



ELEVIDYS®

Delandistrogene moxeparvovec

Solution for infusion

NAME OF THE MEDICINAL PRODUCT

ELEVIDYS

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ELEVIDYS contains 1.33×10^{13} vector genomes (vg).

ELEVIDYS is a preservative-free, sterile, clear, colorless liquid and may have some opalescence. ELEVIDYS may contain white to off-white particles.

Each vial contains an extractable volume of 10.0 mL. The total number of vials in each finished pack corresponds to the dosing requirement for the individual patient, depending on their weight.

For the full list of excipients, see section 11.

PHARMACEUTICAL FORM

Solution for infusion.

CLINICAL PARTICULARS

Caregiver safety information guide and Patient safety information card

The marketing of ELEVIDYS is subject to a risk management plan (RMP) including Safety information materials (caregiver guide and patient card). These materials emphasize important safety information that the caregiver and patient should be aware of before and during treatment. Please explain to the caregiver and patient the need to review these materials before starting treatment.

Health Care Professional (HCP) guide

This product is marketed with an HCP guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

1 INDICATIONS AND USAGE

ELEVIDYS is indicated 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.

2 DOSAGE AND ADMINISTRATION

For single-dose intravenous infusion only.

2.1 Patient Selection

Select patients for treatment with ELEVIDYS with anti-AAVrh74 total binding antibody titers <1:400. Currently available tests may vary in accuracy and design.

2.2 Dose

The recommended dose of ELEVIDYS is 1.33×10^{14} vector genomes per kilogram (vg/kg) of body weight (or 10 mL/kg body weight). For the number of vials required, refer to Table 7 [see *How Supplied/Storage and Handling (16.1)*].

Calculate the dose as follows:

$$\text{ELEVIDYS dose (in mL)} = \text{patient body weight (in kilogram)} \times 10$$

The multiplication factor 10 represents the per kilogram dose (1.33×10^{14} vg/kg) divided by the amount of vector genome copies per mL of the ELEVIDYS solution (1.33×10^{13} vg/mL).

Number of ELEVIDYS vials needed = ELEVIDYS dose (in mL) divided by 10 (round to the nearest number of vials).

Example: Calculation of volume needed for a 19.6 kg patient

$$19.6 \text{ kg} \times 10 = 196 \text{ mL}$$

Number of ELEVIDYS vials needed = 196 divided by 10, rounded to the nearest number of vials = 20 vials

Prior to ELEVIDYS infusion:

- Due to the increased risk of serious systemic immune response, postpone ELEVIDYS in patients with infections until the infection has resolved. Clinical signs or symptoms of infection should not be evident at the time of ELEVIDYS administration.
- Assess liver function [see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.6)*].
- Obtain platelet count and troponin-I levels [see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.3)*].
- Measure baseline anti-AAVrh74 antibody titers using a Total Binding Antibody enzyme-linked immunosorbent assay (ELISA) [see *Dosage and Administration (2)*, *Clinical Pharmacology (12.6)*].

ELEVIDYS administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers ($\geq 1:400$). Re-administration of ELEVIDYS is not recommended [see *Warnings and Precautions (5.4)*, *Clinical Pharmacology (12.6)*].

Immune responses to the AAVrh74 vector can occur after administration of ELEVIDYS [see *Clinical Pharmacology (12.6)*]. To reduce the risk associated with an immune response, corticosteroids should be administered starting 1 day prior to ELEVIDYS infusion. Initiate a corticosteroid regimen following the appropriate schedule (see Table 1). This regimen is recommended for a minimum of 60 days after the infusion, unless earlier tapering is clinically indicated. Table 2 includes the recommended corticosteroid regimen dose modification for patients with liver function abnormalities following ELEVIDYS infusion. If acute serious liver injury is suspected, a consultation with a specialist is recommended.

For patients previously taking corticosteroids at baseline, taper off the additional peri-ELEVIDYS corticosteroids (back to baseline corticosteroid dose) over 2 weeks, or longer as needed. For patients not previously taking corticosteroids at baseline, taper the added peri-ELEVIDYS corticosteroids off (back to no corticosteroids) over 4 weeks, or longer, as needed, and the corticosteroids should not be stopped abruptly.

Table 1: Recommended pre- and post-infusion corticosteroid dosing

Baseline corticosteroid dosing ^a	Peri-ELEVIDYS infusion corticosteroid dose (prednisone equivalent) ^b	Recommended maximum total daily dose (prednisone equivalent) ^b
Daily or intermittent dose	Start 1 day prior to infusion: 1 mg/kg/day (and continue baseline dose)	60 mg/day
High dose for 2 days per week	Start 1 day prior to infusion: 1 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	60 mg/day
Not on corticosteroids	Start 1 week prior to infusion: 1.5 mg/kg/day	60 mg/day

^a Patient continues to receive this dose

^b Deflazacort is not recommended for use as a peri-ELEVIDYS infusion corticosteroid

Table 2: Recommended corticosteroid regimen dose modification for liver function abnormalities following ELEVIDYS infusion^a

Peri-ELEVIDYS infusion corticosteroid dosing	Modified corticosteroid dose following ELEVIDYS infusion (prednisone equivalent) ^b	Recommended maximum total daily dose (prednisone equivalent) ^b
Baseline + 1 mg/kg/day	Increase to 2 mg/kg/day (and continue baseline dose)	120 mg/day
Baseline + 1 mg/kg/day taken on days without high-dose corticosteroid treatment	Increase to 2 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	120 mg/day
1.5 mg/kg/day	Increase from 1.5 mg/kg/day to 2.5 mg/kg/day	120 mg/day

^a GGT \geq 150 U/L and/or other clinically significant liver function abnormalities (e.g., total bilirubin $>$ 2 x ULN) following infusion. For GGT or bilirubin elevations that do not respond to these oral corticosteroid increases, IV bolus corticosteroids may be considered.

^b Deflazacort is not recommended for use as a peri-ELEVIDYS infusion corticosteroid

2.3 Preparation

General precautions

- Prepare ELEVIDYS using aseptic technique.
- Verify the required dose of ELEVIDYS based on the patient's body weight.
- Confirm that the kit contains sufficient number of vials to prepare the ELEVIDYS infusion for the patient.
- Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. ELEVIDYS may contain white to off-white particles.

Recommended supplies and materials:

- 60 mL siliconized polypropylene syringes
- 21-gauge or smaller stainless steel needles

Preparing ELEVIDYS infusion

1. Thaw ELEVIDYS before use.
 - When thawed in the refrigerator, ELEVIDYS vials are stable for up to 14 days in the refrigerator (2°C to 8°C).
 - Frozen ELEVIDYS vials will thaw in approximately 2 hours when placed at room temperature (up to 25°C) when removed from original packaging.
2. Inspect vials to ensure no ice crystals are present prior to preparation.
3. When thawed, swirl gently.
 - Do not shake.
 - Do not refreeze.
 - Do not place back in the refrigerator.
4. Visually inspect each vial of ELEVIDYS. ELEVIDYS is a clear, colorless liquid that may have some opalescence. ELEVIDYS may contain white to off-white particles.
 - Do not use if the solution in the vials is cloudy or discolored.
5. Remove the plastic flip-off cap from the vials and disinfect the rubber stopper with a sterilizing agent (e.g., alcohol wipes).
6. Withdraw 10 mL of ELEVIDYS from each vial provided in the customized ELEVIDYS kit (refer to Table 7).
 - Do not use filter needles during preparation of ELEVIDYS.
 - Multiple syringes will be required to withdraw the required volume.
 - Remove air from the syringes and cap the syringes.
7. Maintain syringes at room temperature (up to 25°C) prior to and during administration, and use ELEVIDYS within 6 hours of drawing into syringe.
 - Sealed ELEVIDYS thawed vials are stable up to 24 hours at room temperature (up to 25°C).
 - Once transferred from the vial to the syringe, ELEVIDYS should be infused immediately because the medicine does not contain any antimicrobial-preservative.
 - If ELEVIDYS is transferred from the vial to the syringe under aseptic conditions in the healthcare environment, the medicine in the capped syringe can be used within 6 hours of drawing into syringe.
 - Syringes should be maintained at room temperature prior to and during administration.

2.4 Administration

Recommended supplies and materials:

- Syringe infusion pump
- 0.2-micron PES* in-line filter
- PVC* (non-DEHP*), polyurethane IV infusion tubing and catheter

*PVC = Polyvinyl chloride, DEHP = Di(2-ethylhexyl) phthalate, PES = Polyether sulfone

Administer ELEVIDYS as a single-dose intravenous infusion through a peripheral venous catheter:

Consider application of a topical anesthetic to the infusion site prior to administration of IV insertion.

Recommend inserting a back-up catheter.

1. Flush the intravenous access line prior to the ELEVIDYS infusion at the same infusion rate.
2. Administer ELEVIDYS via intravenous infusion using a syringe infusion pump with an in-line 0.2-micron filter at a duration of approximately 1 to 2 hours, or longer at care team discretion, through a peripheral limb vein.
3. Infuse at a rate of less than 10 mL/kg/hour.
 - Do not administer ELEVIDYS as an intravenous push.
 - Do not infuse ELEVIDYS in the same intravenous access line with any other product.
 - Use ELEVIDYS within 6 hours after drawing into syringe. Discard the vector-containing syringe if the drug is not infused within the 6-hour timeframe. If the infusion is interrupted, the remaining dose of ELEVIDYS cannot be administered if the infusion cannot be completed within this 6-hour timeframe.
4. Flush the intravenous access line with 0.9% Sodium Chloride Injection after the ELEVIDYS infusion.
 - Discard unused ELEVIDYS [see *How Supplied/Storage and Handling (16.2)*].
 - Dispose of the needle and syringe [see *How Supplied/Storage and Handling (16.2)*].

Monitoring Post-ELEVIDYS Administration

- Assess liver function (clinical exam, GGT, and total bilirubin) weekly for the first 3 months. Continue monitoring if clinically indicated, until results are unremarkable (normal clinical exam, GGT and total bilirubin levels return to near baseline levels) [see *Warning and Precautions (5.1)*, *Specific Populations (8.6)*].
- Obtain platelet counts weekly for the first two weeks [see *Adverse Reactions (6.1)*]. Continue monitoring if clinically indicated.
- Measure troponin-I weekly for the first month [see *Warning and Precautions (5.3)*]. Continue monitoring if clinically indicated.

3 DOSAGE FORMS AND STRENGTHS

ELEVIDYS is a preservative-free, sterile, clear, colorless liquid that may have some opalescence and may contain white to off-white particles.

ELEVIDYS is a solution for infusion with a nominal concentration of 1.33×10^{13} vg/mL.

ELEVIDYS is provided in a customized kit containing ten to seventy 10 mL single-dose vials, with each kit constituting a dosage unit based on the patient's body weight [see *How Supplied/Storage and Handling (16.1)*].

The intravenous dosage is determined by patient body weight, with a recommended dose of 1.33×10^{14} vector genomes (vg)/kg.

4 CONTRAINDICATIONS

ELEVIDYS is contraindicated in patients with:

- Any deletion in exon 8 and/or exon 9 in the *DMD* gene [see *Warnings and Precautions (5.2)*].
- Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Serious Liver Injury

Acute serious liver injury has been observed with ELEVIDYS. Administration of ELEVIDYS may result in elevations of liver enzymes (e.g., GGT, ALT) and total bilirubin, typically seen within 8 weeks.

Patients with preexisting liver impairment, chronic hepatic condition or acute liver disease (e.g., acute hepatic viral infection) may be at higher risk of acute serious liver injury. Postpone ELEVIDYS administration in patients with acute liver disease until resolved or controlled. Patients with hepatic impairment, acute liver disease, chronic hepatic condition or elevated GGT have not been studied in clinical trials with ELEVIDYS [see *Specific Populations (8.6)*].

In clinical studies, liver function test increased (including increases in GGT, GLDH, ALT, AST, or total bilirubin) was commonly reported typically within 8 weeks following ELEVIDYS infusion, with the majority of cases being asymptomatic [see *Adverse Reactions (6.1)*]. Cases resolved spontaneously or with systemic corticosteroids and resolved without clinical sequelae within 2 months. No cases of liver failure were reported.

Prior to ELEVIDYS administration, perform liver enzyme test [see *Dosage and Administration (2.2)*]. Monitor liver function (clinical exam, GGT, and total bilirubin) weekly for the first 3 months following ELEVIDYS infusion. Continue monitoring if clinically indicated, until results are unremarkable (normal clinical exam, GGT and total bilirubin levels return to near baseline levels) [see *Dosage and Administration (2.4)*].

Systemic corticosteroid treatment is recommended for patients before and after ELEVIDYS infusion [see *Dosage and Administration (2.2)*]. Adjust corticosteroid regimen when indicated [see *Dosage and Administration (2.2)*]. If acute serious liver injury is suspected, a consultation with a specialist is recommended.

5.2 Immune-mediated Myositis

In clinical trials, immune-mediated myositis has been observed approximately 1 month following ELEVIDYS infusion in patients with deletion mutations involving exon 8 and/or exon 9 in the *DMD* gene. Symptoms of severe muscle weakness, including dysphagia, dyspnea and hypophonia, were observed. In a life-threatening case of immune-mediated myositis, symptoms resolved during hospitalization following additional immunomodulatory treatment; muscle strength gradually improved but did not return to baseline level. These immune reactions may be due to a T-cell based response from lack of self-tolerance to a specific region encoded by the transgene corresponding to exons 1-17 of the *DMD* gene.

Limited data are available for ELEVIDYS treatment in patients with mutations in the *DMD* gene in exons 1 to 17 and/or exons 59 to 71 [see *Clinical Studies (14)*]. Patients with deletions in these regions may be at risk for a severe immune-mediated myositis reaction. ELEVIDYS is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene due to the increased risk for a severe immune-mediated myositis reaction [see *Contraindications (4)*].

Advise patients to contact a physician immediately if they experience any unexplained increased muscle pain, tenderness, or weakness, including dysphagia, dyspnea or hypophonia as these may be symptoms of myositis. Consider additional immunomodulatory treatment (immunosuppressants [e.g., calcineurin-inhibitor] in addition to corticosteroids) based on patient's clinical presentation and medical history if these symptoms occur.

5.3 Myocarditis

Acute serious myocarditis and troponin-I elevations have been observed following ELEVIDYS infusion in clinical trials.

Monitor troponin-I before ELEVIDYS infusion and weekly for the first month following infusion [see *Dosage and Administration (2.4)*]. Continue monitoring if clinically indicated. More frequent monitoring may be warranted in the presence of cardiac symptoms, such as chest pain or shortness of breath.

Advise patients to contact a physician immediately if they experience cardiac symptoms.

5.4 Pre-existing Immunity against AAVrh74

In AAV-vector based gene therapies, preexisting anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with ELEVIDYS all subjects developed anti-AAVrh74 antibodies. Perform baseline testing for the presence of anti-AAVrh74 total binding antibodies prior to ELEVIDYS administration [see *Dosage and Administration (2.1)*].

ELEVIDYS administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers ($\geq 1:400$).

6 ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 5\%$) reported in clinical studies were vomiting, nausea, liver function test increased, pyrexia, and thrombocytopenia.

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Acute serious liver injury [see *Warnings and Precautions (5.1)*]
- Immune-mediated myositis [see *Warnings and Precautions (5.2)*]
- Myocarditis [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to a one-time intravenous infusion of ELEVIDYS in 85 male subjects with a confirmed mutation of the *DMD* gene in three on-going clinical studies, including two open-label studies and one study that included a double-blind, placebo-controlled period. Prior to ELEVIDYS infusion, patients in the ELEVIDYS treatment group had a mean age of 7.08 years (range: 3 to 20) and mean weight of 25.91 kg (range: 12.5 to 80.1). 73 subjects received the recommended dose of 1.33×10^{14} vg/kg, and 12 received a lower dose. Table 3 below presents adverse reactions from these three clinical studies.

The most common adverse reactions (incidence $\geq 5\%$) across all studies are summarized in Table 3.

Adverse reactions were typically seen within the first 2 weeks (nausea, vomiting, thrombocytopenia, pyrexia), or within the first 2 months (immune-mediated myositis, liver function test increased). Vomiting may occur as early as on the day of the infusion.

Table 3. Adverse reactions (Incidence $\geq 5\%$) following treatment with ELEVIDYS in Clinical Studies

Adverse reactions	ELEVIDYS (N=85) %
Vomiting	61
Nausea	40
Liver function test increased ^a	37
Pyrexia	24
Thrombocytopenia ^b	12

^a Includes: AST increased, ALT increased, GGT increased, GLDH increased, hepatic enzyme increased, transaminases increased, blood bilirubin increased

^b Transient, mild, asymptomatic decrease in platelet counts

In the double-blind, placebo-controlled trial (Study 1 Part 1), subjects 4 to 7 years of age (N=41) received either ELEVIDYS (N=20) at the recommended dose of 1.33×10^{14} vg/kg (n=8) or lower dose (n=12) or received placebo (N=21). Table 4 below presents the most frequent adverse reactions from Study 1 Part 1.

Table 4. Adverse reactions occurring in ELEVIDYS-treated subjects and at least 10% more frequently than in placebo in Study 1, Part 1

Adverse reactions	ELEVIDYS (N=20) %	Placebo (N=21) %
Vomiting	65	33
Nausea	35	10
Liver function test increased ^a	25	0
Pyrexia	20	5

^a Includes: AST increased, ALT increased, GGT increased, GLDH increased, hepatic enzyme increased, transaminases increased, blood bilirubin increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

7 DRUG INTERACTIONS

Prior to initiating the corticosteroid regimen required before ELEVIDYS administration, consider the patient's vaccination status. Patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines. Vaccinations should be completed at least 4 weeks prior to initiation of the corticosteroid regimen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ELEVIDYS is not intended for use in pregnant women.

8.2 Lactation

Risk Summary

There is no information available on the presence of ELEVIDYS in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

ELEVIDYS is indicated for the treatment of ambulatory pediatric patients 4 through 5 years of age with Duchenne muscular dystrophy with a confirmed mutation in the *DMD* gene. This indication is based on expression of ELEVIDYS micro-dystrophin protein in skeletal muscle observed in DMD patients treated with ELEVIDYS. The effectiveness and safety of ELEVIDYS has not been established in pediatric patients younger than 3 years of age. The effectiveness of ELEVIDYS has not been established in pediatric patients 3 years of age and in pediatric patients 6 years of age and older [see *Clinical Pharmacology (12.2), Clinical Studies (14)*].

8.5 Geriatric Use

The safety and efficacy of ELEVIDYS in geriatric patients with DMD have not been studied.

8.6 Hepatic Impairment

The safety and efficacy of ELEVIDYS in patients with hepatic impairment or elevated GGT have not been studied.

Postpone ELEVIDYS administration in patients with acute liver disease until resolved or controlled. ELEVIDYS therapy should be carefully considered in patients with preexisting liver impairment or chronic hepatic viral infection. These patients may be at increased risk of acute serious liver injury [see *Warnings and Precautions (5.1)*].

In clinical trials, liver function test increase was commonly reported in subjects following ELEVIDYS infusion [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*].

11 DESCRIPTION

ELEVIDYS (delandistrogene moxeparovec) is a recombinant gene therapy designed to deliver the gene encoding the ELEVIDYS micro-dystrophin protein. ELEVIDYS is a non-replicating, recombinant, adeno-associated virus serotype rh74 (AAVrh74) based vector containing the ELEVIDYS micro-dystrophin transgene under the control of the MHCK7 promoter. The genome within the ELEVIDYS AAVrh74 vector contains no viral genes and consequently is incapable of replication or reversion to a replicating form. The micro-dystrophin protein expressed by ELEVIDYS is a shortened version (138 kDa, compared to 427 kDa size of dystrophin expressed in normal muscle cells) that contains selected domains of dystrophin expressed in normal muscle cells.

ELEVIDYS is a preservative-free, sterile, clear, colorless liquid that may have some opalescence and may contain white to off-white particles. ELEVIDYS is a solution for infusion with a nominal concentration of 1.33×10^{13} vg/mL and supplied in a single-dose 10 mL vial. Each vial contains an extractable volume of 10 mL and the following excipients: sodium chloride, tromethamine HCl, tromethamine, magnesium chloride, poloxamer 188 and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ELEVIDYS is the recombinant gene therapy product that is comprised of a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) capsid and a ssDNA expression cassette flanked by inverted terminal repeats (ITRs) derived from AAV2. The cassette contains: 1) an MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α -myosin heavy chain enhancer, and 2) the DNA transgene encoding the engineered ELEVIDYS micro-dystrophin protein.

Vector/Capsid: Clinical and nonclinical studies have demonstrated AAVrh74 serotype transduction in skeletal muscle cells. Additionally, in nonclinical studies, AAVrh74 serotype transduction has been demonstrated in cardiac and diaphragm muscle cells.

Promoter: The MHCK7 promoter/enhancer drives transgene expression and has been shown in animal models to drive transgenic ELEVIDYS micro-dystrophin protein expression predominantly in skeletal muscle (including diaphragm) and cardiac muscle. In clinical studies, muscle biopsy analyses have confirmed ELEVIDYS micro-dystrophin expression in skeletal muscle.

Transgene: DMD is caused by a mutation in the *DMD* gene resulting in lack of functional dystrophin protein. ELEVIDYS carries a transgene encoding a micro-dystrophin protein consisting of selected domains of dystrophin expressed in normal muscle cells.

ELEVIDYS micro-dystrophin has been demonstrated to localize to the sarcolemma.

12.2 Pharmacodynamics

In 61 subjects who received ELEVIDYS in clinical studies, ELEVIDYS micro-dystrophin protein expression from muscle biopsies (gastrocnemius) was quantified by western blot and localized by immunofluorescence staining (fiber intensity and percentage ELEVIDYS micro-dystrophin).

ELEVIDYS micro-dystrophin expression (expressed as change from baseline) as measured by western blot was the primary objective of Study 1 and Study 2. Muscle biopsies were obtained at baseline prior to ELEVIDYS infusion and at Week 12 after ELEVIDYS infusion in all subjects. The absolute quantity of ELEVIDYS micro-dystrophin was measured by western blot assay, adjusted by muscle content and expressed as a percent of control (levels of wild-type dystrophin in subjects without DMD or Becker muscular dystrophy) in muscle biopsy samples. Results of subjects receiving 1.33×10^{14} vg/kg ELEVIDYS are presented in Table 5.

Table 5: ELEVIDYS Micro-Dystrophin Expression in Studies 1 and 2 (Western Blot Assay)^{abcd}

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)

^a All patients received 1.33×10^{14} vg/kg, as measured by ddPCR

^b Muscle biopsies were obtained from the gastrocnemius

^c Change from baseline was statistically significant

^d Adjusted for muscle content. Control was level of wild-type (normal) dystrophin in normal muscle.

For subjects aged 4 through 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS micro-dystrophin expression levels (change from baseline) at Week 12 following ELEVIDYS infusion were 95.7% (N=3, SD: 17.9%) in Study 1 Parts 1 and 2 and 51.7% (N=11, SD: 41.0%) in Study 2 Cohort 1.

Assessment of ELEVIDYS micro-dystrophin levels can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, valid comparisons of ELEVIDYS micro-dystrophin measurements obtained from different assays cannot be made.

12.3 Pharmacokinetics

Vector Distribution and Vector Shedding

Nonclinical Data

Biodistribution of ELEVIDYS was evaluated in tissue samples collected from healthy mice and Dmd^{mdx} mice following intravenous administration in toxicology studies. At 12 weeks following ELEVIDYS administration at dose levels of 1.33×10^{14} to 4.02×10^{14} vg/kg, vector DNA was detected in all major organs with the highest quantities detected in the liver, followed by lower levels in the heart, adrenal glands, skeletal muscle, and aorta. ELEVIDYS was also detected at low levels in the spinal cord, sciatic nerve and gonads (testis). Protein expression of ELEVIDYS micro-dystrophin was highest in cardiac tissue, exceeding physiologic dystrophin expression levels in healthy mice, with lower levels in the skeletal muscle and diaphragm. In some studies, micro-dystrophin was also detected at low levels in the liver.

Clinical Data

Following IV administration, ELEVIDYS vector genome undergoes distribution via systemic circulation and distributes into target muscle tissues followed by elimination in the urine and feces. ELEVIDYS biodistribution and tissue transduction are detected in the target muscle tissue groups and quantified in the gastrocnemius or biceps femoris biopsies obtained from patients with mutations in the *DMD* gene. Evaluation of ELEVIDYS vector genome exposure in clinical muscle biopsies at Week 12 post-dose expressed as copies per nucleus revealed ELEVIDYS drug distribution and transduction with a mean change from baseline of 2.91 and 3.44 copies per nucleus at the recommended dose of 1.33×10^{14} vg/kg for Study 1 and Study 2 Cohort 1, respectively.

In Study 2 Cohort 1, the biodistribution and vector shedding of ELEVIDYS in the serum and excreta were quantified, respectively. The mean maximum concentration (C_{max}) in the serum was 0.0049×10^{13} copies/mL and 4.11×10^5 copies/mL in the urine, 4.72×10^7 copies/mL in the saliva, and 2.32×10^7 copies/ μ g in the feces. The median time to achieve maximum concentration (T_{max}) was 5.3 hours post-dose in the serum, followed by 6.7 hours, 6.4 hours and 13.5 days post-dose in the saliva, urine, and feces, respectively. The median time to achieve first below limit of quantification (BLOQ) sample followed by 2 consecutive BLOQ samples were 63 days post-dose for serum. The median time to achieve complete elimination as the first below limit of detection (BLOD) sample followed by 2 consecutive BLOD samples were 49.8 days, 123 days and 162 days post-dose for saliva, urine and feces, respectively. The estimated elimination half-life of ELEVIDYS vector genome in the serum is approximately 12 hours, and the majority of the drug is expected to be cleared from the serum by 1-week post-dose. In the excreta, the estimated elimination half-life of ELEVIDYS vector genome is 40 hours, 55 hours, and 60 hours in the urine, feces, and saliva, respectively. As an AAV-based gene therapy that consists of a protein capsid containing the transgene DNA genome of interest, ELEVIDYS capsid proteins are broken down through proteasomal degradation following AAV entry into target cells. As such, ELEVIDYS is not likely to exhibit the drug-drug interaction potential mediated by known drug metabolizing enzymes (cytochrome P450-based) and drug transporters.

12.6 Immunogenicity

The observed incidence of anti-AAVrh74 antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-AAVrh74 antibodies in the studies described below with the incidence of anti-AAVrh74 antibodies in other studies.

In ELEVIDYS clinical studies, patients were required to have baseline anti-AAVrh74 total binding antibodies of $\leq 1:400$, measured using an investigational total binding antibody enzyme-linked immunosorbent assay (ELISA), and only patients with baseline anti-AAVrh74 total binding antibodies $< 1:400$ were enrolled in those studies. The safety and efficacy of ELEVIDYS in patients with elevated anti-AAVrh74 total binding antibody titer ($\geq 1:400$) have not been evaluated [see *Clinical Studies (14)*].

Across clinical studies evaluating a total of 84 patients, elevated anti-AAVrh74 total binding antibodies titers were observed in all patients following a one-time ELEVIDYS infusion. Anti-AAVrh74 total binding antibody titers reached at least 1:409,600 in every subject, and the maximum titers exceeded 1:26,214,400 in certain subjects. The safety of re-administration of ELEVIDYS or any other AAVrh74 vector-based gene therapy in the presence of high anti-AAVrh74 total binding antibody titer has not been evaluated in humans [see *Warnings and Precautions (5.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the effects of ELEVIDYS on carcinogenicity, mutagenesis, or impairment of fertility.

14 CLINICAL STUDIES

ELEVIDYS was evaluated primarily based on data from Study 1 and Study 2 described below.

Study 1 is an ongoing multi-center study including:

- Part 1: a 48-week, randomized, double-blind, placebo-controlled period
- Part 2: a 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 male ambulatory DMD patients (N=41) 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.

Patients were randomized 1:1 to receive either ELEVIDYS (N=20) or placebo (N=21), as a single intravenous infusion via a peripheral limb. Randomization was stratified by age (i.e., aged 4 to 5 years vs. aged 6 to 7 years). In the ELEVIDYS group, eight patients received 1.33×10^{14} vg/kg of ELEVIDYS, and 12 patients received lower doses. Key demographic and baseline characteristics are presented in Table 6 below.

Table 6: Key Demographic and Baseline Characteristics (Part 1)

Characteristic	All (n=41)	ELEVIDYS (n=20)	Placebo (n=21)	ELEVIDYS Aged 4 through 5-year-old subgroup (n=8)	Placebo Aged 4 through 5-year-old subgroup (n=8)
Race group White (%)	73.2	65	81	75	100
Mean age [range] (years)	6.27 [4.34 – 7.98]	6.29 [4.47 – 7.85]	6.24 [4.34 – 7.98]	4.98 [4.47 – 5.39]	5.15 [4.93 – 5.91]
Mean weight [range] (kg)	22.4 [15.0 – 34.5]	23.3 [18.0 – 34.5]	21.6 [15.0 – 30.0]	20.1 [18.0 – 23.5]	19.8 [15.0 – 21.5]
Mean NSAA total score [range]	21.2 [13 – 29]	19.8 [13 – 26]	22.6 [15 – 29]	20.1 [17 – 23]	20.4 [15 – 24]
Mean time to rise from floor [range] (seconds)	4.3 [2.7 – 10.4]	5.1 [3.2 – 10.4]	3.6 [2.7 – 4.8]	3.9 [3.2 – 5.2]	3.8 [3.2 – 10.4]

All subjects were on a stable dose of corticosteroids for DMD for at least 12 weeks prior to ELEVIDYS infusion. All randomized subjects had baseline anti-AAVrh74 antibody titers <1:400 as determined by an investigational total binding antibody ELISA.

One day prior to treatment with ELEVIDYS or placebo, the subject's background dose of corticosteroid for DMD was increased to at least 1 mg/kg of a corticosteroid (prednisone equivalent) daily and was continued at this level for at least 60 days after the infusion, unless earlier tapering was clinically indicated.

The primary objectives of Study 1 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.

Results of ELEVIDYS micro-dystrophin measured by western blot are presented in Table 5 [see *Clinical Pharmacology (12.2)*].

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 subjects 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 subjects aged 6 through 7 years, the LS mean changes (SE) in NSAA total 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, multi-center study which includes a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years. All 20 subjects have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the *DMD* gene.

At study entry, 75% of subjects were white with a mean age of 5.81 years (range: 4.38 to 7.94), mean weight of 21.2 kg (range: 15.2 to 33.1), mean NSAA total score of 22.1 points (range: 18 to 26), and mean time to rise from floor of 4.2 seconds (range: 2.4 to 8.2). Subjects received corticosteroids for DMD before infusion according to Table 1 [see *Dosage and Administration (2.2)*]. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 as determined by the investigational total binding antibody ELISA and received a single intravenous infusion of 1.33×10^{14} vg/kg ELEVIDYS.

The primary objective of the study was to evaluate the effect of ELEVIDYS micro-dystrophin expression as measured by western blot. Results are presented in Table 5 [see *Clinical Pharmacology (12.2)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ELEVIDYS is shipped frozen ($\leq -60^{\circ}\text{C}$) in 10 mL vials.

ELEVIDYS is supplied as a customized kit to meet dosing requirements for each patient [see *Dosage and Administration (2.1)*]. Each kit contains:

- Ten (10) to seventy (70) single-dose vials of ELEVIDYS
- One alcohol wipe per vial

Each ELEVIDYS pack may contain a maximum of two different drug product lots.

The total number of vials in each kit corresponds to the dosing requirement for the individual patient, based on the patient's body weight, and is specified on the package [see *Dosage and Administration (2.2)*]. Each kit includes a specified number of ELEVIDYS vials (with a minimum of 10 vials for a patient with 10.0 – 10.4 kg body weight range, and a maximum of 70 vials for a patient with body weight of 69.5 kg and above).

Kit sizes are provided in Table 7.

Table 7: ELEVIDYS Multi-vial Kits

Patient Weight (kg)	Total Vials per Kit	Total Dose Volume per Kit (mL)
10.0 – 10.4	10	100
10.5 – 11.4	11	110
11.5 – 12.4	12	120

Patient Weight (kg)	Total Vials per Kit	Total Dose Volume per Kit (mL)
12.5 – 13.4	13	130
13.5 – 14.4	14	140
14.5 – 15.4	15	150
15.5 – 16.4	16	160
16.5 – 17.4	17	170
17.5 – 18.4	18	180
18.5 – 19.4	19	190
19.5 – 20.4	20	200
20.5 – 21.4	21	210
21.5 – 22.4	22	220
22.5 – 23.4	23	230
23.5 – 24.4	24	240
24.5 – 25.4	25	250
25.5 – 26.4	26	260
26.5 – 27.4	27	270
27.5 – 28.4	28	280
28.5 – 29.4	29	290
29.5 – 30.4	30	300
30.5 – 31.4	31	310
31.5 – 32.4	32	320
32.5 – 33.4	33	330
33.5 – 34.4	34	340
34.5 – 35.4	35	350
35.5 – 36.4	36	360
36.5 – 37.4	37	370
37.5 – 38.4	38	380
38.5 – 39.4	39	390
39.5 – 40.4	40	400
40.5 – 41.4	41	410
41.5 – 42.4	42	420

Patient Weight (kg)	Total Vials per Kit	Total Dose Volume per Kit (mL)
42.5 – 43.4	43	430
43.5 – 44.4	44	440
44.5 – 45.4	45	450
45.5 – 46.4	46	460
46.5 – 47.4	47	470
47.5 – 48.4	48	480
48.5 – 49.4	49	490
49.5 – 50.4	50	500
50.5 – 51.4	51	510
51.5 – 52.4	52	520
52.5 – 53.4	53	530
53.5 – 54.4	54	540
54.5 – 55.4	55	550
55.5 – 56.4	56	560
56.5 – 57.4	57	570
57.5 – 58.4	58	580
58.5 – 59.4	59	590
59.5 – 60.4	60	600
60.5 – 61.4	61	610
61.5 – 62.4	62	620
62.5 – 63.4	63	630
63.5 – 64.4	64	640
64.5 – 65.4	65	650
65.5 – 66.4	66	660
66.5 – 67.4	67	670
67.5 – 68.4	68	680
68.5 – 69.4	69	690
69.5 and above	70	700

A 10 mL single-dose vial carton for ELEVIDYS is not sold individually.

16.2 Storage and Handling

- ELEVIDYS is shipped and delivered at $\leq -60^{\circ}\text{C}$.
- ELEVIDYS can be refrigerated for up to 14 days when stored at 2°C to 8°C .
- Do not refreeze.
- Do not shake.
- Do not place back in the refrigerator once brought to room temperature.
- Follow local guidelines on handling of biological waste.

Shelf-life:

- When stored at $\leq -60^{\circ}\text{C}$, the expiry date of the product is indicated on the packaging materials.

MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079

MARKETING AUTHORISATION NUMBER(S):

176-89-37834-00

MANUFACTURER

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