April 18, 2025

Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Gene Therapy Product, 2. Viral Vector Product
Non-proprietary Name	Delandistrogene moxeparvovec
Brand Name	Elevidys for Intravenous Infusion
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 14, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on April 18, 2025, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The conditional and time-limited approval is applicable to the product. The approval conditions and the time limit of approval are as follows.

The following approval conditions must be satisfied.

Approval Conditions

1. During the period between the conditional and time-limited approval and the reapplication for marketing approval, the applicant is required to conduct a post-marketing approval condition assessment through clinical studies aiming at confirmation of the product's long-term efficacy and safety and post-marketing surveillance covering all patients treated with the product.
2. The product should be used by physicians with adequate knowledge of and experience with Duchenne muscular dystrophy who fully understand the clinical study results and adverse events, etc. of the product and at medical institutions with an established treatment system for Duchenne muscular dystrophy, in accordance with "INDICATION OR PERFORMANCE" and "DOSAGE AND ADMINISTRATION OR METHOD OF USE." To this end, the applicant is required to take necessary measures including the dissemination of the proper use guidelines developed jointly with the relevant academic societies.
3. The product must be used in compliance with the Type 1 Use Regulations approved under the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). To this end, the applicant is required to take necessary measures including the dissemination of the relevant use regulations.

Duration of Approval

3 years

Review Report

April 10, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Elevidys for Intravenous Infusion
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Non-proprietary Name	Delandistrogene moxeparvovec
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 14, 2024

Shape, Structure, Active Ingredients, Quantities, or Definition
Elevidys is a non-replicating, recombinant adeno-associated virus (AAV) containing AAV serotype rh74 capsid proteins and carrying a gene that expresses the delandistrogene moxeparvovec micro-dystrophin protein under the control of the α-myosin heavy-chain creatine kinase 7 promotor/enhancer.

Application Classification (1-1) New regenerative medical product

Items Warranting Special Mention
Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 16 of 2020 [*R2 sai*]; PSB/MDED Notification No. 0730-1 dated July 30, 2024, by the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of Cellular and Tissue-based Products

Results of Review
On the basis of the data submitted, PMDA has concluded that the product is expected to have a certain level of efficacy in the treatment of Duchenne muscular dystrophy, and that the product has acceptable safety (see Attachment). In view of limited information currently available, the efficacy of the product is subject to further evaluation for confirmation after marketing approval.

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval

conditions. The approval should be conditional and time-limited in accordance with Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Indication or Performance

Duchenne muscular dystrophy exclusively meeting all of the following criteria:

- Anti-AAVrh74 antibody-negative patients
- Ambulatory patients
- Patients aged 3 to less than 8 years

Dosage and Administration or Method of Use

The usual dose of Elevidys is 1.33×10^{14} vector genomes (vg)/kg for patients weighing 10 to less than 70 kg or 9.31×10^{15} vg for patients weighing 70 kg or greater. Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Do not re-administer Elevidys. Calculate the total dose volume as per the table below.

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
10.0-10.4	10	100
10.5-11.4	11	110
11.5-12.4	12	120
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

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
41.5-42.4	42	420
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	70	700

Approval Conditions

1. During the period between the conditional and time-limited approval and the reapplication for marketing approval, the applicant is required to conduct a post-marketing approval condition assessment through clinical studies aiming at confirmation of the product's long-term efficacy and safety and post-marketing surveillance covering all patients treated with the product.
2. The product should be used by physicians with adequate knowledge of and experience with Duchenne muscular dystrophy who fully understand the clinical study results and adverse events, etc. of the product and at medical institutions with an established treatment system for Duchenne muscular dystrophy, in accordance with "INDICATION OR PERFORMANCE" and "DOSAGE AND ADMINISTRATION OR METHOD OF USE." To this end, the applicant is required to take necessary measures including the dissemination of the proper use guidelines developed jointly with the relevant academic societies.
3. The product must be used in compliance with the Type 1 Use Regulations approved under the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). To this end, the applicant is required to take necessary measures including the dissemination of the relevant use regulations.

Attachment

Review Report (1)

February 19, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Elevidys for Intravenous Infusion
Classification	Gene Therapy Product, 2. Viral Vector Product
Non-proprietary Name	Delandistrogene moxeparvovec
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 14, 2024

Shape, Structure, Active Ingredients, Quantities, or Definition

Elevidys is a non-replicating, recombinant adeno-associated virus (AAV) containing AAV serotype rh74 capsid proteins and carrying a gene that encodes the delandistrogene moxeparvovec micro-dystrophin protein under the control of the α-myosin heavy-chain creatine kinase 7 (MHCK7) promotor/enhancer.

Proposed Indication or Performance

Duchenne muscular dystrophy (excluding patients with any genetically-confirmed deletion in exon 8 and/or exon 9 in the *DMD* gene) exclusively in anti-AAVrh74 antibody-negative patients

Proposed Dosage and Administration or Method of Use

The usual dose of Elevidys is 1.33×10^{14} vector genomes (vg)/kg for patients weighing 10 to less than 70 kg or 9.31×10^{15} vg for patients weighing 70 kg or greater. Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Do not re-administer Elevidys. Calculate the total dose volume as per the table below.

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
10.0-10.4	10	100
10.5-11.4	11	110
11.5-12.4	12	120
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

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
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
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	70	700

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Elevidys is a regenerative medical product, which is a non-replicating, recombinant AAV containing a DNA transgene encoding a shortened form of dystrophin that retains only the essential functional domains of the human dystrophin protein (delandistrogene moxeparvovec micro-dystrophin [hereinafter referred to as "micro-dystrophin"). Once intravenously administered Elevidys infects the patient's skeletal and cardiac muscle cells, the expression construct in Elevidys remains as an episome in the nucleus of the cell and expresses a functional micro-dystrophin protein in cardiac, respiratory, and skeletal muscles. The expressed micro-dystrophin is expected to reduce muscle loss and improve muscle function by stabilizing the sarcolemma and preventing muscle breakdown.

Elevidys was designated as an orphan regenerative medical product with the intended indication or performance of "Duchenne muscular dystrophy" as of July 30, 2024 (Orphan Regenerative Medical Product Designation No. 16 of 2020 [*R2 sai*]).

1.2 Development history, etc.

Duchenne muscular dystrophy (DMD) is an X-linked, degenerative, neuromuscular disease caused by mutations in the *DMD* gene. Dystrophin is expressed in multiple tissue types including skeletal muscle, smooth muscle, and cardiac muscle. Dystrophin is a critically important part of the protein complex connecting the cytoskeleton of muscle fibers to the cell membrane and the extracellular matrix and is thought to prevent sarcolemma membrane damage during eccentric contraction.

The incidence of DMD is approximately 1 in 5,000 live male births worldwide (*Ann Neurol.* 2012;71:304-13, *Orphanet J Rare Dis.* 2020;15:141). The first clinical symptoms of DMD are delay in motor developmental milestones, such as walking. As the disease progresses, walking gradually becomes more difficult. The natural history of DMD is that by 8 years of age, most patients lose the ability to rise from the floor or climb stairs. Between 10 and 14 years of age, patients lose ambulation, eventually leading to a fatal outcome due to cardiac and respiratory muscle weakness.

At present, corticosteroids are recommended as standard of care for DMD in Japan and overseas. In Japan, prednisolone has been approved as a treatment for DMD. However, corticosteroids do not address the underlying cause of the disease. As exon 53 skipping therapy to increase dystrophin production, viltolarsen has been approved under conditional early approval system in Japan. However, only approximately 8% of DMD patients can be treated by skipping exon 53 (*Hum Mutat*. 2009; 30: 293-9).

Sarepta initiated a foreign phase I/IIa study of Elevidys in ambulatory patients with DMD aged 4 to <8 years (Study 101) in November 2017. Then, a foreign phase II study in ambulatory patients with DMD aged 4 to <8 years (Study 102) was initiated in December 2018. Furthermore, a foreign phase Ib study in various age groups of ambulatory or non-ambulatory patients with DMD (Study 103) and a global phase III study in ambulatory

patients with DMD aged 4 to <8 years (Study 301) were initiated in November 2020 and October 2021, respectively.

In the US, Elevidys was granted accelerated approval[1)] for ambulatory patients with DMD, as shown below, in June 2023, based mainly on the results from Studies 101, 102, and 103.

ELEVIDYS is an adeno-associated virus vector-based gene therapy 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. This indication is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin in skeletal muscle 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).

Then, a supplemental application was submitted for the proposed indication of "For treatment of Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the *DMD* gene" based mainly on the results from Studies 103 and 301, and the approval of Elevidys was expanded for the following indications in June 2024. The DMD indication in non-ambulatory patients received accelerated approval.[2)]

ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated in individuals at least 4 years of age:

- For the treatment of Duchenne muscular dystrophy (DMD) in patients who are ambulatory and have a confirmed mutation in the *DMD* gene.
- For the treatment of DMD in patients who are non-ambulatory and have a confirmed mutation in the *DMD* gene

The DMD indication in non-ambulatory patients is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin (noted hereafter as “micro-dystrophin”). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

An EU application[3)] was submitted based mainly on the results from Study 301 in May 2024 and is under review as of January 2025.

In Japan, Sarepta started enrollment of Japanese patients in Study 301 in [redacted] 2022.

The applicant has now submitted a marketing application for Elevidys based mainly on the results from Study

[1)] The review team concluded that based on available data, the potential benefit associated with accelerated approval did not outweigh the identified or potential risks associated with Elevidys. However, the CBER director concluded that the results of a surrogate endpoint, micro-dystrophin expression, etc., were sufficient to meet the standard for accelerated approval, leading to accelerated approval of the product for use in ambulatory patients aged 4 to 5 years.

[2)] The review team concluded that available data did not demonstrate the benefit of Elevidys in ambulatory patients aged 4-5 years, ambulatory patients aged ≥5 years, or non-ambulatory patients. However, the CBER director concluded that the results of motor function endpoints in ambulatory patients aged ≥4 years were sufficient to meet the standard for traditional approval, and that the results of a surrogate endpoint, micro-dystrophin expression, etc., in non-ambulatory patients were sufficient to meet the standard for accelerated approval. Thus, FDA granted traditional approval or accelerated approval for the above indications.

[3)] The proposed indication is for the treatment of DMD in ambulatory patients aged 3 to 7 years.

301.

2. Quality and Outline of the Review Conducted by PMDA

Elevidys comprises a capsid derived from AAVrh74. The expression construct delivered by Elevidys contains an expression cassette flanked by inverted terminal repeats (ITRs) derived from AAV2. The cassette contains the MHCK7 promoter/enhancer,[4)] a chimeric simian virus 40 (SV40) intron, a codon-optimized human micro-dystrophin complementary DNA, and a synthetic polyadenylation signal.

Elevidys is unable to replicate due to the removal of the *rep* and *cap* genes from the wild-type AAV genome. The AAV2 Rep/AAVrh74 Cap packaging component; the E2a, E4, and VA RNA packaging component; and the micro-dystrophin expression cassette, which are used for the production of Elevidys, are divided into 3 plasmids. Elevidys has been designed not to generate a replication competent virus by homologous recombination.

Taking account of the genome packaging limit of AAV capsids, the micro-dystrophin transgene in Elevidys is designed to encode only the essential functional domains of the dystrophin protein (Table 1) and contains exons 1-17, exons 59-71, and exon 79 of the dystrophin gene.

Table 1. Domains of dystrophin included in micro-dystrophin protein

Domain of dystrophin *	Reason for selection, etc.
N-terminus (ABD)	Important for internal actin cytoskeletal linkage.
Hinge 1 (H1)	To provide intramolecular flexibility between the N-terminal domain and spectrin-like repeats.
Spectrin-like repeats 1-3 (R1-3)	Important for binding to the sarcolemma to maintain contractile force.
Hinge 2 (H2)	For intramolecular flexibility.
A novel junction	To minimize synthetic linkages that could disrupt protein function or create immunogenic epitopes and to mimic naturally existing functional shortened dystrophins found in nature.
Spectrin-like repeat 24 (R24)	Necessary for organization of the internal microtubule network.
Hinge 4 (H4)	H4 contains domains involved in protein-protein interaction and anchoring at sarcolemma.
Cysteine-rich domain (CR)	Important for DAPC assembly.
[redacted]	[redacted]

*Exons 1-17 correspond to ABD to H2, exons 59-69 correspond to R24 to CR, and [redacted].

2.1 Drug substance

2.1.1 Plasmid

Three plasmids (transgene plasmid, packaging plasmid, helper plasmid) are used for the production of a viral vector. The transgene plasmid contains the micro-dystrophin gene under the control of the MHCK7 promoter. The packaging plasmid contains the AAV2 *Rep* gene and the AAVrh74 *Cap* gene. The helper plasmid contains the genes encoding E2a, E4, and VA RNA, respectively. The controls of these plasmids consist of [redacted], bacterial endotoxin, sterility, [redacted], [redacted], [redacted]

[4)] The MHCK7 promoter/enhancer is derived from the MCK and MHC promoter/enhancer and drives transgene expression predominantly in skeletal muscle (including diaphragm) and cardiac muscle.

[redacted], mycoplasma, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

2.1.2 Generation and control of the cell substrate for the production of drug substance

Human embryonic kidney 293 (HEK293) cells are used to produce the drug substance. HEK293 cells supplied from [redacted] were used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, the WCB, and cells at the limit-of-in-vitro-cell-age (LIVCA) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1) and Q5D guidelines. Tests for adventitious agents performed are shown in Table 2. No viral or non-viral adventitious agents were detected in any of the tests conducted.

The MCB and WCB are stored at ≤[redacted]°C. The MCB [redacted], and the WCB [redacted].

Table 2. Tests for adventitious agents for MCB, WCB, and LIVCA

Sterility test
Test for mycoplasma
Transmission electron microscopy[*1]
Reverse transcriptase activity assay[*1]
Retrovirus infectivity test (S^+L^-focus assay, XC plaque assay)[*1]
In vitro tests (MRC-5 cells, Vero cells, HEK293 cells)
In vivo tests (suckling and adult mice, guinea pigs, embryonated eggs)[*1]
Tests for bovine viruses (9CFR; BAV, BRSV, BTV, IBR,[*2] PI-3, Rabies, and Reo [BT cells and Vero cells], BPV and BVD [BT cells])
Tests for porcine viruses (9CFR; PAV [PK-15 cells], PPV and TGEV [ST Neb cells], PHEV [HCT-8 cells], PRRSV [MA104 cells], PRV and Rabies [BT cells and Vero cells], Reo [Vero cells], EMC [Vero cells and ST Neb cells])[*1]
Tests for human viruses (B19, JC, BK, HHV-7, HIV-1, HIV-2, HHV-8, HHV-6, HPV-16, HPV-18, HBV, HAV, HTLV-1, HTLV-2, HCV, CMV, EBV)[*1]
Tests for HSV I and HSV II DNA[*1]
Test for SV40 DNA[*1]
Test for AAV2[*1]
Test for human ADV5 DNA[*1]
Test for MVM[*1]

*1 MCB and LIVCA were tested.
*2 MCB only was tested.

2.1.3 Manufacturing process

The manufacturing process for the drug substance consists of thawing of the WCB, cell expansion, [redacted] culture, transfection and virus production, [redacted] and harvest, [redacted], [redacted], [redacted], [redacted] and filtration, [redacted] chromatography, [redacted] chromatography, filtration for virus removal, [redacted], formulation and filtration, storage, and testing.

[redacted], [redacted], [redacted], [redacted] chromatography, [redacted] chromatography, and filtration for virus removal have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.4 Safety evaluation of adventitious agents

Table 3 shows raw materials of biological origin etc. other than HEK293 cells used in the drug substance manufacturing process, both of which have been confirmed to conform to the Standard for Biological Ingredients.

Table 3. Raw materials of biological origin etc. other than HEK293 cells

Raw material	Animal species	Specific part of animal used	Process step
[redacted]CS	Bovine	Blood	Preparation of MCB and WCB
FBS	Bovine	Blood	Preparation of WCB Cell culture ([redacted])

In the drug substance manufacturing process, *in vitro* test for adventitious viruses and tests for mycoplasma and bioburden are included as in-process controls for unprocessed bulk before cell lysis.

Viral clearance studies of the drug substance purification process were performed with model viruses. The results demonstrated the robustness of the purification process (Table 4).

Table 4. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})			
	XMuLV	PRV	Reo-3	MVM
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] virus inactivation*	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Filtration for virus removal	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>21.54	>19.29	>14.67	7.31

[redacted]

2.1.5 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, and [redacted] [the proposed commercial process]).

- Process A→Process B: change in [redacted], change in [redacted], modification of [redacted], change in [redacted] step, and change in [redacted] step
- Process B→[redacted] (the proposed commercial process): change in [redacted], updating of [redacted], change in [redacted] step, and change in [redacted] step

In non-clinical studies, the test materials manufactured using Process A, Process B, and the proposed commercial process were used. Table 5 shows the manufacturing processes of the drug substances used for the production of the drug products used in different clinical studies.

Table 5. Manufacturing processes of drug substances used for the production of drug products used in clinical studies

Process A	Study [redacted], Study [redacted]
[redacted] (the proposed commercial process)	Study [redacted], Study 301

For these process changes, the comparability of quality attributes was assessed. Since Process A [redacted], [redacted] manufactured using [redacted] was used for assessment.

Comparison between [redacted] and [redacted] showed differences in percent full capsid etc. The applicant explains as follows: It is difficult to determine the comparability of quality attributes between the drug products derived from the drug substances manufactured using these processes. However, the results of non-clinical and clinical studies indicate that the observed differences in quality attributes do not impact the efficacy or safety of Elevidys.

Comparison of [redacted] demonstrated the comparability of quality attributes between the drug products derived from the drug substances manufactured using these processes.

2.1.6 Characterization

2.1.6.1 Structure and properties

Table 6 shows characterization tests performed.

Table 6. Characterization attributes

Expression construct	DNA sequence, ORF analysis
Analyses of capsid protein	ratios of [redacted], primary sequence and post-translational modifications (N-terminal sequence, C-terminal sequence, [redacted])
Activity	*in vivo* study ([redacted] and [redacted] functional improvements in [redacted]) and *in vitro* study (micro-dystrophin expression and localization to sarcolemma in cells isolated from [redacted])
Impurities	[redacted]

2.1.6.2 Product-related substances/Product-related impurities

Although no product-related substances have been identified, Impurity A, Impurity B , Impurity C, Impurity D, Impurity E, and Impurity F were considered product-related impurities, based on the results of characterization tests presented in Section 2.1.6.1. The product-related impurities other than Impurity B and Impurity C are adequately controlled by the drug substance and drug product specifications. The levels of Impurity B and Impurity C are controlled by the manufacturing process.

2.1.6.3 Process-related impurities

Impurity G, host cell protein (HCP), host cell DNA, Impurity H, Impurity I, Impurity J , Impurity K, and Impurity L were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process. Impurity G, HCP, host cell DNA, and Impurity I are adequately controlled by the drug substance specification.

2.1.7 Control of drug substance

The proposed specifications for the drug substance consist of quantity, appearance, identity ([redacted]), osmolality, pH, purity ([redacted]), host cell DNA, HCP, [redacted], bacterial endotoxin, microbial limits, [redacted],

and [redacted]. [redacted] is not tested at release of the drug substance, but is tested for stability evaluation.

2.1.8 Stability of drug substance

Table 7 shows an overview of the primary stability studies on the drug substance.

Table 7. Overview of primary stability studies on drug substance

Study	No. of batches*	Storage condition	Testing period	Storage package
Long-term	3	≤−60°C	[redacted] months	[redacted] and bag with [redacted] port

*The drug substance manufactured using the proposed commercial process was used.

Under the long-term condition, purity tests ([redacted]) showed a trend towards increased [redacted], a trend towards lowered [redacted], and a trend towards decreased [redacted]. [redacted] was not evaluated until [redacted] months, but was evaluated at [redacted] months and met the acceptance criteria.

Based on the above, a shelf-life of [redacted] months was proposed for the drug substance when stored in [redacted] and [redacted] bag with [redacted] port at ≤−60°C.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an injectable formulation in 10-mL vials each containing 10 mL of 1.33×10^{13} vg/mL of delandistrogene moxeparvovec. It contains excipients including sodium chloride, tromethamol hydrochloride, trometamol, magnesium chloride hexahydrate, poloxamer 188, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of thawing, [redacted], sterile filtration, filling/stoppering/capping, testing, freeze/storage, labeling/storage, packaging, and storage/testing.

[redacted] and [redacted] have been defined as critical steps.

Process validation of the commercial-scale drug product manufacturing process has been performed.

2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development: addition of [redacted] step, change in [redacted] step, change in [redacted] step, change in [redacted], and change in [redacted] (The pre-change process is referred to as Process 1, and the post-change process is referred to as Process 2 [the proposed commercial process]).

Table 8 shows the manufacturing processes of the drug products used in different clinical studies.

Table 8. Manufacturing processes of drug products used in clinical studies

Process 1	Study 101, Study 102
Process 2 (the proposed commercial process)	Study 103, Study 301

The process change from Process 1 to Process 2 [redacted] the change to [redacted] in the [redacted] step , and the comparability of quality attributes between pre-change and post-change drug produces was assessed [redacted] [see Section 2.1.5].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identity ([redacted]), osmolality, pH, purity ([redacted]), bacterial endotoxin, extractable volume, [redacted], insoluble particulate matter, sterility, [redacted], and [redacted].

2.2.5 Stability of drug product

Table 9 shows an overview of the primary stability studies on the drug product.

Table 9. Overview of primary stability studies on drug product

Study	Number of batches[*1]	Storage conditions	Testing period	Storage package
Long-term	3	≤−60°C	24 months[*2]	A cyclic olefin polymer vial with [redacted] rubber stopper
Accelerated	3	[redacted]°C	[redacted] months[*3]	
Stress	1	5 ± 3°C	14 days	
Photostability	1	An overall illumination of 1.2 million lux·hr and an integrated near ultraviolet energy of 200 W·h/m^2, [redacted]°C, [redacted]%RH		

*1 The drug product produced using the proposed commercial process from the drug substance manufactured using the proposed commercial process was used.
*2 In progress up to [redacted] months
*3 [redacted]-month stability data for 1 batch and [redacted]-month stability data for 1 batch have been obtained. The study will be continued up to [redacted] months for 2 batches and up to [redacted] months for 1 batch.

Under the long-term condition, evaluation of [redacted] by [redacted] showed a trend towards increased [redacted].

Under the accelerated condition, evaluation of [redacted] by [redacted] showed an increase in [redacted].

Under the stress condition, no significant changes in quality attributes occurred throughout the testing period.

Photostability data showed that the drug product is photostable.

Based on the above, a shelf-life of 24 months was proposed for the drug product when packaged in a cyclic olefin polymer vial with [redacted] rubber stopper and stored at ≤−60°C.

2.3 Quality control strategy

Based on the following studies etc., a quality control strategy for Elevidys was established through the combination of the control of process parameters, in-process controls, and the specification [for the control of product-related impurities and process-related impurities, see Sections 2.1.6.2 and 2.1.6.3].

- Identification of critical quality attributes (CQAs)

  The following CQAs were identified based on the information obtained during the development of Elevidys, the relevant knowledge, etc.

  - CQAs of the drug substance or the drug product

    adventitious viruses, mycoplasma, bioburden, bacterial endotoxin, sterility, osmolarity, pH, appearance, [redacted], [redacted], [redacted] and Impurity F, [redacted], extractable volume, [redacted], identity ([redacted], [redacted]), [redacted], [redacted], [redacted], Impurity M, Impurity N, Impurity G, Impurity H, Impurity K, Impurity J, Impurity I

- Process characterization

  Process parameters were classified by risk assessment based on their impact on CQAs, and each process step was characterized.

2.R Outline of the Review Conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following studies in young DMD^{MDX} mice[5)] or DMD^{MDX} rats[6)] corresponding to children of 2 to 11 years, etc., as the primary pharmacodynamics or performance data.

3.1 Study in DMD^{MDX} mice (CTD4.2.1.1-4)

Male DMD^{MDX} mice in the Elevidys group received a single intravenous dose of Elevidys 1.33×10^{14} vg/kg or 2.66×10^{14} vg/kg, and male DMD^{MDX} mice in the control group received a single intravenous dose of saline. At 12 weeks post-administration (Week 12), the expression of micro-dystrophin protein by immunofluorescence staining and Western blot, its localization to the sarcolemma by immunofluorescence staining, and muscle function[7)] by muscle physiology apparatus were assessed.

Immunofluorescence staining showed micro-dystrophin expression in skeletal muscles, diaphragm, and heart and its localization to the sarcolemma in both dose groups of Elevidys.

[5)] A mouse model of DMD carrying a spontaneous mutation in exon 23 of the *DMD* gene
[6)] A rat model of DMD generated by introducing a mutation into exon 23 of the *DMD* gene, using a gene-editing technique
[7)] Electrodes were inserted into the left tibialis anterior muscles of anesthetized mice, and eccentric contractions elicited by 150 Hz electric stimulation were measured.

Western blot analysis revealed micro-dystrophin expression in skeletal muscles, diaphragm, and heart in the Elevidys 1.33×10^{14} vg/kg group and micro-dystrophin expression in skeletal muscles, diaphragm, heart, and liver in the Elevidys 2.66×10^{14} vg/kg group, whereas micro-dystrophin expression in other organs (spinal cord, brain, lymph node, gonads, pancreas, stomach, kidney, spleen, lung) was not observed at either dose level. The level of micro-dystrophin expression was lower in the liver than in skeletal muscles, diaphragm, and heart.

The results of muscle function assessment are shown in Table 10. There was a trend towards higher specific force in both dose groups of Elevidys compared to the control group.

Table 10. Specific force of skeletal muscle and diaphragm at Week 12

Animal	Test article	Dose (vg/kg)	Specific force (mN/mm^2)	
			Skeletal muscle	Diaphragm
DMD^{MDX} mouse	Saline	-	120.3 ± 35.6	80.1 ± 23.7
	Elevidys	1.33×10^{14}	160.7 ± 19.6	96.2 ± 15.8
		2.66×10^{14}	183.0 ± 15.6	122.4 ± 15.7

Mean ± SD

3.2 Studies in DMD^{MDX} rats

3.2.1 Study in young DMD^{MDX} rats (CTD4.2.1.1-7)

Male DMD^{MDX} rats (3-5 weeks of age) in the Elevidys group received a single intravenous dose of Elevidys 1.33×10^{14} vg/kg, and male DMD^{MDX} rats in the control group received a single intravenous dose of saline. At Week 12, Week 24, and the terminal survival timepoint (up to 28 months of age, at Week 119), the expression of micro-dystrophin protein by immunofluorescence staining and Western blot and its localization to the sarcolemma by immunofluorescence staining were assessed. Motor function[8)] at Weeks 12 and 24 and survival were assessed.

Immunofluorescence staining showed micro-dystrophin expression in skeletal muscles, diaphragm, and heart and its localization to the sarcolemma at all time points.

Western blot analysis revealed micro-dystrophin expression in skeletal muscles, diaphragm, and heart at all time points.

The results of motor function assessment are shown in Table 11. There was a trend towards improvements in ambulation and vertical activity in the Elevidys group compared to the control group at Weeks 12 and 24.

Table 11. Ambulation and vertical activity at Weeks 12 and 24

Animal	Test article	Dose (vg/kg)	Number of beam breaks per hour			
			Ambulation		Vertical activity	
			Week 12	Week 24	Week 12	Week 24
DMD^{MDX} rat	Saline	-	4,066.6 ± 1562.7	2,860.7 ± 1044.3	51.5 ± 35.8	23.6 ± 13.3
	Elevidys	1.33×10^{14}	6,525.2 ± 1,251.5	4,723.1 ± 973.4	108.8 ± 34.4	47.1 ± 20.1

Mean ± SD

As to survival, all animals in the control group died by Month 17, and the median survival was 13 months,

[8)] Ambulation and vertical activity in rats were measured based on the number of beam breaks per hour in an activity cage.

whereas a longer survival was observed in the Elevidys group, i.e., the maximum survival was 28 months, and the median survival was 26 months.

3.2.2 Study in adolescent DMD^{MDX} rats (CTD4.2.1.1-8)

Male DMD^{MDX} rats (5-6 weeks of age) in the Elevidys group received a single intravenous dose of Elevidys 7.0×10^{13} vg/kg or 1.33×10^{14} vg/kg, and male DMD^{MDX} rats in the control group received a single intravenous dose of saline. At Weeks 12 and 52, the expression of micro-dystrophin protein by immunofluorescence staining and Western blot and its localization to the sarcolemma by immunofluorescence staining were assessed. Motor function[8)] was also assessed.

Immunofluorescence staining showed micro-dystrophin expression in skeletal muscles at Week 12 and micro-dystrophin expression in skeletal muscles and heart at Week 52 and its localization to the sarcolemma in the Elevidys 7.0×10^{13} vg/kg group and micro-dystrophin expression in skeletal muscles and heart at Weeks 12 and 52 and its localization to the sarcolemma in the Elevidys 1.33×10^{14} vg/kg group.

Western blot analysis revealed micro-dystrophin expression in skeletal muscles and heart at both dose levels and at both time points, but micro-dystrophin expression was not detected in other organs (the lung and liver).

The results of motor function assessment are shown in Table 12. There was a trend towards improvements in ambulation and vertical activity in the Elevidys group compared to the control group at Weeks 12 and 52.

Table 12. Ambulation and vertical activity at Weeks 12 and 52

Animal	Test article	Dose (vg/kg)	Number of beam breaks per hour			
			Ambulation		Vertical activity	
			Week 12	Week 52	Week 12	Week 52
DMD^{MDX} rat	Saline	-	3,719.3 ± 1,605.4	3,070.3 ± 858.0	38.2 ± 21.8	31.3 ± 9.9
	Elevidys	7.0×10^{13}	6,890.2 ± 2,169.8	3,736.6 ± 522.0	86.2 ± 31.6	23.8 ± 12.5
		1.33×10^{14}	7,379.6 ± 1,794.4	3,938.4 ± 956.3	108.8 ± 42.8	33.2 ± 12.2

Mean ± SD

3.R Outline of the Review Conducted by PMDA

PMDA's review strategy:

Among the submitted data, the pivotal studies to evaluate the mechanism of action of Elevidys are studies to assess the expression of the micro-dystrophin transgene in muscle tissues, its localization to the sarcolemma, and the effects on muscle strength and motor function. PMDA decided to focus its review on these studies.

The applicant's explanation about the effects of Elevidys in DMD:

In vivo studies showed micro-dystrophin expression in skeletal muscles, diaphragm, and heart and its localization to the sarcolemma in DMD^{MDX} mice or DMD^{MDX} rats treated with Elevidys. In the Elevidys group compared to the control group, there was a trend towards improvements in muscle function and motor function, and a longer survival was observed. In the Elevidys group of a study in adolescent DMD^{MDX} rats, mobility was reduced at Week 52 compared with Week 12, which is explained by an age-related decline in mobility due to

increased body weight, etc. Given micro-dystrophin expression in muscle tissues and the results of ambulation etc., the effects of Elevidys were maintained also at Week 52.

Based on the above, Elevidys is expected to stabilize the sarcolemma, prevent muscle breakdown, and improve muscle strength and motor function by inducing the expression of micro-dystrophin protein in skeletal and cardiac muscle cells and its localization to the sarcolemma.

PMDA's conclusion:
Although the reason for no differences in vertical activity at Week 52 between the Elevidys and control groups in the study in adolescent DMD^{MDX} rats is unclear, the applicant's explanation about the effects of Elevidys is understandable.

4. Non-clinical Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted the results from single-dose biodistribution studies in DMD^{MDX} mice or DMD^{MDX} rats as the data on the non-clinical biological disposition of Elevidys.

4.1 Analytical methods

For the evaluation of the non-clinical biological disposition of Elevidys, Elevidys genomic DNA (gDNA) levels were determined by quantitative polymerase chain reaction (qPCR) in mice and by droplet digital polymerase chain reaction (ddPCR) in rats. The expression level of micro-dystrophin protein was evaluated by Western blot.

4.2 Non-clinical biodistribution

4.2.1 Biodistribution of vector

The studies with Elevidys presented in Table 13 were conducted, and the tissue distribution of Elevidys gDNA was evaluated.

Table 13. Single intravenous dose biodistribution studies of Elevidys

Test system	Observation period	Dose (vg/kg)	Summary of findings	Attached document
Male mouse (DMD^{MDX})	12 weeks 24 weeks*1	1.33×10^{14} 4.01×10^{14}	• The level of Elevidys gDNA in plasma peaked at the first time point, i.e., Day 2, and showed a biphasic disposition characterized by a rapid distribution phase of up to 10 days post-dose followed by a slower terminal elimination phase. Elevidys gDNA in plasma was below the LLOQ at Day 44 at both dose levels. • At Weeks 12 and 24, Elevidys gDNA was detected in all tissues (adrenal gland, brain [prefrontal cortex], colon, epididymis, eye, Harderian gland, heart, jejunum, kidney, liver, lung, skeletal muscle, sciatic nerve, skin, spleen, testis, thymus, thyroid, trachea) at both dose levels. • At Weeks 12 and 24, Elevidys gDNA levels in the liver, heart, adrenal gland, and skeletal muscle were higher than those in other tissues at both dose levels.	4.2.2.2-1
Male mouse (DMD^{MDX})	12 weeks	1.33×10^{14} 2.66×10^{14}	• At Week 12, Elevidys gDNA was detected in all tissues (skeletal muscle, heart, diaphragm, liver, kidney, lung, spleen, gonads, stomach, pancreas, hepatic portal vein, brain, spinal cord, dorsal root ganglia, lymph node, femoral artery, fat) at both dose levels. • At both dose levels, higher levels of Elevidys gDNA were detected in the liver compared with other tissues, and Elevidys gDNA was detected at low levels in the dorsal root ganglia, brain, and spinal cord.	4.2.2.3-5*2
Male mouse (DMD^{MDX})	12 weeks	1.33×10^{14} 4.02×10^{14}	• At Week 12, Elevidys gDNA was detected in all tissues (adrenal gland, aorta, bone, brain, cecum, colon, duodenum, esophagus, eye, Harderian gland, heart, ileum, jejunum, kidney, liver, lung, skeletal muscle, pancreas, salivary gland, sciatic nerve, skin, spinal cord [cervical spine, lumbar spine, thoracic spine], spleen, stomach, testis, thymus, thyroid, trachea) at both dose levels. • At both dose levels, higher levels of Elevidys gDNA were detected in the liver, adrenal gland, skeletal muscle, heart, and aorta compared with other tissues, and Elevidys gDNA was detected at low levels in the brain, sciatic nerve, and spinal cord.	4.2.2.3-8
Male rat (DMD^{MDX})	12 weeks 24 weeks Terminal survival timepoint (up to 28 months of age, at Week 119)	1.33×10^{14}	• Elevidys gDNA was detected in all tissues other than the stomach (skeletal muscle, heart, diaphragm, kidney, lung, spleen, gonads, lymph node, brain, liver, fat) at Week 12. • Elevidys gDNA was detected in all tissues other than the stomach and spleen (skeletal muscle, heart, diaphragm, kidney, lung, gonads, lymph node, brain, liver, fat) at Week 24. • At all time points, the highest levels of Elevidys gDNA were detected in the liver followed by the heart. • Elevidys gDNA was detected in all tissues evaluated at the terminal survival timepoint (skeletal muscle, heart, diaphragm, liver).	4.2.2.3-11*2

*1 Plasma gDNA levels were determined up to 44 days post-dose.

*2 The analytical procedures for assay have not been validated.

4.2.2 Biodistribution of micro-dystrophin protein (CTD4.2.2.3-11)

Male DMD^{MDX} rats received a single intravenous dose of Elevidys 1.33×10^{14} vg/kg. The distribution of micro-dystrophin expression in skeletal muscles, heart, and diaphragm was evaluated at Week 12, Week 24, and the terminal survival timepoint (up to 28 months of age, at Week 119). At all time points, micro-dystrophin expression was detected in all tissues [see Section 3.2.1].

4.3 Shedding (CTD4.2.2.2-1 and CTD4.2.2.2-2)

DMD^{MDX} mice received a single intravenous dose of Elevidys 1.33×10^{14} vg/kg or 4.01×10^{14} vg/kg. Urine and feces samples were collected starting from Day 2 up to Day 44 after administration every 3 days and evaluated for Elevidys gDNA by qPCR. At both dose levels, Elevidys gDNA levels in urine and feces peaked at Day 2. In the 1.33×10^{14} vg/kg group, Elevidys gDNA was quantifiable in urine up to Day 7 and in feces up to Day 13. In the 4.01×10^{14} vg/kg group, Elevidys gDNA was quantifiable in urine up to Day 4 and in feces up to Day 28.

4.R Outline of the Review Conducted by PMDA

The applicant's explanation about the biological disposition of Elevidys:

In a single intravenous dose biodistribution study of Elevidys in mice, Elevidys gDNA levels in the liver, heart, adrenal gland, and skeletal muscle tended to be higher than those in other tissues. Particularly a liver tropism was observed, and Elevidys gDNA was detected at low levels in the central nervous system.

In a single intravenous dose biodistribution study of Elevidys in rats, high levels of Elevidys gDNA were detected in the liver and heart, and particularly a liver tropism was observed. Elevidys gDNA was distributed also to skeletal muscle.

The long-term persistence of micro-dystrophin expression in skeletal muscles, heart, and diaphragm following administration of Elevidys was suggested. Although Elevidys has a liver tropism, micro-dystrophin expression was lower in the liver than in skeletal muscles, diaphragm, and heart in a pharmacology study in DMD^{MDX} mice [see Section 3.1], indicating low expression in off-target tissues due to the control of transgene expression by the MHCK7 promoter.

PMDA accepted the applicant's explanation.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results from single-dose toxicity studies in mice and an *in vivo* genome integration study in cynomolgus monkeys as the data on the non-clinical safety of Elevidys.

5.1 Single-dose toxicity

A single intravenous dose toxicity study in male mice (a 12-week or 24-week observation period), a single intravenous dose toxicity study in male mice (a 12-week observation period), a single intravenous dose toxicity study to evaluate dilatation of brain ventricles in male mice (a 12-week observation period), and a single intravenous dose toxicity study in male and female neonatal mice were conducted with Elevidys.

In the single intravenous dose toxicity study in male mice (a 12-week or 24-week observation period), hepatocyte hypertrophy and single cell necrosis, etc., with associated liver enzyme abnormalities were observed in the liver of wild-type (C57BL/6J) mice, but not in DMD^{MDX} mice. These findings other than

hepatocyte vacuolation were minimal or slight in severity, which had resolved at Week 24 and were reversible. Hepatocyte vacuolation observed at Week 24 is considered an adaptive change. Thus, the applicant explained that all those findings were of little toxicological significance.

In the single intravenous dose toxicity study in male mice (a 12-week or 24-week observation period) and the single intravenous dose toxicity study in male mice (a 12-week observation period), unscheduled deaths occurred in DMD^{MDX} mice in the saline and Elevidys groups. Brain ventricle dilatation was noted in multiple animals including unscheduled deaths, and the finding was considered possibly related to Elevidys based on the relationship between its severity and the dose. The incidence of naturally occurring enlargement of lateral ventricles has been reported to be high in DMD^{MDX} mice (*Neuromuscul Disord*. 2015;25:764-72, *Neuromuscul Disord*. 2020;30:368-88). In the single intravenous dose toxicity study to evaluate dilatation of brain ventricles in male mice (a 12-week observation period), any mouse with a domed head, which is an external finding related to brain ventricle dilatation, was removed prior to dosing. The study showed no correlation between the severity of the finding and the dose. Thus, the applicant explained that the finding was not related to Elevidys and was an event unique to DMD^{MDX} mice.

Although dorsal root ganglia toxicity related to AAV vector administration is known (*Front Neuroanat.* 2014; 8: 42, *Hum Gene Ther*. 2018; 29: 285-98, etc.), there were no Elevidys-related histopathological changes in the spinal cord or peripheral nerves or effects on the neurologic function in clinical observations.

Table 14. Single intravenous dose toxicity studies of Elevidys

Test system	Observation period	Dose (vg/kg)	Noteworthy findings	Attached document
Male mouse (wild-type [C57BL/6J], DMD^{MDX})	12 weeks 24 weeks	0 (saline) 1.33×10^{14} 4.01×10^{14}	[C57BL/6J mice] Mortality: none 1.33×10^{14} vg/kg group: increased AST/ALT, hepatocyte hypertrophy, oval cell hyperplasia in the liver, pigment in the liver, hepatocyte single cell necrosis, increased hepatocyte mitosis, hepatocyte vacuolation[*1] 4.01×10^{14} vg/kg group: increased MCHC, rough surface of the liver These findings were reversible (except for hepatocyte vacuolation). [DMD^{MDX} mice] Mortalities[*2]: 1 of 20 mice (saline group), 2 of 20 mice (1.33×10^{14} vg/kg group), 1 of 20 mice (4.01×10^{14} vg/kg group) Saline group: brain ventricle dilatation 1.33×10^{14} vg/kg group: decreased body weight gain, increased MCHC, decreases in white blood cell count/neutrophil count/monocyte count/platelet count, decreases in AST/ALT/GLDH/BUN Reversibility: Brain ventricle dilatation, decreased platelet count, and decreases in AST and GLDH were noted at Week 12 and at Week 24.	4.2.3.1-2
Male mouse (wild-type [C57BL/6J], DMD^{MDX})	12 weeks	0 (saline) 1.33×10^{14} 4.02×10^{14}	[C57BL/6J mice] Mortality: none 1.33×10^{14} vg/kg group: increased spleen weights [DMD^{MDX} mice] Mortalities[*2]: 2 of 15 mice (4.02×10^{14} vg/kg group) Saline group: brain ventricle dilatation[*3] 1.33×10^{14} vg/kg group: brain ventricle dilatation,[*3] decreases in white blood cell count/neutrophil count, decreased ALT, decreased liver weights 4.02×10^{14} vg/kg group: decreased general activity, piloerection, thin, hunched posture, decreases in body weight/body weight gain, decreased monocyte count, decreased AST	4.2.3.1-3
Male mouse (DMD^{MDX})	12 weeks	0 (saline), 0 (vehicle)[*4], 2.0×10^{14}, 4.01×10^{14}	Saline, vehicle, and 4.01×10^{14} vg/kg groups: brain ventricle dilatation[*5]	4.2.3.1-4 Reference data
Male and female juvenile mice (C57BL/6J, postnatal day 1)	90 days	0 (saline), 1.33×10^{14}, 4.01×10^{14}	1.33×10^{14} vg/kg group: increased bone mineral density (female) 4.01×10^{14} vg/kg group: decreased body weight gain (male and female), decreased food consumption (male)	4.2.3.5.4-2

*1 Hepatocyte vacuolation was not observed at Week 12, but was observed at Week 24.
*2 The number of animals found dead or sacrificed moribund excluding deaths considered related to blood sampling procedure or incidental
*3 The severity of the finding was minimal in the saline and 1.33×10^{14} vg/kg groups and moderate to severe in the 4.02×10^{14} vg/kg group.
*4 Vehicle (20 mmol/L trometamol, 1 mmol/L sodium chloride, and 0.001% poloxamer 188) was administered.
*5 There were no differences in the incidence or severity of the finding among the treatment groups. Brain ventricles were not evaluated in the 2.0×10^{14} vg/kg group.

5.2 Other safety evaluation

5.2.1 Potential chromosomal integration

Table 15 shows the results of evaluation of vector integration in liver tissues from cynomolgus monkeys treated with Elevidys surrogate,[9)] which showed the random distribution and low frequency of insertion mutations and general lack of proximity to cancer-associated genes.

[9)] Like Elevidys, the surrogate product contains a recombinant AAVrh74 capsid and ITRs. Meanwhile, the surrogate product carries a GFP gene, instead of the micro-dystrophin gene, and a CMV promoter, instead of the MHCK7 promoter.

Table 15. Evaluation of vector integration in liver tissues

Test system	Test method	Results	Attached document
Cynomolgus monkey	Elevidys surrogate was administered intravenously at 1.33×10^{14} vg/kg, and liver tissues were collected from 5 monkeys 12 weeks later. Vector integration site analysis was performed on the liver tissues, using TES.	• Integration sites were random, and the frequency of each integration site was low (The highest relative contribution was 0.166%). • As to the frequencies of integration sites in proximity to cancer-associated genes, the highest relative contribution was found for *EXT2*, *FLT4*, and *MAP2K1*, each constituting 0.13%.	4.2.3.3.1-1 (Reference data)

The applicant's explanation:

In addition to the study results in Table 15, though the wild-type AAV can insert its genome at a specific site in human chromosome 19, Elevidys lacks the *rep* gene encoding the Rep proteins, which are involved in genome integration [see Section 2], and does not carry integration machinery. Thus, the risk of integration of Elevidys into the host genome should be low.

5.2.2 Tumorigenic and carcinogenic potential

The applicant's explanation:

The risk of tumorigenesis and carcinogenesis associated with the use of Elevidys should be low, based on the following points:

- The risk of integration of Elevidys into the host genome is considered low [see Section 5.2.1].
- Since dystrophin is unlikely to contribute to tumor formation, the risk of tumorigenicity/carcinogenicity associated with the expression of micro-dystrophin that retains only the essential functional domains of the human dystrophin protein [see Section 2] should be low.
- Although wild-type AAV2 integrations occurred in proximity to known cancer driver genes in multiple cases with human hepatocellular carcinomas (*Nat Genet*. 2015; 47: 1187-93), at present, there is no report that recombinant AAVrh74 vectors are associated with tumorigenicity in humans.

5.2.3 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted with Elevidys.

5.2.4 Safety assessment of process-related impurities

The applicant's explanation:

The process-related impurities in Elevidys [see Section 2.1.6.3] were present also in the test article used in toxicity studies. Given the specification limits for impurities established for the test article used in toxicity studies and the impurity levels in the commercial product, the safety of the process-related impurities has been assessed in toxicity studies of Elevidys. The process-related impurities are adequately reduced by the manufacturing process. Thus, the process-related impurities in Elevidys pose little safety concern in the clinical use of Elevidys.

5.2.5 Safety assessment of excipients

The applicant's explanation about the safety of the excipients of the product, i.e., sodium chloride, trometamol,

tromethamol hydrochloride, magnesium chloride hexahydrate, and poloxamer 188:
Given that these excipients have been used in the approved pharmaceutical products in Japan, etc., there are no safety concerns about the clinical use of Elevidys.

5.R Outline of the Review Conducted by PMDA

Based on the presented data and the following considerations, PMDA concluded that there are no particular concerns about the non-clinical safety of Elevidys.

5.R.1 Hepatotoxicity

Since hepatotoxicity due to an immune response to an AAV capsid is known with an AAV vector product approved in Japan, i.e., onasemnogene abeparvovec (Review Report on Zolgensma Intravenous Infusion as of February 7, 2020), PMDA asked the applicant to explain if the liver findings observed in mice treated with Elevidys are indicative of hepatotoxicity and explain about the safety of Elevidys in humans.

The applicant's explanation:
Given the following considerations and the safety information from clinical studies of Elevidys [see Section 7], the possibility of acute liver injury associated with Elevidys cannot be excluded. Thus, a precautionary statement about acute liver injury will be included in the package insert.

- Liver toxicity induced by systemic administration of high-dose recombinant AAV is known and may be mediated by recombinant AAV vector DNA overload per hepatocyte, toxic transgene overexpression, immune responses against recombinant AAV components, etc. (*Toxicol Pathol*. 2022; 50: 118-46).
- The liver findings in mice treated with Elevidys are considered inflammatory reactions and associated adaptative changes after Elevidys administration.
- Given the following points, histopathological changes or changes in liver injury markers such as liver enzyme levels associated with the function of the expressed protein, and hepatotoxicity due to an immune response are unlikely to occur following administration of Elevidys in humans, but the possibilities of these effects cannot be excluded.
  - In a pharmacology study in DMD^{MDX} mice [see Section 3.1], micro-dystrophin expression was detected at low levels in the liver following administration of Elevidys.
  - Micro-dystrophin protein expressed by Elevidys is highly homologous to endogenous human dystrophin protein. The possibility that a part of micro-dystrophin that is different from endogenous dystrophin is recognized as an epitope cannot be excluded.

PMDA accepted the applicant's explanation. Hepatotoxicity of Elevidys will be discussed also in the clinical section.

5.R.2 The risk of reproductive and developmental toxicity in male patients with DMD treated with Elevidys

The applicant's explanation:

Given the following points, the risk of germline integration and the risk of affecting the offspring are low when Elevidys is administered to male DMD patients.

- The risk of integration of Elevidys into the host genome should be low [see Section 5.2.1].
- In a single intravenous dose toxicity study in male mice (a 12-week or 24-week observation period), Elevidys gDNA was detected in the testicular tissues of mice at Weeks 12 and 24 (Table 13), but at lower levels than in the liver, heart, adrenal gland, and skeletal muscle. Elevidys gDNA levels in testicular tissues tended to be lower at Week 24 than at Week 12. These findings indicate that Elevidys gDNA is distributed to the testis at low levels and declines over time.
- According to the following study results, Elevidys was distributed to the interstitial space only and was not distributed to the germ cells including spermatogonia.
  - In a single intravenous dose toxicity study in male and female juvenile mice (Table 14), *in situ* hybridization was performed on the testes of mice at approximately 70 days after Elevidys administration to evaluate the micro-dystrophin transgene and AAV vector genome mRNA. The micro-dystrophin transgene and AAV vector genome mRNA was detected in the interstitial space of the testis.
  - In a pharmacology study of Elevidys in male mice (CTD4.2.1.1-2, Reference data), *in situ* hybridization was performed on the testicular tissues from DMD^{MDX} mice at 12 weeks after a single intravenous administration of up to 4.01×10^{14} vg/kg of Elevidys to evaluate the micro-dystrophin transgene and AAV vector genome mRNA. The micro-dystrophin transgene and AAV vector genome mRNA was detected in the interstitial space of the testis and was considered to be distributed to the vascular endothelial and Leydig cells.

Since Elevidys was distributed to the testis [see Section 4.2.1], and the micro-dystrophin transgene and AAV vector genome mRNA was detected in the interstitial space of the testis, PMDA asked the applicant to explain about the effect of Elevidys on male fertility.

The applicant's response:

Based on the following points, there is little concern about the effect of Elevidys on fertility.

- In a single intravenous dose toxicity study in male mice and a single intravenous dose toxicity study in male and female juvenile mice, histopathological examination revealed no Elevidys-related abnormalities in male reproductive organs [see Section 5.1].
- In a study using an AAV vector containing an AAVrh74 capsid, an MHCK7 promoter, and [redacted], which are the same as those of Elevidys, and [redacted] and a gene, which are different from those of Elevidys, male mice treated with the AAV vector or saline as a control were mated with untreated female mice. There were no differences in the number of pregnant females.
- AAV vector genome was detected in the testes of male mice dosed with valoctocogene roxaparvovec

(Roctavian) containing an AAV5 capsid. In a study in which these male mice were bred with naïve females, there were no effects on fertility parameters such as the number of pups born per mating (*Gene Ther.* 2023; 30: 581-6).

PMDA's conclusion:

As to effects on the offspring, although complete elimination of Elevidys from gonadal tissue was not achieved during the observation period of a single intravenous dose toxicity study in male mice (a 12-week or 24-week observation period), given its quantities distributed and declining trend, detection of Elevidys in gonadal tissue should be transient, and after its clearance, Elevidys is unlikely to affect the offspring via germline integration. Thus, taking into account that the target population for Elevidys is DMD patients aged 3 to <8 years, the risk of affecting the offspring and exposure through semen should be low in the clinical use of Elevidys. However, information on Elevidys dissemination to the testis should be provided, and if the age limit for Elevidys therapy is changed in future, a precautionary statement including contraception requirements in the package insert should be considered. Based on the applicant's explanation, the risk of affecting male fertility should be low.

6. Clinical Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted the results from Studies 103 and 301 etc. as the data on the clinical biological disposition of Elevidys.

6.1 Analytical methods

Elevidys gDNA in skeletal muscle, serum, saliva, urine, and feces was quantified using ddPCR. The lower limits of quantification (LLOQs) in the samples in each study are shown in Table 16.

Table 16. LLOQs in samples in each study

	Study 103	Study 301
Skeletal muscle	25.0 vg/μL	25.0 vg/μL
Serum	4.5 vg/μL	2.4 vg/μL
Saliva	25.0 vg/μL	−
Urine	25.0 vg/μL	−
Feces	25.0 vg/μL	−

Table 17 shows the assay method, assay sensitivity, and threshold for assay positivity for anti-AAVrh74 capsid antibodies, anti-micro-dystrophin antibodies, or interferon-gamma (IFN-γ) in each study. The IFNγ enzyme-linked immunosorbent spot (ELISpot) assay was performed for the immune response against AAVrh74 capsid or micro-dystrophin in peripheral blood mononuclear cells (PBMCs).

Table 17. Assay method, assay sensitivity, and threshold for assay positivity for anti-AAVrh74 capsid antibodies, anti-micro-dystrophin antibodies, or IFN-γ in Studies 103 and 301

	Assay method	Assay sensitivity	Threshold for assay positivity
Anti-AAVrh74 capsid antibodies	ELISA	−	1:400*
Anti-micro-dystrophin antibodies	ECLIA	77.9 ng/mL	1.36
IFN-γ	ELISpot	≥3 Spot Forming Unit	10 Spot Forming Unit/4.00 × 10^5 PBMCs

* Samples with an OD value of ≥0.043 at >1:400 dilution were considered positive.

6.2 Clinical biological disposition

Table 18 shows the dosing regimen, samples, and sampling time points in Studies 103 and 301. In Study 103, Elevidys gDNA levels in serum and shedding were evaluated in Cohorts 1 to 4 only.

Table 18. Samples, dosing regimen, and sampling time points in each study

Study ID	Dosing regimen	Samples	Sampling time points
Study 103	Body weight <70 kg: Elevidys 1.33×10^{14} vg/kg administered by single IV infusion Body weight ≥70 kg: Elevidys 9.31×10^{15} vg (fixed dose) by single IV infusion	Skeletal muscle Serum Saliva Urine Feces	[Elevidys gDNA] Skeletal muscle: Quantified at baseline and Week 12. Serum: The day of administration (Day 1), Day 2, and Weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 24, 36, and 52 Saliva, urine, and feces: Day 1, Day 2, and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 36, 52, 78, and 104 (quantified until 3 consecutive samples below LLOQ) [Immune response] Anti-AAVrh74 capsid antibodies: Screening, Day 2, and Weeks 1, 2, 4, 8, 10, 12, 24, 52, and 104 Anti-micro-dystrophin antibodies: Screening, Day 2, and Weeks 1, 2, 4, 8, 10, 12, 24, 52, and 104 IFN-γ: Baseline, Day 2, and Weeks 1, 2, 4, 8, 10, 12, 24, 52, and 104
Study 301	[Part 1] Elevidys 1.33×10^{14} vg/kg or placebo administered by single IV infusion	Skeletal muscle Serum	[Elevidys gDNA] Skeletal muscle: Quantified at Week 12. Serum: Day 1 and Weeks 4, 8, and 12 [Immune response] Anti-AAVrh74 capsid antibodies: Screening and Weeks 2, 4, 8, 12, 24, and 52 Anti-micro-dystrophin antibodies: Baseline and Weeks 2, 4, 8, 12, 24, and 52 IFN-γ: Baseline and Weeks 1, 2, 4, 8, 12, 24, and 52

6.2.1 Elevidys gDNA levels in serum

6.2.1.1 Elevidys gDNA levels in serum in Study 103

Elevidys gDNA levels in serum were evaluated in patients in Cohorts 1 to 4 of Study 103. Table 19 shows the maximum concentration, the time to the maximum concentration, and the time to achieve clearance for Elevidys gDNA in serum in patients in each cohort (20 in Cohort 1, 6 in Cohort 2, 6 in Cohort 3, 7 in Cohort 4), and the level of Elevidys gDNA in serum showed a biphasic disposition characterized by a rapid distribution phase of up to 10 days post-dose followed by a slow and flat terminal elimination phase.

Table 19. Biological disposition of Elevidys gDNA in serum in Study 103 (Data cutoff date of July 24, 2023)

	Cohort 1 (N = 20)	Cohort 2 (N = 6)	Cohort 3 (N = 6)	Cohort 4 (N = 7)
Maximum concentration (vg/L)[*1]	$0.561 \times 10^{14} \pm 0.101 \times 10^{14}$	$0.949 \times 10^{14} \pm 0.153 \times 10^{14}$	$1.53 \times 10^{14} \pm 0.295 \times 10^{14}$	$1.03 \times 10^{14} \pm 0.291 \times 10^{14}$
	0.560×10^{14} (0.415×10^{14}, 0.827×10^{14})	0.897×10^{14} (0.774×10^{14}, 1.18×10^{14})	1.56×10^{14} (1.08×10^{14}, 1.86×10^{14})	1.17×10^{14} (0.617×10^{14}, 1.34×10^{14})
Time to maximum concentration (h)[*1]	2.4 ± 0.00	2.56 ± 0.291	3.03 ± 0.705	1.38 ± 0.228
	2.4 (2.4, 2.4)	2.4 (2.4, 3.12)	2.88 (2.4, 3.8)	1.3 (1.27, 1.9)
Time to achieve clearance (days)[2]	85.0 (57.0, 253)	41.0 (22.0, 107)	80.5 (23.0, 191)	41.0 (14.0, 369)

*1 Upper row, Mean ± SD; Lower row, Median (Min., Max.)

*2 Median (Min., Max.)

6.2.1.2 Elevidys gDNA levels in serum in Study 301

Elevidys gDNA levels in serum were evaluated in 64 patients including 3 Japanese patients in Study 301. Table 20 shows the maximum concentration, the time to the maximum concentration, and the time to achieve clearance for Elevidys gDNA in serum. There was no trend towards major differences in Elevidys gDNA levels in serum between the 3 Japanese patients and non-Japanese patients, though the results should be interpreted with care due to the limited numbers of patients and sampling time points.

Table 20. Biological disposition of Elevidys gDNA in serum in Study 301 (Data cutoff date of September 13, 2023)

	Study 301 (n = 59)[*1]
Maximum concentration (vg/L)[*2]	$1.45 \times 10^{14} \pm 0.733 \times 10^{14}$
	1.36×10^{14} (4.12×10^{8}, 6.14×10^{14})
Time to maximum concentration (days)[*2]	0.176 ± 0.0156
	0.172 (0.127, 0.234)
Time to achieve clearance (days)[*3]	85.0 (1.00, 106) (n = 64)

*1 Patients without Elevidys gDNA levels in serum on Day 1 were excluded from the analysis.

*2 Upper row, Mean ± SD; Lower row, Median (Min., Max.)

*3 Median (Min., Max.)

6.2.2 Elevidys gDNA levels in skeletal muscle

6.2.2.1 Elevidys gDNA levels in skeletal muscle in Study 103

Elevidys gDNA levels (vg/nucleus levels) in skeletal muscle were measured in patients in Cohorts 1 to 5 of Study 103. Elevidys gDNA was not detected at baseline, and the results at Week 12 are shown in Table 21.

Table 21. Elevidys gDNA levels in skeletal muscle at Week 12 in Study 103 (Data cutoff date of July 24, 2023)

	Cohort 1 (N = 20)	Cohort 2 (N = 6)	Cohort 3 (N = 6)	Cohort 4 (N = 7)	Cohort 5a (N = 6)	Cohort 5b (N = 2)
Mean ± SD	3.44 ± 2.38	1.61 ± 0.53	2.76 ± 1.08	3.00 ± 1.33	2.49 ± 1.34	2.41 ± 0.07
Median (Min., Max.)	2.72 (0.74, 9.77)	1.57 (0.94, 2.35)	2.79 (1.59, 4.62)	3.52 (1.11, 4.76)	2.36 (0.47, 4.33)	2.41 (2.36, 2.47)

Unit: vg/nucleus

6.2.2.2 Elevidys gDNA levels in skeletal muscle in Study 301

Elevidys gDNA levels (vg/nucleus levels) in skeletal muscle were measured using ddPCR in 17 patients in the Elevidys group and 14 patients in the placebo group with muscle biopsy samples in Part 1 of Study 301. The

results at Week 12 are shown in Table 22.

Table 22. Elevidys gDNA levels in skeletal muscle at Week 12 in Study 301 (Data cutoff date of September 13, 2023)

	Elevidys (N = 17)	Placebo (N = 14)
Mean ± SD	2.26 ± 1.55	0.00
Median (Min., Max.)	1.77 (0.77, 6.92)	0.00 (0.00, 0.00)

Unit: vg/nucleus

6.3 Shedding

6.3.1 Shedding in Study 103

Elevidys gDNA in saliva, urine, and feces from patients in Cohorts 1 to 4 of Study 103 was quantified through Week 104 until complete elimination[10)] was achieved, and Elevidys shedding was evaluated.

At Week 4, Elevidys gDNA levels in saliva, urine, and feces decreased to <0.5% of the peak levels (8.17×10^7 vg/mL in saliva, 2.75×10^6 vg/mL in urine, 1.04×10^8 vg/μg in feces). The results until complete elimination was achieved in each sample are shown in Table 23.

Table 23. Time to achieve complete elimination of Elevidys gDNA in saliva, urine, and feces in Study 103 (Data cutoff date of July 24, 2023)

	Time to achieve complete elimination (weeks)
Saliva[*1]	10.02 ± 8.61
	7.29 (4.1, 51.1)
Urine[*2]	14.16 ± 11.53
	11.00 (2.3, 37.1)
Feces[*3]	27.18 ± 11.02
	25.07 (6.3, 52.4)

Upper row, Mean ± SD; Lower row, Median (Min., Max.)

*1 n = 20 in Cohort 1, n = 7 in Cohort 2, n = 6 in Cohort 3, n = 5 in Cohort 4

*2 n = 20 in Cohort 1, n = 7 in Cohort 2, n = 6 in Cohort 3, n = 7 in Cohort 4

*3 n = 14 in Cohort 1, n = 7 in Cohort 2, n = 5 in Cohort 3, n = 7 in Cohort 4

6.4 Immune response associated with Elevidys administration

The results of evaluation of immune response to Elevidys are shown below.

- Anti-AAVrh74 capsid antibodies

  In Cohorts 1 to 3 of Study 103, 16 of 32 patients tested positive, and the remaining 16 patients tested negative at Week 1. All of 7 patients in Cohort 4 tested negative. In Cohort 5, 4 of 8 patients tested positive, and the 4 patients tested negative. At Week 2, 46 of the 47 patients in Cohorts 1 to 5 tested positive. As shown in Figure 1, there was no impact of anti-AAVrh74 capsid antibodies at Week 1 on Elevidys gDNA concentration-time profiles in serum in Cohorts 1 to 3.

  In Study 301, all of 63 patients tested positive at Week 2. In patients in Cohort 1 of Study 103 and patients in Part 1 of Study 301, anti-AAVrh74 capsid antibodies detected after Elevidys administration

[10)] Complete elimination was defined as 3 consecutive samples below LLOQ after Elevidys administration.

reached peak levels at Week 10. The antibody titers persisted through Week 104 in Study 103.

- Anti-micro-dystrophin antibodies

  In Cohorts 1 to 5 of Study 103, the proportion of anti-micro-dystrophin antibody-positive patients increased from Week 4 to Week 8, reaching 56.2% at Week 12, which persisted even at Week 104. In Part 1 of Study 301, the proportion of anti-micro-dystrophin antibody-positive patients was highest at 42.9% at Week 12, which persisted even at Week 52.

- IFN-γ production

  The proportion of patients with positive ELISpot results (IFN-γ released in response to the stimulation of PBMCs with AAVrh74 capsid) was highest at Week 4 in Study 103 and at Weeks 4 and 52 in Study 301. In both studies, T-cell mediated cellular immune responses against AAVrh74 capsid persisted throughout the follow-up period.

  The proportion of patients with positive ELISpot results (IFN-γ released in response to the stimulation of PBMCs with micro-dystrophin) was highest at Weeks 8 to 12 in Study 103 and at Weeks 8 and 24 in Study 301. In both studies, T-cell mediated cellular immune responses against micro-dystrophin persisted throughout the follow-up period. In Study 103, the frequency of IFN-γ producing PBMCs tended to be high in patients with immune-mediated myositis.

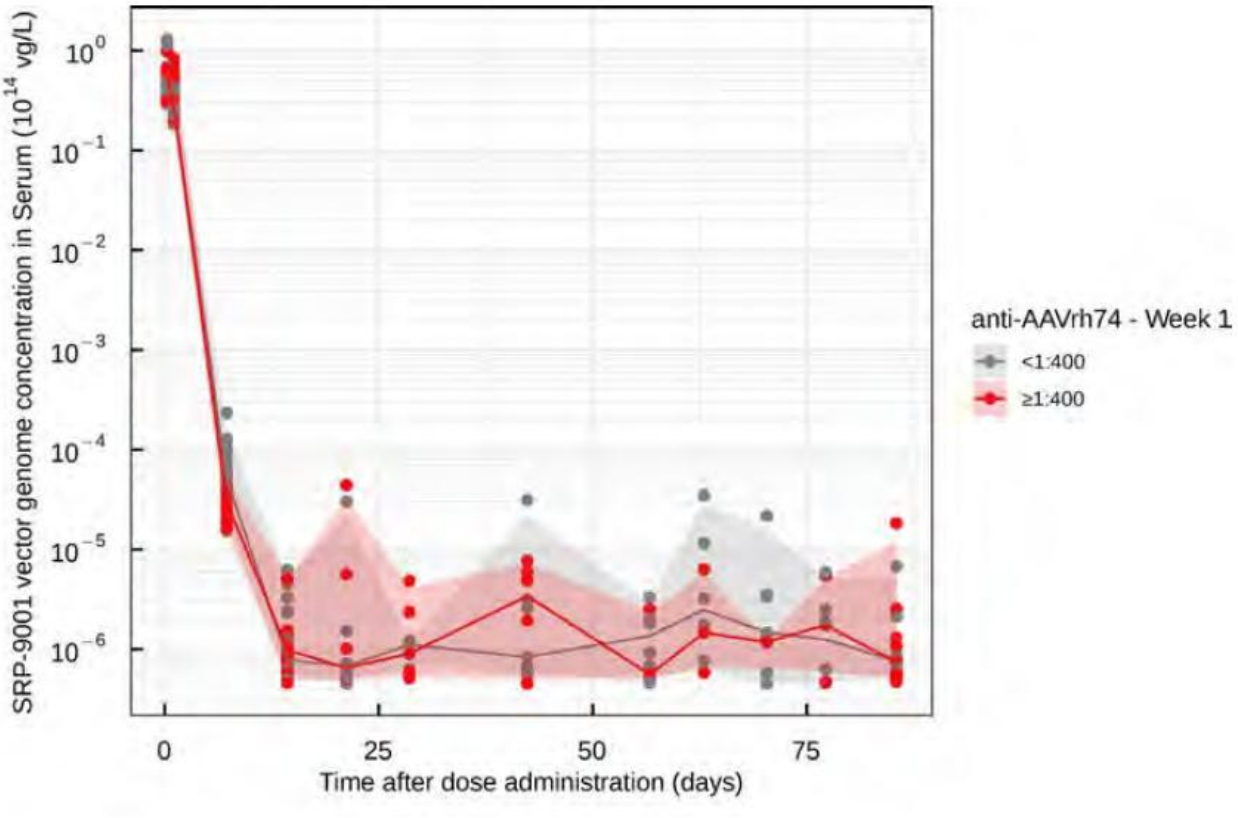

Figure 1. Elevidys gDNA concentration-time profiles in serum by anti-AAVrh74 capsid antibody status at Week 1 in Cohorts 1-3 of Study 103

6.R Outline of the Review Conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there are no particular concerns about the clinical biological disposition of Elevidys.

6.R.1 Clinical biological disposition of Elevidys and immune response

The applicant's explanation about the clinical biological disposition of Elevidys and evaluation of immune response:

- Biological disposition and shedding

  The estimated half-life of Elevidys in serum is approximately 12 hours, and the majority of Elevidys is expected to be cleared from the serum by 1-week post-dose. Elevidys gDNA levels were lower in saliva, urine, and feces than in serum. In all cohorts of Study 103, shedding was decreased to <0.5% of the peak level at Week 4. Furthermore, the distribution of Elevidys to target muscle tissues was observed at Week 12. Given these findings, following intravenous administration, Elevidys is considered to undergo rapid distribution via the systemic circulation and widely distributes into muscle tissues followed by elimination in urine and feces. Although vector shedding in the excreta of patients treated with Elevidys and an exposure to the patient's blood or the infusion solution after a needle stick injury may lead to unintended exposure of third parties, as the amount of shed vector is small, this is very unlikely to become a clinically relevant problem.

- Biological disposition and shedding in Japanese patients

  There was no trend towards major differences in Elevidys gDNA concentration-time profiles in serum between 3 Japanese patients and non-Japanese patients. For the following reasons, Elevidys gDNA levels in serum, Elevidys exposure in skeletal muscle, and shedding in saliva, urine, and feces in the Japanese population are unlikely to differ from those in the non-Japanese population.

  - Elevidys is not a substrate of the known drug-metabolizing enzymes or transporters.
  - The amino acid sequence of AAVrh74 shows the highest homology to AAV8, and AAV8 binds a cell-surface receptor, the 37/67-kDa laminin receptor. There is no report that there are racial differences in the expression level and polymorphism of this receptor.
  - There is no report that there are racial differences in the glomerular pores, glomerular membrane charge, and the renal function.

- Immune response associated with Elevidys administration

  Given that there were no clear differences in Elevidys gDNA concentration-time profiles in serum according to anti-AAVrh74 capsid antibody status at Week 1, immune response associated with Elevidys administration had no clear impact on Elevidys levels in serum.

  PMDA accepted the applicant's explanation. Since the immune response to micro-dystrophin protein expressed by Elevidys is considered associated with the risk of immune-mediated myositis, this risk will be discussed also in the clinical section.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 4 clinical studies presented in Table 24.

Table 24. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Foreign	101	I/IIa	Ambulatory patients with DMD aged 4 to <8 years	4	Elevidys 2×10^{14} vg/kg[*1] by single IV infusion	Safety Efficacy
	Foreign	102	II	Ambulatory patients with DMD aged 4 to <8 years	41	[Part 1] Elevidys 2×10^{14} vg/kg[*2] or placebo by single IV infusion [Part 2] Placebo group in Part 1: Elevidys 1.33×10^{14} vg/kg by single IV infusion Elevidys group in Part 1: Placebo by single IV infusion	Efficacy Safety
	Foreign	103	Ib	Cohort 1: Ambulatory patients with DMD aged 4 to <8 years Cohort 2: Ambulatory patients with DMD aged 8 to <18 years Cohort 3: Non-ambulatory patients with DMD Cohort 4: Ambulatory patients with DMD aged 3 to <4 years Cohort 5: The following DMD patients with mutations in exons 1-17 Cohort 5a: Ambulatory patients with DMD aged 4 to <9 years Cohort 5b: Non-ambulatory patients with DMD	Cohort 1: 20 Cohort 2: 7 Cohort 3: 6 Cohort 4: 7 Cohort 5: 8 (5a: 6, 5b: 2)	Body weight <70 kg: Elevidys 1.33×10^{14} vg/kg by single IV infusion Body weight ≥70 kg: Elevidys 9.31×10^{15} vg (fixed dose) by single IV infusion	Efficacy Safety
	Global	301	III	Ambulatory patients with DMD aged 4 to <8 years	131	[Part 1] Elevidys 1.33×10^{14} vg/kg or placebo by single IV infusion [Part 2] Placebo group in Part 1: Elevidys 1.33×10^{14} vg/kg by single IV infusion Elevidys group in Part 1: Placebo by single IV infusion	Efficacy Safety

*1 The dose as determined by a qPCR method using a supercoiled standard, which was used at the timing of conducting the clinical study. Then, a qPCR method using a linear standard was established, and the batches used in the clinical study were retrospectively reanalyzed by linear standard qPCR, which ascertained that a dose amount of 1.33×10^{14} vg/kg had been administered in the study.

*2: The dose as determined by supercoiled standard qPCR, which was used at the time of conducting the clinical study. Then, linear standard qPCR was established, and 3 batches used in the clinical study were retrospectively reanalyzed by linear standard qPCR, which ascertained that 3 different dose amounts (6.29×10^{13} vg/kg [N = 6], 8.94×10^{13} vg/kg [N = 6], 1.33×10^{14} vg/kg [N = 8]) had been administered in Part 1.

7.1 Evaluation data

7.1.1 Foreign clinical studies

7.1.1.1 Foreign phase I/IIa study (CTD 5.3.5.2-1, 5.3.5.2-2, Study 101 [November 2017 to April 2023])

An open-label, uncontrolled study was conducted at 1 site in the US to evaluate the safety and efficacy of Elevidys in non-Japanese male patients with DMD (target sample size, 12 subjects).

Table 25 shows the main inclusion and exclusion criteria.

Table 25. Main inclusion and exclusion criteria

Inclusion criteria	• Male patients with DMD aged 4 to <8 years • Frameshift (deletion or duplication), or premature stop codon mutation between exons 18 to 58 in the *DMD* gene • CK elevation >1,000 U/L and below-average 100-meter walk/run defined as ≤80% predicted • Stable dose equivalent of oral corticosteroids for ≥12 weeks prior to screening, with the dose expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the first year of the study
Exclusion criteria	• Signs of cardiomyopathy, including echocardiogram with left ventricular ejection fraction <40% • Has received any investigational medication (other than corticosteroids) or exon skipping medications in the last 6 months prior to screening • Has had gene therapy, cell-based therapy, or CRISPR/Cas9 • AAVrh74 or AAV8 antibody titers >1:400 as determined by ELISA

The study consisted of a pre-infusion period (60 days to 2 days prior to the Day 1 infusion), a treatment period (the day of Elevidys infusion and the day before and after the Day 1 infusion) and a follow-up period (60 months post-treatment). This study was originally designed to enroll a total 12 subjects, in 2 cohorts: 6 subjects in Cohort B (4 to <8 years of age), followed by 6 subjects in Cohort A (3 months to <4 years of age). However, after 4 subjects were enrolled in Cohort B, Study 102 with similar inclusion criteria was initiated. Thus, further enrollment in the study was stopped.

Elevidys 2×10^{14} vg/kg (as determined by supercoiled standard qPCR. The dose was found to be equivalent to 1.33×10^{14} vg/kg based on linear standard qPCR.) was to be administered as a single intravenous infusion. One day prior to Elevidys infusion, subjects were to begin receiving corticosteroid 1 mg/kg/day in addition to their continued baseline[11)] prednisolone dose, which was to be continued for ≥30 days post-treatment.

All of 4 subjects enrolled in the study received Elevidys and were included in the full analysis set (FAS). The FAS was used as the safety population and the efficacy population.

Regarding efficacy, Table 26 shows the change in micro-dystrophin expression (Western blot, immunofluorescence [IF] fiber intensity, percent dystrophin-positive fibers as measured by immunofluorescence staining) from baseline[11)] to Day 90.

[11)] At screening during the pre-infusion period

Table 26. Change in micro-dystrophin expression from baseline to Day 90[*1] (Study 101, FAS)

Subject Number	Western blot[*2]	IF fiber intensity[*3]	Percent dystrophin-positive fibers as measured by immunofluorescence staining[*4]
Subject A	38.76	79.84	78.03
Subject B	13.50	58.76	73.45
Subject C	47.18	77.95	77.07
Subject D	182.63	157.82	96.19
Mean ± SD	70.52 ± 76.10	93.59 ± 43.86	81.18 ± 10.19
Median (Range)	42.97 (13.50, 182.63)	78.90 (58.77, 157.82)	77.55 (73.45, 96.19)

*1 Measured value at Day 90 (%) − baseline value (%)

*2 Percentage of normal dystrophin expression level (muscle biopsy samples from enrolled patients vs. non-DMD control muscle biopsy samples) (%)

*3 Percentage of normal dystrophin protein IF intensity (muscle biopsy samples from enrolled patients vs. non-DMD control muscle biopsy samples) (%)

*4 Percentage of dystrophin-positive fibers in muscle fibers (dystrophin-positive and dystrophin-negative fibers) after immunofluorescence staining of dystrophin protein (%)

As to motor function endpoints, the changes in the North Star Ambulatory Assessment (NSAA) total score,[12] time to rise from the floor (seconds), time of 10-meter walk/run (seconds), time of 100-meter walk/run (seconds), and time to ascend 4 steps (seconds) from baseline to Year 5 (mean ± SD) are shown in Table 27.

Table 27. Changes in motor function endpoints from baseline to Year 5 (Study 101, FAS)

	Elevidys (N = 4)				
	NSAA total score	Time to rise from the floor (seconds)	Time of 10-meter walk/run (seconds)	Time of 100-meter walk/run (seconds)	Time to ascend 4 steps (seconds)
Baseline	20.5 ± 3.70	3.68 ± 0.48	4.89 ± 0.48	56.40 ± 8.54	3.47 ± 1.20
	19.0 [18, 26]	3.80 [3.0, 4.1]	4.90 [4.33, 5.43]	54.55 [49.3, 67.2]	3.59 [1.90, 4.80]
Change at Year 1	5.5 ± 2.65	−0.35 ± 0.82	−0.68 ± 0.69	−9.05 ± 9.84	−1.27 ± 1.12
	6.0 [2, 8]	−0.15 [−1.5, 0.4]	−0.76 [−1.30, 0.10]	−5.10 [−23.6, −2.4]	−1.09 [−2.80, −0.10]
Change at Year 2	7.0 ± 2.31	−0.17 ± 0.81*	−0.71 ± 0.72*	−8.33 ± 0.74*	−0.76 ± 0.96*
	7.0 [5, 9]	0.20* [−1.1, 0.4]	−0.53* [−1.50, −0.10]	−8.60* [−8.9, −7.5]	−1.03* [−1.55, 0.31]
Change at Year 3	7.5 ± 3.42	−0.10 ± 0.74	−0.77 ± 0.72	−10.30 ± 6.30*	−1.14 ± 1.36*
	7.0 [4, 12]	0.05 [−1.1, 0.6]	−0.82 [−1.53, 0.10]	−10.50* [−16.5, −3.9]	−0.93* [−2.60, 0.10]
Change at Year 4	7.0 ± 2.94	−0.07 ± 0.59	−0.34 ± 0.52	−6.95 ± 6.00	−1.07 ± 1.41
	6.5 [4, 11]	−0.15 [−0.7, 0.7]	−0.41 [−0.83, 0.30]	−7.10 [−13.5, −0.1]	−1.19 [−2.60, 0.70]
Change at Year 5	7.5 ± 2.38	1.08 ± 0.43	−0.34 ± 0.37	−4.02 ± 4.64	−0.82 ± 1.14
	7.5 [5, 10]	0.90 [0.8, 1.7]	−0.48 [−0.60, 0.20]	−2.90 [−10.6, 0.3]	−0.74 [−2.20, 0.40]

Upper row, Mean ± SD; Lower row, Median [Range]
*Results from 3 subjects

Regarding safety, adverse events occurred in all 4 subjects. The events reported by ≥2 subjects were vomiting; and upper respiratory tract infection (4 subjects each); hepatic enzyme increased (3 subjects); and gastrooesophageal reflux disease; fatigue; Covid-19; procedural pain; decreased appetite; and cough (2 subjects each). Adverse reactions occurred in 3 subjects (vomiting; and hepatic enzyme increased [3 subjects each]; decreased appetite [2 subjects]; and nausea; asthenia; and fatigue [1 subject each). There were no deaths or

[12] The NSAA is a functional rating scale developed to measure ambulatory performance in boys with DMD aged ≥4 years (*PLoS One*. 2019; 14: e0221097, *Neuromuscul Disord*. 2015; 25: 14-8). The NSAA scale is composed of 17 items and rates performance on various functional activities, such as standing and running. Each of the 17 items is scored from 0 to 2, and scores range from 0 to 34, with higher scores indicating better motor function.

serious adverse events.

7.1.1.2 Foreign phase II study (CTD 5.3.5.1-1, 5.3.5.1-2, and 5.3.5.1-3, Study 102 [December 2018 to August 2023])

A placebo-controlled, randomized, double-blind study was conducted at 2 sites in the US to evaluate the efficacy and safety of Elevidys in non-Japanese male patients with DMD (target sample size,[13] 44 subjects [22 per group]).

Table 28 shows the main inclusion and exclusion criteria.

Table 28. Main inclusion and exclusion criteria

Inclusion criteria	• Male patients with DMD aged 4 to <8 years • Frameshift (deletion or duplication), or premature stop codon mutation between exons 18 to 58 in the *DMD* gene • CK elevation >1,000 U/L and below-average 100-meter walk/run defined as <95% predicted • Stable dose equivalent of oral corticosteroids for ≥12 weeks prior to screening, with the dose expected to remain constant (except for potential modifications to accommodate changes in weight) throughout Part 1 and Part 2
Exclusion criteria	• Signs of cardiomyopathy, including echocardiogram with left ventricular ejection fraction <40% • Has received any investigational medication (other than corticosteroids) or exon skipping medications in the last 6 months prior to screening • Has had gene therapy, cell-based therapy, or CRISPR/Cas9 • AAVrh74 antibody titers >1:400 as determined by ELISA

The study consisted of a screening/baseline period (Week −4 to Day −2), Part 1 (Elevidys or placebo was administered, 48 weeks of follow-up), Part 2 (patients randomized to Elevidys in Part 1 crossed over to receive placebo, and patients randomized to placebo in Part 1 crossed over to receive Elevidys, 48 weeks of follow-up), and Part 3 (an open-label follow-up period, 212 weeks of follow-up).

At the start of Part 1, subjects were to receive a single intravenous infusion of Elevidys 2×10^{14} vg/kg (as determined by supercoiled standard qPCR) or placebo. Subsequent retrospective analysis using linear standard qPCR, which was established after the initiation of the study, ascertained that 3 different dose amounts (6.29×10^{13} vg/kg in 6 subjects, 8.94×10^{13} vg/kg in 6 subjects, 1.33×10^{14} vg/kg in 8 subjects) had been administered in Part 1. In Part 2, patients randomized to Elevidys in Part 1 were to cross over to receive a single intravenous infusion of placebo, and patients randomized to placebo in Part 1 were to cross over to receive a single intravenous infusion of Elevidys 1.33×10^{14} vg/kg (as determined by linear standard qPCR). For immunosuppression and the prevention of adverse events, one day prior to study drug infusion, subjects were to begin receiving corticosteroid 1 mg/kg/day (prednisone equivalent) for immunosuppression, in addition to their continued baseline[14] stable oral corticosteroid dose for the treatment of DMD, which was to be continued for ≥60 days[15] post-infusion, unless earlier tapering was judged by the study investigator to be in the patient's best interest.

[13] A total sample size of 44 (22 per group) was needed to provide approximately 90% power to detect a difference between the Elevidys and placebo groups in the change from baseline to Week 48 in the NSAA total score of 5 points (the primary endpoint), with a standard deviation of 5 in each treatment group, and a two-sided significance level of 5%.
[14] At screening during the screening/baseline period
[15] Before Protocol Amendment 5 (as of July 2, 2019), the increased dose was to be continued for ≥30 days.

Among 43 subjects who were enrolled in the study and randomized, 41 subjects (20 in the Elevidys group, 21 in the placebo group) after excluding 2 subjects who withdrew their consent (1 each in the Elevidys and placebo groups) received Elevidys or placebo in Part 1 and were included in the safety population and the intention-to-treat (ITT) population. The ITT population was used as the efficacy population. Thirty-nine subjects[16] (18 in the Elevidys group, 21 in the placebo group) who completed Part 1 entered Part 2, all of whom entered Part 3.

Regarding efficacy, the change in micro-dystrophin expression by Western blot from baseline to Week 12 (Part 1) was chosen as the primary biomarker endpoint, and the change in the NSAA total score from baseline to Week 48 (Part 1) was chosen as the primary motor function endpoint for this study. Multiplicity adjustment for hypothesis testing of 2 co-primary endpoints was conducted to control the overall type I error rate of the study at 5%.[17] The study plan did not specify the following point: Success of the study was to be concluded if both co-primary endpoints were statistically significant, or if one of the 2 co-primary endpoints was statistically significant after adjusting for multiplicity in hypothesis testing.

Table 29 shows the primary biomarker endpoint of the change in micro-dystrophin expression by Western blot from baseline to Week 12, and there was a statistically significant difference between the Elevidys and placebo groups.

Table 29. Change in micro-dystrophin expression[*1] from baseline to Week 12 (Part 1 of Study 102, ITT population, data cutoff date of January 19, 2021)

	Elevidys	Placebo
Baseline (%)	4.23 ± 6.83 (n = 20)	1.91 ± 1.28 (n = 21)
Change at Week 12 in Part 1[*2] (%)	23.82 ± 39.76 (n = 20)	0.14 ± 1.24 (n = 21)
P-value[*3]	<0.0001	

Mean ± SD

*1 Percentage of normal dystrophin expression level (muscle biopsy samples from enrolled patients vs. non-DMD control muscle biopsy samples) (%)

*2 Measured value at Week 12 (%) − baseline value (%)

*3 A re-randomization test using a two-sample Welch t-test as the test statistic. A two-sided significance level of 1%. For adjustment of multiplicity in hypothesis testing, see footnote 17).

The primary motor function endpoint was the change in the NSAA total score from baseline to Week 48 (Part 1), and the least-squares (LS) mean change difference between the Elevidys and placebo groups [95% CI] was 0.8 [−1.0, 2.7], which showed no statistically significant difference and failed to demonstrate the superiority of Elevidys over placebo (Table 30).

16) Two subjects in the Elevidys group discontinued the study due to adverse events.

17) A two-sided alpha of 1% and a two-sided alpha of 4% were allocated to the primary biomarker endpoint and the primary motor function endpoint, respectively. If one of the co-primary endpoints was statistically significant, the other co-primary endpoint was to be tested at a two-sided alpha of 5%.

Table 30. Change in NSAA total score from baseline to Week 48
(Part 1 of Study 102, ITT population, data cutoff date of January 19, 2021)

		Elevidys	Placebo
Baseline	Mean ± SD	19.8 ± 3.3 (n = 20)	22.6 ± 3.3 (n = 21)
	Range (Min., Max.)	(13, 26)	(15, 29)
Change at Week 48	Mean ± SD	1.6 ± 2.9 (n = 19)	1.0 ± 2.6 (n = 21)
	Range (Min., Max.)	(−3, 6)	(−4, 6)
LS mean treatment difference [95% CI] *P*-value*		0.8 [−1.0, 2.7] 0.3730	

* A two-sided significance level of 5%. A mixed model for repeated measures (MMRM) with treatment group, age group, visit, treatment group-by-visit interaction, baseline NSAA total score, and baseline NSAA total score-by-visit interaction as covariates. The MMRM model assumed an unstructured variance-covariance matrix. For multiplicity adjustment for hypothesis testing, see footnote 17).

As to secondary motor function endpoints, Table 31 shows the changes in the time to rise from the floor, time of 10-meter walk/run, time of 100-meter walk/run, and time to ascend 4 steps from baseline to Week 48 (Part 1).

Table 31. Changes in motor function endpoints from baseline to Week 48
(Part 1 of Study 102, ITT population, data cutoff date of January 19, 2021)

		Elevidys	Placebo
Time to rise from the floor (seconds)	Baseline	5.10 ± 2.17 (n = 20)	3.56 ± 0.65 (n = 21)
	Change at Week 48	−0.21 ± 1.13 (n = 19)	0.44 ± 0.91 (n = 21)
	LS mean treatment difference* [95% CI]	−0.50 [−1.22, 0.23]	
Time of 10-meter walk/run (seconds)	Baseline	5.35 ± 1.14 (n = 20)	4.83 ± 0.72 (n = 21)
	Change at Week 48	0.70 ± 1.16 (n = 19)	0.01 ± 0.69 (n = 21)
	LS mean treatment difference* [95% CI]	0.49 [−0.08, 1.06]	
Time of 100-meter walk/run (seconds)	Baseline	61.04 ± 12.71 (n = 20)	53.86 ± 8.30 (n = 21)
	Change at Week 48	8.67 ± 27.98 (n = 19)	2.49 ± 7.52 (n = 21)
	LS mean treatment difference* [95% CI]	−2.00 [−13.42, 9.43]	
Time to ascend 4 steps (seconds)	Baseline	3.69 ± 1.46 (n = 20)	3.10 ± 0.98 (n = 21)
	Change at Week 48	0.26 ± 1.35 (n = 19)	0.03 ± 0.87 (n = 21)
	LS mean treatment difference* [95% CI]	0.14 [−0.61, 0.90]	

Mean ± SD

* A mixed model for repeated measures (MMRM) with treatment group, age group, visit, treatment group-by-visit interaction, baseline value, and baseline value-by-visit interaction as covariates. The MMRM model assumed an unstructured variance-covariance matrix.

Regarding safety, in Part 1, adverse events occurred in 20 of 20 subjects (100%) in the Elevidys group and 21 of 21 subjects (100%) in the placebo group. Adverse reactions occurred in 17 of 20 subjects (85.0%) in the Elevidys group and 9 of 21 subjects (42.9%) in the placebo group. Adverse events reported by ≥20% of subjects in either group and adverse reactions reported by ≥10% of subjects in either group are shown in Table 32 and Table 33, respectively.

Table 32. Adverse events reported by ≥20% of subjects in either group
(Part 1 of Study 102, Safety population, data cutoff date of January 19, 2021)

	Elevidys (N = 20)	Placebo (N = 21)
Any adverse event	20 (100)	21 (100)
Vomiting	13 (65.0)	7 (33.3)
Upper respiratory tract infection	13 (65.0)	13 (61.9)
Cough	9 (45.0)	6 (28.6)
Ecchymosis	9 (45.0)	4 (19.0)
Viral infection	8 (40.0)	9 (42.9)
Decreased appetite	8 (40.0)	0
Nausea	7 (35.0)	2 (9.5)
Abdominal pain	5 (25.0)	2 (9.5)
Abdominal pain upper	5 (25.0)	4 (19.0)
Procedural pain	5 (25.0)	7 (33.3)
Gamma-glutamyltransferase increased	5 (25.0)	0
Arthralgia	5 (25.0)	1 (4.8)
Pain in extremity	5 (25.0)	5 (23.8)
Pyrexia	4 (20.0)	1 (4.8)
Skin abrasion	4 (20.0)	2 (9.5)
Headache	4 (20.0)	6 (28.6)
Rhinorrhoea	4 (20.0)	3 (14.3)

MedDRA ver.20.1
n (%)

Table 33. Adverse reactions reported by ≥10% of subjects in either group
(Part 1 of Study 102, Safety population, data cutoff date of January 19, 2021)

	Elevidys (N = 20)	Placebo (N = 21)
Any adverse reaction	17 (85.0)	9 (42.9)
Vomiting	12 (60.0)	4 (19.0)
Nausea	6 (30.0)	2 (9.5)
Decreased appetite	6 (30.0)	0
Gamma-glutamyltransferase increased	5 (25.0)	0
Abdominal pain	3 (15.0)	0
Abdominal pain upper	3 (15.0)	1 (4.8)
Blood bilirubin increased	2 (10.0)	0
Pain in extremity	2 (10.0)	1 (4.8)
Rhabdomyolysis	2 (10.0)	1 (4.8)

MedDRA ver.20.1
n (%)

There were no deaths. Serious adverse events occurred in 3 subjects in the Elevidys group (rhabdomyolysis; liver injury and rhabdomyolysis; and transaminases increased) and 2 subjects in the placebo group (rhabdomyolysis; and humerus fracture). All those events were classified as adverse reactions, except for 1 case (humerus fracture) in the placebo group.

During the entire period, adverse events occurred in 41 of 41 subjects (100%), and adverse reactions occurred in 37 of 41 subjects (90.2%). Adverse events and adverse reactions reported by ≥20% of subjects are shown in Table 34 and Table 35, respectively.

Table 34. Adverse events reported by ≥20% of subjects (Study 102, Entire period, Safety population)

	All subjects treated with Elevidys (N = 41)
Any adverse event	41 (100)
Upper respiratory tract infection	29 (70.7)
Vomiting	29 (70.7)
Decreased appetite	23 (56.1)
Pain in extremity	23 (56.1)
Procedural pain	20 (48.8)
COVID-19	19 (46.3)
Irritability	18 (43.9)
Nausea	18 (43.9)
Cough	16 (39.0)
Abdominal pain upper	15 (36.6)
Pyrexia	14 (34.1)
Injection site haemorrhage	13 (31.7)
Viral infection	13 (31.7)
Headache	12 (29.3)
Arthralgia	11 (26.8)
Diarrhoea	11 (26.8)
Gamma-glutamyltransferase increased	11 (26.8)
Ecchymosis	10 (24.4)
Gastroenteritis viral	10 (24.4)
Rhinorrhoea	10 (24.4)
Fatigue	9 (22.0)
Gastrooesophageal reflux disease	9 (22.0)

MedDRA ver.24.1
n (%)

Table 35. Adverse reactions reported by ≥20% of subjects (Study 102, Entire period, Safety population)

	All subjects treated with Elevidys (N = 41)
Any adverse reaction	37 (90.2)
Vomiting	28 (68.3)
Decreased appetite	21 (51.2)
Nausea	17 (41.5)
Abdominal pain upper	11 (26.8)
Gamma-glutamyltransferase increased	11 (26.8)

MedDRA ver.24.1
n (%)

There were no deaths. Serious adverse events occurred in 9 subjects (femur fracture [2 subjects]; rhabdomyolysis [2 subjects]; rhabdomyolysis and femur fracture; liver injury and rhabdomyolysis; transaminases increased; appendicitis; and humerus fracture), and those reported by 4 subjects (rhabdomyolysis [2 subjects]; liver injury and rhabdomyolysis; and transaminases increased) were classified as adverse reactions.

7.1.1.3 Foreign phase Ib study (CTD 5.3.5.2-3 and 5.3.5.2-4, Study 103 [November 2020 to data cutoff date of July 24, 2023])

An open-label, uncontrolled study was conducted at 5 sites in the US to evaluate the efficacy and safety of Elevidys in non-Japanese male patients with DMD (target sample size, 20 in Cohort 1, 6 each in Cohorts 2, 3, and 4, 6 in Cohort 5a, 2 in Cohort 5b).

Table 36 shows the main inclusion and exclusion criteria.

Table 36. Main inclusion and exclusion criteria

Inclusion criteria	• Cohort 1: Male ambulatory patients aged 4 to <8 years with an NSAA total score of >17 and ≤26 at screening • Cohort 2: Male ambulatory patients aged 8 to <18 years with an NSAA total score of 15-26 at screening • Cohort 3 and Cohort 5b: Male patients, non-ambulatory for a minimum of 9 months, with an NSAA total score of "0" and inability to perform the 10-meter walk/run at screening, and with a Performance Upper Limb (PUL) entry item score ≥2. Onset of loss of ambulation is defined as patient- or caregiver-reported age at continuous wheelchair use, approximated to the nearest month. • Cohort 4: Male ambulatory patients aged 3 to <4 years at screening • Cohort 5a: Male ambulatory patients aged 4 to <9 years with time to rise from the floor ≤7 seconds at screening • Cohorts 1-4: a definitive diagnosis of DMD prior to screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the *DMD* gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein. In Cohorts 2 and 4, patients with mutations in exons 1-17 (inclusive) are ineligible.* • Cohort 5: a definitive diagnosis of DMD prior to screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the *DMD* gene partially or fully contained between exons 1 to 17 (inclusive) that is expected to lead to absence of dystrophin protein. Patients with a deletion fully contained between exons 9-13 are ineligible. • Cohorts 1-3 and 5: Stable daily dose of oral corticosteroids for ≥12 weeks prior to screening, with the dose expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the study • Cohort 4: Patients who do not yet require use of chronic corticosteroids for treatment of DMD in the opinion of the investigator, and are not receiving corticosteroids at the time of screening • AAVrh74 antibody titers ≤1:400 as determined by ELISA
Exclusion criteria	• Cohorts 1-5: Echocardiogram with left ventricular ejection fraction <40%, or clinical signs and/or symptoms of cardiomyopathy • Cohorts 2, 3, and 5b: an FVC <50% of predicted at screening, and/or the need for nocturnal ventilatory support • Has had gene therapy, cell-based therapy, or CRISPR/Cas9 at any time • Use of human growth factor or vamorolone within 12 weeks of Day 1 • Any investigational medication or any treatment designed to increase dystrophin expression within 6 months of Day 1 • Abnormal laboratory values considered clinically significant: ➢ γ-glutamyl transferase (GGT) >2 × ULN ➢ Glutamate dehydrogenase (GLDH) >15 U/L ➢ Total bilirubin > ULN (Note; elevations in total bilirubin confirmed to be due to Gilbert' s syndrome are not exclusionary.) ➢ White blood cell count >18,500/μL ➢ Platelets ≤150,000/μL

*Before Protocol Amendment 5, patients with mutations in exons 1-17 (inclusive) were eligible in Cohorts 1-4. Protocol Amendment 5 made patients with mutations in exons 1-17 (inclusive) ineligible in Cohorts 2 and 4. Except for 1 patient in Cohort 2 enrolled per Protocol Amendment 5, patients in Cohorts 1-3 were enrolled before Protocol Amendment 5 (i.e., patients with mutations in exons 1-17 (inclusive) were eligible). All of 7 patients in Cohort 4 were enrolled per Protocol Amendment 5 that made patients with mutations in exons 1-17 (inclusive) ineligible.

The study consisted of screening and baseline periods (up to 31 days), Part 1 (Elevidys infusion, 12 weeks of follow-up), and Part 2 (a follow-up period, 144 weeks of follow-up).

Patients weighing <70 kg on Day 1 were to receive a single intravenous infusion of Elevidys 1.33×10^{14} vg/kg or patients weighing ≥70 kg on Day 1 were to receive a single intravenous infusion of Elevidys 9.31×10^{15} vg (both determined by linear standard qPCR). For immunosuppression and the prevention of adverse events, one day prior to Elevidys infusion, patients in Cohorts 1 to 3 and 5 were to begin receiving corticosteroid 1 mg/kg/day (prednisone equivalent) for immunosuppression, in addition to their continued baseline[18)] stable oral corticosteroid dose for the treatment of DMD, which was to be continued for ≥60 days post-treatment.

[18)] At screening during the screening and baseline periods

Patients in Cohort 4 who were not on oral corticosteroids for DMD at screening were to start corticosteroid 1.5 mg/kg/day (prednisone equivalent) 1 week prior to Elevidys infusion, and corticosteroid treatment was to continue for ≥60 days after Elevidys infusion.

All of 48 enrolled subjects (20 in Cohort 1, 7 in Cohort 2, 6 in Cohort 3, 7 in Cohort 4, 8 in Cohort 5) received Elevidys and were included in the safety population and the FAS. The FAS was used as the efficacy population. As of the data cutoff date of July 24, 2023, all patients in Cohorts 1 to 4 and 7 patients in Cohort 5 had completed Part 1.

The primary efficacy endpoint of the change in micro-dystrophin expression by Western blot from baseline to Week 12 is shown in Table 37.

Table 37. Change in micro-dystrophin expression[*1] from baseline to Week 12 (Part 1 of Study 103, FAS[*2])

	Cohort 1 (N = 20)	Cohort 2 (N = 7)	Cohort 3 (N = 6)	Cohort 4 (N = 7)	Cohort 5a (N = 6)	Cohort 5b (N = 2)
Baseline (%)	0	0	0	0	0	0
Change at Week 12[*3] (%)	54.21 ± 42.57	11.92 ± 4.21[*4]	45.53 ± 40.59	99.64 ± 51.97	22.82 ± 21.63	23.64 ± 6.93

Mean ± SD
*1 Percentage of normal dystrophin expression level (muscle biopsy samples from enrolled patients vs. non-DMD control muscle biopsy samples) (%)
*2 Cohorts 1-3, data cutoff date of April 6, 2022; Cohorts 4-5, data cutoff date of July 24, 2023
*3 Measured value at Week 12 (%) − baseline value (%)
*4 Results from 6 subjects

As to motor function endpoints, Table 38 shows the changes in the NSAA total score, time to rise from the floor, time of 10-meter walk/run, time of 100-meter walk/run, and time to ascend 4 steps from baseline to Week 104 in Cohorts 1, 2, and 4 of ambulatory patients.[19)]

Table 38. Changes in motor function endpoints from baseline to Week 104 (Study 103, FAS[*1])

		Cohort 1 (N = 20)	Cohort 2 (N = 7)	Cohort 4 (N = 7)
NSAA total score[*2]	Baseline	22.1 ± 3.0 (n = 20)	20.7 ± 3.4 (n = 7)	12.9 ± 2.1 (n = 7)
	Change at Week 52	4.0 ± 3.5 (n = 20)	−0.1 ± 6.6 (n = 7)	6.0 ± 1.8 (n = 7)
	Change at Week 104	3.6 ± 4.3 (n = 20)	−2.7 ± 7.2 (n = 6)	—
Time to rise from the floor (seconds)	Baseline	4.17 ± 1.43 (n = 20)	5.87 ± 2.05 (n = 7)	5.17 ± 1.02 (n = 6)
	Change at Week 52	−0.48 ± 1.47 (n = 20)	0.35 ± 1.33 (n = 6)	−0.95 ± 1.23 (n = 6)
	Change at Week 104	−0.03 ± 2.59 (n = 19)	2.18 ± 4.20 (n = 4)	—
Time of 10-meter walk/run (seconds)	Baseline	5.11 ± 0.82 (n = 20)	5.54 ± 1.00 (n = 7)	7.55 ± 1.29 (n = 6)
	Change at Week 52	−0.77 ± 0.84 (n = 20)	0.97 ± 1.08 (n = 7)	−1.60 ± 1.20 (n = 6)
	Change at Week 104	−0.11 ± 1.42 (n = 20)	2.27 ± 1.95 (n = 6)	—
Time of 100-meter walk/run (seconds)	Baseline	60.11 ± 12.14 (n = 20)	67.43 ± 17.64 (n = 7)	110.20 ± 30.00 (n = 5)
	Change at Week 52	−8.02 ± 9.21 (n = 20)	12.17 ± 14.60 (n = 7)	−25.95 ± 16.48 (n = 2)
	Change at Week 104	−3.22 ± 17.31 (n = 20)	21.42 ± 20.42 (n = 6)	—
Time to ascend 4 steps (seconds)	Baseline	3.55 ± 0.96 (n = 20)	3.69 ± 1.27 (n = 7)	7.30 ± 2.00 (n = 7)
	Change at Week 52	−0.79 ± 0.88 (n = 20)	0.69 ± 1.27 (n = 7)	−2.26 ± 1.32 (n = 7)
	Change at Week 104	−0.15 ± 1.38 (n = 19)	1.52 ± 1.64 (n = 6)	—

Mean ± SD
*1 Cohort 1, data cutoff date of April 6, 2022; Cohorts 2 and 4, data cutoff date of July 24, 2023
*2 The sum of the scores of 8 items only suitable for DMD patients aged ≤3 years (E*xpert Rev Pharmacoecon Outcomes Res*. 2010; 10: 385-96) was used for Cohort 4.

Regarding safety, adverse events occurred in all subjects. Adverse reactions occurred in 18 of 20 subjects

[19)] As of the data cutoff date of April 6, 2022, the data from Cohort 5a were not available.

(90.0%) in Cohort 1, 5 of 7 subjects (71.4%) in Cohort 2, 5 of 6 subjects (83.3%) in Cohort 3, 6 of 7 subjects (85.7%) in Cohort 4, and 8 of 8 subjects (100%) in Cohort 5. Adverse events reported by ≥30% of subjects in any cohort and adverse reactions reported by ≥30% of subjects in any cohort are shown in Table 39 and Table 40, respectively.

Table 39. Adverse events reported by ≥30% of subjects in any cohort (Study 103, Safety population, data cutoff date of July 24, 2023)

	Cohort 1 (N = 20)	Cohort 2 (N = 7)	Cohort 3 (N = 6)	Cohort 4 (N = 7)	Cohort 5 (N = 8)
Any adverse event	20 (100)	7 (100)	6 (100)	7 (100)	8 (100)
Vomiting	11 (55.0)	3 (42.9)	3 (50.0)	4 (57.1)	7 (87.5)
Nausea	8 (40.0)	5 (71.4)	3 (50.0)	0	7 (87.5)
Abdominal pain upper	5 (25.0)	1 (14.3)	1 (16.7)	1 (14.3)	3 (37.5)
Constipation	6 (30.0)	0	0	3 (42.9)	1 (12.5)
Pyrexia	6 (30.0)	0	0	1 (14.3)	2 (25.0)
COVID-19	6 (30.0)	3 (42.9)	0	4 (57.1)	0
Upper respiratory tract infection	3 (15.0)	0	1 (16.7)	5 (71.4)	2 (25.0)
Influenza	3 (15.0)	0	1 (16.7)	4 (57.1)	0
Viral infection	2 (10.0)	1 (14.3)	0	3 (42.9)	0
Ear infection	1 (5.0)	0	0	3 (42.9)	0
Glutamate dehydrogenase increased	9 (45.0)	1 (14.3)	2 (33.3)	1 (14.3)	2 (25.0)
Troponin I increased	6 (30.0)	0	0	0	2 (25.0)
Hepatic enzyme increased	0	0	0	3 (42.9)	0
Decreased appetite	10 (50.0)	1 (14.3)	1 (16.7)	3 (42.9)	0
Headache	3 (15.0)	2 (28.6)	1 (16.7)	0	4 (50.0)

MedDRA ver.24.1
n (%)

Table 40. Adverse reactions reported by ≥30% of subjects in any cohort (Study 103, Safety population, data cutoff date of July 24, 2023)

	Cohort 1 (N = 20)	Cohort 2 (N = 7)	Cohort 3 (N = 6)	Cohort 4 (N = 7)	Cohort 5 (N = 8)
Any adverse reaction	18 (90.0)	5 (71.4)	5 (83.3)	6 (85.7)	8 (100)
Vomiting	11 (55.0)	3 (42.9)	3 (50.0)	3 (42.9)	7 (87.5)
Nausea	8 (40.0)	4 (57.1)	3 (50.0)	0	7 (87.5)
Glutamate dehydrogenase increased	9 (45.0)	1 (14.3)	2 (33.3)	1 (14.3)	2 (25.0)
Hepatic enzyme increased	0	0	0	3 (42.9)	0
Decreased appetite	9 (45.0)	0	1 (16.7)	3 (42.9)	0

MedDRA ver.24.1
n (%)

There were no deaths. Serious adverse events occurred in 5 subjects (2 subjects in Cohort 1 [hypertransaminasaemia; and vomiting], 2 subjects in Cohort 2 [immune-mediated myositis; and myocarditis and vomiting], and 1 subject in Cohort 5a [immune-mediated myositis]) and were classified as adverse reactions. All those events resolved.

7.1.2 Global study

7.1.2.1 Global phase III study (CTD 5.3.5.1-4, Study 301 [October 2021 to data cutoff date of September 13, 2023])

A placebo-controlled, randomized, double-blind study was conducted at 42 sites in 9 countries or regions[20)] to

[20)] Belgium, Germany, Hong Kong, Italy, Japan, Spain, Taiwan, the UK, and the US

evaluate the efficacy and safety of Elevidys in male patients with DMD aged 4 to <8 years (target sample size,[21] 120 subjects [60 per group]).

Table 41 shows the main inclusion and exclusion criteria.

Table 41. Main inclusion and exclusion criteria

Inclusion criteria	• Male ambulatory patients aged 4 to <8 years at the time of randomization • A definitive diagnosis of DMD prior to screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the *DMD* gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein. ➢ Mutations between or including exons 1 to 17 are not eligible. ➢ In-frame deletions, in-frame duplications, and variants of uncertain significance (VUS) are not eligible. ➢ Mutations fully contained within exon 45 (inclusive) are not eligible. • An NSAA total score >16 and <29 at screening • Time to rise from the floor <5 seconds at screening • Stable daily dose of oral corticosteroids for ≥12 weeks prior to screening, with the dose expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the study • rAAVrh74 antibody titers <1:400 as determined by ELISA
Exclusion criteria	• Echocardiogram with left ventricular ejection fraction <40%, or clinical signs and/or symptoms of cardiomyopathy • Treatment with gene therapy, cell-based therapy, or CRISPR/Cas9 at any time • Use of human growth factor or vamorolone within 12 weeks of Day 1 • Any investigational medication or any treatment designed to increase dystrophin expression within 6 months of Day 1 • Abnormal laboratory values considered clinically significant: ➢ γ-glutamyl transferase (GGT) >2 × ULN ➢ Glutamate dehydrogenase (GLDH) >15 U/L ➢ Total bilirubin > ULN (Note; elevations in total bilirubin confirmed to be due to Gilbert' s syndrome are not exclusionary.) ➢ White blood cell count >18,500/μL ➢ Platelets ≤150,000/μL

The study consisted of screening and baseline periods (31 days prior to study drug infusion), Part 1 (Elevidys or placebo was administered, 52 weeks of follow-up), and Part 2 (Patients who received Elevidys in Part 1 received placebo, and patients who received placebo in Part 1 received Elevidys, 52 weeks of follow-up).

In Part 1, Elevidys 1.33×10^{14} vg/kg (as determined by linear standard qPCR) or placebo was to be administered as a single intravenous infusion over 60 to 120 minutes. In Part 2, patients who received Elevidys in Part 1 were to receive placebo, and patients who received placebo in Part 1 were to receive Elevidys 1.33×10^{14} vg/kg as a single intravenous infusion over 60 to 120 minutes. For immunosuppression and the prevention of adverse events, one day prior to study drug infusion, patients were to begin receiving corticosteroid 1 mg/kg/day (prednisone equivalent) for immunosuppression, in addition to their continued baseline[22] stable oral corticosteroid dose for the treatment of DMD, which was to be continued for ≥60 days post-infusion.

[21] Assuming a standard deviation of 3.5 in each treatment group and a 10% dropout rate, with a type 1 error rate of 5% (two-sided), a target sample size of 120 (60 per group) would provide approximately 90% power to detect a difference of 2.2 in change in NSAA total score from baseline to Week 52 (the primary endpoint) between the Elevidys and placebo groups.

[22] At screening during the screening and baseline periods

Among 131 enrolled subjects, 129 subjects after excluding 2 subjects who met the exclusion criteria were randomized, and 125 subjects (63 in the Elevidys group, 62 in the placebo group) after excluding 4 subjects who discontinued the study before receiving study drug (2 in the Elevidys group [adverse events], 2 in the placebo group [investigator decision]) received Elevidys or placebo and were included in the safety population and the modified intention-to-treat (mITT) population. The mITT population was used as the efficacy population. As of the data cutoff date of September 13, 2023, among 125 subjects who completed Part 1 (63 in the Elevidys group, 62 in the placebo group), 99 subjects (49 in the Elevidys group, 50 in the placebo group) entered Part 2, and 97 subjects after excluding 2 subjects in the Elevidys group received Elevidys or placebo.[23)] Five Japanese patients were enrolled in the study, of whom 4 patients (2 each in the Elevidys and placebo groups) were included in the safety population and the mITT population. The remaining 1 patient was not included in the safety population or the mITT population because the patient was additionally enrolled after the completion of randomization for Part 1.

Randomization was stratified by age group at randomization (4 to <6 years, 6 to <8 years) and by the NSAA total score at screening (≤22, >22).

The primary efficacy endpoint was the change in the NSAA total score from baseline to Week 52. The LS mean treatment difference [95% CI] was 0.65 [−0.45, 1.74], which showed no statistically significant difference and failed to demonstrate the superiority of Elevidys over placebo (Table 42).

Table 42. Change in NSAA total score from baseline to Week 52
(Part 1 of Study 301, mITT population, data cutoff date of September 13, 2023)

		Elevidys	Placebo
Baseline	Mean ± SD	23.10 ± 3.75 (n = 63)	22.82 ± 3.78 (n = 62)
	Range (Min., Max.)	(14, 32)	(15.5, 30)
Change at Week 52	Mean ± SD	2.52 ± 3.31 (n = 63)	1.86 ± 3.18 (n = 61)
	Range (Min., Max.)	(−8, 10)	(−5, 8.5)
LS mean treatment difference [95% CI]		0.65 [−0.45, 1.74]	
P-value*		0.2441	

* A two-sided significance level of 5%. A mixed model for repeated measures (MMRM) with treatment group, age group, visit, treatment group-by-visit interaction, baseline NSAA total score, and baseline NSAA total score-by-visit interaction as covariates. The MMRM model assumed an unstructured variance-covariance matrix.

As to motor function endpoints, Table 43 shows the changes in the time to rise from the floor, time of 10-meter walk/run, time of 100-meter walk/run, and time to ascend 4 steps from baseline to Week 52.

[23)] As of October 25, 2024 after the completion of Part 2, all of 63 subjects who received Elevidys in Part 1 received placebo in Part 2. Among 62 subjects who received placebo in Part 1, 60 subjects after excluding 2 subjects who completed Part 1 and then discontinued the study before participating in Part 2 (Both had AAVrh74 antibody titers ≥1:400 prior to the start of Part 2) received Elevidys in Part 2.

Table 43. Changes in motor function endpoints from baseline to Week 52
(Part 1 of Study 301, mITT population, data cutoff date of September 13, 2023)

		Elevidys (N = 63)	Placebo (N = 62)
Time to rise from the floor (seconds)	Baseline	3.52 ± 0.81 (n = 63)	3.60 ± 0.68 (n = 62)
	Change at Week 52	−0.26 ± 0.95 (n = 63)	0.39 ± 1.39 (n = 61)
	LS mean treatment difference* [95% CI]	−0.64 [−1.06, −0.23]	
Time of 10-meter walk/run (seconds)	Baseline	4.82 ± 0.79 (n = 63)	4.92 ± 0.73 (n = 62)
	Change at Week 52	−0.34 ± 0.69 (n = 63)	0.09 ± 1.03 (n = 61)
	LS mean treatment difference* [95% CI]	−0.42 [−0.71, −0.13]	
Time of 100-meter walk/run (seconds)	Baseline	60.67 ± 15.55 (n = 63)	63.01 ± 17.01 (n = 59)
	Change at Week 52	−6.65 ± 14.54 (n = 59)	−4.18 ± 18.46 (n = 57)
	LS mean treatment difference* [95% CI]	−3.29 [−8.28, 1.70]	
Time to ascend 4 steps (seconds)	Baseline	3.17 ± 1.01 (n = 63)	3.37 ± 1.09 (n = 61)
	Change at Week 52	−0.41 ± 0.85 (n = 62)	−0.12 ± 1.28 (n = 60)
	LS mean treatment difference* [95% CI]	−0.36 [−0.71, −0.01]	

Mean ± SD

* A mixed model for repeated measures (MMRM) with treatment group, age group, visit, treatment group-by-visit interaction, NSAA total score at screening, baseline value for secondary endpoint, and baseline value for secondary endpoint-by-visit interaction as covariates. The MMRM model assumed an unstructured variance-covariance matrix.

The mean micro-dystrophin expression[24)] by Western blot at Week 12 (mean ± SD) (%) was 34.29 ± 41.04 in the Elevidys group (17 subjects) and 0 in all 14 subjects in the placebo group.

Regarding safety, in Part 1, adverse events occurred in 62 of 63 subjects (98.4%) in the Elevidys group and 57 of 62 subjects (91.9%) in the placebo group. Table 44 shows adverse events reported by ≥10% of subjects in either group. Adverse reactions occurred in 48 of 63 subjects (76.2%) in the Elevidys group and 17 of 62 subjects (27.4%) in the placebo group. Table 45 shows adverse reactions reported by ≥10% of subjects in either group.

[24)] Percentage of normal dystrophin expression level (muscle biopsy samples from enrolled patients vs. non-DMD control muscle biopsy samples) (%). Only patients who provided consent were evaluated for micro-dystrophin expression.

Table 44. Adverse events reported by ≥10% of subjects in either group
(Part 1 of Study 301, Safety population, data cutoff date of September 13, 2023)

	Elevidys (N = 63)	Placebo (N = 62)
Any adverse event	62 (98.4)	57 (91.9)
Vomiting	40 (63.5)	12 (19.4)
Nausea	25 (39.7)	8 (12.9)
Decreased appetite	20 (31.7)	3 (4.8)
Pyrexia	20 (31.7)	15 (24.2)
COVID-19	17 (27.0)	9 (14.5)
Glutamate dehydrogenase increased	17 (27.0)	2 (3.2)
Cough	12 (19.0)	18 (29.0)
Upper respiratory tract infection	12 (19.0)	17 (27.4)
Abdominal pain upper	10 (15.9)	9 (14.5)
Fatigue	9 (14.3)	6 (9.7)
Influenza	9 (14.3)	4 (6.5)
Irritability	9 (14.3)	4 (6.5)
Nasopharyngitis	9 (14.3)	12 (19.4)
Contusion	7 (11.1)	9 (14.5)
Headache	7 (11.1)	8 (12.9)
Pain in extremity	7 (11.1)	12 (19.4)
Diarrhoea	6 (9.5)	13 (21.0)
Abdominal pain	5 (7.9)	7 (11.3)
Fall	5 (7.9)	7 (11.3)
Rhinorrhoea	5 (7.9)	7 (11.3)
Nasal congestion	1 (1.6)	7 (11.3)

MedDRA ver.26.0
n (%)

Table 45. Adverse reactions reported by ≥10% of subjects in either group
(Part 1 of Study 301, Safety population, data cutoff date of September 13, 2023)

	Elevidys (N = 63)	Placebo (N = 62)
Any adverse reaction	48 (76.2)	17 (27.4)
Vomiting	34 (54.0)	0
Nausea	20 (31.7)	5 (8.1)
Decreased appetite	17 (27.0)	1 (1.6)
Glutamate dehydrogenase increased	15 (23.8)	2 (3.2)
Pyrexia	10 (15.9)	0
Abdominal pain upper	8 (12.7)	1 (1.6)

MedDRA ver.26.0
n (%)

There were no deaths. Serious adverse events occurred in 14 subjects in the Elevidys group (COVID-19 [2 subjects]; and transaminases increased; craniocerebral injury and intracranial haemorrhage; vomiting and abdominal pain; liver injury; hepatotoxicity; rhabdomyolysis; hepatic enzyme increased; gamma-glutamyltransferase increased; vomiting, myocarditis, pyrexia, and nausea; rotavirus infection; pneumonia and prescription drug used without a prescription; and appendicitis) and 5 subjects in the placebo group (vomiting and pyrexia; upper limb fracture; COVID-19 and influenza; anal abscess; and toxic shock syndrome streptococcal, left ventricular dysfunction, and arterial injury). Serious adverse reactions occurred in 7 subjects in the Elevidys group (transaminases increased; liver injury; hepatotoxicity; rhabdomyolysis; hepatic enzyme increased; gamma-glutamyltransferase increased; and vomiting, myocarditis, pyrexia, and nausea), but not in the placebo group.

7.R Outline of the Review Conducted by PMDA

7.R.1 Use of foreign clinical study data

For the present application, the applicant submitted the results from a global study (Study 301) and Studies 101, 102, and 103 in non-Japanese patients as evaluation data. Due to the very limited number of Japanese patients who are candidates for Elevidys therapy, clinical study results from Japanese patients are the results from only 5 Japanese patients from Study 301.

PMDA asked the applicant to explain the appropriateness of evaluating the efficacy and safety of Elevidys in Japanese patients based mainly on the results from clinical studies in non-Japanese patients, after examining intrinsic and extrinsic ethnic factors that may affect the efficacy and safety of Elevidys.

The applicant's response:

For the following reasons, the efficacy and safety of Elevidys in Japanese patients can be evaluated, using the results of a global study and clinical studies in non-Japanese patients.

• There are no major differences in the diagnostic criteria for DMD, pharmacological therapy, or the standard of care including non-drug rehabilitation between Japan and overseas (Japanese Society of Neurology. Clinical Practice Guideline for Duchenne muscular dystrophy 2014 [in Japanese], *Lancet Neurol*. 2018; 17: 251-67, etc.).

• As to the pharmacokinetics of Elevidys, while the mutation rate in the dystrophin gene, i.e., the gene responsible for DMD, may differ from country to country, the treatment effect of Elevidys, a gene therapy product for patients with a diagnosis of DMD confirmed by genetic testing, is unlikely to be affected by differences in the genetic mutation rate among the countries. Although the distribution of body weights of patients at the time of Elevidys infusion may differ from country to country, as Elevidys is dosed per body weight, the effect of differences in body weight is small.

PMDA accepted the applicant's explanation..

7.R.2 Efficacy

7.R.2.1 Review strategy for efficacy evaluation

PMDA review strategy:

The pivotal clinical study to evaluate the efficacy of Elevidys is a global phase III study involving Japanese patients (Study 301). Given the applicant's explanation about the results of Studies 301 and 102 [see Section 7.R.2.2.1] and evaluation based on long-term data [see Section 7.R.2.2.2], taking account of the natural history of the NSAA total score etc. in DMD patients, PMDA decided to evaluate the efficacy of Elevidys based mainly on the long-term data after Elevidys infusion and the efficacy of Elevidys in Japanese patients based on the results from 5 Japanese patients in Study 301 [see Section 7.R.2.2.3].

7.R.2.2 Results of efficacy assessment

7.R.2.2.1 Results of Studies 301 and 102

The applicant's explanation about the results of the primary and secondary endpoints in Studies 301 and 102, taking account of the natural history of the NSAA total score etc. in patients with DMD:

(1) Natural history of the NSAA total score etc. in patients with DMD

In the natural history of patients with DMD, the NSAA total score peaks at 6.3 years of age and begins to decline after that (*PLoS One*. 2019; 14: e0221097). Given the age of the patient population enrolled in Studies 301, 102, and 101 and Cohort 1 of Study 103 (4 to <8 years), among the patients enrolled in these clinical studies, generally, the NSAA total score is expected to increase from baseline, peak, and then decline in patients aged <6.3 years, while the NSAA total score is expected to decrease from baseline in patients aged ≥6.3 years. In the natural history, DMD patients lose the ability to get up from the floor as assessed by the time to rise from the floor, first, as compared to the abilities assessed by other tests, and the loss of function occurs in the following order: climbing 4 stairs, 6-minute walk, and 10-meter walk/run (*Muscle Nerve*. 2018; 58: 631-8). Moreover, according to a cross-sectional analysis of the time of 100-meter walk/run, the time of 100-meter walk/run tends to improve with age in DMD patients aged 4 to 6 years, or gradually worsen in patients aged ≥7 years (*Neuromuscul Disord*. 2017 ;27:452-7).

(2) The results of Study 301

In Part 1 of Study 301, in accordance with the EMA guideline, "Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. Jul 2016," the change in the NSAA total score from baseline to Week 52 was chosen as the primary endpoint, and the time to rise from the floor, time of 10-meter walk/run, time of 100-meter walk/run, and time to ascend 4 steps were chosen as secondary endpoints. There was no statistically significant difference in the primary endpoint of the change in the NSAA total score from baseline to Week 52 between the Elevidys and placebo groups (Table 42). However, there were improvements in the secondary endpoints of the time to rise from the floor, time of 10-meter walk/run, and time to ascend 4 steps in the Elevidys group compared to the placebo group, and there was also a trend towards improvement in the time of 100-meter walk/run in the Elevidys group (Table 43).

Assessment of the time to rise from the floor and time of 10-meter walk/run as additional measures of motor function is recommended (*PLoS One*. 2013; 8: e52512). As described above, the loss of the ability to rise from the floor occurs first. Thus, motor functional decline can be detected earlier with the time to rise from the floor than with the NSAA score. Longer time to rise from the floor and longer time of 10-meter walk/run are associated with major disease milestones, even in the case of stable NSAA score (*Dev Med Child Neurol.* 2022; 64: 979-88) and are considered prognostic factors for a decline in motor function in ambulatory patients with DMD (*PLoS One*. 2016; 11: e0151445). On the other hand, the NSAA is a scale that rates performance on daily functional activities as a graded change. Especially, a score of 1 for each item represents a broad range of abilities, and the score can only change by 1 if a relatively great improvement in motor function is observed. Thus, the NSAA score may change slower than the time to rise from the floor and time of 10-meter walk/run, which assess the speed of activity.

Taking account of the natural history of the NSAA total score etc. in DMD patients as described above, subgroup analyses of Study 301 according to age group were performed. The results of the primary endpoint and secondary motor function endpoints tended to differ between the subgroup of patients aged 4 to <6 years and the subgroup of patients aged 6 to <8 years (Table 46).

Table 46. Changes in motor function endpoints from baseline to Week 52 by age subgroup (Part 1 of Study 301, mITT population, data cutoff date of September 13, 2023)

		4 to <6 years		6 to <8 years	
		Elevidys	Placebo	Elevidys	Placebo
NSAA total score	Baseline	22.28 ± 3.76 (n = 30)	22.02 ± 3.39 (n = 29)	23.83 ± 3.65 (n = 33)	23.53 ± 4.01 (n = 33)
		22.00 [14, 30]	22.00 [15.5, 28]	24.50 [17, 32]	24.00 [16.5, 30]
	Change at Week 52	3.95 ± 2.28 (n = 30)	2.64 ± 3.51 (n = 29)	1.21 ± 3.58 (n = 33)	1.16 ± 2.72 (n = 32)
		4.00 [−0.5, 10]	2.50 [−3, 8.5]	1.50 [−8, 7]	1.00 [−5, 7]
Time to rise from the floor (seconds)	Baseline	3.39 ± 0.69 (n = 30)	3.47 ± 0.69 (n = 29)	3.64 ± 0.90 (n = 33)	3.72 ± 0.66 (n = 33)
		3.20 [2.35, 4.8]	3.50 [2.25, 5]	3.55 [1.85, 5.75]	3.75 [2.35, 4.9]
	Change at Week 52	−0.44 ± 0.62 (n = 30)	0.04 ± 0.93 (n = 29)	−0.10 ± 1.16 (n = 33)	0.71 ± 1.66 (n = 32)
		−0.45 [−2.5, 0.65]	−0.05 [−1.6, 2.6]	−0.30 [−1.75, 5.1]	0.18 [−1.15, 7.5]
Time of 10-meter walk/run (seconds)	Baseline	4.83 ± 0.77 (n = 30)	4.99 ± 0.65 (n = 29)	4.81 ± 0.83 (n = 33)	4.85 ± 0.79 (n = 33)
		4.65 [3.5, 6.5]	5.00 [3.7, 7]	4.60 [3.2, 6.85]	4.80 [3.65, 6.7]
	Change at Week 52	−0.59 ± 0.52 (n = 30)	−0.29 ± 0.63 (n = 29)	−0.12 ± 0.76 (n = 33)	0.43 ± 1.20 (n = 32)
		−0.55 [−1.45, 1]	−0.45 [−1.2, 1.35]	−0.20 [−1.4, 2.1]	0.18 [−0.9, 6]
Time of 100-meter walk/run (seconds)	Baseline	62.53 ± 17.59 (n = 30)	67.14 ± 16.95 (n = 29)	58.98 ± 13.48 (n = 33)	59.01 ± 16.35 (n = 30)
		59.50 [38, 129.2]	63.70 [48.7, 118.1]	56.00 [38.6, 94.2]	56.80 [38.7, 108.7]
	Change at Week 52	−12.66 ± 15.42 (n = 29)	−9.85 ± 21.67 (n = 29)	−0.83 ± 11.05 (n = 30)	1.69 ± 12.22 (n = 28)
		−14.00 [−58.8, 29.7]	−6.70 [−70, 39.2]	−2.20 [−22.1, 39.3]	1.25 [−39.7, 28.3]
Time to ascend 4 steps (seconds)	Baseline	3.35 ± 1.19 (n = 30)	3.50 ± 1.17 (n = 29)	3.01 ± 0.80 (n = 33)	3.24 ± 1.01 (n = 32)
		3.00 [1.8, 7.1]	3.10 [1.9, 7.1]	2.80 [1.6, 4.4]	3.10 [1.5, 5.5]
	Change at Week 52	−0.78 ± 0.72 (n = 30)	−0.60 ± 0.75 (n = 29)	−0.06 ± 0.82 (n = 32)	0.34 ± 1.51 (n = 31)
		−0.65 [−2.5, 0.8]	−0.60 [−3.1, 0.8]	−0.10 [−1.4, 2]	−0.10 [−2, 4.7]

Upper row, Mean ± SD; Lower row, Median [Range]

In patients aged 4 to <6 years, there was a trend towards improvement in the NSAA total score in both the Elevidys and placebo groups, and the change was greater in the Elevidys group. A similar trend was observed also for motor function endpoints, e.g., the time to rise from the floor and time of 10-meter walk/run.

In patients aged 6 to <8 years, there was a trend towards slight improvement in the NSAA total score in both groups, but the treatment difference was smaller as compared with patients aged 4 to <6 years. The time to rise from the floor, time of 10-meter walk/run, and time of 100-meter walk/run increased in the placebo group, but decreased in the Elevidys group.

As described above, due to the age of DMD patients enrolled in Study 301 and the characteristics of the NSAA score, the NSAA score may not have been sensitive enough to detect a difference from placebo at 52 weeks.

(3) The results of Study 102

In Part 1 of Study 102, there were no differences between the Elevidys and placebo groups with respect to the primary endpoint of the change in the NSAA total score from baseline to Week 48 (Table 30) and the secondary endpoints of the time to rise from the floor, time of 10-meter walk/run, time of 100-meter walk/run, and time to ascend 4 steps (Table 31).

As the reasons for these findings, the following points may have affected the efficacy of Elevidys:
There were imbalances in baseline patient characteristics between the 2 groups; and 12 of 20 patients in the Elevidys group in Part 1 received a dose lower than the target dose due to the effect of the assay method (6.29×10^{13} vg/kg in 6 patients, 8.94×10^{13} vg/kg in 6 patients).

However, it was difficult to identify the definitive cause based on the results of analyses adjusted for the imbalances in patient characteristics and the efficacy results by dose level.

PMDA's discussion:
With respect to the reason that Studies 301 and 102 failed to demonstrate the superiority of Elevidys over placebo in the primary endpoint of the NSAA total score, given the above explanation by the applicant, the applicant's explanation (The NSAA total score may not have been sensitive enough to detect a difference between the Elevidys and placebo groups at 52 or 48 weeks post-infusion, for the patient population enrolled in Studies 301 and 102) is understandable.

As to motor function endpoints other than the NSAA total score, there were improvements in the time to rise from the floor, time of 10-meter walk/run, and time to ascend 4 steps in the Elevidys group compared to the placebo group in Study 301 (Table 43). Meanwhile, there were no differences in these endpoints between the Elevidys and placebo groups in Part 1 of Study 102 (Table 31). Due to the lack of consistency of the results between the studies, there are limitations to explaining the efficacy of Elevidys based only on the results of motor function endpoints such as the time to rise from the floor and time of 10-meter walk/run.

7.R.2.2.2 Evaluation based on long-term data

The applicant's explanation about the long-term data after Elevidys infusion:
As described in Section 7.R.2.2.1 (1) and (2), given the natural history of DMD patients and the characteristics of the NSAA score, it is important to evaluate the efficacy of Elevidys in patients aged 4 to <8 years based on the long-term data, i.e. ≥3 years after Elevidys infusion.

Since DMD is a progressive, life-threatening disease, it is difficult to include a long-term follow-up period after placebo administration, and there are no >1-year data from the placebo group in clinical studies of Elevidys. Thus, the applicant discussed the long-term data obtained from clinical studies of Elevidys in ambulatory patients aged 4 to <8 years (Study 101, Study 102, Cohort 1 of Study 103) as follows.

Table 27 shows the change in motor function from baseline to Year 5 in 4 subjects treated with Elevidys in Study 101. These 4 subjects were 4 to 6 years of age at the time of Elevidys infusion, and 5 years later, they became 9 to 11 years of age, at which motor function decline is expected in the natural history of DMD patients (*Muscle Nerve*. 2024; 69: 93-8). Improvements in the NSAA total score were sustained, which has clinical significance.

Table 47 shows the change in motor function from baseline to Year 4 or Year 3, which was assessed in Part 3, in patients treated with Elevidys in Part 1 or 2 of Study 102. Unlike the long-term data from other clinical studies, there were no consistent improvements in the NSAA total score in Study 102.

Table 47. Changes in motor function endpoints from baseline to Year 4 (Study 102, ITT population)

		Patients who received Elevidys in Part 1 (N = 20)[*1]	Patients who received Elevidys in Part 2 (N = 21)
NSAA total score	Baseline[*2]	19.8 ± 3.3 (n = 20)	23.6 ± 3.7 (n = 21)
		20.0 [13, 26]	24.0 [13, 30]
	Change at Year 1	1.6 ± 2.9 (n = 19)	2.4 ± 4.4 (n = 20)
		2.0 [−3, 6]	2.0 [−5, 11]
	Change at Year 2	0.1 ± 6.6 (n = 19)	0.5 ± 5.2 (n = 19)
		2.0 [−17, 9]	−1.0 [−7, 10]
	Change at Year 3	−2.7 ± 8.2 (n = 16)	2.9 ± 5.7 (n = 12)
		−1.5 [−19, 11]	4.0 [−10, 11]
	Change at Year 4	−2.6 ± 7.6 (n = 11)	—
		−3.0 [−17, 7]	—
Time to rise from the floor (seconds)	Baseline[*2]	5.10 ± 2.17 (n = 20)	4.02 ± 1.30 (n = 21)
		4.30 [3.2, 10.4]	3.90 [2.4, 7.2]
	Change at Year 1	−0.21 ± 1.13 (n = 19)	0.18 ± 1.33 (n = 20)
		−0.40 [−1.8, 2.8]	−0.25 [−1.4, 4.2]
	Change at Year 2	0.31 ± 2.12 (n = 15)	0.92 ± 2.04 (n = 17)
		−0.50 [−1.4, 5.9]	0.70 [−1.2, 7.0]
	Change at Year 3	0.30 ± 0.70 (n = 11)	1.66 ± 3.87 (n = 12)
		0.00 [−0.6, 1.6]	0.55 [−1.4, 13.1]
	Change at Year 4	2.40 ± 2.08 (n = 9)	—
		1.60 [−0.3, 5.6]	—
Time of 10-meter walk/run (seconds)	Baseline[*2]	5.35 ± 1.14 (n = 20)	4.84 ± 1.12 (n = 21)
		5.00 [4.1, 8.9]	4.70 [3.8, 9.1]
	Change at Year 1	0.70 ± 1.16 (n = 19)	−0.14 ± 0.75 (n = 20)
		0.38 [−0.6, 3.5]	−0.15 [−1.9, 1.2]
	Change at Year 2	0.79 ± 1.84 (n = 17)	0.53 ± 1.54 (n = 19)
		0.20 [−1.2, 5.2]	0.20 [−1.5, 4.1]
	Change at Year 3	0.66 ± 1.67 (n = 13)	0.64 ± 3.33 (n = 12)
		0.10 [−0.9, 5.4]	−0.50 [−1.7, 10.9]
	Change at Year 4	1.60 ± 1.99 (n = 10)	—
		1.25 [−1.1, 5.8]	—
Time of 100-meter walk/run (seconds)	Baseline[*2]	61.04 ± 12.71 (n = 20)	55.98 ± 10.21 (n = 21)
		57.10 [42.3, 99.3]	55.00 [41.5, 80.1]
	Change at Year 1	8.67 ± 27.98 (n = 19)	0.84 ± 8.84 (n = 20)
		3.50 [−8.2, 119.4]	0.50 [−12.7, 17.6]
	Change at Year 2	10.44 ± 19.10 (n = 17)	8.46 ± 20.53 (n = 19)
		3.20 [−14.8, 55.8]	4.10 [−13.3, 59.6]
	Change at Year 3	4.78 ± 12.98 (n = 12)	0.28 ± 11.70 (n = 11)
		2.75 [−10.7, 38.9]	0.80 [−14.3, 26.8]
	Change at Year 4	16.70 ± 19.01 (n = 9)	—
		7.80 [−7.8, 43.4]	—
Time to ascend 4 steps (seconds)	Baseline[*2]	3.69 ± 1.46 (n = 20)	3.09 ± 1.09 (n = 21)
		3.30 [2.1, 6.5]	2.80 [1.8, 6.2]
	Change at Year 1	0.26 ± 1.35 (n = 19)	−0.20 ± 1.08 (n = 20)
		−0.30 [−1.6, 3.2]	−0.45 [−1.8, 2.0]
	Change at Year 2	1.89 ± 5.43 (n = 17)	0.98 ± 3.42 (n = 19)
		−0.30 [−2.3, 18.4]	0.10 [−2.1, 13.0]
	Change at Year 3	0.18 ± 1.77 (n = 12)	1.15 ± 6.16 (n = 12)
		−0.10 [−2.8, 4.1]	−0.70 [−2.3, 20.5]
	Change at Year 4	0.72 ± 2.24 (n = 9)	—
		0.10 [−2.6, 4.0]	—

Upper row, Mean ± SD; Lower row, Median [Range]
*1 Including patients treated with Elevidys 1.33×10^{14} vg/kg and patients treated with Elevidys 6.29×10^{13} vg/kg or 8.94×10^{13} vg/kg
*2 Baseline value in Part 2 is pre-infusion value in Part 2.

Table 48 shows the changes in motor function endpoints from baseline to Year 3 in patients treated with Elevidys (patients aged 4 to <8 years) in Cohort 1 of Study 103. Improvements in the NSAA total score tended to be sustained through 3 years after Elevidys infusion.

Table 48. Changes in motor function endpoints from baseline to Year 3 (Study 103 Cohort 1, FAS, data cutoff date of October 4, 2024)

		Elevidys (N = 20)
NSAA total score	Baseline	22.1 ± 3.0 (n = 20)
		22.0 [18, 26]
	Change at Year 1	4.0 ± 3.5 (n = 20)
		5.0 [−3, 10]
	Change at Year 2	3.6 ± 4.3 (n = 20)
		4.0 [−8, 11]
	Change at Year 3	1.0 ± 6.8 (n = 20)
		3.0 [−17, 9]
Time to rise from the floor (seconds)	Baseline	4.17 ± 1.43 (n = 20)
		3.85 [2.40, 8.20]
	Change at Year 1	−0.48 ± 1.47 (n = 20)
		−0.70 [−3.80, 3.70]
	Change at Year 2	−0.03 ± 2.59 (n = 19)
		−0.30 [−4.10, 9.60]
	Change at Year 3	0.46 ± 2.09 (n = 18)
		0.10 [−3.70, 5.90]
Time of 10-meter walk/run (seconds)	Baseline	5.11 ± 0.82 (n = 20)
		4.95 [3.50, 6.70]
	Change at Year 1	−0.77 ± 0.84 (n = 20)
		−0.90 [−2.20, 1.90]
	Change at Year 2	−0.11 ± 1.42 (n = 20)
		−0.20 [−2.20, 4.70]
	Change at Year 3	0.11 ± 1.40 (n = 19)
		−0.10 [−2.10, 3.70]
Time of 100-meter walk/run (seconds)	Baseline	60.11 ± 12.14 (n = 20)
		59.10 [42.7, 79.8]
	Change at Year 1	−8.02 ± 9.21 (n = 20)
		−8.85 [−24.5, 19.9]
	Change at Year 2	−3.22 ± 17.31 (n = 20)
		−6.20 [−26.6, 51.1]
	Change at Year 3	7.48 ± 27.78 (n = 18)
		−2.75 [−29.7, 86.0]
Time to ascend 4 steps (seconds)	Baseline	3.55 ± 0.96 (n = 20)
		3.60 [1.9; 5.5]
	Change at Year 1	−0.79 ± 0.88 (n = 20)
		−1.20 [−2.0, 1.0]
	Change at Year 2	−0.15 ± 1.38 (n = 19)
		−0.40 [−2.2, 3.3]
	Change at Year 3	0.14 ± 2.04 (n = 19)
		−0.60 [−1.8, 7.0]

Upper row, Mean ± SD; Lower row, Median [Range]

Furthermore, the NSAA total score, time to rise from the floor, and time of 10-meter walk/run at 3 years post-infusion in patients treated with Elevidys 1.33×10^{14} vg/kg in clinical studies of Elevidys (Study 101, Study 102, Study 103 Cohort 1) were compared with the external control data (Patients meeting the entry criteria for the clinical studies of Elevidys were identified from 3 clinical studies[25)]). The results are shown in Table 49. Decline in motor function was slower in the Elevidys group compared to the external control data, and the treatment difference tended to be greater over time.

Table 49. Changes from baseline in motor function endpoints comparison to external controls (Study 101, Study 102,[*1] Study 103 Cohort 1)

		Elevidys	External control	LS mean treatment difference[*2] [95% CI]
NSAA total score	Baseline[*3]	22.1 ± 3.8 22.0 [13, 30] (n = 53)	21.4 ± 2.8 21.0 [13, 30] (n = 141)	—
	Change at Year 1[*2]	2.41 [1.79, 3.03] (n = 53)	−0.38 [−1.01, 0.24] (n = 139)	2.79 [1.91, 3.67]
	Change at Year 2[*2]	0.77 [−0.29, 1.82] (n = 53)	−1.86 [−3.02, −0.70] (n = 109)	2.63 [1.06, 4.20]
	Change at Year 3[*2]	−1.43 [−3.08, 0.22] (n = 50)	−4.63 [−6.75, −2.52] (n = 66)	3.20 [0.52, 5.89]
Time to rise from the floor (seconds)	Baseline[*3]	4.48 ± 1.82 4.00 [2.40, 10.40] (n = 53)	4.52 ± 1.03 4.30 [1.90, 10.20] (n = 141)	—
	Change at Year 1[*2]	−0.36 [−0.87, 0.16] (n = 53)	1.47 [0.95, 1.99] (n = 137)	−1.83 [−2.56, −1.09]
	Change at Year 2[*2]	3.25 [1.56, 4.94] (n = 53)	5.41 [3.58, 7.23] (n = 108)	−2.16 [−4.64, 0.33]
	Change at Year 3[*2]	4.88 [2.86, 6.90] (n = 50)	10.10 [7.60, 12.6] (n = 66)	−5.22 [−8.43, −2.01]
Time of 10-meter walk/run (seconds)	Baseline[*3]	5.14 ± 1.09 4.90 [3.50, 9.10] (n = 53)	5.19 ± 0.62 5.10 [3.40, 8.60] (n = 141)	—
	Change at Year 1[*2]	−0.21 [−0.55, 0.13] (n = 53)	0.55 [0.20, 0.90] (n = 138)	−0.76 [−1.24, −0.27]
	Change at Year 2[*2]	0.76 [0.08, 1.43] (n = 52)	1.80 [1.05, 2.56] (n = 109)	−1.05 [−2.05, −0.04]
	Change at Year 3[*2]	3.51 [1.99, 5.03] (n = 49)	4.89 [2.89, 6.90] (n = 66)	−1.38 [−3.90, 1.13]

*1 Patients treated with Elevidys 1.33×10^{14} vg/kg only were included in the analyses, and patients treated with 6.29×10^{13} vg/kg or 8.94×10^{13} vg/kg were not included.

*2 A propensity score-weighted multiple regression model with treatment group, visit, baseline age group, baseline value, baseline age group-by-baseline value interaction, treatment group-by-visit interaction, and baseline value-by-visit interaction as covariates. The model assumed an unstructured variance-covariance matrix. Propensity scores were estimated using a logistic regression model with baseline age group, baseline NSAA total score, baseline time to rise from the floor, baseline time of 10-meter walk/run, body weight, height, and BMI as covariates.

*3 Upper row, Mean ± SD; Lower row, Median [Range]

Evaluation of the efficacy of Elevidys will be continued after marketing, based on the data from Part 2 of Study 301, comparison between the long-term data from Study 301 and external control data [see Section 8.1.1], etc.

[25)] The following 3 clinical studies

- Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS):
  A global study conducted at 21 centers prospectively collected the comprehensive natural history data of patients with DMD aged 2 to <29 years, and 441 patients were enrolled in the study.
- Study BioMarin PRO-DMD-01:
  A prospective, observational study of physical impairment, activity limitation, and quality of life in DMD patients, focusing on ambulatory patients aged ≥3 years, and 265 patients were enrolled in the study.
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) study:
  A multicenter, double-blind, parallel-group study to compare 3 corticosteroid regimens (daily prednisone [unapproved in Japan] [0.75 mg/kg/day], intermittent prednisone [0.75 mg/kg/day for 10 days alternating with 10 days off], daily deflazacort [unapproved in Japan] [0.9 mg/kg/day]) in DMD patients aged 4 to <8 years. As external control data, the results from patients treated with daily corticosteroid (prednisone or deflazacort) (194 patients) were used to be matched for corticosteroid use with patients in the Elevidys group.

PMDA's discussion:
In a confirmatory study, Study 301, there was no statistically significant improvement in the primary endpoint of the change in the NSAA total score from baseline to Week 52 in the Elevidys group compared to the control group.

However, given the applicant's explanation, at the age of the patient population of Study 301, the patient's physical growth antagonizes the progression of DMD, and it was difficult to evaluate the efficacy of Elevidys based on the change in the NSAA total score in a short-duration study, which is understandable. The efficacy of Elevidys should be evaluated based on the change in the NSAA total score in a study of longer duration in which assessment will occur at the age at which the effects of DMD progression are prominent as compared with the patient's physical growth.

Taking account of the above points, the efficacy of Elevidys was evaluated based mainly on the long-term data after Elevidys infusion, and the following results have been obtained at present. Thus, Elevidys is expected to have a certain level of efficacy in improving motor function or slowing decline in motor function in ambulatory patients with DMD.

- The long-term data from Study 101 and Cohort 1 of Study 103 showed that improvements in the NSAA total score were sustained through 3 to 5 years after Elevidys infusion.
- The changes in motor function from baseline to Year 3 in patients treated with Elevidys 1.33×10^{14} vg/kg in Studies 101 and 102 and Cohort 1 of Study 103 were compared with the external control data. Although it should be noted that the external control data were used for comparison, decline in motor function was slower in the Elevidys group than in external controls, and the treatment difference tended to be greater over time.

However, such clear results were not obtained from Study 102, and the long-term data after Elevidys infusion are limited at present. Thus, after marketing, the data on motor function endpoints, focusing on the NSAA total score, including the data from Japanese patients, should be obtained by long-term follow-up of patients in Study 301, etc., and evaluation of the efficacy of Elevidys should be continued.

7.R.2.2.3 Efficacy of Elevidys in Japanese patients

The applicant's explanation about the efficacy of Elevidys in Japanese patients:
The number of Japanese patients was very limited, i.e., 4 Japanese patients (2 each in the Elevidys and placebo groups) were included in the primary analysis of Study 301, and 1 Japanese patient was additionally enrolled after the completion of randomization for Part 1. However, there were no major differences in baseline patient characteristics between the Japanese subgroup and the overall population (Table 50 and Table 51).

Table 50. Baseline characteristics of Japanese patients (Study 301)

	Elevidys		Placebo		Additionally enrolled patient (treated with Elevidys)
Subject Number	Subject E	Subject F	Subject G	Subject H	Subject I
Age	6-7 years	4-5 years	6-7 years	6-7 years	4-5 years
Height (cm)	10[redacted].7	10[redacted].3	11[redacted].5	11[redacted].5	10[redacted].2
Body weight (kg)	1[redacted].7	1[redacted].3	2[redacted].8	1[redacted].4	1[redacted].7
Years since diagnosis of DMD	6.13	2.67	3.09	4.20	5.06
Years since glucocorticoid treatment started	1.27	0.30	2.41	0.41	0.34

Table 51. Baseline patient characteristics in overall population (Study 301, mITT population)

	Elevidys (N = 63)	Placebo (N = 62)
Age	5.98 ± 1.06	6.08 ± 1.05
Height (cm)	108.64 ± 6.74	110.68 ± 7.44
Body weight (kg)	21.29 ± 4.62	22.37 ± 6.42
Years since diagnosis of DMD	2.62 ± 1.73	2.60 ± 1.78
Years since glucocorticoid treatment started	1.07 ± 0.92	0.97 ± 0.83

Mean ± SD

Table 52 shows the efficacy results in Japanese patients. In 1 subject in the Elevidys group included in the primary analysis (Subject Number, Subject E), the primary endpoint of the change in the NSAA total score from baseline to Week 52 was −2.5 points, but all of the secondary endpoints showed improvements. In another subject in the Elevidys group (Subject Number, Subject F), the NSAA total score increased by 3.5 points, and all of the secondary endpoints showed improvements. In 1 subject in the Elevidys group who was additionally enrolled and was not included in the mITT population (Subject Number, Subject I), the NSAA total score increased by 4.5 points; there was slight improvement in the time of 100-meter walk/run; the time to ascend 4 steps remained unchanged; and the time to rise from the floor and time of 10-meter walk/run worsened. However, the scores for "rise from floor" and "10-meter run test" as the items in the NSAA remained 2, indicating functions were not lost. In 1 subject in the placebo group (Subject Number, Subject H), the NSAA total score increased by 5.5 points, and the time to rise from the floor was only the secondary endpoint worsened, and others improved. In another subject in the placebo group (Subject Number, Subject G), the NSAA total score worsened by 1.0 point, and the time to ascend 4 steps was only the secondary endpoint improved, and others worsened.

Table 52. Efficacy results in Japanese patients (Study 301)

		Elevidys		Placebo		Additionally enrolled patient (treated with Elevidys)
Subject Number		Subject E	Subject F	Subject G	Subject H	Subject I
NSAA total score	Baseline	21	28.5	28	26.5	27.5
	Change at Week 52	−2.5	3.5	−1.0	5.5	4.5
Time to rise from the floor	Baseline	4.25	2.65	2.7	3.2	2.9
	Change at Week 52	−0.40	−0.05	0.20	0.15	0.3
Time of 10-meter walk/run	Baseline	5.5	4.5	3.85	4.35	4.05
	Change at Week 52	−1.05	−0.90	0.15	−0.60	0.05
Time of 100-meter walk/run	Baseline	64.7	50.3	44.1	50	49.1
	Change at Week 52	−2.4	−15	1.4	−8.5	−0.7
Time to ascend 4 steps	Baseline	4.4	3.2	2.6	2.3	2.4
	Change at Week 52	−0.8	−0.9	−0.2	−0.1	0

As described above, in the 2 Japanese patients in the Elevidys group included in the mITT population of Study 301, regardless of the change in the NSAA total score, both of the time to rise from the floor and time of 10-meter walk/run improved. These endpoints are associated with major disease milestones (*Dev Med Child Neurol.* 2022; 64: 979-88) and are considered prognostic factors for a decline in motor function in ambulatory patients with DMD (*PLoS One*. 2016; 11: e0151445). In the 2 patients in the placebo group, these endpoints worsened except that the time of 10-meter walk/run improved in 1 patient. In the 1 patient in the Elevidys group who was additionally enrolled and was not included in the mITT population, the NSAA total score increased by 4.5 points. The time to rise from the floor and time of 10-meter walk/run worsened, whereas there were no changes in scores for rise from floor and 10-meter run test as the items in the NSAA. Based on the above, there were no clear differences between the Japanese subgroup and the overall population, and the results suggested improvement in motor function with Elevidys also in Japanese patients.

PMDA's discussion:

Although there is no particular problem with the applicant's explanation that Study 301 showed no major differences between the results in Japanese patients at present and the results in the overall population, no long-term data from Japanese patients are available. Thus, after marketing, it is necessary to obtain long-term data on the NSAA total score etc. from Japanese patients and continue to evaluate the efficacy of Elevidys in Japanese patients, by comparing the long-term data from Study 301 with the external control data [see Section 8.1.1] etc.

7.R.3 Safety

7.R.3.1 Safety profile of Elevidys

The applicant's explanation about the safety profile of Elevidys based on safety information from Part 1 of Study 301 and from patients treated with Elevidys in Studies 301, 101, 102, and 103 ("the pooled population")[26]:

Safety data from Study 301 and from the pooled population are summarized in Table 53 and Table 54,

[26] Study 301, 114 patients (63 patients who received Elevidys in Part 1, 50 patients who received Elevidys in Part 2 by the data cutoff date of September 13, 2023, 1 Japanese patient additionally enrolled); Study 101, 4 patients; Study 102, 41 patients; and Study 103, 20 patients in Cohort 1, 7 patients in Cohort 2, 6 patients in Cohort 3, 7 patients in Cohort 4, 6 patients in Cohort 5a, and 2 patients in Cohort 5b

respectively. The majority of adverse events were mild or moderate in severity, and there were no deaths.

Table 53. Summary of safety data from Part 1 of Study 301 (Safety population, data cutoff date of September 13, 2023)

	Elevidys (N = 63)	Placebo (N = 62)
All adverse events	62 (98.4)	57 (91.9)
Adverse reactions	48 (76.2)	17 (27.4)
Serious adverse events	14 (22.2)	5 (8.1)
Severe adverse events	13 (20.6)	5 (8.1)
Adverse events leading to study discontinuation	0	0
Adverse events leading to death	0	0

n (%)

Table 54. Summary of safety data from the pooled population*

	Elevidys (N = 207)
All adverse events	198 (95.7)
Adverse reactions	171 (82.6)
Serious adverse events	30 (14.5)
Severe adverse events	31 (15.0)
Adverse events leading to study discontinuation	0
Adverse events leading to death	0

n (%)

*Study 301 (data cutoff date of September 13, 2023; data cutoff date of October 11, 2023 for additionally enrolled Japanese patient), Study 101 (data cutoff date of April 25, 2023), Study 102 (data cutoff date of September 29, 2023), Study 103 (data cutoff date of July 24, 2023)

The most commonly observed events after Elevidys infusion in clinical studies were nausea/vomiting and pyrexia.

The incidences of adverse events of nausea/vomiting (MedDRA PTs "nausea," "vomiting," "abdominal discomfort," "abdominal pain," "abdominal pain upper," and "decreased appetite") were 77.8% (49 of 63 subjects) in the Elevidys group and 43.5% (27 of 62 subjects) in the placebo group in Part 1 of Study 301 (data cutoff date of September 13, 2023), showing a higher incidence in the Elevidys group than in the placebo group. Among those events, 2 events in the Elevidys group and 1 event in the placebo group remained unresolved, and all of the other events resolved. Serious events occurred in 2 subjects in the Elevidys group and 1 subject in the placebo group, all of which resolved. Forty-four subjects (69.8%) in the Elevidys group and 13 subjects (21.0%) in the placebo group experienced adverse events of nausea/vomiting within the first 2 weeks after study drug infusion, and the treatment difference in the incidence was greater in this time frame than in other time frames.

In the pooled population, the incidence of adverse events of vomiting/nausea was 83.6% (173 of 207 subjects). Among the observed events, 21 events remained unresolved, 2 events had an unknown outcome, and all of the other events resolved. The majority of the observed events were mild or moderate in severity. Six severe events occurred in 4 subjects, of which 4 events reported by 3 subjects (vomiting [3], nausea [1]) occurred on Days 1 to 3 after Elevidys infusion. These events were all serious and classified as adverse reactions. The remaining 1 subject experienced 2 severe events (abdominal pain [1] and vomiting [1]) on Day 173 after Elevidys infusion. Both events were serious and were considered unrelated to Elevidys. The severe events all resolved following

treatment with ondansetron etc. The median time to the first onset of nausea/vomiting was 3.0 days, and nausea/vomiting occurred within the first 2 weeks in 162 of the 173 patients.

The incidences of adverse events of pyrexia (MedDRA PTs "pyrexia" and "body temperature increased") were 31.7% (20 of 63 subjects) in the Elevidys group and 24.2% (15 of 62 subjects) in the placebo group in Part 1 of Study 301 (data cutoff date of September 13, 2023). Adverse events of pyrexia occurring within the first 2 weeks after study drug infusion were observed in 11 subjects (17.5%) in the Elevidys group, but not in the placebo group. All of the reported events resolved. Serious pyrexia occurred in 2 subjects (1 subject each in the Elevidys and placebo groups).

In the pooled population, the incidence of adverse events of pyrexia was 25.6% (53 of 207 subjects). Those reported by 27 subjects (13.0%) were classified as adverse reactions. The majority of adverse events were mild or moderate in severity, and severe pyrexia occurred on Day 1 after Elevidys infusion in 1 subject. All of the reported events resolved. Serious pyrexia occurred in 2 subjects in Part 1 or Part 2 of Study 301, and both events were classified as adverse reactions.

Between the primary data cutoff (September 14, 2023 for Study 301, July 25, 2023 for Study 103) and October 31, 2024, serious adverse events of nausea/vomiting or pyrexia occurred in 4 subjects in Study 301 (2 subjects in Part 1 [vomiting and pyrexia (2 subjects)], 2 subjects in Part 2 [vomiting and pyrexia (1 subject), vomiting (1 subject)]) and 1 subject in Study 103 (pyrexia). The events reported by 2 subjects in Part 1 of Study 301 occurred on Days 385 to 392 after Elevidys infusion. The events reported by 2 subjects in Part 2 of Study 301 occurred on Days 2 to 3 after Elevidys infusion. The event reported by 1 subject in Study 103 occurred on Day 69 after Elevidys infusion. All those events had an outcome of "resolved." In Study 303,[27] 3 cases (nausea [2 subjects], nausea and vomiting [1 subject]) were reported. Those events occurred on Days 3 to 5 after Elevidys infusion and resolved except for 1 case.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, 2 cases of serious adverse events of nausea/vomiting and 2 cases of serious adverse events of pyrexia were reported. As to the events with the onset date, treatment, and outcome reported, the time to onset was 3 to 11 days after Elevidys infusion, and the events of nausea/vomiting resolved within 1 to 2 days following treatment with corticosteroids and fluids.

Regarding long-term safety, safety information from Study 102 is summarized in Table 55, and no delayed adverse reactions were reported. After the data cutoff date of August 16, 2023, 1 death occurred. The patient was [redacted] years old at the time of Elevidys infusion, had severe myalgia at 4 years and 11 months post-infusion, and died on the same day. The autopsy findings were not indicative of any specific cause of death other than DMD, and its causal relationship to Elevidys was denied.

[27] A placebo-controlled, double-blind study in non-ambulatory DMD patients (Cohort 1) and ambulatory DMD patients aged 8 to <18 years (Cohort 2) (Study start date, May 31, 2023).

Table 55. Summary of long-term safety data by time period after Elevidys infusion (Study 102, Safety population, data cutoff date of August 16, 2023)

	<1 year (N = 41)	1-2 years (N = 41)	2-3 years (N = 41)	3-4 years (N = 30)	≥4 years (N = 12)
All adverse events	41 (100)	37 (90.2)	33 (80.5)	17 (56.7)	3 (25.0)
Adverse reactions	37 (90.2)	2 (4.9)	1 (2.4)	0	0
Serious adverse events	5 (12.2)	1 (2.4)	2 (4.9)	0	0
Severe adverse events	6 (14.6)	1 (2.4)	2 (4.9)	0	0
Adverse events leading to study discontinuation	0	0	0	0	0
Adverse events leading to death	0	0	0	0	0

n (%)

Regarding safety by age group and by ambulatory status, safety data from the pooled population are summarized in Table 56. Although the number of ambulatory patients aged 3 years or ≥8 years and the number of non-ambulatory patients were limited, there should be no differences in safety profile according to the age group or ambulatory status.

Table 56. Safety data by patient characteristics (Pooled population[*1])

	Ambulatory					Non-ambulatory (N = 8)
	3 years (N = 7)	4 to <6 years (N = 64)	6 to <8 years (N = 99)	≥8 years (N = 29)	Total (N = 199)	
All adverse events	7 (100)	61 (95.3)	94 (94.9)	28 (96.6)	190 (95.5)	8 (100)
Adverse reactions	6 (85.7)	47 (73.4)	86 (86.9)	25 (86.2)	164 (82.4)	7 (87.5)
Severe adverse events	0	7 (10.9)	19 (19.2)	5 (17.2)	31 (15.6)	0
Serious adverse events	0	7 (10.9)	18 (18.2)	5 (17.2)	30 (15.1)	0
Adverse events of nausea/vomiting[*2]	6 (85.7)	51 (79.7)	84 (84.8)	26 (89.7)	167 (83.9)	6 (75.0)
Adverse events of pyrexia[*3]	1 (14.3)	21 (32.8)	24 (24.2)	7 (24.1)	53 (26.6)	0

n (%)
*1 Study 301 (data cutoff date of September 13, 2023), Study 101 (data cutoff date of April 25, 2023), Study 102 (data cutoff date of September 29, 2023), Study 103 (data cutoff date of July 24, 2023)
*2 Adverse events coded to MedDRA PTs "nausea," "vomiting," "abdominal discomfort," "abdominal pain," "abdominal pain upper," and "decreased appetite"
*3 Adverse events coded to MedDRA PTs "pyrexia" and "body temperature increased"

In addition, the applicant's explanation about safety in Japanese patients:
The results from Japanese patients enrolled in Study 301 (2 in the Elevidys group, 2 in the placebo group) are shown below.

In 2 subjects in the Elevidys group, 7 moderate adverse events (vomiting [2 subjects, 2 events]; nasopharyngitis [1 subject, 2 events]; constipation [1 subject, 1 event]; pyrexia [1 subject, 1 event]; and influenza [1 subject, 1 event]) and 5 mild adverse events (malaise [1 subject, 1 event]; glutamate dehydrogenase increased [1 subject, 1 event]; COVID-19 [1 subject, 1 event]; nausea [1 subject, 1 event]; and pyrexia [1 subject, 1 event]) occurred. Of these events, 2 events of vomiting, 2 events of pyrexia, 1 event of constipation, 1 event of nausea, 1 event of malaise, and 1 event of glutamate dehydrogenase increased were classified as adverse reactions. The 1 subject additionally enrolled experienced 4 moderate adverse events (influenza; conjunctivitis allergic; upper respiratory tract infection; and pyrexia [1 event each]) and 9 mild adverse events (vomiting [2 events]; and abdominal pain; pyrexia; decreased appetite; glutamate dehydrogenase increased; urinary occult blood positive; lip dry; and arthropod bite [1 event each]). Of these events, abdominal pain; pyrexia; decreased appetite; vomiting; glutamate dehydrogenase increased; and urinary occult blood positive (1 event each) were

classified as adverse reactions, and all resolved. One of the 2 subjects in the placebo group experienced 1 moderate adverse event and 1 mild adverse event (both nasopharyngitis), and their causal relationship was denied. The other subject had no adverse events. No serious or severe adverse events were reported in Japanese patients.

Although interpretation of the results has limitations due to the limited number of Japanese patients (5 patients), there were no new safety concerns unique to the Japanese population.

As described above, the results of clinical studies showed favorable tolerability of Elevidys. Although nausea, vomiting, and pyrexia frequently occurred early after Elevidys infusion in clinical studies and the overseas marketing experience, as the majority of the events were mild or moderate in severity, and even severe events resolved, these events are considered manageable. Thus, to provide precautions, nausea, vomiting, and pyrexia will be listed in the following section of the package insert: 11. DEFECTS/ADVERSE REACTIONS, 11.2 Other Adverse Reactions. Information materials will also provide precautions.

PMDA's discussion:
Although serious adverse reactions were reported in clinical studies, Elevidys is tolerable as long as physicians with adequate knowledge of and experience in DMD manage and take appropriate measures. Nausea, vomiting, and pyrexia occurred frequently early after Elevidys infusion in clinical studies of Elevidys and the overseas marketing experience, and some of those events required medication therapy for recovery or were serious adverse events. Thus, the package insert should include an adequate precautionary statement regarding the management of these events occurring early after infusion.

There should be no problems with the applicant's explanation (No particular problematic events were reported in Japanese patients; and there are no differences in safety profile according to the age group or ambulatory status). However, as the number of patients included in clinical studies was limited, it is necessary to collect post-marketing information.

In the following sections, adverse events that are considered to require attention following administration of Elevidys are assessed. For assessment, the information from clinical studies not included in the clinical data package for the present application (Study 303, Study 305,[28)] Study 104[29)]) is also referenced.

7.R.3.2 Hepatotoxicity

The applicant's explanation about hepatotoxicity associated with Elevidys (1) the incidence of hepatotoxicity in clinical studies and (2) corticosteroid use in clinical studies:

[28)] A long-term follow-up (5 years) study in patients who have previously received Elevidys (study start date, September 27, 2023). In the sub-study, ambulatory patients who participated in Study 101, 102, 103 (Cohorts 1 and 4), or 301 and were 3 to <8 years of age at the time of participation in their previous study are planned to be followed for approximately 10 years post-infusion.
[29)] An open-label study to evaluate the safety and efficacy of Elevidys following imlifidase (a selective immunosuppressant) infusion in DMD patients with pre-existing anti-AAVrh74 antibodies, aged 4 to <10 years

(1) Incidence of hepatotoxicity in clinical studies

In Part 1 of Study 301, the incidences of hepatotoxicity based on SMQ search[30] were 41.3% (26 of 63 subjects) in the Elevidys group and 8.1% (5 of 62 subjects) in the placebo group, showing a higher incidence in the Elevidys group than in the placebo group. Those events reported by 24 of 63 subjects (38.1%) in the Elevidys group and 3 of 62 subjects (4.8%) in the placebo group were classified as adverse reactions. The observed events resolved except for the events reported by 2 subjects in the placebo group. The events reported by 6 subjects in the Elevidys group and 1 subject in the placebo group were severe in severity, and the other events were mild or moderate in severity. Serious adverse events occurred in 5 subjects in the Elevidys group (transaminases increased; liver injury; hepatotoxicity; hepatic enzyme increased; and gamma-glutamyltransferase increased), but not in the placebo group. The majority of adverse events occurred within 90 days of study drug administration. The events reported by 1 subject in the Elevidys group and 3 subjects in the placebo group occurred beyond 90 days post-infusion, none of which required an increase in corticosteroid dose.

The incidence of hepatotoxicity based on laboratory values[31] was similar to the incidence of hepatotoxicity based on SMQ search. The median time to the first onset (range) was 42.0 (7-106) days, the median time from onset to peak (range) was 1.0 (1-37) day, and the median duration (range) was 24.0 (6-77) days.

In the pooled population, adverse events of hepatotoxicity based on SMQ search occurred in 80 of 207 subjects (38.6%). The majority of the events (75 of 207 subjects [36.2%]) were classified as adverse reactions. Severe adverse events occurred in 13 subjects. Of the reported 159 events, 15 events remained unresolved, 1 event had an unknown outcome, and the other events resolved. Serious adverse events occurred in 10 subjects, all of which were classified as adverse reactions. The time to onset was 31 to 56 days post-infusion. Except for the event reported by 1 subject (The event occurred 8 days prior to the data cutoff date for Part 2 of Study 301 and was persisting at that time), all serious adverse events resolved on Days 67 to 119 after Elevidys infusion.

The time to the first onset of hepatotoxicity based on SMQ search was 2 weeks to 60 days after Elevidys infusion in the majority of cases (55 subjects [26.6%]), and the time to the first onset was 60 to 90 days post-infusion in 6 subjects (2.9%). The events reported by these 6 subjects were all non-serous, including 4 mild cases and 2 moderate cases. All those events were classified as adverse reactions and resolved. The time to the first onset was >90 days (157-254 days) after Elevidys infusion in 4 subjects. Among the events reported by these 4 subjects, the events of glutamate dehydrogenase increased reported by 2 subjects were classified as adverse reactions, and prothrombin time prolonged reported by 1 subject and hypertransaminasaemia reported by 1 subject were considered unrelated to Elevidys. All those events were mild in severity and resolved without additional corticosteroid treatment.

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[30] Events in the SMQs "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "hepatitis, non-infectious," "cholestasis and jaundice of hepatic origin," "liver related investigations, signs and symptoms," or "liver-related coagulation and bleeding disturbances"

[31] Any of the following laboratory criteria were met.
GGT >3 × ULN, GLDH >2.5 × ULN, alkaline phosphatase (ALP) >2 × ULN, ALT >3 × baseline (excluding ALT elevation from muscle)

Hepatotoxicity based on laboratory values[32] occurred in 82 of 207 subjects (39.6%). GLDH increased >2.5 × ULN occurred in 72 of 207 subjects (34.8%), GGT increased >3 × ULN in 32 of 207 subjects (15.5%), total bilirubin increased > 2 × ULN in 6 of 207 subjects (2.9%), and ALT increased >3 × baseline in 23 of 207 subjects (11.1%). Among the 82 subjects with hepatotoxicity based on laboratory values, 61 had adverse events of hepatotoxicity based on SMQ search. The median time to the first onset (range) was 43.5 (6-898) days, the median time from onset to peak (range) was 1.0 (1-598) day, and the median duration (range) was 25.0 (3-386) days.

(2) Corticosteroid use in clinical studies

In clinical studies, one day prior to study drug infusion, patients were to begin receiving corticosteroid 1 mg/kg/day (prednisone equivalent) for immunosuppression, in addition to their continued baseline corticosteroid dose, which was to be continued for ≥60 days post-infusion in Studies 301 and 103. If hepatotoxicity occurred after Elevidys infusion, the corticosteroid dose was to be increased to the specified dose, according to the baseline corticosteroid dosing regimen [see Section 7.R.6.3].

In the pooled population, 14 of 76 subjects[33] with adverse events of hepatotoxicity based on SMQ search were treated with intravenous corticosteroids, of whom 13 subjects received high dose IV pulses of steroids. On Days 61 to 90 after Elevidys infusion, the median corticosteroid dose in patients who received additional corticosteroids to treat hepatotoxicity was approximately 2-fold that in patients who did not receive additional corticosteroids. At ≥91 days after Elevidys infusion, the corticosteroid dose returned to baseline.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, serious adverse events of hepatotoxicity based on SMQ search occurred in 7 subjects in Study 301 (4 subjects in Part 1 [hepatotoxicity (2 subjects); liver injury (1 subject); and hepatic enzyme increased (1 subject)], 3 subjects in Part 2 [hepatotoxicity; liver injury; and hepatic enzyme increased]), all of which were classified as adverse reactions. The events reported by 4 subjects in Part 1 occurred on Days 406 to 456 after Elevidys infusion, were treated with corticosteroids, and resolved 1 to 2 months after onset. The events reported by 3 subjects in Part 2 occurred within 60 days after Elevidys infusion and resolved following corticosteroid treatment within 2 months. In 1 subject in Study 303, serious hepatic dysfunction occurred on Day 37 after Elevidys infusion and was classified as an adverse reaction. This event resolved following corticosteroid treatment approximately 4 months after onset.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, 33 serious adverse events of hepatotoxicity based on SMQ search occurred in 17 patients, all of which were classified as adverse reactions. According to the reported cases with clinical course, the events occurred within

[32] Any of the following laboratory criteria were met.
GGT >3 ×ULN, GLDH >2.5 × ULN, ALT >3 × baseline, total bilirubin >2 × ULN, total bilirubin >2 mg/dL
[33] Excluding 4 subjects in Study 101 from whom adverse event treatment data were not collected, from 80 subjects.

60 days after Elevidys infusion and were treated with intravenous corticosteroids. As to the outcome, 10 events had an outcome of resolved, 5 events had an outcome of resolving, 9 events had an outcome of not resolved, and 9 events had an unknown outcome.

Given (1) and (2), although the majority of hepatotoxicity events observed in clinical studies and the overseas marketing experience occurred within 60 days, and there were also serious adverse events, as those events were responsive to corticosteroid treatment, and decreased hepatic functional reserve or hepatic failure was not observed, hepatotoxicity is manageable by monitoring liver function parameters and administering corticosteroids after marketing in the same manner as in clinical studies.

After marketing, the package insert will advise the following points concerning monitoring for hepatotoxicity and corticosteroid dosing.

- Perform liver function tests prior to Elevidys infusion.
- Monitor liver function weekly for the first 3 months after Elevidys infusion (clinical symptoms, γ-GTP, total bilirubin, etc.) and continue until test results return to normal.
- Administer prednisolone before and after Elevidys infusion, according to the doses specified in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section.

PMDA's discussion:
Since serious hepatotoxicity has been reported in clinical studies of Elevidys and the overseas marketing experience, close attention should be paid to the possible occurrence of hepatotoxicity following administration of Elevidys. Thus, information on the incidence of hepatotoxicity and corticosteroid dosing and the method of monitoring liver function to mitigate hepatotoxicity should be provided appropriately to healthcare professionals in clinical practice, using the package insert etc.

7.R.3.3 Immune-mediated myositis

The applicant's explanation about the risk of immune-mediated myositis associated with Elevidys:
In Part 1 of Study 301, the incidences of adverse events indicative of immune-mediated myositis[34)] were 6.3% (4 of 63 subjects) in the Elevidys group and 6.5% (4 of 62 subjects) in the placebo group, and the reported events were asthenia (2 subjects), dysphonia (1 subject), and myositis (1 subject) in the Elevidys group and asthenia (2 subjects) and muscular weakness (2 subjects) in the placebo group. Except that the event reported by 1 subject in the Elevidys group (myositis) was moderate in severity, all those events were mild in severity. The events reported by 3 subjects in the Elevidys group (asthenia [2 subjects]; and myositis [1 subject]) and the event reported by 1 subject in the placebo group (asthenia) were classified as adverse reactions. All those events were non-serious, and except for the event reported by 1 subject in the placebo group (muscular weakness), all events resolved. According to a detailed review using an algorithm for assessment of immune-mediated myositis (*Best Pract Res Clin Rheumatol*. 2020; 34: 101486), none of the events were considered

[34)] Events coded to the MedDRA PTs (autoimmune myositis, dermatomyositis, eosinophilia myalgia syndrome, focal myositis, immune-mediated myositis, juvenile polymyositis, myositis, myositis-like syndrome, polymyositis, asthenia, dysphonia, dysphagia, muscular weakness)

confirmed immune-mediated myositis cases.

In the pooled population, the incidence of adverse events indicative of immune-mediated myositis was 5.8% (12 of 207 subjects), and the reported events were asthenia (6 subjects), muscular weakness (3 subjects), immune-mediated myositis (2 subjects), dysphonia (1 subject), and myositis (1 subject). The events reported by 6 subjects occurred within 60 days after Elevidys infusion. Nine events reported by 8 of the 12 subjects were classified as adverse reactions (asthenia [5 subjects], immune-mediated myositis [2 subjects], muscular weakness [1 subject], myositis [1 subject]). Among the observed events, 2 events remained unresolved, 3 events resolved with sequelae, and the other events resolved. Eleven events reported by 10 subjects were mild or moderate in severity, and these patients carried mutations between exons 18 and 58. Three severe events occurred in 2 subjects (immune-mediated myositis and muscular weakness[35)]; and immune-mediated myositis[36)]) and were classified as serious adverse events and adverse reactions. All those events resolved with sequelae. The results of the ELISpot assay including *ex vivo* epitope mapping obtained from these 2 subjects suggested that patients with deletions in the *DMD* gene that involve exon 8 and/or exon 9 are at highest risk of immune-mediated myositis.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, a serious adverse event indicative of immune-mediated myositis occurred in 1 patient who entered Study 305 from Study 103 and was classified as an adverse reaction. The event occurred on Day 362 after Elevidys infusion and was treated with immunosuppressants including corticosteroids, with an outcome of unresolved.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, 2 serious adverse events of immune-mediated myositis occurred in 2 patients, both of which were classified as adverse reactions. The 1 patient[37)] had an exon 61-79 deletion, and the other patient[38)] had an exon 12-25 deletion.

As described above, immune-mediated myositis occurred after Elevidys infusion in clinical studies and the overseas marketing experience. Immune-mediated myositis causes muscle injury and is life-threatening in the acute phase. In addition, immune-mediated myositis in the subacute and chronic phases may worsen the course

35) A patient with an exon 3-43 deletion aged 8 years enrolled in Cohort 2 of Study 103. The patient had serious immune-mediated myositis on Day 35 after Elevidys infusion and presented with muscular weakness, dysphagia, dyspnoea, dysphonia, fatigue, and difficulty in sitting or walking. Guillain-Barre syndrome was suspected, and the symptoms improved following plasmapheresis. However, cerebrospinal fluid findings denied a diagnosis of Guillain-Barre syndrome, and the patient was diagnosed with autoimmune myositis. Although treatment with tacrolimus was initiated, and the event resolved on Day 100 after Elevidys infusion, muscle strength did not return to baseline.

36) A patient with an exon 8-9 deletion aged 7 years enrolled in Cohort 5a of Study 103. The patient had serious immune-mediated myositis on Day 27 after Elevidys infusion. The patient was infected with Streptococcus and rhinovirus/enterovirus over the same period of time. On Day 30, the patient had weakness worsened, weak cough with congestion, fatigue, sore throat, and oral intake reduced. The event was treated with intravenous methylprednisolone, immunoglobulin, and tacrolimus and resolved with sequelae on Day 36.

37) A patient with an exon 61-79 deletion aged [redacted] years. The patient had the event on Day 32 after Elevidys infusion and presented with severe weakness and dyspnoea. The event was treated with intravenous methylprednisolone, immunoglobulin, and oral prednisolone and resolved without sequelae on Day 104 after Elevidys infusion, and motor function returned to baseline.

38) A patient with an exon 12-25 deletion aged [redacted] years. On Day 25 after Elevidys infusion, dysphonia, muscular weakness, dyspnoea, dysphagia, and pyrexia occurred and worsened, leading to severe muscular weakness and motor dysfunction. The patient was diagnosed with immune-mediated myositis and bilateral pneumonia and received treatment with antibiotics, antivirals, intravenous methylprednisolone, immunoglobulin, plasmapheresis, etc. At approximately 1 month after onset, dysphagia, dysphonia, and respiratory distress improved, but severe muscular weakness and motor dysfunction were persisting.

of DMD by decreasing myofunction. Thus, Elevidys will be contraindicated in patients with any deletion in exon 8 and/or exon 9 who are at increased risk of immune-mediated myositis. Since the possibility that mutations other than deletions in the *DMD* gene that involve exon 8 and/or exon 9 cause immune-mediated myositis cannot be excluded, the package insert etc. will advise that the patient's muscle strength should be closely monitored after Elevidys infusion and that acute signs of muscular weakness and associated adverse events should be appropriately managed.

PMDA's discussion:
Since serious immune-mediated myositis has been reported in clinical studies of Elevidys and the overseas marketing experience, close attention should be paid to the possible occurrence of immune-mediated myositis following administration of Elevidys. Thus, information on the incidence of immune-mediated myositis should be provided appropriately to healthcare professionals in clinical practice, using the package insert etc. Mutations for which Elevidys is contraindicated will be discussed in Section 7.R.5.2.

7.R.3.4 Myocarditis (including elevated troponin)

The applicant's explanation about the risk of myocarditis associated with Elevidys:
In Part 1 of Study 301, elevated troponin I >3 × ULN (or >3 × baseline for patients with increased baseline values) occurred in 2 of 63 subjects (3.2%) in the Elevidys group and 2 of 62 subjects (3.2%) in the placebo group. Adverse events related to elevated troponin and associated myocarditis (events in the MedDRA HLTs "cardiomyopathies" and "noninfectious myocarditis," PTs "troponin increased," "troponin I increased," and "troponin T increased") occurred in 2 subjects in the Elevidys group (myocarditis, troponin I increased, and troponin increased; and troponin I increased) and 2 subjects in the placebo group (troponin I increased). The event reported by 1 subject in the Elevidys group (myocarditis) was classified as a serious adverse event. Among the observed events, the event reported by 1 subject in the Elevidys group (troponin increased) and the event reported by 1 subject in the placebo group (troponin I increased) remained unresolved, and the other events resolved. Only the event of myocarditis observed in the Elevidys group was classified as an adverse reaction.

In the pooled population, elevated troponin I >3 × ULN (or >3 × baseline for patients with increased baseline values) occurred in 17 of 207 subjects (8.2%). There was no trend towards frequent occurrence in a specific time frame. Elevated troponin I was observed at baseline in 18 of 207 subjects. Of the 18 subjects, 6 subjects had elevated troponin I >3 × baseline after Elevidys infusion and reported adverse events indicative of myocarditis. One of the 6 subjects had serious myocarditis. Thirty-three adverse events related to elevated troponin and associated myocarditis (MedDRA HLTs "cardiomyopathies" and "noninfectious myocarditis," PTs "troponin increased," "troponin I increased," and "troponin T increased") occurred in 26 of 207 subjects (12.6%). Those events reported by 9 subjects were classified as adverse reactions, and these patients were identified also by search for patients with elevated troponin I >3 × ULN or baseline. The majority of the events

were mild or moderate in severity. Severe events occurred in 2 subjects (myocarditis[39]), both of which were classified as serious adverse reactions. Of the observed 33 events, 9 events remained unresolved, 3 events resolved with sequelae, and 1 event had an unknown outcome. The other events resolved. Eight subjects had cardiomyopathy. In 1 of the 8 subjects, the event occurred on Day 4 after Elevidys infusion and was classified as an adverse reaction. The event was moderate in severity and resolved by Day 254 after Elevidys infusion. This patient had also a serious adverse reaction of myocarditis. In the remaining 7 subjects, the time to onset ranged from 407 to 1826 days. The events occurred with prolonged study period and remained unresolved. These events were due to the underlying disease of DMD and were considered unrelated to Elevidys.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, serious adverse events of myocarditis or elevated troponin occurred in 2 subjects in Study 301 (troponin I increased [2 events], myocarditis), and the 1 event of troponin I increased only was classified as an adverse reaction. This event occurred on Day 420 after Elevidys infusion and resolved without treatment 2 days after onset.

In other clinical studies of Elevidys, a total of 4 cases of serious adverse events of myocarditis or elevated troponin were reported.

The details of these cases are as follows:
Myopericarditis and troponin I increased; and immune-mediated myositis and myocarditis were reported by 2 subjects in Study 305 (1 patient entered from Study 102, 1 patient entered from Study 103). The events of immune-mediated myositis and myocarditis reported by 1 subject were classified as adverse reactions. In this subject, the event of immune-mediated myositis occurred on Day 362 after Elevidys infusion, and the event of myocarditis occurred on Day 400 after Elevidys infusion. These events were treated with intravenous methylprednisolone, immunoglobulin, etc., both of which had an outcome of unresolved. In Study 303, myocarditis; and troponin I increased were reported by 2 subjects, both of which were classified as adverse reactions. The event of myocarditis reported by 1 subject occurred on Day 8 after Elevidys infusion and resolved following treatment with prednisolone etc. 15 days after onset. The event of troponin I increased reported by 1 subject occurred on Day 2 after Elevidys infusion and resolved without treatment 22 days after onset.

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[39] A 1[redacted]-year-old patient enrolled in Study 103. The patient had a history of cardiomyopathy and a normal left ventricular ejection fraction on echocardiogram at baseline. The patient was hospitalized due to severe vomiting on Day 3 after Elevidys infusion and experienced severe, serious myocarditis on the following day. On Day 6 after Elevidys infusion, troponin I increased to >40,000 pg/mL, and methylprednisolone was administered intravenously. On Day 8 after Elevidys infusion, cardiac MRI revealed extensive late enhancement mainly in the lateral wall. Since troponin I improved, and ECG and echocardiogram findings were stable on Day 12 after Elevidys infusion, the patient was discharged, and myocarditis was considered resolved with sequelae. At approximately 4 months after discharge, echocardiogram findings returned to the condition before the onset of myocarditis, and elevated troponin I persisted, which was likely to be attributed to DMD, rather than myocarditis. Based on the Brighton criteria, a definitive diagnosis of myocarditis was made due to elevated troponin I and late enhancement on the cardiac MRI.

Another case was a [redacted]-year-old patient enrolled in Study 301, and echocardiogram findings were normal at baseline. The patient was hospitalized due to pyrexia, vomiting, and nausea and experienced serious myocarditis on Day 1 after Elevidys infusion. The patient was transferred to the intensive care unit on the following day. Though troponin I increased, there were no major changes from baseline in ECG and echocardiogram. The patient was treated with ondansetron and fluids and discharged on Day 3 after Elevidys infusion. Troponin I decreased to the normal range on Day 21 after Elevidys infusion, and the outcome of myocarditis was considered "resolved." Based on the Brighton criteria, the event was likely to be myocarditis because of elevated troponin I and clinical symptoms.

After October 31, 2024, a new event that was likely to be myocarditis was reported in 1 non-ambulatory patient in Study 303.[40)]

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, a serious adverse event of myocarditis or elevated troponin occurred in 1 patient (troponin I increased) and was classified as an adverse reaction. The event occurred on Day 142 after Elevidys infusion and resolved following treatment with prednisolone 24 days after onset.

As described above, elevated troponin I and myocarditis occurred after Elevidys infusion in clinical studies and the overseas marketing experience. Myocarditis may seriously affect DMD patients and may become a problem especially in patients with pre-existing DMD cardiomyopathy. Thus, in order to reduce the risk of myocarditis, the package insert will mention the risk of myocarditis and advise that troponin I should be monitored after Elevidys infusion. Post-marketing information on the relationship between Elevidys and myocarditis will be collected.

PMDA's discussion:
Myocarditis has been reported in clinical studies of Elevidys etc., and attention should be paid to the possible occurrence of myocarditis following administration of Elevidys. Thus, information on the incidence of myocarditis and the need for troponin I monitoring, etc. should be provided appropriately to healthcare professionals in clinical practice, using the package insert etc. In addition to the measures proposed by the applicant, the package insert etc. should advise that there is no clinical experience with Elevidys in patients with left ventricular ejection fraction <40% on echocardiogram or clinical signs or symptoms of cardiomyopathy, because these patients were excluded from Study 301 etc.

7.R.3.5 Rhabdomyolysis

The applicant's explanation about the risk of rhabdomyolysis associated with Elevidys:
Adverse events related to rhabdomyolysis (acute onset or worsening of MedDRA PTs "rhabdomyolysis," "myoglobinuria," "chromaturia," and "myalgia") occurred in 8 of 63 subjects (12.7%) in the Elevidys group and 9 of 62 subjects (14.5%) in the placebo group in Part 1 of Study 301. According to a detailed review using an algorithm for assessment of rhabdomyolysis[41)] (*Medicine*. 1982; 61: 141-52, *Eur J Intern Med*. 2007 ; 18: 90-100), no events were classified as "probable rhabdomyolysis," 3 events reported by 2 subjects were classified as "possible rhabdomyolysis" (1 subject each in the Elevidys and placebo groups), and other events

[40)] A 1[redacted]-year-old patient did not have concurrent cardiac disorder at baseline. Nausea, grade 4 supraventricular tachycardia, chest pain, and troponin I increased occurred within 24 hours after Elevidys infusion. The cardiac MRI revealed signs of inflammation consistent with myocarditis, and echocardiogram showed worsened left ventricular ejection fraction. Following treatment with intravenous corticosteroids, antiarrhythmics, etc., the event resolved on Day 5 after Elevidys infusion.

[41)] The events were to be categorized according to the following definitions.

- "Probable rhabdomyolysis": Signs/symptoms of a) myalgia, b) weakness or inability to walk, and c) reddish-brown urine or myoglobinuria are all present, with acute CPK elevation (≥2 × baseline).
- "Possible rhabdomyolysis": Two of signs/symptoms of a), b), and c) are present with acute CPK elevation (≥2 × baseline).
- "Unlikely rhabdomyolysis or unassessable": One of signs/symptoms of a), b), and c) are present with acute CPK elevation (≥2 × baseline).

were classified as "unlikely rhabdomyolysis or unassessable." In the 1 subject with "possible rhabdomyolysis" in the Elevidys group, 2 events of rhabdomyolysis were reported as serious events on Days 3 and 171 after Elevidys infusion, and the event occurring on Day 3 post-infusion was classified as an adverse reaction.

Adverse events related to rhabdomyolysis based on SMQ "rhabdomyolysis/myopathy" search occurred in 10 of 63 subjects (15.9%) in the Elevidys group and 14 of 62 subjects (22.6%) in the placebo group. The majority of these events were considered unrelated to study drug and were also mild or moderate in severity. Severe events occurred in 1 subject in the Elevidys group (rhabdomyolysis) and 1 subject in the placebo group (blood creatine phosphokinase increased), of which, rhabdomyolysis in the Elevidys group was classified as a serious adverse event. The events reported by 3 subjects in the Elevidys group and 2 subjects in the placebo group occurred within 2 weeks of study drug administration, but the other events all occurred beyond 2 weeks post-infusion. Among the observed events, 3 events in the placebo group remained unresolved, and the other events resolved.

In the pooled population, adverse events related to rhabdomyolysis occurred in 24 of 207 subjects (11.6%). Adverse events related to rhabdomyolysis based on SMQ search occurred in 36 of 207 subjects (17.4%). Those reported by 18 subjects were classified as adverse reactions. The majority of the events were mild or moderate in severity. Six severe events occurred in 5 subjects (rhabdomyolysis [4 subjects, 5 events]; and muscular weakness [1 subject, 1 event]), all of which were classified as serious adverse events. Except for 2 events of rhabdomyolysis, 4 events reported by 4 subjects were classified as adverse reactions. Among the 5 serious adverse events of rhabdomyolysis reported by 4 subjects, 2 events occurred early after Elevidys infusion (Days 3 and 16), and the other 3 events were late-onset (Days 156, 171, and 790). Although the time to onset varied widely, all events resolved within several days after onset. The serious adverse reaction of muscular weakness occurred on Day 35 after Elevidys infusion and resolved on Day 100 after Elevidys infusion. No patients reported events related to the kidney, heart, or abnormal electrolytes.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, 2 serious adverse events related to rhabdomyolysis (rhabdomyolysis) occurred in 1 subject in Study 301, both of which were classified as adverse reactions. Those events occurred on Days 457 and 605 after Elevidys infusion. The former resolved following treatment with prednisolone and fluids 3 days after onset, and the latter resolved following treatment with fluids only 8 days after onset.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, serious adverse events related to rhabdomyolysis, i.e., myalgia; and blood creatine phosphokinase increased, occurred in 2 patients, both of which were classified as adverse reactions. The event of myalgia (the date of onset and action taken were unknown) had an outcome of resolved, and the event of blood creatine phosphokinase increased occurred on Day 267 after Elevidys infusion and was treated with fluids, with an unknown outcome.

As described above, serious rhabdomyolysis and serious adverse events related to rhabdomyolysis were

reported in clinical studies of Elevidys and the overseas marketing experience, but were manageable. Post-marketing information on the incidence of rhabdomyolysis will be collected.

PMDA's discussion:
Since serious rhabdomyolysis has been reported in clinical studies of Elevidys and the overseas marketing experience, attention should be paid to the possible occurrence of rhabdomyolysis following administration of Elevidys. Thus, information on the incidence of rhabdomyolysis should be provided to healthcare professionals in clinical practice, using the package insert etc. Moreover, post-marketing safety information should be collected, and the obtained information should be provided to healthcare professionals in clinical practice.

7.R.3.6 Hypersensitivity-related adverse events (including infusion-related reactions)

The applicant's explanation about the risk of hypersensitivity associated with Elevidys:
Adverse events of hypersensitivity[42)] occurred in 19 of 63 subjects (30.2%) in the Elevidys group and 21 of 62 subjects (33.9%) in the placebo group in Part 1 of Study 301. The majority of these events were considered unrelated to study drug, and adverse reactions occurred in 5 of 63 subjects (7.9%) in the Elevidys group and 1 of 62 subjects (1.6%) in the placebo group. Among the observed events, the events reported by 4 subjects in the Elevidys group and the events reported by 4 subjects in the placebo group remained unresolved, and the other events resolved. A causal relationship to study drug was denied for all of the unresolved events.

In the pooled population, adverse events of hypersensitivity occurred in 63 of 207 subjects (30.4%). Of whom, 15 subjects had a first onset within 2 weeks after Elevidys infusion, and 11 subjects had a first onset at >2 weeks to 60 days post-infusion. The remaining 37 patients had a first onset beyond 60 days after Elevidys infusion. Among the observed events, the events reported by 13 subjects remained unresolved, the event reported by 1 subject resolved with sequelae, and the other events resolved. A causal relationship to study drug was denied for all of the unresolved events. Adverse reactions of hypersensitivity occurred in 10 of 207 subjects (4.8%), and those reported by ≥2 subjects were complement factor C4 decreased (3 subjects); and myocarditis (2 subjects). The majority of the events of hypersensitivity were mild or moderate in severity. Severe events were myocarditis (2 subjects) and classified as serious adverse reactions [see Section 7.R.3.4].

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, no serious adverse events of hypersensitivity were reported in the pooled population. In other clinical studies of Elevidys, serious adverse events of hypersensitivity reported were anaphylactoid reaction (1 subject) (Study 303) and urticaria (1 subject) (Study 104), both of which were classified as adverse reactions. Those events occurred on the day of Elevidys infusion and resolved following treatment with antihistamines etc. 1 to 5 hours later.

[42)] The following events:
- Events coded to the MedDRA PTs "anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, angioedema, epiglottic oedema, laryngeal oedema, laryngotracheal oedema, lip oedema, swollen tongue, tongue oedema, and tracheal oedema"
- Severe (CTCAE Grade ≥3) events in the MedDRA SMQ "hypersensitivity"
- Severe (CTCAE Grade ≥3) events coded to the MedDRA PTs "haemolytic uraemic syndrome, atypical haemolytic uraemic syndrome, acute kidney injury, arteritis, myocarditis, myositis, polymyositis, pneumonitis, thrombotic microangiopathy, and microangiopathic haemolytic anaemia"

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, serious adverse events of hypersensitivity were observed in 2 patients (anaphylactic reaction; and rash erythematous, erythema, urticaria, hypersensitivity, and flushing). All those events were classified as adverse reactions, occurred within 1 hour after Elevidys infusion, and resolved on that day following treatment with antihistamines etc.

A search of adverse events in the MedDRA SMQ "hypersensitivity (narrow and broad)" and other adverse events occurring within 24 hours of Elevidys infusion was conducted using the safety data from all clinical studies of Elevidys and the overseas marketing experience (November 3, 2017 to March 8, 2024), and whether the relevant events were consistent with infusion-related reactions was assessed medically. The events of infusion-related reactions occurred during or within 24 hours of Elevidys infusion in 2 of 216 subjects treated with Elevidys in clinical studies (1 non-serious case, 1 serious case) and 7 patients representing 6.5% of all patients treated with Elevidys in the overseas marketing experience (5 non-serious cases, 2 serious cases). As to the 6 non-serious cases, the events other than 1 event of unreported severity were mild in severity and resolved shortly without treatment or following drug therapy (antihistamines, corticosteroids, etc.), and Elevidys infusion was completed.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, 2 cases of serious adverse events of hypersensitivity were reported in Studies 303 and 104, and 2 cases of serious adverse events of hypersensitivity were reported in the overseas marketing experience. All those events were considered infusion-related adverse events.

As described above, serious hypersensitivity (infusion-related reaction) was reported in clinical studies of Elevidys and the overseas marketing experience, but was manageable with a reduction in infusion rate, stopping infusion, or medical intervention. Thus, the package insert will list the risk of infusion-related reactions and advise that Elevidys should be administered in a setting where treatment for infusion-related reactions is immediately available.

PMDA's discussion:
Since serious hypersensitivity (infusion-related reaction) has been reported in clinical studies of Elevidys and the overseas marketing experience, adequate caution is needed when administering Elevidys. A relevant precautionary statement should be included in the package insert, and post-marketing information on the incidence of hypersensitivity should be collected.

7.R.3.7 Thrombocytopenia (including thrombotic microangiopathy)

The applicant's explanation about the risk of thrombocytopenia (including thrombotic microangiopathy) associated with Elevidys:
Adverse events of thrombocytopenia (events in the MedDRA SMQ "haematopoietic thrombocytopenia")

occurred in 2 of 63 subjects (3.2%) in the Elevidys group in Part 1 of Study 301. No events were reported in the placebo group. Among the events observed in the Elevidys group, the event reported by 1 subject occurred on Day 8 after Elevidys infusion and was classified as an adverse reaction. The event was mild in severity and resolved by Day 14 after Elevidys infusion. The other event occurred on Day 43 after Elevidys infusion and was considered unrelated to Elevidys because platelet clumping at the time of sampling was reported.

In the pooled population, the incidence of adverse events of thrombocytopenia was 8.7% (18 of 207 subjects). In 15 of the 18 subjects, the event occurred within 2 weeks after Elevidys infusion. All those events were mild or moderate in severity and non-serious. The events other than 2 events of thrombocytopenia were classified as adverse reactions, and all events resolved. There was no clear correlation between thrombocytopenia reported within 2 weeks after Elevidys infusion and adverse events of bleeding.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, no serious adverse events of thrombocytopenia were reported in the pooled population. In 1 patient in Study 305 (1 patient entered from Study 103), serious thrombocytopenia occurred on Day 403 after Elevidys infusion. The event was classified as an adverse reaction, but resolved without treatment 2 days after onset.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, no serious adverse events of thrombocytopenia were reported.

As thrombotic microangiopathy, events coded to the MedDRA PTs "haemolytic uraemic syndrome, atypical haemolytic uraemic syndrome, thrombotic microangiopathy, acute kidney injury, microangiopathic haemolytic anaemia, and red cell fragmentation syndrome" were counted. Thrombotic microangiopathy occurred in 1 subject in the placebo group (acute kidney injury) only, but not in the Elevidys group, in Part 1 of Study 301. In the pooled population, no relevant adverse events were reported. In all clinical studies and the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, no relevant serious adverse events were reported.

In 207 subjects in the pooled population, the mean platelet count at baseline was 317.05 × 10^9/L, which decreased shortly after Elevidys infusion, and the mean change from baseline to Week 1 was −111.11 × 10^9/L. Then, platelet counts returned to baseline levels at Week 36 onwards. Platelet counts fell to <75 × 10^9/L in 8 subjects, and 2 of the 8 subjects had Grade 3 (<50 × 10^9/L) decreases. Although Grade 3 decreases in these 2 subjects occurred on Days 43 and 74 after Elevidys infusion, platelet clumping seen in these samples suggested that the measurements of low platelet counts were most likely not accurate. There were no Grade 4 (<25 × 10^9/L) decreases.

Hemoglobin levels <10 g/dL and lactate dehydrogenase ≥2 × baseline during the first 2 weeks following administration of Elevidys were reviewed for signs of potential thrombotic microangiopathy. No hemoglobin values <10 g/dL were found up to Week 2. There were 5 patients with lactate dehydrogenase ≥2 × baseline

during the first 2 weeks after Elevidys infusion, none of whom had hemoglobin values <10 g/dL.

As described above, though thrombocytopenia occurred early after Elevidys infusion in clinical studies, there were no clinically problematic events, and no serious thrombocytopenia or thrombotic microangiopathy was reported in clinical studies or the overseas marketing experience. However, as decreased platelet counts were observed early after Elevidys infusion in clinical studies, the package insert will advise that platelet counts should be monitored after Elevidys infusion.

PMDA's discussion:
Although thrombotic microangiopathy has not been reported in clinical studies of Elevidys or the overseas marketing experience, decreased platelet counts were observed early after Elevidys infusion in clinical studies in which Elevidys was administered, and caution should be exercised when administering Elevidys. Thus, the package insert etc. should advise that platelet counts should be monitored, and post-marketing information on the incidences of thrombocytopenia and thrombotic microangiopathy should be collected and provided appropriately to healthcare professionals in clinical practice.

7.R.3.8 Adverse events attributable to additional corticosteroid use

The applicant's explanation about adverse events attributable to additional corticosteroid use required for Elevidys administration:
In the pooled population, as adverse events attributable to additional corticosteroid use, adverse events in the MedDRA SOC "infections" were counted. The incidence of those events within 12 weeks after Elevidys infusion (53 of 207 subjects [25.6%]) was similar to that at >12 weeks to 24 weeks after Elevidys infusion (54 of 207 subjects [26.1%]), which did not indicate that additional corticosteroid use early after Elevidys infusion increased infections.

Between the primary data cutoff (July 24, 2023 for Study 103, September 13, 2023 for Study 301) and October 31, 2024, in the pooled population, serious adverse events attributable to additional corticosteroid use[43)] occurred on Day 458 after Elevidys infusion in 1 subject (forearm fracture) in Study 301 and on Day 62 after Elevidys infusion in 1 subject (gastroenteritis) in Study 303. These serious adverse events were considered unrelated to Elevidys, and had an outcome of resolved.

In the overseas marketing experience between the launch date of June 22, 2023 and October 31, 2024, no serious adverse events attributable to additional corticosteroid use were reported. Six cases of serious adverse events in the MedDRA SOC "infections" were reported, but were not attributable to additional corticosteroid use.

As described above, a few cases of serious adverse events attributable to additional corticosteroid use after

[43)] Events considered by the investigator as adverse events attributable to additional corticosteroid use

Elevidys infusion were reported in clinical studies, but were considered manageable because there were no unexpected abnormalities. The package insert etc. will advise about the risk of infections due to administration of corticosteroids.

PMDA's discussion:
Serious adverse events attributable to additional corticosteroid use have been reported in clinical studies of Elevidys. Adequate caution is needed when administering an even higher dose of corticosteroids to patients on background chronic corticosteroid therapy. Thus, the package insert etc. should advise about the risk associated with additional corticosteroid use, and post-marketing information on the incidence of adverse events attributable to additional corticosteroid use should be collected and provided appropriately to healthcare professionals in clinical practice.

7.R.3.9 Malignancies

The applicant's explanation about the risk of malignancies associated with Elevidys:
By October 31, 2024, no adverse events in the MedDRA SMQ (broad) "malignancies" were reported in clinical studies in which Elevidys was administered and the overseas marketing experience. However, as the investigation is limited at present, the incidence of malignancies will be monitored after marketing.

PMDA's discussion:
Although there were no malignancies in clinical studies of Elevidys and the overseas marketing experience, as the number of patients treated with Elevidys is limited, post-marketing information on the incidence of malignancies should be collected.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of Elevidys:
DMD is an X-linked degenerative neuromuscular disease caused by mutations in the dystrophin gene and subsequent deficiency of dystrophin protein, which is critical for maintaining muscle fiber integrity etc. Treatments include drug therapy, rehabilitation, pain management, orthopedic surgery, and respiratory management. As drug therapy, corticosteroids are recommended as standard of care in Japan and overseas (Japanese Society of Neurology. Clinical Practice Guideline for Duchenne muscular dystrophy 2014 [in Japanese]). Prednisolone has been approved in Japan, and vamorolone, which has similar effects to corticosteroids and fewer adverse reactions, has been approved in Western countries, none of which treats the underlying cause of DMD. As exon 53 skipping therapy to increase dystrophin protein, viltolarsen has been approved under conditional early approval system in Japan, but only approximately 8% of DMD patients can be treated with viltolarsen that works by skipping exon 53 (*Hum Mutat*. 2009; 30: 293-9). Furthermore, viltolarsen is an intravenous infusion that is administered once weekly, and a once-weekly visit is a burden for DMD patients and their families and caregivers. Rehabilitation, pain management, orthopedic surgery, and respiratory management are just supportive care according to disease progression.

Elevidys is a novel therapeutic product with a mode of action different from the currently approved drugs. In clinical studies, Elevidys improved motor function or slowed decline in motor function. Elevidys will become a new treatment option for patients with DMD because it addresses the underlying cause of DMD and is expected to improve clinical outcomes of the disease.

PMDA accepted the above explanation by the applicant. The appropriateness of "INDICATION OR PERFORMANCE" for Elevidys will be discussed in Section "7.R.5 Indication or performance."

7.R.5 Indication or Performance

The proposed indication or performance statement is as follows:

"Duchenne muscular dystrophy (excluding patients with any genetically-confirmed deletion in exon 8 and/or exon 9 in the *DMD* gene) exclusively in anti-AAVrh74 antibody-negative patients"

The following statements were included in the PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE section.

1. Administer Elevidys to patients with Duchenne muscular dystrophy confirmed based on genetic testing etc.
2. Administer Elevidys to patients who test negative for anti-AAVrh74 antibodies. The approved *in vitro* diagnostic or medical device should be used for testing. The safety and efficacy of Elevidys in patients with elevated anti-AAVrh74 antibody titers have not been evaluated. Information on the approved *in vitro* diagnostic or medical device is available from the following website: XX
3. Eligible patients must be selected by physicians with a full understanding of the information presented in the section of "17. CLINICAL STUDIES" concerning the characteristics of patients (age, ambulatory status, etc.) enrolled in the clinical study and of the efficacy and safety of Elevidys.
4. Administer Elevidys to patients aged 3 to less than 8 years. The efficacy and safety of Elevidys in patients aged <3 years or patients aged ≥8 years have not been established.
5. The efficacy and safety of Elevidys in non-ambulatory patients have not been established.
6. No clinical studies in female patients have been conducted.

Based on Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning of Elevidys" and the following considerations, PMDA concluded that the following statements should be included in the INDICATION OR PERFORMANCE and PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE sections.

Indication or Performance (Underline denotes additions, and strikethrough denotes deletions.)

Duchenne muscular dystrophy ~~(excluding patients with any genetically-confirmed deletion in exon 8 and/or exon 9 in the *DMD* gene)~~ exclusively ~~in anti-AAVrh74 antibody-negative patients~~ meeting all of the following criteria:

- Anti-AAVrh74 antibody-negative patients

- Ambulatory patients
- Patients aged 3 to less than 8 years

Precautions Concerning Indication or Performance (Underline denotes additions, and strikethrough denotes deletions.)

1. Administer Elevidys to patients with Duchenne muscular dystrophy confirmed based on genetic testing etc.
2. Administer Elevidys to patients who test negative for anti-AAVrh74 antibodies. The approved *in vitro* diagnostic or medical device should be used for testing. ~~The safety and efficacy of Elevidys in patients with elevated anti-AAVrh74 antibody titers have not been evaluated.~~ Information on the approved *in vitro* diagnostic or medical device is available from the following website: ~~XX~~ https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
3. Eligible patients must be selected by physicians with a full understanding of the information presented in the section of "17. CLINICAL STUDIES" concerning the characteristics of patients (age, ambulatory status, etc.) enrolled in the clinical study and of the efficacy and safety of Elevidys.
4. ~~Administer Elevidys to patients aged 3 to less than 8 years. The efficacy and safety of Elevidys in patients aged <3 years or patients aged ≥8 years have not been established.~~
5. ~~The efficacy and safety of Elevidys in non-ambulatory patients have not been established.~~
6. No clinical studies in female patients have been conducted.

7.R.5.1 Patients who test positive for anti-AAVrh74 antibodies

The applicant's explanation about limiting the use of Elevidys to patients who test negative for anti-AAVrh74 antibodies:

In clinical studies of Elevidys, patients who tested negative for anti-AAVrh74 antibodies only were allowed to be enrolled. Study 104 in which Elevidys is administered to patients with pre-existing anti-AAVrh74 antibodies is ongoing, and 1 event of urticaria occurred as a serious adverse event in this clinical study. The patient had serious, severe urticaria with marked flushing, rash, oedema, nausea, malaise, etc., at 8 minutes after starting Elevidys infusion, and the infusion of Elevidys was stopped. As reference information, when an AAV vector containing an AAVrh74 capsid, which is the same as Elevidys, was readministered to rhesus monkeys with anti-AAVrh74 antibody titers of ≥1:400, microdystrophin expression was attenuated compared with sero-negative animals (*Mol Ther.* 2014; 22: 338-47). In a non-GLP study, when Elevidys was readministered to rhesus monkeys with elevated anti-AAVrh74 antibody titers after Elevidys administration, acute systemic findings (increases in respiratory rate and heart rate, lethargy, rash) indicative of immune-medicated effects were observed.

Based on the above, when Elevidys is administered to patients who test positive for anti-AAVrh74 antibodies, adverse events may occur, and efficacy may be reduced. The efficacy and safety of Elevidys in these patients have not been established. Thus, patients who test positive for anti-AAVrh74 antibodies are not eligible for Elevidys therapy.

PMDA accepted the above explanation by the applicant.

7.R.5.2 Patients with any deletion in exon 8 and/or exon 9

The applicant's explanation about the basis for contraindication of Elevidys in patients with any deletion in exon 8 and/or exon 9 and the use of Elevidys in patients with other genetic mutations:

The micro-dystrophin transgene in Elevidys contains exons 1-17, exons 59-71, and exon 79 of the dystrophin gene [see Section 2]. At the time of regulatory submission, 17 of 207 patients treated with Elevidys in clinical studies had mutations in exons 1-17, of whom 2 patients with deletion mutations involving exon 8 and/or exon 9 in the *DMD* gene experienced serious immune-mediated myositis with severe muscular weakness at approximately 1 month post-infusion, which may have resulted from a T-cell response due to a lack of self-tolerance to a specific region of micro-dystrophin protein expressed by Elevidys. On the other hand, in 15 patients with mutations in exons 1-17 (deletions in 7 patients, duplications in 5 patients, micro/point mutations in 3 patients) other than these 2 patients and 16 patients with mutations in exons 59-79 (deletions in 2 patients, duplications in 1 patient, micro/point mutations in 7 patients, intron mutations in 6 patients), no adverse events related to skeletal muscular weakness or immune-mediated myositis were reported. In addition, only 3 amino acids are derived from exon 79, and a deletion of this exon is unlikely to induce an immune response, etc. Thus, the risk of immune-mediated myositis should be low in patients with a deletion in exon 79.

Patients with mutations in exon 45 were excluded from Study 301 because they exhibit a milder phenotype and thus may impact efficacy results. In other clinical studies, 8 patients with mutations in exon 45 received Elevidys, and none of them experienced adverse events related to skeletal muscular weakness or immune-mediated myositis.

Based on the above, Elevidys will be contraindicated in patients with any deletion in exon 8 and/or exon 9 due to the increased risk for immune-mediated myositis. On the other hand, patients with any deletion in exons 1-17 and/or exons 59-71 will be eligible for Elevidys therapy, with the package insert advising that safety and efficacy information is limited, because at present, there has been no sufficient risk to contraindicate Elevidys in these patients. Since there are no safety concerns about mutations in exon 45 or exon 79, a contraindication and a precautionary statement are unnecessary. In patients with mutations other than deletions (duplications or micro/point mutations, etc.) in exons 1-17 and exons 59-71, a certain level of expression of a protein containing the dystrophin sequence may occur, and self-tolerance to micro-dystrophin protein expressed by Elevidys should arise. Thus, a contraindication and a precautionary statement are unnecessary.

PMDA's discussion:

Although the above explanation by the applicant is understandable, as information on the safety of Elevidys in patients with mutations other than those in exon 8 and/or exon 9 is limited, it is necessary to collect post-marketing information on the relationship between mutation sites and immune-mediated myositis and appropriately provide the information to healthcare professionals in clinical practice. Given that patients with

any deletion in exon 8 and/or exon 9 will be listed in the CONTRAINDICATIONS section of the package insert, a relevant statement in the INDICATION OR PERFORMANCE section is a repetition and may thus be deleted from this section.

7.R.5.3 Non-ambulatory patients

Non-ambulatory patients enrolled in clinical studies were only 6 patients in Cohort 3 and 2 patients in Cohort 5b of Study 103, and limited information on the efficacy and safety of Elevidys in these patients was provided. PMDA asked the applicant to provide a justification for including non-ambulatory patients in the indication for Elevidys.

The applicant's response:

The results from Cohorts 3 and 5b of Study 103 in which non-ambulatory DMD patients were enrolled raised no particular safety concerns. A clinical study in non-ambulatory DMD patients and ambulatory DMD patients aged 8 to <18 years to evaluate the efficacy and safety of Elevidys (Study 303) is currently ongoing. Given that the efficacy and safety results of Elevidys in non-ambulatory patients are insufficient at present, the following information will be included in the PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE section: "The efficacy and safety of Elevidys in non-ambulatory patients have not been established."

PMDA's discussion:

At present, there is very limited experience with Elevidys in non-ambulatory patients with DMD in clinical studies, and the benefits of administering Elevidys to non-ambulatory patients are unknown. Thus, the INDICATION OR PERFORMANCE section should clearly state that Elevidys should be used only in "ambulatory patients."

7.R.5.4 Age restriction for the use of Elevidys

The applicant's explanation about the age restriction for the use of Elevidys:

(1) Patients aged 4 to less than 8 years

In Study 301 (Table 46), the change in the NSAA total score from baseline to Week 52 was greater in the Elevidys group than in the placebo group among patients aged 4 to <6 years. A similar trend was observed also for motor function endpoints, e.g., the time to rise from the floor and time of 10-meter walk/run. In patients aged 6 to <8 years, there were no differences in the change in the NSAA total score from baseline to Week 52 between the Elevidys and placebo groups. However, taking account of the results of the time to rise from the floor, time of 10-meter walk/run, and time of 100-meter walk/run, motor function tended to worsen in the placebo group, whereas there was a trend towards no change in motor function in the Elevidys group [see Section 7.R.2.2.1].

As shown in Table 49, decline in motor function was slower in patients treated with Elevidys 1.33×10^{14} vg/kg in Studies 101 and 102 and Cohort 1 of Study 103 than in external controls [see Section 7.R.2.2.2]. A subgroup analysis of the NSAA total score according to the age group (4 to <6 years, 6 to <8 years) also showed similar

results between the age subgroups (Table 57).

Table 57. Change from baseline in NSAA total score comparison to external controls by age subgroup (Study 101, Study 102,[*1] Study 103 Cohort 1)

	4 to <6 years		6 to <8 years	
	Elevidys	External control	Elevidys	External control
Baseline[*2]	21.5 ± 3.0 21.0 [18, 27] (n = 19)	24.1 ± 3.6 24.0 [13, 30] (n = 53)	22.0 ± 4.3 22.5 [13, 30] (n = 28)	24.4 ± 4.7 26.0 [13, 30] (n = 104)
Change at Year 1[*2]	5.2 ± 2.4 5.0 [1, 10] (n = 19)	1.7 ± 3.5 2.0 [−8, 9] (n = 53)	1.0 ± 2.9 1.0 [−5, 7] (n = 28)	−0.4 ± 3.6 0.0 [−10, 6] (n = 102)
LS mean treatment difference[*3] [95% CI]	3.32 [1.54, 5.10]		2.53 [1.26, 3.79]	
Change at Year 2[*2]	5.0 ± 3.0 4.0 [−1, 11] (n = 19)	1.2 ± 4.8 2.0 [−9, 10] (n = 35)	−1.4 ± 6.0 0.5 [−17, 7] (n = 28)	−1.1 ± 5.1 0.0 [−13, 8] (n = 82)
LS mean treatment difference[*3] [95% CI]	5.57 [2.97, 8.17]		1.67 [−0.61, 3.94]	
Change at Year 3[*2]	4.3 ± 3.9 4.0 [−3, 12] (n = 19)	0.5 ± 6.5 1.0 [−17, 9] (n = 22)	−4.5 ± 8.5 −3.0 [−25, 6] (n = 26)	−4.8 ± 7.4 −4.5 [−22, 10] (n = 52)
LS mean treatment difference[*3] [95% CI]	3.68 [−0.22, 7.59]		2.70 [−1.00, 6.39]	

*1 Patients treated with Elevidys 1.33×10^{14} vg/kg only were included in the analyses, and patients treated with 6.29×10^{13} vg/kg or 8.94×10^{13} vg/kg were not included.
*2 Upper row, Mean ± SD; Lower row, Median [Range]
*3 A propensity score-weighted multiple regression model with treatment group, visit, baseline score, treatment group-by-visit interaction, and baseline score-by-visit interaction as covariates. The model assumed an unstructured variance-covariance matrix. Propensity scores were estimated using a logistic regression model with baseline age group, baseline NSAA total score, baseline time to rise from the floor, baseline time of 10-meter walk/run, body weight, height, and BMI as covariates.

The natural history of DMD is that by 8 years of age, most patients lose the ability to get up from the floor or climb stairs. At the age of 13 years, patients lose ambulation and become wheelchair dependent (*Lancet.* 2018; 391: 451-61). Loss of ambulation is an extremely important disease milestone for patients with DMD. Preservation of ambulation as long as possible directly impacts the activities of daily living and the quality of life and is clinically meaningful for both patients and their caregivers. Among the motor function endpoints chosen for Study 301 etc., especially, the time to rise from the floor has been shown to be a prognostic factor for the course of the disease, and there is a positive correlation between the time to rise from the floor and the age of loss of ambulation. In patients aged around 6 years, lower time to rise from the floor at baseline was associated with older age at loss of ambulation (*Dev Med Child Neurol*. 2022; 64: 979-88). Tables 46, 49, and 57 indicate that in ambulatory patients aged 4 to <8 years, Elevidys is expected to improve motor function or slow decline in motor function and may contribute to prolongation of ambulation.

(2) Patients aged 3 years

Muscle damage in DMD is evident early after birth, and damaged muscle fibers are replaced by fat and fibrosis leading to irreversible muscle loss. Thus, earlier gene therapy intervention may provide greater therapeutic benefits. As to the efficacy of Elevidys in DMD patients aged 3 years, the results presented in Table 38 were obtained from 7 patients enrolled in Cohort 4 of Study 103, and there was a trend towards improvements in all endpoints. Micro-dystrophin expression levels in these 7 patients were equal to or greater than those in patients aged 4 to <8 years (Study 301 and Cohort 1 of Study 103) [see Table 37 and Section 7.1.2.1].

Based on the above, the efficacy of Elevidys is expected also in patients aged 3 years.

In addition, as shown in Table 56, there were no differences in the safety profile of Elevidys among the age subgroups of 3 years, 4 to <6 years, and 6 to <8 years, and Elevidys is considered tolerable across all age groups.

Based on the above, as the benefit-risk balance of Elevidys was favorable in ambulatory patients with DMD aged 3 to <8 years, Elevidys should be indicated for use in patients aged 3 to <8 years.

(3) Patients aged <3 years or ≥8 years
A clinical study in patients aged <3 years (Cohort 6 of Study 103) and clinical studies in ambulatory patients aged 8 to <18 years (Cohort 2 of Study 103 and Study 303) are ongoing. Since the efficacy and safety of Elevidys in these age groups of patients have not been established, the lower limit of age should be ≥3 years, and the upper limit of age should be <8 years.

On the basis of the above considerations (1) to (3), the applicant considers that Elevidys should be indicated for use in patients aged 3 to <8 years. The following statements will be included in the PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE section: "Administer Elevidys to patients aged 3 to less than 8 years. The efficacy and safety of Elevidys in patients aged <3 years or patients aged ≥8 years have not been established."

PMDA's discussion:
The efficacy of Elevidys is expected in patients aged 4 to <8 years based on the long-term data up to 3 years post-infusion. Including these patients in the indication for Elevidys is acceptable. As to patients aged 3 years, the information is limited, e.g., no long-term data are available. However, given that the efficacy of Elevidys is expected based on the currently available results from 7 patients enrolled in Cohort 4 of Study 103, and that it is important to initiate treatment as early as possible and offer a treatment option that may prevent loss of ambulation, including also patients aged 3 years in the indication for Elevidys is acceptable.

If the age restriction for the use of Elevidys is changed in future, a partial change application for Elevidys should be submitted based on the data from clinical studies in an additional age group of patients, and the appropriateness of the change should be assessed in the review. Thus, the age restriction for the use of Elevidys should be specified in the INDICATION OR PERFORMANCE section.

7.R.5.5 Female patients

Male patients only were enrolled in clinical studies, and the efficacy and safety of Elevidys in female patients have not been evaluated. PMDA asked the applicant to provide a justification for including female patients in the indication for Elevidys.

The applicant's response:
Females with mutations in the *DMD* gene are carriers, and some carriers may manifest progressive muscular weakness or cardiomyopathy in adulthood, whereas epidemiological information on female carriers is limited in Japan and overseas (Japanese Society of Neurology. Clinical Practice Guideline for Duchenne muscular dystrophy 2014 [in Japanese]). Since no animal reproductive and developmental toxicity studies have been conducted with Elevidys, there is no information on the effects of Elevidys on human fertility. In addition, female patients were excluded from clinical studies in which Elevidys was administered, and there is no clinical experience with Elevidys in female patients. It is envisaged that Elevidys will be used mainly in male patients after marketing. However, some female patients with mutations in the *DMD* gene may manifest progressive muscular weakness or cardiomyopathy, and there is a possibility that female carriers are diagnosed with DMD.

Based on the above, though female patients are not excluded from the indication for Elevidys, the use of Elevidys is not recommended. Thus, "No clinical studies in female patients have been conducted." will be included in the PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE section, and "There is no information on the effects of Elevidys on human fertility. No animal reproductive and developmental toxicity studies have been conducted." will be included in the section of "9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS, 9.4 Patients with Reproductive Potential" of the package insert.

PMDA's discussion:
The efficacy and safety of Elevidys in female patients have not been evaluated in clinical studies, and there is no information on the effects of Elevidys on human reproduction. However, given that it is difficult to conduct a clinical study due to the very limited number of female patients, and that DMD is a progressive disease, and there are very limited treatment options, offering the option of Elevidys to female patients, with appropriate precautionary statements in the package insert, instead of excluding female patients from the indication for Elevidys, is acceptable. The precautionary statements in the package insert should be amended to include the following information: "Not only fertility effects, but also embryo-fetal effects are unknown, etc." If Elevidys is administered to female patients after marketing, safety and efficacy information should be collected.

7.R.6 Dosage and Administration or Method of Use
The proposed dosage and administration or method of use for Elevidys is shown below. The dosing regimens of corticosteroids to reduce the risk of immune responses to the AAVrh74 vector after administration of Elevidys was included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section.

Dosage and Administration or Method of Use

The usual dose of Elevidys is 1.33×10^{14} vector genomes (vg)/kg for patients weighing 10 to less than 70 kg or 9.31×10^{15} vg for patients weighing 70 kg or greater. Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Do not re-administer Elevidys. Calculate the total dose volume as per the table below.

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
10.0-10.4	10	100
10.5-11.4	11	110
11.5-12.4	12	120
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
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

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
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	70	700

Precautions Concerning Dosage and Administration or Method of Use (Relevant text only)

Since immune responses to the AAVrh74 vector can occur after the administration of Elevidys, prednisolone should be administered as per the table below.

Table a. Recommended pre- and post-infusion prednisolone dosing

1. Patients on once-daily or intermittent dose of baseline corticosteroid
   - From 1 day prior to Elevidys infusion, start additional dose of prednisolone at 1 mg/kg/day (continue the baseline dose). The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days after the infusion, then consider tapering back to the baseline dose over 2 weeks.
2. Patients on baseline high-dose corticosteroid for 2 days per week
   - From 1 day prior to Elevidys infusion, start prednisolone at 1 mg/kg/day (continue the baseline dose). Take 1 mg/kg/day also on days without high-dose corticosteroid treatment. The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days after the infusion, then consider tapering back to the baseline dose over 2 weeks.
3. Patients not on baseline corticosteroid
   - From 1 week prior to Elevidys infusion, start prednisolone at 1.5 mg/kg/day. The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days, then consider tapering back to no corticosteroids over 4 weeks.

Table b. Recommended prednisolone dose modification for liver function abnormalities following Elevidys infusion[Note)]

1. Patients on baseline + additional prednisolone 1 mg/kg/day
   - Increase to 2 mg/kg/day (continue the baseline dose). The maximum total daily dose is 120 mg/day. Consider tapering back to the baseline dose over 2 weeks as needed.
2. Patients on baseline high-dose corticosteroid (2 days per week) + prednisolone 1 mg/kg/day
   - Increase to 2 mg/kg/day taken on days without high-dose corticosteroid treatment (continue the baseline dose). The maximum total daily dose is 120 mg/day. Consider tapering back to the baseline dose over 2 weeks as needed.
3. Patients on prednisolone 1.5 mg/kg/day
   - Increase from 1.5 mg/kg/day to 2.5 mg/kg/day. The maximum total daily dose is 120 mg/day. Then, consider tapering back to no corticosteroids over 4 weeks.

Note) Consider IV bolus corticosteroids for liver function abnormalities that do not respond to increased oral corticosteroids.

Based on Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning of Elevidys" and the following considerations, PMDA concluded that the proposed statements in the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections are appropriate.

7.R.6.1 Dosage and Administration or Method of Use for Elevidys

The applicant's explanation about the rationale for the proposed dosage and administration or method of use:
The proposed dosage and administration or method of use for Elevidys is based on the results of clinical studies conducted to date.

Following administration of Elevidys 1.33×10^{14} vg/kg in DMD patients in clinical studies, the distribution of Elevidys to muscle tissues and micro-dystrophin expression were observed. The efficacy results as shown in Section 7.R.2.2 were obtained. Elevidys at this dose level was well tolerated.

A dose cap of 9.31×10^{15} vg for patients weighing ≥70 kg is based on weight-based dosing with a dose cap in Study 103.[44)] Only 1 patient weighing ≥70 kg in Cohort 3 of Study 103 received Elevidys. There were no major differences between all 6 patients enrolled in Cohort 3 and this 1 patient weighing ≥70 kg with respect to micro-dystrophin expression (by Western blot), vector genome copies per nucleus, serum CK, Performance of Upper Limb (PUL)ver.2.0 total score, forced vital capacity, and peak expiratory flow. No results suggesting reduced efficacy of Elevidys in dose-capped patients weighing ≥70 kg have been obtained at present. Although these results were obtained from non-ambulatory patients treated with Elevidys, the mechanism of action of Elevidys is the same in all ambulatory and non-ambulatory patients, and these results can be used to justify this dose in ambulatory patients. Based on the growth trajectory in patients with DMD, a weight-cap of 70 kg is expected to cover the majority of the target DMD population up to 18 years of age.

As to the infusion rate, since Elevidys was infused over 60 to 120 minutes[45)] in Study 301, [DOSAGE AND ADMINISTRATION OR METHOD OF USE] will specify that Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Though not reported in clinical studies, infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur during or up to several hours following Elevidys administration. Thus, the package insert will advise that if abnormalities are observed during Elevidys administration, slow or stop the infusion based on the patient's clinical presentation.

PMDA accepted the above explanation by the applicant.

7.R.6.2 Re-administration

PMDA asked the applicant to explain the appropriateness of "Do not re-administer Elevidys." in the package insert.

The applicant's response:
As described in Section 7.R.5.1, when an AAV vector containing an AAVrh74 capsid, which is the same as

[44)] A dose cap of 9.31×10^{15} vg was chosen as the dose predicted below the safety threshold of liver exposure established in non-clinical safety studies in DMD^{MDX} mice.
[45)] As the dose volume is high in heavy patients, an infusion over 60 to 240 minutes was also permitted in clinical studies, and the protocol advised against IV bolus dosing. However, the rate of IV bolus administration is generally 10 mL/kg/hour, and the infusion rate of Elevidys is <10 mL/kg/hour even in heavy patients (1 vial of 10 mL per kg body weight (up to 70 vials) is infused over 60 to 120 minutes). Thus, the applicant explained that there is no need for specifying the infusion rate separately for heavy patients.

Elevidys, was readministered to anti-AAVrh74 antibody-positive rhesus monkeys, microdystrophin expression was attenuated compared with sero-negative animals. When Elevidys was readministered to rhesus monkeys with elevated anti-AAVrh74 antibody titers after Elevidys administration, acute systemic findings indicative of immune-medicated effects were observed.

In Studies 101, 102, 103, and 301, patients were screened for pre-existing antibodies to AAVrh74 prior to study drug administration, and anti-AAVrh74 antibody-positive patients were excluded. In Study 301, a neutralizing antibody assay was performed at multiple time points after Elevidys infusion, and elevated anti-AAVrh74 antibody titers persisted until Week 52 in the Elevidys group in Part 1.

An open-label study to evaluate the safety and efficacy of Elevidys following imlifidase (a selective immunosuppressant) infusion in DMD patients with pre-existing anti-AAVrh74 antibodies aged 4 to <10 years (Study 104) and an open-label study to evaluate the safety and efficacy of Elevidys following plasmapheresis in DMD patients with pre-existing antibodies to AAVrh74 aged 4 to <9 years (Study 105) have been conducted, but the results have not become available at present. As of October 2024, Elevidys has been approved in 7 countries. To date, there is no clinical experience in re-administering Elevidys.

As described above, the efficacy and safety of Elevidys in patients who test positive for anti-AAVrh74 antibodies have not been established at present, and re-administration of Elevidys can lead to reduced efficacy and safety concerns. Thus, "Do not re-administer Elevidys." was included in the package insert.

PMDA accepted the above explanation by the applicant.

7.R.6.3 Corticosteroid dosing

The applicant's explanation about pre- and post-infusion oral corticosteroid dosing:

In clinical studies of Elevidys, except for Cohort 4 of Study 103, patients on a stable daily dose of oral corticosteroids for ≥12 weeks prior to screening for the treatment of DMD were enrolled, and the dose and regimen were to remain constant (except for modifications to accommodate changes in weight) throughout the study. For immunosuppression and the prevention of adverse events, one day prior to study drug infusion, patients were to begin receiving corticosteroid 1 mg/kg/day (prednisone equivalent), in addition to their continued baseline stable oral corticosteroid dose, which was to be continued for ≥60 days post-treatment in Studies 301 and 103.[46)]

Patients aged <4 years who were not on oral corticosteroids for DMD in Cohort 4 of Study 103 were to start corticosteroid 1.5 mg/kg/day (prednisone equivalent) 1 week prior to study drug infusion.

[46)] In Study 102, the increased corticosteroid dose was to be continued for ≥60 days after study drug infusion (≥30 days before the protocol amendment 5), unless earlier tapering was judged by the investigator to be in the patient's best interest. In Study 101, one day prior to Elevidys infusion, subjects were to begin receiving additional corticosteroid 1 mg/kg/day, which was to be continued for ≥30 days post-treatment.

The clinical studies were conducted with the above dosing regimens, which indicated that immune-mediated adverse events such as hepatotoxicity are manageable. Thus, the dosing regimens of corticosteroids used in the clinical studies will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section.

PMDA's discussion:
Since the dosing regimens of prednisolone and the criteria for starting tapering are very important information for the management of adverse events such as hepatotoxicity associated with Elevidys, this information should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section of the package insert. Since many of patients with DMD for whom Elevidys is indicated have already been on chronic corticosteroid treatment, it is necessary to adequately alert physicians to the risk associated with an even higher dose of corticosteroids required for Elevidys administration. Post-marketing information on the appropriate dosing regimens of prednisolone should be collected. If new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice as soon as possible.

8. Risk Analysis and Outline of the Review Conducted by PMDA

8.1 Post-marketing investigations

The applicant's explanation about a post-marketing clinical study and a use-results survey intended to assess the efficacy of Elevidys and collect further safety information, etc., by a specified time limit after marketing:

8.1.1 Post-marketing clinical study

A confirmatory study, Study 301 failed to demonstrate the superiority of Elevidys over placebo in the primary endpoint of the change from baseline in the NSAA total score [see Section 7.R.2.2.1]. As the NSAA score was not sensitive enough to detect a difference from placebo at 52 weeks, evaluation of the long-term efficacy of Elevidys was considered important. Thus, a post-marketing clinical study to confirm the efficacy of Elevidys was planned as shown in Table 58.

Table 58. Outline of post-marketing clinical study

Objective	To confirm the efficacy of Elevidys by pooling the results at Year 3 from patients treated with Elevidys in Parts 1 and 2 of Study 301 to be compared with retrospectively collected external control data.
Study design	An open-label, non-interventional study to compare with external controls
Population	Elevidys group: Patients who participated in Study 301 and received Elevidys External control group: Patients who meet the following entry criteria* in the external dataset • 4 to <10 years of age at baseline • Baseline NSAA total score of 12-34 • Baseline time to rise from the floor of ≤11.75 seconds • Baseline time of 10-meter walk/run of ≤10.90 seconds • Is on a stable dose of oral corticosteroids for ≥12 weeks at baseline
Evaluation period	3 years after Elevidys infusion
Target sample size	Elevidys group: approximately 100 patients External control group: approximately 170 patients [Basis for sample size determination] As the Elevidys group, patients treated with Elevidys in Part 1 or 2 of Study 301 will be evaluated. As external controls, all patients in the overall external dataset who meet the above entry criteria and have baseline value and at least 1 post-baseline value (at Year 1, 2, or 3) will be evaluated. Taking account of the diversity of the pathology of DMD itself, the number of patients in an external control study conducted [see Section 7.R.2.2.2], etc., assuming a standard deviation of 7.6 in each treatment group with a one-sided significance level of 5%, a sample size of 100 patients each in the Elevidys and external control groups will provide approximately 77.8% power to detect a difference of 2.6 points between the treatment groups.
Efficacy endpoints	[Primary endpoint] • Change in the NSAA total score from baseline to Year 3 [Secondary endpoints] • Change in the time to rise from the floor and velocity from baseline to Year 3 • Change in the time of 10-meter walk/run and velocity from baseline to Year 3
Analysis of the primary efficacy endpoint	Compare the change in the NSAA total score at Year 3 in the Elevidys group with the external control data using a propensity score-weighted mixed model for repeated measures with a one-sided significance level of 5%.

*For patients matched for baseline characteristics with Study 301, the entry criteria were established based on baseline data in Parts 1 and 2 of Study 301.

The study was designed with NSAA total score chosen as the primary efficacy endpoint, which was the primary endpoint of Study 301. In the natural history of patients with DMD, the NSAA total score peaks at 6.3 years of age and begins to decline after that (*PLoS One.* 2019; 14: e0221097). Since the patient population enrolled in Study 301 will reach a mean age of approximately 9 years (Part 1) or approximately 10 years (Part 2) at Year 3, etc., a difference between the Elevidys and external control groups can be shown at 3 years after Elevidys administration.

Three datasets,[25)] i.e., CINRG DNHS, FOR-DMD, and BioMarin PRO-DMD-01, will be used as the external control data because the results from ≥3 years of efficacy evaluation are available etc.

8.1.2 Use-results survey

The applicant planned a use-results survey, covering all patients treated with Elevidys, to assess the long-term safety profile and long-term efficacy of Elevidys in clinical practice. The main survey items of the use-results survey are shown in Table 59. The NSAA total score is not included in the survey items for efficacy because it is difficult to maintain the quality of assessment over a long period of time in clinical practice, and rigorous assessment is difficult in the use-results survey.

Table 59. Outline of use-results survey (draft) (Main survey items)

Safety	Incidence of adverse events Key survey items: infusion reactions (including hypersensitivity), acute liver injury, immune-mediated myositis, myocarditis, thrombotic microangiopathy, long-term safety, malignancies related to vector integration into somatic cell DNA (carcinogenicity)
Efficacy	ADL, time to rise from the floor, time of 10-meter walk/run, upper limb function (Brooke score), cardiac function (left ventricular ejection fraction), respiratory function, the use of ventilator, the date/age of ventilator initiation, the time/age of wheelchair dependence, the time/age of loss of the ability to get up, the time/age of loss of ambulation, the age of regaining ambulation

8.R Outline of the Review Conducted by PMDA

8.R.1 Post-marketing clinical study

PMDA's discussion on the post-marketing clinical study plan (draft) proposed by the applicant:
The applicant's policy (Since a confirmatory study, Study 301 failed to demonstrate the superiority of Elevidys over placebo in the primary endpoint, a post-marketing clinical study to confirm the efficacy of Elevidys will be conducted.) is appropriate.

As to the design of the post-marketing clinical study, new patients should be enrolled, including a control group, and data should be collected prospectively in order to improve the objectivity in assessment. However, since DMD is a rare disease, etc., the plan of confirming the efficacy of Elevidys based on the NSAA total score at 3 years post-infusion in patients previously treated with Elevidys in Study 301 is acceptable. As the current treatment options are very limited for the intended patient population for Elevidys, it is considered difficult to prospectively collect data from the control group in parallel with a post-marketing clinical study. Thus, the plan of comparing with retrospectively collected external control data is unavoidable.

As to the efficacy endpoint and the timing of the endpoint, given that the NSAA total score is an important measure of efficacy of DMD drugs and taking account of the results of comparison between the pooled population from Studies 101 and 102 and Cohort 1 of Study 103 and the external control data (Table 49), the effects of Elevidys can be evaluated at 3 years post-infusion. Thus, the change in the NSAA total score from baseline to Year 3 as the primary efficacy endpoint is justified.

The details of the post-marketing clinical study plan will be finalized, taking also account of comments from the Expert Discussion.

8.R.2 Use-results survey

PMDA's discussion on the use-results survey plan (draft) proposed by the applicant:
Since there is very limited clinical experience with Elevidys in Japanese patients, it is necessary to conduct a post-marketing use-results survey, covering all patients treated with Elevidys, in order to collect information on the safety and efficacy of Elevidys in a prompt and unbiased manner, and to provide the obtained safety information to healthcare professionals in clinical practice as soon as possible.

As to the survey items for safety, based on the considerations in Section "7.R.3 Safety," rhabdomyolysis,

thrombocytopenia, and the risk associated with additional corticosteroid use should also be assessed. As to the survey items for efficacy, since information on the NSAA total scores can be collected with a certain level of quality even in clinical practice, the NSAA total scores should also be collected and assessed, as in the post-marketing clinical study.

The details of the use-results survey will be finalized, taking also account of comments on efficacy and safety evaluation of Elevidys from the Expert Discussion.

9. Regulations on Type-1 Use of Living Modified Organisms under Article 4 of the Act on Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms ("the Cartagena Act")

The use of Elevidys is classified as Type 1 Use of Living Modified Organisms under Article 4 of the Cartagena Act, and the Regulations on Type-1 Use of Living Modified Organisms have been approved (Approval Number: 20-36V-0006).

10. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

10.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

10.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.1-4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

11. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Elevidys is expected to have a certain level of efficacy in improving motor function or slowing decline in motor function in ambulatory patients with DMD, and that Elevidys has acceptable safety in view of its benefits. Though the information on the efficacy and safety of Elevidys is limited at present, offering Elevidys as a treatment option for ambulatory patients with DMD to clinical practice has its significance.

PMDA has concluded that Elevidys may be approved if Elevidys is not considered to have any particular

problems based on comments from the Expert Discussion. The approval should be conditional and time-limited in accordance with Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The conditions require the applicant to assess the efficacy of Elevidys and collect further safety information by a specified time limit after marketing, etc. The time limit according to the Article will be finalized, taking account of the post-marketing clinical study and post-marketing surveillance plans (e.g., preparation time for marketing, patient enrollment period, observation period for each case, preparation time for reapplication for approval), based on comments from the Expert Discussion.

Review Report (2)

April 9, 2025

Product Submitted for Approval

Brand Name	Elevidys for Intravenous Infusion
Non-proprietary Name	Delandistrogene moxeparvovec
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 14, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusion:

As a result of the discussion in Section "7.R.2 Efficacy" in the Review Report (1), based primarily on the long-term data after administration, Elevidys is expected to have a certain level of efficacy in improving motor function or slowing decline in motor function of ambulatory patients with DMD. However, because of extremely limited efficacy data, the product’s post-marketing efficacy should be further evaluated.

At the Expert Discussion, many expert advisors supported the above conclusion by PMDA. At the same time, some expert advisors commented that it was too early to draw a conclusion on the efficacy of Elevidys for the following reasons.

- Study 301, a confirmatory study, failed to demonstrate a statistically significant improvement in the primary endpoint, i.e., the change in the NSAA total score from baseline to Week 52 in the Elevidys group compared with the placebo control group. The applicant views that the Elevidys group showed improvements in the secondary endpoints including time to rise from the floor, time of 10-meter walk/run, etc. compared with the placebo control group, these changes were, however, not marked.
- Although the study results suggest that the effects of Elevidys will last for 3 to 5 years after infusion, the current limited data do not provide insufficient information on the magnitude and durability of the effects.

Nevertheless, during the discussion, PMDA explained the purpose of the conditional and time-limited approval system and their intention to make the final conclusion on the efficacy of Elevidys in the review of the reapplication that will be conducted within the timeframe of the conditional and time-limited approval. The expert advisors finally supported PMDA's conclusion.

The expert advisors made the following comment:
Long-term data on the duration of micro-dystrophin expression and how effectively Elevidys slows ambulation loss compared with the natural history would help explain the efficacy of Elevidys.

Taking account of the comments from the Expert Discussion, PMDA requested the applicant to collect information on the long-term expression of micro-dystrophin protein as long-term follow-up data from clinical studies, which was, however, found to be difficult to obtain for the following reasons.

- Highly invasive muscle biopsies will increase burdens on patients and their caregivers.
- Foreign regulatory authorities have advised against muscle biopsies.

Long-term follow-up data on ambulation loss have been collected from Study 305.[28)] PMDA asked the applicant to explain the time to ambulation loss after Elevidys administration, based on the latest information.

The applicant's response:
Many of DMD patients lose ambulation at the age of around 10 years (Clinical Practice Guidelines for Duchenne muscular dystrophy 2014 [in Japanese]. Nankodo; 2014. p2-3).

In clinical studies of Elevidys, 177 patients were 3 to <8 years of age at the time of Elevidys infusion (the intended patient population for Elevidys in post- marketing use) (the median age [range] was 6.28 [3.29-7.96]). Patients who were treated with Elevidys infusion at the age of 3 to <8 are estimated to have reached the age of 6 to 13 years. However, long-term information after Elevidys infusion has been available from only limited number of patients until now, and evaluation based on further long-term follow-up is necessary.

PMDA's discussion:
As the applicant has explained, the difficulty in evaluating the effect of Elevidys on the time to ambulation loss and the necessity of discussion based on longer follow-up are understandable. The effect of Elevidys on the time to ambulation loss should be further evaluated through long-term post-marketing follow-up of patients who entered Study 305 from Studies 101, 102, 103, and 301, etc.

1.2 Safety

PMDA's conclusion:
Based on the discussion in Section "7.R.3 Safety" in the Review Report (1), adverse events that require particular attention following Elevidys treatment are hepatotoxicity, immune-mediated myositis, myocarditis, rhabdomyolysis, hypersensitivity, thrombocytopenia, and adverse events attributable to additional

corticosteroid use, which were observed in clinical studies of Elevidys, and thrombotic microangiopathy, which is considered a potential risk associated with Elevidys in connection with thrombocytopenia. These adverse events of Elevidys warrant attention. Elevidys is tolerable as long as physicians with adequate knowledge of and experience in DMD take appropriate measures, e.g., adverse event monitoring and management at medical institutions with adequate facilities for the management of relevant adverse events.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

After the Review Report (1) was fixed, 1 death was reported in a foreign, long-term, multicenter, prospective, observational study that compared the efficacy and safety of Elevidys against the standard of care in patients with DMD (Study 401).[47)] At the time of Elevidys infusion, the patient was 16 years old and non-ambulatory, and died of intracranial hemorrhage caused by acute hepatic failure on Day 83. At present, although no autopsy report available, the acute hepatic failure is considered causally related to Elevidys and potentially associated with CMV infection or reactivation of CMV in light of the laboratory results, etc. indicative of CMV infection.

PMDA's discussion:
The lack of autopsy report precludes a conclusion on the necessity of additional cautionary advice on acute hepatic failure and infections at present. However, these events are related to hepatotoxicity and adverse events attributable to additional corticosteroid use (infections) that are listed in the current package insert as adverse events requiring attention in the use of Elevidys. In this view, the package insert, etc. should caution against both events. Post-marketing information about the events should be continuously collected, and healthcare professionals should be appropriately updated with new information.

1.3 Indication or Performance

PMDA's conclusion:
Based on the considerations in Section "7.R.5 Indication or performance" in the Review Report (1), the statements presented in the section should be included in the INDICATION OR PERFORMANCE and PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE sections accordingly.

At the Expert Discussion, the expert advisors made the following comments on the age restriction for the use of Elevidys and patterns of *DMD* gene mutations ineligible for Elevidys therapy.

- The lack of long-term efficacy data from patients aged 3 years precludes a conclusion on whether early administration of Elevidys maximizes its efficacy at this time. Thus, there is no solid evidence for the inclusion of patients aged 3 years in the intended population for Elevidys therapy.
- The decision to contraindicate Elevidys for patients with deletion in exon 8 and/or exon 9 in the *DMD* gene is understandable. However, a single deletion of exon 6 or other exon deletions upstream of exon 8

[47)] The primary objective of the study is to compare the change from baseline in the time of 10-meter walk/run in DMD patients who are ambulatory at baseline receiving Elevidys as part of clinical care with that in those patients receiving standard of care in routine clinical practice. In addition to cohorts enrolling patients who are ambulatory at screening (patients who are able to complete the 10-meter walk/run in <30 seconds), a cohort enrolling patients who are non-ambulatory at screening (patients who are unable to complete the 10-meter walk/run in <30 seconds) is also included.

can result in a frameshift of all downstream exons. Thus, physicians in clinical practice must become competent in accurate identification of the types of *DMD* gene mutations for which Elevidys should be contraindicated.

PMDA's discussion based on the comments from the expert advisors above:

- Inclusion of patients aged 3 years in the intended population for Elevidys therapy
  DMD is a progressive disease with limited treatment options. Given this, it is significant to offer a treatment option for patients aged 3 years, despite the lack of long-term efficacy data from the relevant patient population. However, efficacy evaluation of Elevidys in patients aged 3 years should be continued in the post-marketing settings through long-term follow-up of Cohort 4 (ambulatory patients aged 3 to <4 years) of Study 103, etc.

- *DMD* gene mutation types for which Elevidys therapy should be contraindicated
  PMDA asked the applicant to explain their view on the provision of information to healthcare professionals in clinical practice about *DMD* gene mutations for which Elevidys therapy should be contraindicated, including handling of patients with a deletion upstream of exon 8.

The applicant's response:
Information on the safety of Elevidys in patients with mutations upstream of exon 8 is as follows.

- Among patients treated with Elevidys in clinical studies, 1 patient had an exon 3-7 deletion, and 1 patient had an exon 2 duplication. Immune-mediated myositis was not reported from either patient.
- Table 60 shows patients with mutations upstream of exon 8 treated with Elevidys in the US post-marketing settings as of November 2, 2024. Immune-mediated myositis was not reported from these patients.

Table 60. Patients with mutations upstream of exon 8 treated with Elevidys in the US post-marketing experience (as of November 2, 2024)

Mutation type	Exon	Number of patients
Deletion	1*	1
	1-2	1
	2-6*	1
	3-7*	2
Duplication	2*	3
	3-4	1
	3-7*	1
	5-7*	1
Single nucleotide variant (Nonsense substitution)	6	1
	7	1

* A mutation that should result in a frameshift of all downstream exons

The above information etc. does not indicate a sufficient level of current risk that justifies the contraindication of Elevidys in patients with mutations upstream of exon 8. Thus, this patient population should also be eligible for Elevidys, with a caution about limited safety and efficacy information through the package insert.

In addition, information materials etc. will present specific examples of *DMD* gene mutations clearly defined as contraindications for Elevidys.

While understanding the applicant's explanation in light of the clinical information currently available, PMDA also considers that information collection on the relationship between genetic mutation sites (including mutations upstream of exon 8) and immune-mediated myositis should be continued in the post-marketing settings, and that obtained information should be communicated appropriately to healthcare professionals in clinical practice.

Based on the above considerations, PMDA has concluded that the INDICATION OR PERFORMANCE and PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE sections should be described as follows, with the CONTRAINDICATIONS section describing the contraindication for Elevidys as follows.

Indication or Performance

Duchenne muscular dystrophy exclusively meeting all of the following criteria:

- Anti-AAVrh74 antibody-negative patients
- Ambulatory patients
- Patients aged 3 to less than 8 years

Precautions Concerning Indication or Performance

1. Administer Elevidys to patients with Duchenne muscular dystrophy confirmed based on genetic testing, etc.
2. Administer Elevidys to patients tested negative for anti-AAVrh74 antibodies using approved *in vitro* diagnostic or medical device. Information on the approved *in vitro* diagnostic or medical device is available from the following website:
   https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
3. Eligible patients must be selected by physicians with a full understanding of the information presented in the section of "17. CLINICAL STUDIES" concerning the characteristics of patients (age, ambulatory status, etc.) enrolled in the clinical study and of the efficacy and safety of Elevidys.
4. No clinical studies have been conducted in female patients.

Contraindications (Relevant text only)

Patients with a deletion of any portion or the entirety of exon 8 and/or exon 9 in the *DMD* gene [Immune-mediated myositis may occur.]

PMDA requested the applicant to describe the INDICATION OR PERFORMANCE, PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE, and CONTRAINDICATIONS sections as above. The applicant responded accordingly, and PMDA accepted it.

1.4 Dosage and Administration or Method of Use

PMDA's conclusion:

Based on the discussion in Section "7.R.6 Dosage and administration or method of use" in the Review Report (1), the descriptions presented in the section should be reflected in the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

PMDA further made conclusions, i.e., the package insert descriptions should be modified (describe thawing/preparation in the section of "14. PRECAUTIONS CONCERNING USE" instead of the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section; refine the descriptions in Table a and Table b, etc.) and the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections should be described as follows:

Dosage and Administration or Method of Use

The usual dose of Elevidys is 1.33×10^{14} vector genomes (vg)/kg for patients weighing 10 to less than 70 kg or 9.31×10^{15} vg for patients weighing 70 kg or greater. Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Do not re-administer Elevidys. Calculate the total dose volume as per the table below.

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
10.0-10.4	10	100
10.5-11.4	11	110
11.5-12.4	12	120
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

Patient weight range (kg)	Total number of vials required	Total dose volume (mL)
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
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	70	700

Precautions Concerning Dosage and Administration or Method of Use

Elevidys can induce immune responses to the AAVrh74 vector. Prednisolone should be administered as per the table below.

Table a. Recommended pre- and post-infusion prednisolone dosing

1. Patients on once-daily or intermittent dose of baseline corticosteroid • From 1 day prior to Elevidys infusion, start additional dose of prednisolone at 1 mg/kg/day (continue the baseline dose). The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days after the infusion, then consider tapering back to the baseline dose over 2 weeks. 2. Patients on baseline high dose corticosteroid for 2 days per week • From 1 day prior to Elevidys infusion, start prednisolone at 1 mg/kg/day (continue the baseline dose). Take 1 mg/kg/day also on days without high-dose corticosteroid treatment. The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days after the infusion, then consider tapering back to the baseline dose over 2 weeks. 3. Patients not on baseline corticosteroid • From 1 week prior to Elevidys infusion, start prednisolone at 1.5 mg/kg/day. The maximum total daily dose is 60 mg/day. Continue this regimen for at least 60 days, then consider tapering back to no corticosteroids over 4 weeks.

Table b. Recommended prednisolone dose modification for liver function abnormalities following Elevidys infusion[Note)]

1. Patients on baseline + additional prednisolone 1 mg/kg/day • Increase to 2 mg/kg/day (continue baseline dose). The maximum total daily dose is 120 mg/day. Consider tapering back to the baseline dose over 2 weeks as needed. 2. Patients on baseline high-dose corticosteroid (2 days per week) + prednisolone 1 mg/kg/day • Increase to 2 mg/kg/day taken on days without high-dose corticosteroid treatment (continue the baseline dose). The maximum total daily dose is 120 mg/day. Consider tapering back to the baseline dose over 2 weeks as needed. 3. Patients on prednisolone 1.5 mg/kg/day • Increase from 1.5 mg/kg/day to 2.5 mg/kg/day. The maximum total daily dose is 120 mg/day. Then, consider tapering back to no corticosteroids over 4 weeks.

Note) Consider IV bolus corticosteroids for liver function abnormalities that do not respond to increased oral corticosteroids.

PMDA requested the applicant to describe the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections as above. The applicant responded accordingly, and PMDA accepted it.

1.5 Plan of post-marketing approval condition assessment (draft)

The applicant proposed plans of a post-marketing clinical study and use-results survey (draft) for further evaluation of the efficacy and safety of Elevidys after marketing.

PMDA's conclusion:

Based on the discussion in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA," the conduct of a post-marketing clinical study to confirm the efficacy of Elevidys after marketing, as per Table 58, is appropriate. In the use-results survey, the NSAA total scores, commonly used motor function measurements for efficacy evaluation, should also be collected and assessed as an efficacy survey item, as in the post-marketing clinical study. "Rhabdomyolysis," "thrombocytopenia," and "the risk associated with additional corticosteroid use" should be added in the safety specification.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. The expert advisors also expressed their opinion on an additional matter to consider as follows:

- In the treatment for ambulatory function improvement in DMD patients, it is important that Elevidys is used in combination with rehabilitation. In the efficacy evaluation based on the NSAA total score, rehabilitation will be influential to ambulatory performance. Information on the implementation of

rehabilitation should be collected via the use-results survey.

Based on the results of the Expert Discussion, PMDA requested the applicant to revise the use-results survey plan. The applicant responded accordingly and submitted an outline of use-results survey (draft) presented in Table 61, which PMDA accepted.

Table 61. Outline of use-results survey (draft)

Objective	To assess the long-term safety profile of Elevidys in clinical use. To assess the long-term efficacy of Elevidys as a secondary objective.
Population	All patients treated with Elevidys
Survey period*1	Observation period: from the day of Elevidys administration to the day of decision on the reapplication that will be submitted by the time limit of the conditional and time-limited approval
Planned sample size*2	46-86 patients
Main survey items	[Safety] Incidence of adverse events Key survey items: infusion reactions (including hypersensitivity), acute liver injury, myositis, myocarditis, thrombotic microangiopathy, rhabdomyolysis, thrombocytopenia, the risk associated with additional corticosteroid use, long-term safety, malignancies related to vector integration into somatic cell DNA (carcinogenicity) [Efficacy] ADL, time to rise from the floor, time of 10-meter walk/run, upper limb function (Brooke score), cardiac function (left ventricular ejection fraction), respiratory function, the use of ventilator, the date/age of ventilator initiation, the time/age of wheelchair dependence, the time/age of loss of the ability to get up, the time/age of loss of ambulation, the age of regaining ambulation, NSAA total score, the use/the age of onset/the details of rehabilitation etc.

*1 Data cutoff is scheduled at 7 months prior to the reapplication to be submitted by the time limit of the conditional and time-limited approval. The analysis will be used for the reapplication.

*2 The number of patients whose case report forms at Month 3 are expected to be fixed during the survey period. Case report forms are scheduled to be collected at 3 months, 1 year, 2.5 years, and 5 years after administration of Elevidys..

PMDA's conclusion:

The post-marketing clinical study results will be submitted no later than [redacted] 20[redacted]. The duration of the conditional and time-limited approval is 3 years, within which the reapplication is expected to be submitted. A post-marketing approval condition assessment should be conducted based on the results of post-marketing clinical studies and the use-results survey, data on the time to loss of ambulation in Study 305 [see Section 1.1], and long-term follow-up data from patients receiving Elevidys at age 3 years who rolled over from Cohort 4 of Study 103 to Study 305 [see Section 1.3], etc. that will be available during this time period.

1.6 Others

1.6.1 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (Notification Nos. 1105-1 and 1105-2, both dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and the Counselor of Minister's Secretariat, MHLW, respectively). The risks of adventitious agents derived from human- or animal-origin components used in the manufacture of Elevidys and infection transmission in use in an open system are considered extremely low. In this view, PMDA has concluded that Elevidys need not be designated as a specified regenerative medical product.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions, only after offering cautionary advice via the package insert and appropriately disseminating information on the proper product use in the post-marketing setting. The approval should be conditional and time-limited in accordance with Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The duration of approval according to the relevant article should be 3 years. The product need not be designated as a specified regenerative medical product

Indication or Performance

Duchenne muscular dystrophy exclusively meeting all of the following criteria:

- Anti-AAVrh74 antibody-negative patients
- Ambulatory patients
- Patients aged 3 to less than 8 years

Dosage and Administration or Method of Use

The usual dose of Elevidys is 1.33×10^{14} vector genomes (vg)/kg for patients weighing 10 to less than 70 kg or 9.31×10^{15} vg for patients weighing 70 kg or greater. Elevidys should be administered as a one-time intravenous infusion over 60 to 120 minutes. Do not re-administer Elevidys. Calculate the total dose volume as per the table below.

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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

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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
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43.5-44.4	44	440
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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
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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	70	700

Approval Conditions

1. During the period between the conditional and time-limited approval and the reapplication for marketing approval, the applicant is required to conduct a post-marketing approval condition assessment through clinical studies aiming at confirmation of the product's long-term efficacy and safety and post-marketing surveillance covering all patients treated with the product.
2. The product should be used by physicians with adequate knowledge of and experience in Duchenne muscular dystrophy who fully understand the clinical study results and adverse events, etc. of the product and at medical institutions with an established treatment system for Duchenne muscular dystrophy, in accordance with "INDICATION OR PERFORMANCE" and "DOSAGE AND ADMINISTRATION OR METHOD OF USE." To this end, the applicant is required to take necessary measures including the dissemination of the proper use guidelines developed jointly with the relevant academic societies.

3. The product must be used in compliance with the Type 1 Use Regulations approved under the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). To this end, the applicant is required to take necessary measures including the dissemination of the relevant use regulations.

Appendix

List of Abbreviations

AAV	adeno-associated virus
ABD	actin binding domain
ADV	adenovirus
ADL	activities of daily living
ALT	alanine aminotransferase
application	marketing application
AST	aspartate aminotransferase
BAV	bovine adenovirus
BK	polyomavirus BKV
BMD	Becker's muscular dystrophy
BPV	bovine parvovirus
BRSV	bovine respiratory syncytial virus
[redacted]	[redacted]
BTV	bluetongue virus
BT cells	bovine turbinate cells
BUN	blood urea nitrogen
BVD	bovine viral diarrhea virus
B19	parvovirus B19
[redacted]CS	[redacted] calf serum
CI	confidence interval
CK	creatine kinase
CMV	human cytomegalovirus
COVID-19	coronavirus disease
CQA	critical quality attribute
CTCAE	common terminology criteria for adverse events
DAPC	dystrophin-associated protein complex
ddPCR	droplet digital polymerase chain reaction
DMD	duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunosorbent spot
EMC	encephalomyocarditis virus
FAS	Full Analysis Set
FBS	fetal bovine serum
gDNA	genomic DNA
GFP	Green Fluorescent Protein
GLDH	glutamine dehydrogenase
HAV	hepatitis A virus
HBV	hepatitis B virus
HCP	host cell protein
HCT-8 cells	human colon tumor cells
HCV	hepatitis C virus
HEK293 cells	human embryonic kidney 293
HHV	human herpes virus
HIV	human immunodeficiency virus
HLT	High-Level Terms
HPV	human papillomavirus
HSV	herpes simplex virus

HTLV	human T-cell leukemia virus
IBR	infectious bovine rhinotracheitis virus
IFN-γ	interferon-gamma
ITR	inverted terminal repeat
ITT	intention-to-treat
JC	polyomavirus JCV
LIVCA	limit-of-in-vitro-cell-age
LLOQ	lower limit of quantification
MCB	master cell bank
MCHC	mean corpuscular hemoglobin concentration
MCK	muscle creatine kinase
MedDRA	Medical Dictionary for Regulatory Activities
MHC	myosin heavy chain
MHCK7	α-myosin heave-chain creatine kinase 7
mITT	modified intention-to-treat
MRC-5 cells	Human fetal lung fibroblast cells
MRI	Magnetic Resonance Imaging
mRNA	messenger ribonucleic acid
MVM	minute virus of mice
NCH	Nationwide Children's Hospital
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NSAA	North Star Ambulatory Assessment
ORF	open reading frame
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
[redacted]	[redacted]
PHEV	porcine hemagglutinating encephalitis virus
PI-3	parainfluenza-3
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	porcine parvovirus
PRRSV	porcine reproductive and respiratory syndrome virus
PRV	pseudorabies virus
PT	preferred term
qPCR	quantitative polymerase chain reaction
Reo	reo virus
Sarepta	Sarepta Therapeutics, Inc.
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SMQ	standardised MedDRA queries
SOC	system organ class
Study 101	Study SRP-9001-101
Study 102	Study SRP-9001-102
Study 103	Study SRP-9001-103
Study 104	Study SRP-9001-104
Study 105	Study SRP-9001-105
Study 301	Study SRP-9001-301
Study 303	Study SRP-9001-303
Study 305	Study SRP-9001-305
Study 401	Study SRP-9001-401
SV40	simian virus 40
TES	target enrichment sequencing
TGEV	transmissible gastroenteritis virus
The product	Elevidys for Intravenous Infusion

ULN	upper limit of normal
Vero cells	African green monkey kidney epithelial cells
WCB	working cell bank
XMuLV	xenotropic murine leukemia virus