDA has interpreted the "substantial evidence" standard as generally requiring at least two adequate and well-controlled clinical investigations to establish effectiveness.[10]

In addition, section 115(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA), amended section 505(d) of the FD&C Act to provide that "[i]f [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." This modification explicitly recognized the potential for FDA to find that one adequate and well-controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness.

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[8] See section 351(a)(2)(C) of the PHS Act.

[9] In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126) (see former 21 CFR 601.25(d)(2) (2015) (revoked as no longer necessary, 81 FR 7445 (Feb. 12, 2016))). In section 123(f)) of the Food and Drug Administration Modernization Act of 1997, Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FD&C Act. See also 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); Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products, at 3 (October 2023).

[10] See FDA, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; Guidance for Industry, May 1998, (1998 Guidance), at 3; *Warner-Lambert Co. V. Heckler,* 787 F. 2d 147 (3d Cir. 1986). See also, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry (December 2019) (Substantial Evidence of Effectiveness Draft Guidance), at 4, https://www.fda.gov/media/133660/download. When finalized, this draft guidance will represent FDA's current thinking on this topic.

ii. Benefit-Risk Assessment

Because all drugs can have adverse effects, the demonstration of a drug's safety requires a showing that the benefits of the drug outweigh its risks. As such, a benefit-risk assessment is integrated into FDA's regulatory review of marketing applications for new drugs and biological products. As FDA has noted in its guidance, "[the] benefit-risk assessment in FDA's drug regulatory context is making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks) under the conditions of use described in the approved product labeling."[11] In the case of serious rare diseases for which there are few or no approved therapies, FDA has recognized that greater uncertainty or greater risks may be acceptable provided that the standard for substantial evidence of effectiveness has been met.[12]

iii. Evidentiary Criteria for Accelerated Approval

FDA may grant accelerated approval to a product intended to treat a serious or life-threatening disease or condition, upon a determination:

> . . . that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit….[13]

For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but it is not itself a measure of clinical benefit.

Accelerated approval has been reserved for drugs that appear to provide a meaningful advantage over available therapy, and subject to the requirement that "the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit."[14] FDA may require, as appropriate, a confirmatory study or studies to be underway prior to granting accelerated approval, or within a specified time period after the date of accelerated approval, of the applicable product.[15]

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[11] Benefit-Risk Assessment for New Drug and Biological Products; Guidance for Industry, October 2023, (Benefit-Risk Assessment Guidance), at 3-4.
[12] *Id*. at 12.
[13] Section 506(c)(1)(A) of the FD&C Act (21 U.S.C. 356(c)(1)(A)) (see also 21 CFR 601.41).
[14] See FDA's May 2014 guidance for industry Expedited Programs for Serious Conditions—Drugs and Biologics, at 17.
[15] Section 506(c)(2)(D) of the FD&C Act.

II. DISCUSSION

A. Sarepta Has Provided Adequate Evidence to Support Approval of an Expanded Indication for ELEVIDYS

The Petitioner makes several arguments that the data in the BLA for ELEVIDYS are not sufficient to support approving an expanded indication. Based on the limited data cited by Petitioner, we interpret this request as a request not to approve an expanded indication because Sarepta has not provided sufficient information to demonstrate substantial evidence of effectiveness or has not demonstrated that the benefits of ELEVIDYS would outweigh its risks for any expanded indication.

First, the Petitioner repeats several statements contained in a Journal of the American Medical Association (JAMA) viewpoint article by David M. Rind, MD[16], about Study 102, including that the study "'did not achieve statistical significance on the primary functional endpoint of improvement in NSAA total score compared to placebo at 48 weeks post-treatment'"[17] and that "'no dose-response effect was seen with [ELEVIDYS].'"[18] Petitioner also repeats a statement from the JAMA article that ELEVIDYS "'can cause harm'", citing adverse events identified among 85 patients across 3 studies that was assessed as part of the initial approval.[19]

The Petitioner also makes several arguments to suggest that the EMBARK study results do not support an expanded indication for ELEVIDYS. The Petitioner asserts that EMBARK study also did not achieve its primary endpoint, and repeats arguments from the JAMA article that the "'net benefit with [ELEVIDYS] is weak'"[20] and "'if benefits with [ELEVIDYS] are real, they are not large.'"[21]

FDA considered data from Study 102, the EMBARK study, as well as other data and information, during its review of Sarepta's supplemental application requesting that FDA approve an expanded indication for ELEVIDYS. As discussed further in the 2024 Center Director Decisional Memo, we have concluded that Sarepta has verified clinical benefit and has provided substantial evidence of effectiveness to support traditional approval under section 351(a) of the PHS Act in ambulatory individuals 4 years of age and older with DMD with a confirmed mutation in the *DMD* gene who are eligible to receive this therapy. Although the EMBARK study 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 the studies submitted by Sarepta and mechanistic information about the product, provides

[16] Petitioner does not cite the article by name, but based on the quotes in the petition, the article appears to be "The FDA and Gene Therapy for Duchenne Muscular Dystrophy", https://jamanetwork.com/journals/jama/fullarticle/2818205.
[17] Petition, at 1.
[18] *Id.*
[19] *See* Summary Basis for Regulatory Action, at 21, https://www.fda.gov/media/169746/download?attachment.
[20] Petition, at 2.
[21] *Id.*, at 2.

substantial evidence of effectiveness for traditional approval in ambulatory individuals with DMD at least 4 years of age.

In addition, we have also concluded that Sarepta has provided substantial evidence of effectiveness of ELEVIDYS for non-ambulatory individuals 4 years of age and older with DMD with a confirmed mutation in the *DMD* gene who are eligible to receive this therapy, by demonstrating an effect on micro-dystrophin levels which is reasonably likely to predict clinical benefit in this population, to support accelerated approval under section 351(a) of the PHS Act. This is 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.

For these reasons, and as further explained in the 2024 Center Director Decisional Memo[22], we have concluded that there is substantial evidence of effectiveness to support converting ELEVIDYS' accelerated approval indication to traditional approval, and expanding the ELEVIDYS indication, and that the benefits of ELEVIDYS outweigh its risks for the approved indications.[23] We therefore deny your request.

B. ELEVIDYS'S Risk-Benefit Assessment Remains Favorable

Petitioner also requests that FDA re-evaluate the risk-benefit profile for ELEVIDYS. We interpret this as a request to reevaluate whether the benefits of ELEVIDYS outweigh its risks for the initial approved indication and determine that the benefits of ELEVIDYS do not outweigh its risks for this use. As described above, ELEVIDYS was originally approved under accelerated approval for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene. In its Petition, the Petitioner cites the same evidence described above in support of this request.

Evidence from the studies identified by Petitioner, as well as additional data and information, was considered as part of our evaluation of Sarepta's supplement to convert the approved ELEVIDYS indication to traditional approval and expand that approval. 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, which is not yet known, as well

[22] The basis for FDA's licensure decision is set forth in the 2024 Center Director Decisional Memo. This memorandum will be posted on fda.gov. We incorporate by reference the 2024 Center Director Decisional Memo.
[23] Petitioner also makes assertions unrelated to the substantial evidence of ELEVIDYS and the risk-benefit profile for ELEVIDYS, including that expanding the indication "will obstruct the developmental path and availability for disease-stricken patients to obtain treatment with developing therapies that actually show potential for disease modification and physiologic improvement" and "[t]he obstruction or delay of the development of these therapies could be devastating to patients." *Id.,* at 2. However, Petitioner fails to explain why these assertions permit FDA to refuse to approve an expanded indication that meets the standard for approval.

as the significant unmet need. For these reasons, as discussed in the 2024 Center Director Decisional Memo, we conclude that the benefits of ELEVIDYS continue to outweigh its risks for the initial approved indication. We therefore deny your request.

III. CONCLUSION

FDA has considered Petitioner's requests as they relate to ELEVIDYS. For the reasons given above, FDA denies the requests.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Docket Management Staff