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Office Director Memorandum

Office of Clinical Evaluation

Summary of Regulatory Decision on Biologics License Application

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 requested indication and dosage:

> **Proposed Indication**: For the treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the DMD gene.
>
> **Proposed Dosage**: 1.33×10^{14} vector genomes per kilogram (vg/kg) of body weight for patients weighing less than 70 kg and 9.31×10^{15} vg total fixed dose for patients weighing 70 kg or greater.

The primary evidence of effectiveness in the sBLA derives from Study SRP-9001-301 (Study 301), a two-part, multi-center, randomized, double-blind, placebo-controlled (Part 1), study conducted in male, ambulatory patients aged four up to 8 years of age. Patients were required to have a confirmed mutation (see clinical review) in the DMD gene, and to have a minimum North Star Ambulatory Assessment (NSAA) total score at screening of 16 to 28, a Time to Rise from floor at screening of less than 5 seconds, and to be on stable daily dose of oral corticosteroids for at least 12 weeks prior to the screening visit. Patients with AAVrh74 antibody titers exceeding 1:400 were excluded from the study. Patients were stratified at randomization (1:1) by age group (≥4 to <6 years or ≥6 to <8 years), and NSAA Total Score (≤22 or >22) at screening. Patients were randomized to receive Elevidys 1.33×10^{14} vg/kg or placebo in Part 1 of the study. In Part 2, patients randomized to placebo in Part 1 received Elevidys while patients randomized to Elevidys received placebo.

Study 301 was intended as a confirmatory trial "*to verify and describe the clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate benefit*" as described in the approval letter dated June 22, 2023; accelerated approval was granted to Elevidys for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD, with a confirmed mutation in the DMD gene based on the surrogate endpoint of expression of micro-dystrophin at Week 12 after administration of Elevidys.

The primary endpoint and major efficacy endpoint in Study 301 was the change in the NSAA total score from baseline to Week 52. With a sample size of 120 patients (60 patients per arm) Study 301 was powered (90%) to show a statistically significant mean difference of 2.2 (a 10% dropout rate) between the Elevidys group and the placebo group, with a two-sided Type 1 error rate controlled at less than 5% (i.e., p value <0.05 needed to achieve statistical significance). Notably, no other hypothesis was formally tested in Study 301 although the study's analysis plan pre-specified analyses of secondary endpoints in the following sequence with key secondary endpoints are italicized:

- *Quantity of micro-dystrophin protein expression at Week 12, measured by Western blot.*

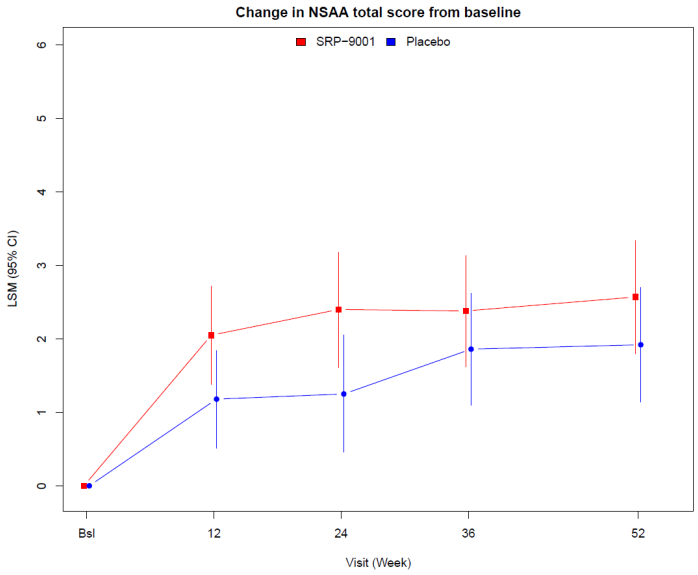
- *Change in time to rise from the floor from Baseline to Week 52.*
- *Change in time of 10-meter timed test from Baseline to Week 52.*
- Change in Stride Velocity 95th Centile from Baseline to Week 52.
- Change in time of 100-meter timed test from Baseline to Week 52.
- Change in time to ascend 4 steps 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.

The protocol also pre-specified subgroup analyses based on age group, NSAA group, race, and body mass index group. Details of the study design and analysis plan are provided in the clinical and statistical reviews.

In the BLA, the Applicant additionally submitted data from Study SRP-9001-103 (Study 103), an open label, single-arm, multi-cohort study intended to provide bridging data to enable a comparison of the investigational agent manufactured using the commercial process to the manufacturing process used in earlier clinical investigation. Data from cohorts 1 – 5 were included in the BLA. The main outcome of Study 103 was micro-dystrophin expression as measured by Western blot of biopsied muscle tissue at Week 12. Study enrolled male patients across cohorts based on ambulatory status (ambulatory or non-ambulatory) and age group (age 2 to 17 years in cohorts included in the BLA). Notably, the only data provided in the BLA on non-ambulatory patients derives from this study, totaling 8 patients. In addition to micro-dystrophin protein expression, Study 103 evaluated functional outcome measures in an exploratory fashion, including NSAA and Performance of Upper Limb (PUL) version 2.0, a clinician-reported outcome measure used to evaluate motor function in the upper limbs of patients with DMD. However, the results of these outcomes in a single-arm, open label study are of limited significance.

Study 301 did not show a statistically significant difference in mean change in NSAA total score from baseline to Week 52 between treatment groups. The Least Square Mean change in NSAA total score was 2.57 (95% Confidence Interval[CI]: 1.80, 3.34)for the Elevidys group, and 1.92 (95% CI: 1.14, 2.70) for the placebo group, a difference of 0.65 points (95% CI: -0.45, 1.74), which was not statistically significant (p value =0.2441). Figure 1 illustrates the LSM change in NSAA total score from baseline over time in each treatment group.

Figure 1. Least Mean Change in North Star Ambulatory Assessment- Baseline to Week 52 (Study 301)



Source: Statistical Review (Figure 1)

Analyses of the key secondary functional outcomes and outcomes in age-defined subgroups (4-5 years and 6-7 years) are shown below in Table 1.

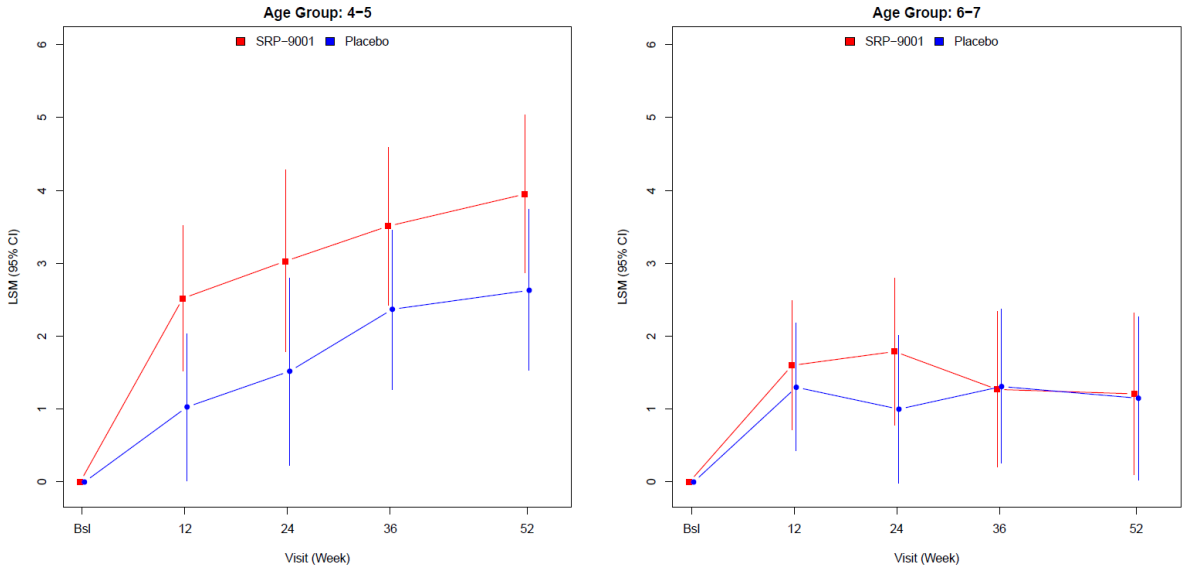
Table 1. Efficacy Results- Primary and Secondary Endpoints (Study 301 Part 1)

Endpoint	Elevidys	Placebo	Difference in LSM (95% CI) at Week 52 in Study 301
Primary endpoint: NSAA total score			-
Overall	2.57 (95% CI: 1.80, 3.34)	1.92 (95% CI: 1.14, 2.70)	0.65 (-0.45, 1.74)
Key secondary endpoint: Time to rise from floor (seconds)			-
Overall	-0.27 (95% CI: -0.56, 0.02)	0.37 (95% CI: 0.08, 0.67)	-0.64 (-1.06, -0.23)
Key secondary endpoint: 10-MWR timed test (seconds)			-
Overall	-0.34 (95% CI: -0.55, -0.14)	0.08 (95% CI: -0.13, 0.29)	-0.42 (-0.71, -0.13)

Source: Clinical Review (Table 13), Statistical Review.

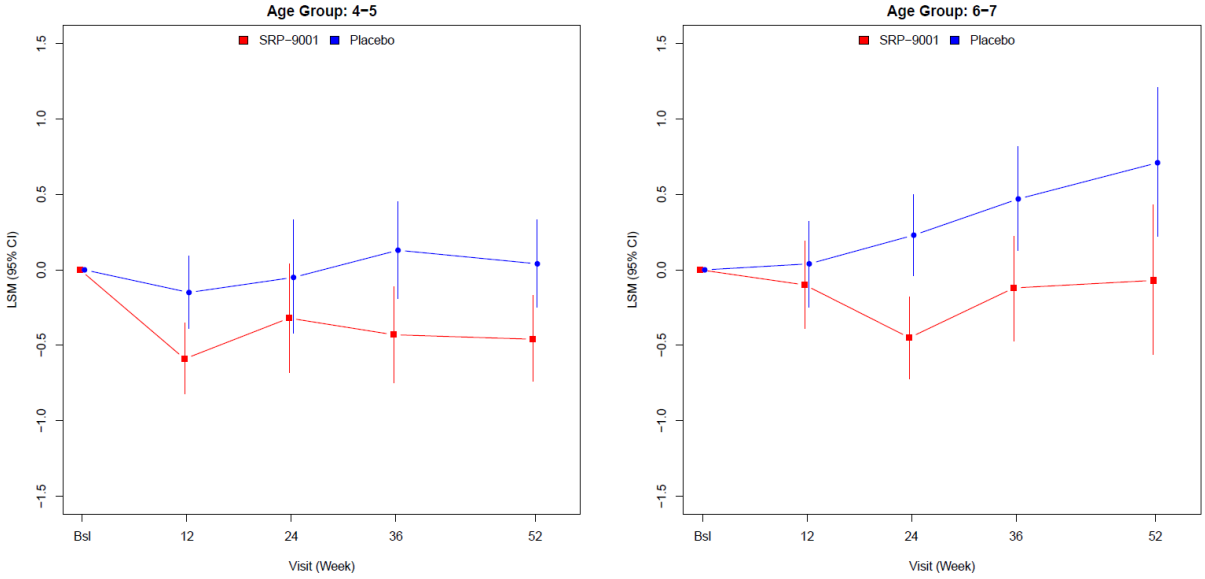
Figure 2, Figure 3, and Figure 4 show subgroup analyses for NSAA, Time to Rise from floor test, and 10-MWR test, respectively.

Figure 2. Least Square Mean Change in NSAA Total score- Age Group (Study 301 Part 1)



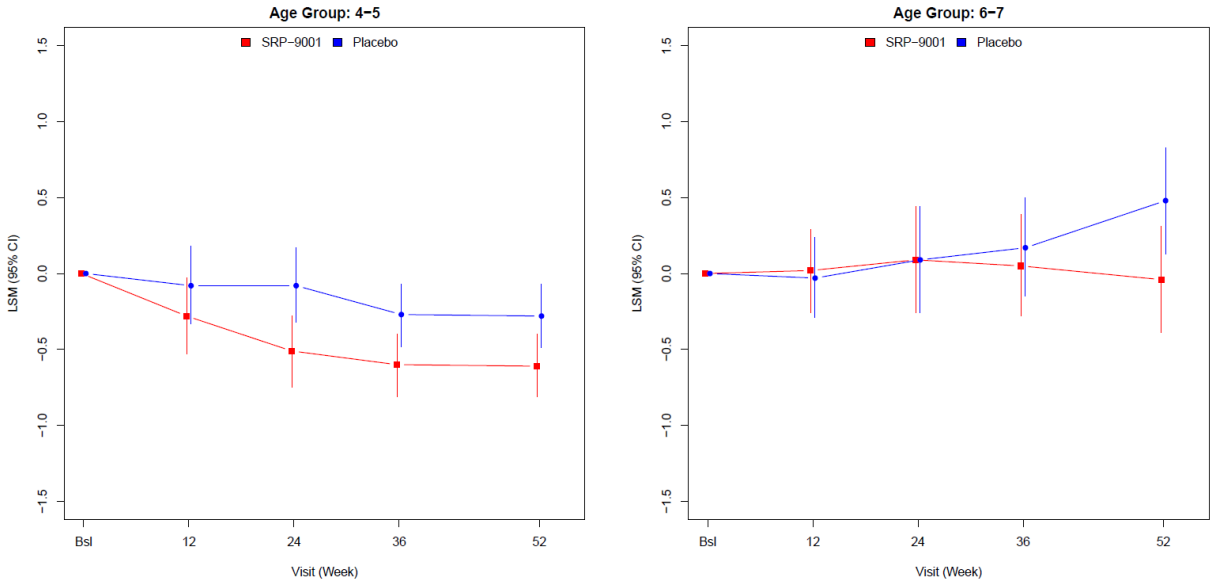
Source: Statistical Review (Figure 2). The LSM treatment difference in change from baseline to Week 52 was 1.32 (-0.23, 2.87) in the 4-5 age group and 0.06 (-1.52, 1.64) in the 6-7 age group.

Figure 3. Least Square Mean change in Time to Rise from Floor test by Age Group (Study 301 Part 1)



Source: Statistical Review (Figure 3). The LSM treatment difference in change from baseline to Week 52 was -0.50 (95% CI: -0.90, -0.09) in the 4-5 age group and -0.78 (95% CI: -1.48, -0.08) in the 6-7 age group.

Figure 4: Least Square Mean Change in 10-MWR Test by Age Group (Study 301 Part 1)



Source: Statistical Review. LSM treatment difference in change from baseline to Week 52 was -0.33 (95% CI: -0.62, -0.03) in the 4-5 age group and -0.52 (95% CI: -1.01, -0.03) in the 6-7 age group.

With respect to the secondary endpoint of micro-dystrophin expression at Week 12, data were available for a mere 25% of patients in Study 301. Micro-dystrophin expression results for Study 301 and Study 103 are shown below in Table 2.

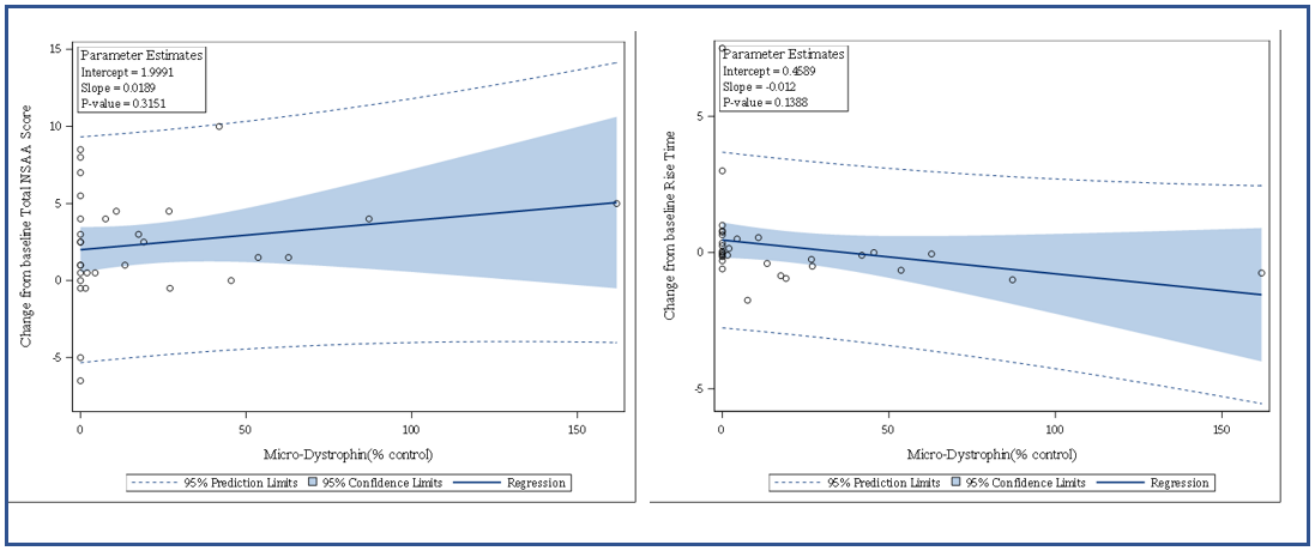
Table 2. Micro-Dystrophin Expression[1] in Muscle Biopsy at Week 12 (Studies 301 & 103)

Micro-Dystrophin Change From Baseline[1]	Study 301[2] N= 125		Study 103 N=48					
	Placebo (n=14)	Elevidys (n=17)	Cohort 1 (n=20)	Cohort 2 (n=7)	Cohort 3 (n=6)	Cohort 4 (n=7)	Cohort 5a (n=6	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: Clinical Review Memo (Table 6)
[1]Change from baseline to Week 12 measured by Western blot assay as percent expression of wild type dystrophin in control patients.
[2]Muscle biopsy samples available for a small subset of patients in Study 301 (14 of 62 in placebo and 17 of 63 in Elevidys arm)
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

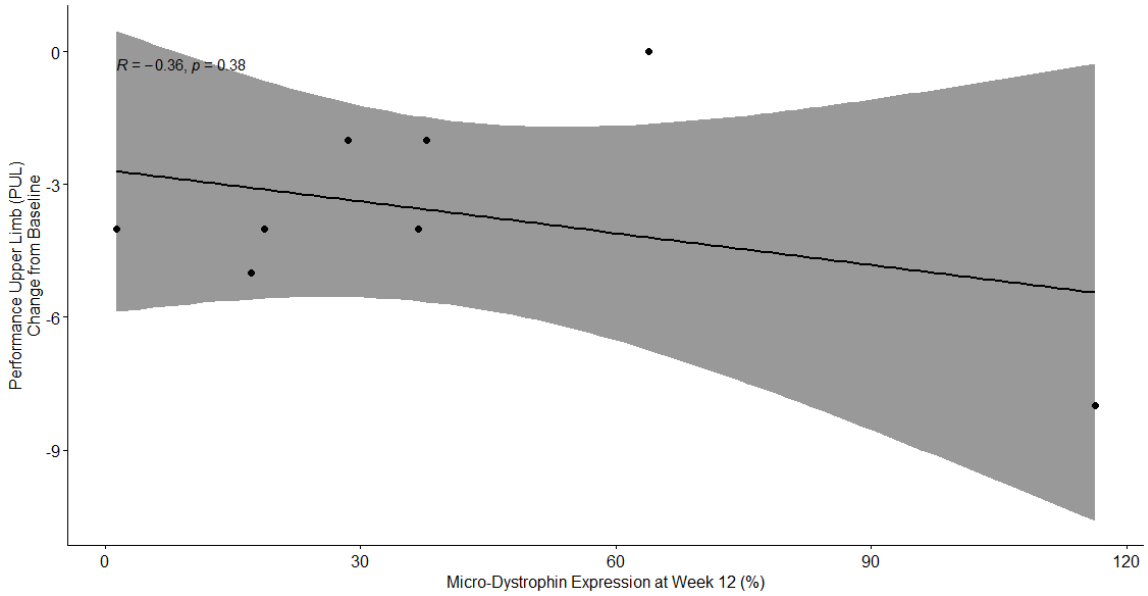
Analysis of micro-dystrophin correlation to the functional outcomes NSAA total score and Time to Rise change from baseline to Week 52 is shown in Figure 5 and Figure 6.

Figure 5. Micro-dystrophin expression & Change in NSAA and Time to Rise from baseline to Week 52 (Study 301)



Source: Clinical Review (Figure 5).

Figure 6. Micro-Dystrophin Expression Level[1] & PUL 2.0 Scores- Non-ambulatory Patients (Study 103)



Source: Clinical Review (Figure 9)
[1]Micro-dystrophic expression level at Week 12 measured by Western blot assay as percent expression of normal control.
Abbreviation: PUL 2.0, Performance of Upper Limb (version 2.0)

Summary and Conclusions

I concur with the clinical, clinical pharmacology, and statistical review teams' assessments of the data presented in this sBLA and with their interpretation of the data (please refer to the respective reviews for more details). Specifically, the results of Study 301 do not constitute substantial evidence of effectiveness. The trial was designed to show a statistically significant difference in the mean change in NSAA total score from baseline to Week 52 in the intention-to-treat population. The study was designed in keeping with accepted standards for statistical rigor for regulatory purposes, with a less than 5% chance that the result would (falsely) show a difference (i.e., that the Elevidys group performed better or worse than the placebo group) when no difference exists, also known as Type 1 error. The Applicant conducted analyses of additional physical function outcome measures and also conducted analyses in age-defined subgroups in Study 301 without controlling for Type 1 error. Given the exploratory nature of these analyses, they are considered potentially hypothesis generating but the results do not constitute substantial evidence of effectiveness due to the high likelihood that observed differences between the treatment groups may be due to chance.

Accelerated approval was granted on the basis that micro-dystrophin expression measured at Week 12 was a surrogate endpoint reasonably likely to predict clinical benefit. Although exploratory analyses of micro-dystrophin expression and the physical function outcomes (NSAA and PUL 2.0) in Study 301 and Study 103 appear to show a negative trend for micro-dystrophin expression and improved physical function, these results neither conclusively refute nor confirm an association due sample size and study design limitations. If an association does exist between micro-dystrophin expression (as evaluated in the Elevidys program) and improvement in physical function outcomes, the data provided to date do not demonstrate it. There remains uncertainty regarding whether micro-dystrophin can be considered a surrogate endpoint to support regulatory decision-making.

Regulatory Recommendation

I also concur with the review teams' recommendation to issue a Complete Response for the submission. Specifically, it is my assessment that the data submitted in the sBLA:

- do not verify the clinical benefit of Elevidys in ambulatory boys aged 4-5 years (i.e., the group for which accelerated approval was granted by Center Director override of the review team and senior CBER leadership recommendation),
- do not demonstrate the benefit of Elevidys in ambulatory patients greater than age 5 years of age, or
- do not demonstrate the benefit of Elevidys in non-ambulatory patients of any age.

The review teams' recommendation for Complete Response and my concurrence with this recommendation was discussed Dr. Nicole Verdun, Super Office Director, Office of Therapeutic Products, who also concurs with a Complete Response (See concurrence below and in the Clinical Review Memo). The review teams' recommendation was also discussed with CBER Center Director, Dr. Peter Marks, who indicated that he would approve the BLA by overriding the Complete Response recommendation from the Office of Clinical Evaluation, the Office of Therapeutic Products, and the Office of Biostatistics and Pharmacovigilance- Division of Biostatistics.

While the results presented in this sBLA and in the original BLA cast significant uncertainty regarding the benefits of treatment of DMD with Elevidys after two failed randomized-controlled trials, there is no doubt that DMD is a serious, progressive condition for which there is an urgent need for effective therapies. Effective therapies are desperately needed for patients with this disease. The results of Study 301 and Study 102 before it, are not necessarily indicative of lack of efficacy in all patients. Indeed, the Applicant previously provided compelling videographic evidence of physical function improvements in patients 4 to 5 years of age who received Elevidys (see Original BLA submission and FDA Advisory Committee meeting), which may suggest that Elevidys may be efficacious in a subset of patients with DMD. Unfortunately, the evidence submitted by the Applicant does not identify the group of patients with DMD in whom there is reasonable assurance of clinical benefit to support marketing authorization of this product. Although my summary does not provide a description of the safety profile of Elevidys, its known risks are acceptable for the indicated population and Study 301 did not identify new safety signals.

Prior to the BLA submission, Elevidys was approved under the provisions of accelerated approval, for patients aged 4 to 5 years who are ambulatory (See Approval Letter for original BLA for specifics of the indication and the basis for approval). In the original BLA, the Applicant submitted as evidence, data from Study 102. Study 102 was similar in design to Study 301 albeit with a smaller sample size and slight differences in the timing of analysis (NSAA total score change from baseline to Week 52 in Study 301 and Week 48 in Study 102); the results of the primary endpoint of NSAA total score change in Study 102 also were not statistically significant. Analyses of physical function outcomes conducted in both studies are inconclusive due to their exploratory nature; in some cases, the results of these analyses have yielded conflicting results, further illustrating the unreliability of exploratory analyses to support regulatory decision-making.

Due to the unmet need for treatments in this disease, and to the fact that that Study 301 and Study 102 did not substantively differ from Study 102 in design, my recommendation would be to explore the Applicant's interest in conducting an additional adequate and well controlled study of Elevidys in the subgroup(s) of patients for which the Applicant believes the effects of Elevidys to be most promising; however, CBER Center Director Dr. Peter Marks has made a determination that approval of the BLA supplement is supported for a broad indication to include patients who are 4 years or age or older who are ambulatory (traditional approval) and non-ambulatory (accelerated approval), rendering this potential path forward highly infeasible to explore in a post-approval setting.

'Lola A. Fashoyin-Aje, MD, MPH

Director, Office of Clinical Evaluation, Office of Therapeutic Products (OTP), CBER

Concurrence provided by **Dr. Nicole Verdun, MD**

Super Office Director, OTP, CBER

I agree with the Office of Clinical Evaluation recommendation for a Complete Response.