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Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Therapuetic Products
Office of Gene Therapy

BLA STN Number: 125781/34

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Reviewer: Sukyoung Sohn, PhD, CBER/OTP/OGT/DGT1/GTB1

Through: Andrew Byrnes, PhD, Division Director, CBER/OTP/OGT/DGT1

Nature of Supplement: To support expansion of the approved indication for ELEVIDYS to all DMD patients and conversion of the accelerated approval to a traditional approval.

Supplement Type: Efficacy

Supplement Numbers: 34

Submission date: December 21, 2024

Review Due date: June 21, 2024

Review Date: June 11, 2024

Related Amendments reviewed: 125781/34.2 (Environmental Assessment) received January 9, 2024

Additional Review: N/A

Executive Summary:

The purpose of the supplement is to support expansion of the approved indication for ELEVIDYS to all Duchenne muscular dystrophy (DMD) patients and conversion of the accelerated approval to a traditional approval.

ELEVIDYS (BLA 125781) was approved on June 22, 2023 through the Accelerated Approval pathway for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.

This efficacy supplement includes results from the placebo controlled confirmatory Study SRP-9001-301 (EMBARK) in ambulatory subjects 4-7 years of age as well as all current results from Study SRP-9001-103, which includes ambulatory and non-ambulatory subjects with DMD ranging in age from 3-20 years, with a maximum weight of 80kg.

There is no change in the product. The in-use hold time described in the Package Insert (PI) remains the same. However, to allow adequate time to complete the infusion, the applicant proposed to add a comment, "If the ELEVIDYS infusion needs to be stopped and restarted, ELEVIDYS should be infused within 12 hours after drawing into the syringe." The stability data included in the original BLA submission as well as the microbial challenge data submitted under CBE-30 Supplement 125781/10 contain sufficient information to support the proposed change in the PI.

There are no CMC issues identified that would prevent approval.

Review of Information supporting the Changes:

There is no change in the product.

Comparison between the DP lots used in Study 301 and commercial DP lots

The same manufacturing process (Process B) is used for both commercial DP lots and the clinical DP lots used in Study 301. However, there were differences in the release specifications between the clinical lots and the commercial lots (Table 1). Bold font depicts the differences between the specifications. Clinical DP lots filled with drug substance (DS) manufactured between (b) (4) were released against the clinical specifications listed in Table 1. Upon our request sent on December 12, 2023, the applicant revised the release specifications for DS and DP to be consistent with those for commercial lots (IND 17763/ Amendment #311 dated February 9, 2024) for all clinical DP lots filled with DS lots manufactured after September 28, 2023.

Table 1. Comparison of Release Specifications for Commercial DP and Clinical DP

Attribute	Analytical Procedure	Commercial AC	Clinical AC*
Appearance	(b) (4) Visual inspection	(b) (4) Cap color: Blue	Clear, colorless liquid, may have some opalescence, **may contain white to off-white particles.** Cap color: Blue
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Identity (vector genome)	(b) (4)	(b) (4)	(b) (4)
Identity (vector capsid)	(b) (4)	(b) (4)	(b) (4)

Sterility	(b) (4)	No growth	No growth
Bacterial Endotoxin	(b) (4)	(b) (4)	(b) (4)
Capsid Purity	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Percent Full Capsid	(b) (4)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
		(b) (4)	(b) (4)
Vector Genome Concentration	(b) (4)	(b) (4)	(b) (4)
Extractable volume	(b) (4)	(b) (4)	(b) (4)
*The AC for clinical lots has been revised to be consistent with those for commercial lots. This change has been made to the DP lots filled with DS lots manufactured after September 28, 2023.			

Reviewer comment: *As of June 10, 2024, a total of 18 commercial DP lots have been approved by FDA for release. I analyzed lot release data for vg titer and % full capsid to compare the clinical DP lots (Process B) and commercial DP lots (Figure 1). Dashed lines correspond to commercial release AC.*

Figure 1. Comparison of Clinical and Commercial DP Lots

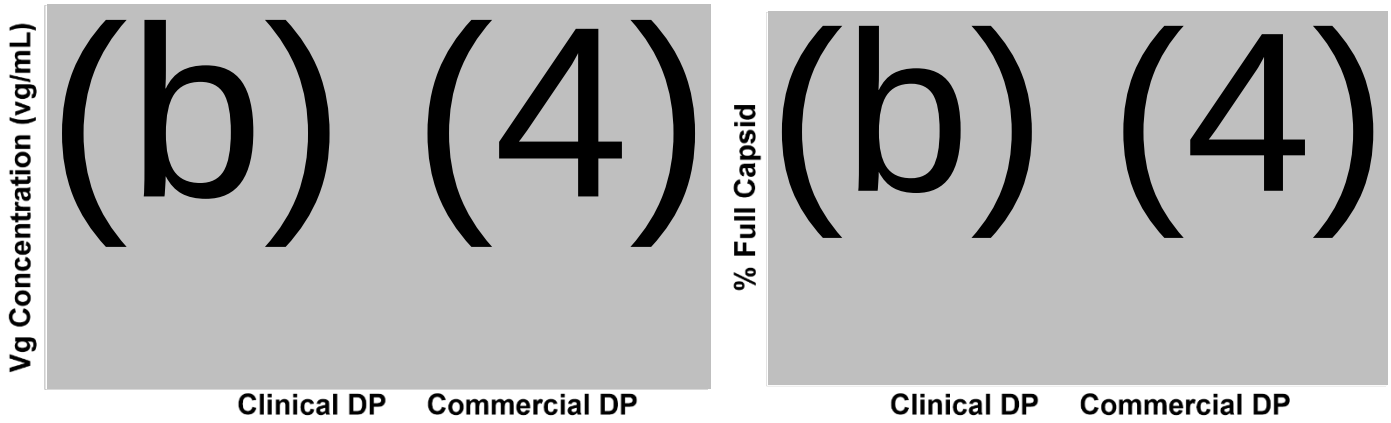

Table 2. Comparison of Clinical and Commercial DP lots

	Vg Concentration (vg/mL)		% Full Capsid	
	Clinical DP	Commercial DP	Clinical DP	Commercial DP
Mean	(b) (4)			
Std. Deviation				

Reviewer comment: *The mean of clinical DP lots is (b) (4) % higher in vg titer and (b) (4) % higher in % full capsid compared to commercial DP lots (Table 2). Due to the wide AC for clinical lots, the clinical lots exhibit higher variability in both attributes. Specifically, the clinical DP lot A634-SRP-9001-20-0010, which was used for Study 103 and Study 301, has (b) (4) % lower vg titer than intended titer and the lower % full capsid (b) (4) %). The consistency and quality of the product is improved for the commercial product, compared to the product used in clinical studies, and the vg titer of commercial lots is more closely aligned with the labeled commercial concentration of 1.33 × 10^{13} vg/mL.*

Overall, the commercial ranges overlap the ranges used in clinical studies. The additional intended patient population will require substantially higher doses of DP, which will also increase the level of impurities. The acceptance criteria for impurities are generally determined based on lots shown to be safe and effective. We do not have sufficient patient safety data in the intended patient population to assess whether reevaluation of the current release AC for commercial lots, originally intended for ambulatory pediatric patients aged 4 through 5 years, is required to support the change in the indicated patient population. We may need to reevaluate the AC for commercial lot release as more lot release data become available.

In-use Stability

The in-use hold time of 6 hours after drawing into syringe, which is described in the Package Insert (PI) Section 2.3 – Preparation, remains the same. However, to allow adequate time to complete the infusion, the applicant proposed to add the following comment in the PI, Section 2.4 - Administration: "If the ELEVIDYS infusion needs to be stopped and restarted, ELEVIDYS should be infused within 12 hours after drawing into the syringe."

Reviewer comment: *I reevaluated the stability data provided in the original BLA submission as well as the microbial challenge study results submitted under CBE-30 Supplement 125781/10, and the information was found to be acceptable for supporting the proposed change in the PI.*

Communications with the Applicant: An information request for the environmental analysis was sent on January 2, 2024; the response was received on January 9, 2024.

Environmental Assessment:
The Applicant submitted environmental (EA) assessment in accordance with 21 CFR 25 requirement. This supplement is not eligible for categorical exclusion, and the Applicant does not make a claim of categorical exclusion for EA.

The product delandistrogene moxeparvovec-rokl (ELEVIDYS) is derived from rhesus serotype 74 AAV (AAVrh74), a nonpathogenic human DNA virus that is incapable of self-replication. The natural DNA genome of AAVrh74 has been replaced with the expression cassette for SRP-9001 microdystrophin. Even in the presence of a helper virus, ELEVIDYS is unable to replicate since it lacks essential genes required for replication and establishment of infection.

ELEVIDYS will be administered in US hospitals or clinic centers. Handling and disposal of any unused medicinal product or waste material will be in accordance with local guidelines on handling of biological waste. Shedding occurs through patient excreta. Caregivers and patient's families will be advised on the proper handling of patients' bodily fluids and waste for a minimum of 4 weeks after the treatment.

Data from the vector shedding study demonstrate that the estimated half-life of ELEVIDYS vector genome in the serum is approximately 12 hours, and majority of the drug is expected to be cleared from the serum by 1-week post-dose. In the excreta, the estimated half-life of the vector genome is 40 hour, 55 hours, and 60 hours in the urine, feces, and saliva, respectively. The data from the viral shedding assessment in clinical patients also show a decrease in shedding from peak to week 4 was greater than 99% for saliva, urine, and feces. Therefore, the Applicant concludes that environmental effects related to the short-term exposure to the viral vector are unlikely and are limited to up to 4 weeks following administration of ELEVIDYS.

The likelihood of germline transmission of vector DNA through semen is negligible. Animal studies showed no indication of paternal germline transmission to the offspring, even with high levels of vector DNA present in gonads.

The manufacturing process is designed to minimize the potential that DNA recombination might result in a virus that contains viral DNA. The product is tested for the presence of replication competent AAV (rcAAV), and all batches have historically tested negative. Even if rcAAV were to form, the virus would still be nonpathogenic and incapable of causing infectious disease without coinfection of cells by a helper virus. Therefore, the Applicant concludes that the risk of complementation, recombination, and rcAAV formation is regarded as negligible.

Based on the Applicant's analysis for the risk to the environment related to the use of ELEVIDYS,

- AAVs have not been associated with any pathogenic disease in humans or animals and are unable to replicate unless the cell is co-infected with a helper virus. In addition, (b) (4) and the finished product is controlled for the absence of replication competent vector.

- The only mechanism by which there could be mobilization is that the same cell was infected simultaneously with the clinical vector, a WT AAV, and a helper virus (triple infection): The likelihood of simultaneous triple infection can be considered very low.
- The recombined particles would have the rep and cap genes encoding for proteins required for replication and capsid formation, but they would still be replication-defective (as the wild-type virus).

Reviewer comment: *Based on the Applicant's risk assessment and the control measures implemented, it is considered that there is no significant environment risk from the approval of this supplement. As such, a finding of no significant impact (FONSI) will be prepared.*

CMC recommendation: There are no CMC issues identified that would prevent approval. CMC defers to Clinical for the final decision on approval.