Elevidys (delandistrogene moxeparvovec-rokl) – New orphan drug approval

- On June 22, 2023, the FDA announced the approval of Sarepta Therapeutics' Elevidys (delandistrogene moxeparvovec-rokl), 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 indication is approved under accelerated approval based on expression of Elevidys micro-dystrophin observed in patients treated with Elevidys. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

- DMD occurs due to a defective *DMD* gene that results in absence of dystrophin, a protein that helps keep the body's muscle cells intact. Patients with DMD may have symptoms such as trouble walking and running, falling frequently, fatigue, learning disabilities/difficulties, heart issues as a result of impact on heart muscle functioning, and breathing problems due to weakening of respiratory muscles involved in lung function.

    — DMD mainly affects males and in rare cases may affect females. About one in every 3,300 boys are affected by this disorder.
    — Although disease severity and life expectancy vary, patients often succumb to the disease in their 20s or 30s because of heart and/or respiratory failure.

- Elevidys is a recombinant gene therapy designed to deliver into the body a gene that leads to production of Elevidys micro-dystrophin, a shortened protein (138 kDa, compared to the 427 kDa dystrophin protein of normal muscle cells) that contains selected domains of the dystrophin protein present in normal muscle cells.

- The accelerated approval of Elevidys was primarily based on data from Study 1 and Study 2.

- Study 1 is an ongoing two-part study including a: (1) 48-week, randomized, double-blind, placebo-controlled period; and (2) 48-week period that began following completion of Part 1. Patients who received placebo during Part 1 were treated with Elevidys, and patients treated with Elevidys during Part 1 received placebo. The study population consisted of 41 male ambulatory DMD patients aged 4 through 7 years with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the *DMD* gene. The primary objectives were to evaluate expression of Elevidys micro-dystrophin in skeletal muscle, and to evaluate the effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score.

    — Refer to the table below for the Elevidys micro-dystrophin expression results for patients who received 1.33×10^{14} vector genomes/kilogram (vg/kg) Elevidys.
    — The change in NSAA total score was assessed from baseline to week 48 after infusion of Elevidys or placebo. The difference between the Elevidys and placebo groups was not statistically significant ($p = 0.37$). The least squares (LS) mean changes in NSAA total score from baseline to week 48 was 1.7 (standard error [SE]: 0.6) points for the Elevidys group and 0.9 (SE: 0.6) points for the placebo group.
    — Exploratory subgroup analyses showed that for patients aged 4 through 5 years, the LS mean changes (SE) in NSAA total score from baseline to week 48 were 4.3 (0.7) points for the Elevidys group, and 1.9 (0.7) points for the placebo group, a numerical advantage for Elevidys. For patients aged 6 through 7 years, the LS mean changes (SE) in NSAA total

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score from baseline to week 48 were -0.2 (0.7) points for the Elevidys group and 0.5 (0.7) points for the placebo group, a numerical disadvantage for Elevidys.

- Study 2 is an ongoing, open-label study which includes a cohort of 20 ambulatory male DMD patients aged 4 through 7 years. All 20 patients have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the *DMD* gene. The primary objective was to evaluate the effect of Elevidys micro-dystrophin expression as measured by western blot. Refer to the table below for the Elevidys micro-dystrophin expression results for patients who received 1.33×10^{14} vg/kg Elevidys.

Western blot (% of Elevidys micro-dystrophin compared to control)	Study 1 (Week 12) Part 1 (N = 6)	Study 1 (Week 12) Part 2 (N = 21)	Study 2 (Week 12) Cohort 1 (N = 20)
Mean change from baseline (SD)	43.4 (48.6)	40.7 (32.3)	54.2 (42.6)
Median change from baseline (Min, Max)	24.3 (1.6, 116.3)	40.8 (0.0, 92.0)	50.6 (4.8, 153.9)

- Elevidys is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.
- Warnings and precautions for Elevidys include acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74.
- The most common adverse reactions (≥ 5%) with Elevidys use were vomiting and nausea, increased liver function test, pyrexia, and thrombocytopenia.
- The recommended dose of Elevidys is 1.33×10^{14} vg/kg of body weight (or 10 mL/kg body weight) via intravenous (IV) infusion as a single-dose. For the number of vials required, refer to the drug label.
    - Patients should be selected for treatment with anti-AAVrh74 total binding antibody titers < 1:400. An FDA-authorized test for the detection of AAVrh74 total binding antibodies is not currently available. Currently available tests may vary in accuracy and design.
- Sarepta Therapeutics' launch plans for Elevidys are pending. Elevidys will be available as a suspension for IV infusion with a nominal concentration of 1.33×10^{13} vg/mL.