CHUGAI PHARMACEUTICAL

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CHUGAI PHARMACEUTICAL CO., LTD.

Chugai Information Meeting on Gene Therapy for Duchenne Muscular Dystrophy

June 17, 2026

Event Summary

[Company Name]	CHUGAI PHARMACEUTICAL CO., LTD.	
[Company ID]	4519-QCODE	
[Event Language]	JPN	
[Event Type]	Analyst Meeting	
[Event Name]	Chugai Information Meeting on Gene Therapy for Duchenne Muscular Dystrophy	
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[Date]	June 17, 2026	
[Number of Pages]	45	
[Time]	13:00 – 14:36 (Total: 96 minutes, Presentation: 61 minutes, Q&A: 35 minutes)	
[Venue]	Webcast	
[Venue Size]		
[Participants]		
[Number of Speakers]	3	
	Hirofumi Komaki, M.D., Ph.D.	Director, Translational Medical Center National Center Hospital, National Center of Neurology and Psychiatry
	Yoko Sano	Elevidys Lifecycle Leader Chugai Pharmaceutical Co., Ltd.
	Kae Miyata	Head of Corporate Communications Dept. Chugai Pharmaceutical Co., Ltd.
[Analyst Names]*	Hiroshi Tanaka	Mizuho Securities
	Seiji Wakao	JPMorgan Securities

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

Presentation

Miyata: Thank you very much for taking the time out of your busy schedule today to attend CHUGAI PHARMACEUTICAL's briefing on gene therapy for Duchenne muscular dystrophy. I'll be serving as today's moderator. My name is Miyata from the Corporate Communications Department. Thank you.

Now, Sano, the Elevidys Lifecycle Leader at CHUGAI PAHRMACEUTICAL, will provide an overview of Elevidys.

Sano: I'm Sano from CHUGAI PHARMACEUTICAL. I will explain the product overview of Elevidys.

I will start with its development history. Elevidys, whose generic name is delandistrogene moxeparvovec, is a gene therapy vector product developed for the treatment of Duchenne muscular dystrophy, DMD.

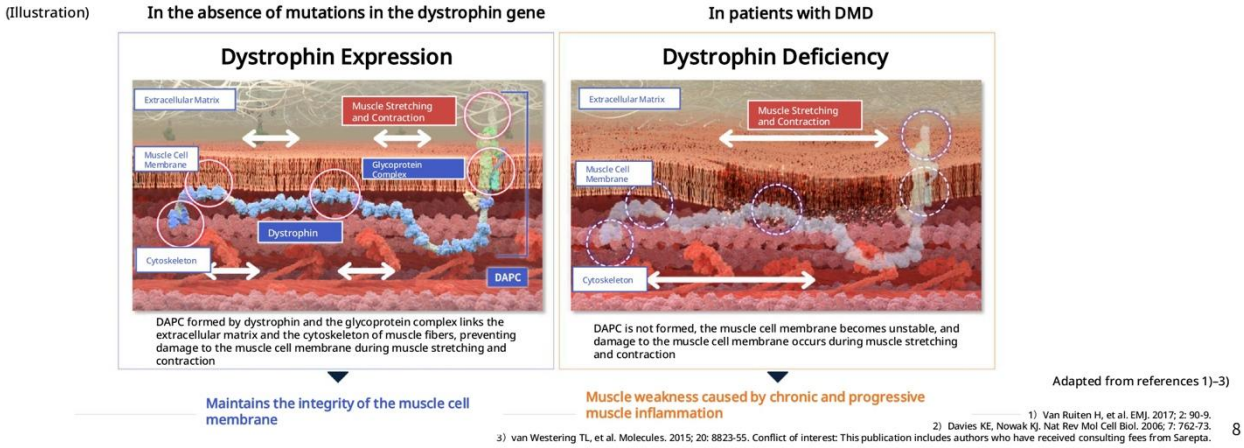
Elevidys was jointly developed by Sarepta and Roche and received its first marketing approval in the United States in June 2023 as a treatment for DMD.

In Japan, we are participating in the EMBARK trial, an international Phase III clinical trial involving ambulatory male and female patients with DMD aged four to seven. Based on the results of this trial and other clinical trials, we obtained marketing authorization last May for this product, the first gene therapy product for DMD, on a conditional and time-limited basis.

As of now, it has been approved in nine countries. In Europe, the recommendation not to grant conditional approval has been accepted, and Roche is currently planning a new international Phase III clinical trial and intends to submit an application in Europe.

Cause of DMD

- DMD is a neuromuscular disorder caused by mutations in the dystrophin gene and follows an X-linked recessive inheritance pattern.[1)]
- When there are mutations in the dystrophin gene, "dystrophin," the protein produced from the dystrophin gene, is absent, or abnormal dystrophin is produced. Dystrophin is expressed in various muscle tissues and forms the dystrophin-associated protein complex (DAPC), linking the cell membrane and extracellular matrix to the cytoskeleton of muscle fibers. [2)]
- When dystrophin is absent, the muscle cell membrane becomes unstable, leading to muscle cell damage and, consequently, decreased muscle strength. [3)]



Now, let's move on to the underlying mechanism.

This is the cause of DMD. Since Dr. Komaki will be covering this in more detail later in his lecture, I'd like to just touch on it briefly here.

DMD is a disorder caused by mutations in the dystrophin gene and follows an X-linked recessive inheritance pattern. When there are mutations in the dystrophin gene, dystrophin, the protein produced from the dystrophin gene, is either absent or produced in an abnormal form.

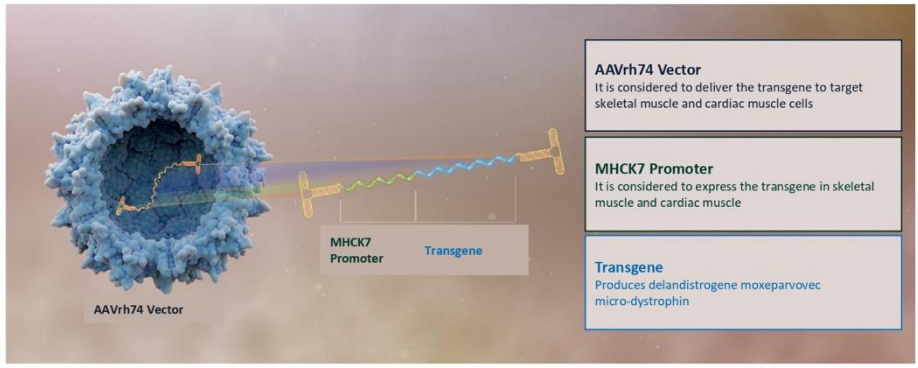
As you can see here on the left, dystrophin is expressed in various muscle tissues, where it helps prevent damage to the muscle cell membrane during muscle extension and contraction. In other words, we believe that the expression of this dystrophin maintains the integrity of the muscle cell membrane.

In patients with Duchenne muscular dystrophy, because this dystrophin is absent, the muscle cell membranes become damaged when the muscles extend and contract, leading to a loss of muscle strength due to chronic and progressive muscle inflammation.

Structure of Elevidys

- Elevidys (generic name: delandistrogene moxeparvovec) is a gene therapy vector product developed for the treatment of DMD.
- It is a non-replicating recombinant adeno-associated virus (recombinant Adeno-Associated Virus: rAAV) vector containing a gene[1] encoding delandistrogene moxeparvovec micro-dystrophin, a functional shortened dystrophin (hereinafter, "micro-dystrophin"), and is controlled by the α-myosin heavy chain creatine kinase 7 (MHCK7) promoter/enhancer, which optimizes expression in skeletal and cardiac muscle. [2]

(Illustration)



Adapted from references 3) and 4)

1) Rodino-Klapac LR, et al. Hum Mol Genet. 2013; 22: 4929-37.
2) Salva MZ, et al. Mol Ther. 2007; 15: 320-9.
3) Review data at the time of approval [Structure of delandistrogene moxeparvovec]
4) Review data at the time of approval [Overview of delandistrogene moxeparvovec]

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This is about the structure of Elevidys.

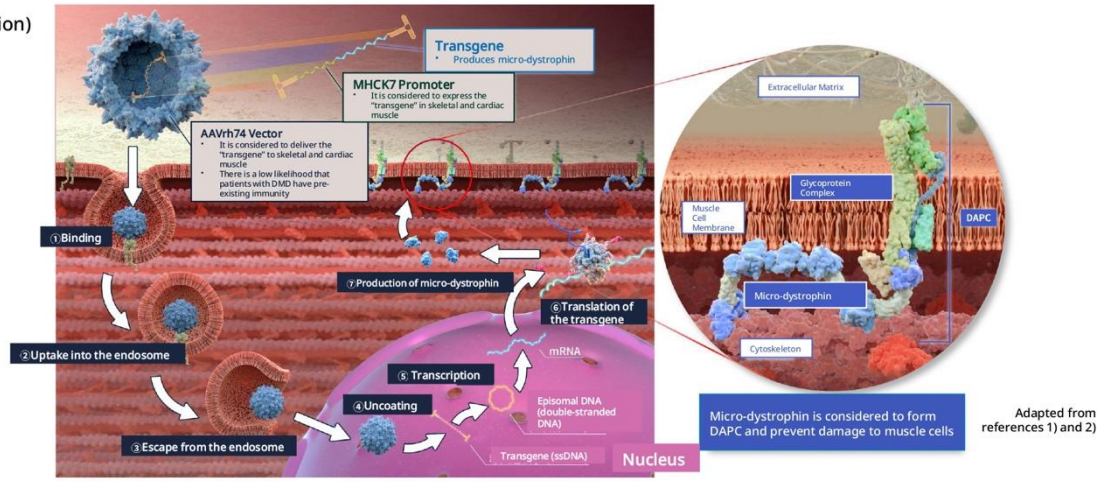
Elevidys is a product that uses an adeno-associated virus vector, which contains micro-dystrophin as the transgene. Since the dystrophin gene is a very large gene, it is extremely difficult to incorporate the full-length version into the AAV vector. For this reason, Elevidys incorporates micro-dystrophin, a functional, truncated form of dystrophin, as a transgene.

The system is designed to carry the transgene to skeletal muscle and cardiac muscle cells where it is then expressed.

Mechanism of Action of Elevidys

- The micro-dystrophin gene carried by Elevidys is considered to be expressed in skeletal and cardiac muscle.[1)]
- It is considered that expression of micro-dystrophin in muscle cells improves muscle function and prevents the loss of muscle strength.[2)]

(Illustration)



Adapted from references 1) and 2)

1) Review data at the time of approval [Structure of delandistrogene moxeparvovec]
2) Review data at the time of approval [Overview of delandistrogene moxeparvovec]

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This is the mechanism of action.

As I mentioned earlier, we believe that by inducing the expression of the introduced micro-dystrophin gene in skeletal and cardiac muscles, we can improve muscle function and prevent muscle weakness.

Basic Information on Elevidys Intravenous Infusion
(delandistrogene moxeparvovec)

- This product is the first gene therapy for Duchenne muscular dystrophy.

Drug Class	Gene therapy product; viral vector product
Efficacy or Effects	Duchenne muscular dystrophy; limited to patients who meet all of the following criteria • Patients who are negative for anti-AAVrh74 antibodies • Ambulatory patients • Patients aged 3 years or older and younger than 8 years
Dosage form	Intravenous administration (the required number of vials for each patient is enclosed in an individual package)
Dosage and administration	In general, a single intravenous infusion is administered over 60 to 120 minutes: 1.33×10^{14} vg/kg for patients weighing ≥10 kg and <70 kg, and 9.31×10^{15} vg for patients weighing ≥70 kg. This product should not be readministered. The dose of this product is calculated based on the table below*.
Orphan designation	Designated on July 30, 2024 (MHLW notification No. 0730-1); Designation No.: (R2 sai) No. 16
Other designation system	Designated intractable disease No. 113 Pediatric Chronic Disease No. 16
NHI reimbursement listing / Launch date	February 20, 2026 Price: JPY 304,972,042 per patient

Packaging

The number of vials required according to patient body weight (1 vial = 10.0 mL) is packaged in an individual box for each patient. The size of the box varies depending on the number of vials.

Although the vials are labeled in English, please refer to the Japanese-labeled package for product information.

*Table refers to the electronic package insert

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Now, let me move on to the basic product information.

Regarding Elevidys, its indications are for Duchenne muscular dystrophy in patients who are negative for anti-AAVrh74 antibodies, are ambulatory, and are aged three years or older and under eight years.

This product is intended for intravenous infusion, and we deliver the appropriate number of vials, based on the patient's weight, to the medical institution after conducting an eligibility test.

The product has received orphan drug designation. Specifically, Duchenne muscular dystrophy is classified as a designated intractable disease and a specified chronic pediatric disease. In February of this year, the product was listed on the NHI drug price list at approximately JPY 300 million per patient and was launched on the same day.

Approval Conditions of Elevidys

Approval Conditions and Time Limit	Approval Conditions 1. During the period until the reapplication for marketing approval of this product after conditional and time-limited approval, post-marketing approval condition evaluation shall be conducted through clinical trials aimed at confirming the long-term efficacy and safety of this product, as well as post-marketing surveillance targeting all cases in which this product is used. 2. Necessary measures shall be taken, including dissemination of proper use guidelines developed in cooperation with relevant academic societies, to ensure that physicians with sufficient knowledge and experience in Duchenne muscular dystrophy use this product in accordance with the "Efficacy or Effects" and "Dosage and Administration" after thoroughly acquiring knowledge of the clinical trial results and adverse events of this product, at medical institutions with established systems for treating Duchenne muscular dystrophy. 3. Necessary measures shall be taken, including dissemination of the usage regulations, to ensure that this product is 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)." Time Limit: 3 years
Expiration of Re-examination Period	Not applicable (conditionally and time-limited approved product)

Elevidys Intravenous Infusion, Electronic Package Insert, Revised February 2026 (3rd edition) 13

Since this is a conditional and time-limited approval, I would also like to outline the conditions for approval. The first condition. During this conditional approval period, we are currently conducting clinical trials to confirm the long-term efficacy and safety of this product, as well as a post-marketing surveillance program covering all cases in which this product is used.

The second condition. We request that this product be used only by physicians with sufficient knowledge of DMD and at medical institutions that have established a system capable of providing proper treatment, after they have thoroughly familiarized themselves with the clinical trial results and adverse events associated with this trial. In this regard, we are working in cooperation with the Japanese Society of Child Neurology that submitted the approval application, and we are also reaching out to medical institutions to request that they use the product in accordance with the guidelines for proper use that the society has developed.

The third and final condition. This is a gene therapy product subject to the Cartagena Act, and we are working with medical institutions to ensure that it is used in strict compliance with the Type 1 usage regulations.

These three conditions were imposed as requirements for approval, and Elevidys is currently being used in medical institutions.

Progress of Post-Approval Safety Measure Review

Year	Date	Event and Actions
2025	May 13	◆ Conditional and time-limited approval (3 years) obtained
	June 16	◆ Report of overseas fatal cases due to acute liver failure in non-ambulatory DMD patients
	June 18	◆ Meeting of the Central Social Insurance Medical Council ✓ Requested thorough review and discussion while gathering information
	August 28	◆ Revision of the electronic package insert ✓ Acute liver failure added as a serious adverse reaction; implementation of liver function monitoring and testing specified; warnings regarding infections related to corticosteroid use added
	October 8	◆ Meeting of the Central Social Insurance Medical Council (regarding handling under the health insurance system and safety) ✓ It was agreed to discuss the handling under the health insurance system, taking into account the need for public confirmation of safety and the importance of providing thorough information.
	November 27	◆ Meeting of the Subcommittee on Safety Measures for Medical Devices and Regenerative Medical Products under the Pharmaceutical Affairs and Food Sanitation Council (Ministry of Health, Labour and Welfare) was held. ✓ As part of the discussions on safety measures, the appropriateness of information materials, the positioning of the expert panel, and the framework for collaboration with relevant academic societies were discussed.
	December 17	◆ A notification was issued by the Director of the Office of Safety Measures, Pharmaceutical Safety Division, Ministry of Health, Labour and Welfare. ✓ Notifications were sent to the presidents of the Japanese Society of Child Neurology and the Japan Society of Hepatology, requesting cooperation in emphasizing clinical experience in DMD in facility accreditation, and in establishing a system capable of ensuring appropriate emergency response and coordination.
2026	January 14	◆ Meeting of the Central Social Insurance Medical Council (regarding handling under the health insurance system and listing on the NHI price list) ✓ Safety measures jointly implemented by the Ministry of Health, Labour and Welfare, relevant academic societies, and the company were reported, and it was agreed that the reimbursement price would be reviewed by the drug pricing organization and that the product would be listed on the NHI reimbursement price list.
	February 13	◆ Meeting of the Central Social Insurance Medical Council (decision on NHI coverage and price listing for Elevidys) ✓ It was agreed that Elevidys would be covered by the NHI and listed on the NHI reimbursement price list on February 20.
	February 20	◆ Listing on the NHI reimbursement price list and launch of Elevidys on the same day

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Finally, I'd like to discuss the progress of the post-approval safety measure review.

After we received conditional approval with certain conditions and a time limit last May, it is with great regret that we must report that two cases of death due to acute liver failure in non-ambulatory DMD patients have been reported overseas.

In light of this, our company considers ensuring patient safety to be our top priority. We are therefore gathering information thoroughly and have begun discussions to carefully evaluate the situation and strengthen safety measures.

As part of this process, we revised the package insert to include a note regarding the occurrence of acute liver failure as a serious adverse reaction, clearly stipulate the need for monitoring and testing of liver function, and, in addition to our existing recommendation for prophylactic administration prior to corticosteroid therapy, we also recommended including a warning about the risk of infection.

Subsequently, through deliberations with various regulatory authorities, including the Central Social Insurance Medical Council, we discussed the specifics of official safety verification and the thorough provision of information, including what types of information materials should be provided and the appropriateness of their content.

As Dr. Komaki will discuss in his lecture later, one of the key points will be how we can ensure patient safety by enlisting the cooperation of expert panels in clinical settings. Furthermore, as part of our efforts to collaborate with relevant academic societies, a notice was sent from the Director of the Office of Safety Measures to the Japanese Society of Child Neurology and the Japan Society of Hepatology, which requests their cooperation in establishing a system capable of implementing emergency response measures.

Following that, after we presented a report on safety measures developed through industry-government-academia collaboration, discussions were held regarding the NHI price list, and the product was finally

launched this past February. We are moving on to Dr. Komaki's presentation, and Elevidys is currently being used at medical institutions in Japan. That's all from me.

Miyata: Next, Dr. Hirofumi Komaki will discuss Duchenne muscular dystrophy, disease and treatment, clinical framework for gene therapy, appropriate use, and clinical positioning.

Thank you very much.

Komaki: Hello everyone. My name is Komaki from the National Center of Neurology and Psychiatry.

I am originally a clinician and a pediatrician. I have been working in Tokyo for many years, with the goal of specializing in pediatric neurology.

Among these are certain neuromuscular disorders, and for some of them, highly innovative treatments, including gene therapy, have been rapidly advanced, particularly over the past decade. With the emergence of drugs that are truly considered game-changers, a major challenge for us is how to build upon and share our knowledge and experience.

I would like to begin by explaining the background of how this drug, Elevidys, became available for clinical use, and, building on that, explain what kind of disease DMD.

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Conflict of Interest (COI) Disclosure

Presenter: Hirofumi Komaki
In relation to the content of this presentation,
the following companies have COI relationships
that should be disclosed by the lead presenter and co-presenters:

Nippon Shinyaku Co., Ltd.: Research funding, lecture fees
Chugai Pharmaceutical Co., Ltd.: Lecture fees
Sarepta Therapeutics, Inc.: Research funding
F. Hoffmann-La Roche Ltd: Consulting fees

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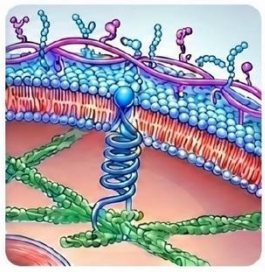
We disclose information regarding conflicts of interest as shown here. I have received research presentation fees and other payments from the companies listed above.

<Illustration>

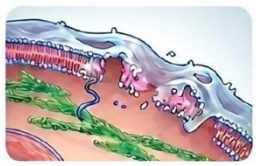
Normal Muscle Cells and the Function of Dystrophin



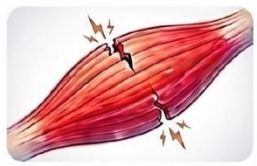
• Structural support: Links the cytoskeleton and cell membrane, providing internal reinforcement.

• Shock absorption: Reduces mechanical stress during muscle contraction and protects the membrane.

Process of Progressive Degeneration in DMD

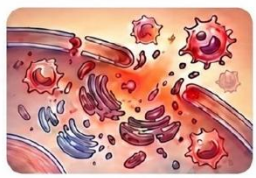


[Step 1] Loss of dystrophin and membrane fragility
Due to the absence of dystrophin, the cell membrane becomes fragile.



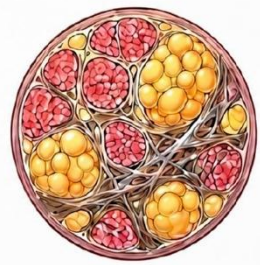
[Step 2] Cell membrane damage caused by contraction
Repeated muscle contraction leads to rupture of the weakened cell membrane.

[Step 3] Excess influx of calcium ions
Calcium ions abnormally flow into the cell through the damaged membrane.



[Step 4] Muscle cell necrosis and chronic inflammation
Excess calcium induces cell death, and inflammation persists.

Irreversible Tissue Degeneration



• Fibrosis and fatty infiltration: Regeneration of muscle cells cannot keep up, and the tissue is replaced by connective tissue and fat.

• Decreased muscle strength: Reduction in muscle mass leads to progressive and severe muscle weakness.

Source: Ali ABB et al. Front Physiol. 2023;14:1183101. Mareedu S et al. Front Physiol. 2021;12:647010.
Prepared by the presenter with reference to the above sources

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First of all, I'm sure you understand that muscular dystrophy is a muscle disease, and I imagine you've at least heard the name before. Since not everyone may be familiar with the details of this disease, I'd like to start by explaining the basics.

So, muscles are actually among the very few organs that can be touched. If you touch it, you can feel the muscle right beneath the skin. Although it actually has various functions, the most obvious and primary one is moving the body. Skeletal muscle. Based on a lever-like principle, muscles essentially span joints, so when they contract, they bend the joint, and when they stretch, they extend in this direction as well. It is an organ that performs such very simple, two-dimensional movements.

In the center of this diagram, you can see a mass of muscle. If you look at it at the microscopic level, you'll see that it's actually made up of bundles of very long, thin fibers. Although we refer to each of these as muscle cells or muscle fibers, please think of these layered structures as the membranes of the muscle cells. This spring-like structure, though this is merely a conceptual diagram, is a schematic representation of a protein called dystrophin.

As for what role they play, skeletal muscles are constantly stimulated and move, you see. So, imagine it as something like a balloon. It's constantly expanding and contracting, and when it's stimulated, it reacts accordingly. It's a protein located on the underside of that membrane, often referred to as a membrane-supporting protein, and the idea is that even when the muscle moves slightly, it provides solid support from behind.

So, to give you an idea, if this building didn't have any columns, it would collapse, right? It's like the columns of a building, or, to use a car analogy, the springs and shock absorbers located behind the tires. Those are what absorb the shocks. I think that's the kind of image I'd like you to have.

Duchenne muscular dystrophy is a disease in which the body cannot produce the dystrophin protein properly. The reason the protein cannot be produced is that there is a problem with the dystrophin gene, which encodes the dystrophin protein. As a result, the body cannot produce the dystrophin protein. Since this spring is lost, the membrane deforms excessively, and eventually, it bursts and breaks. As a result, muscle cells become more susceptible to damage.

Although it says step one, the loss of dystrophin causes the membrane to become fragile and weak. A loss of dystrophin weakens the cell membrane. Although it is described as contraction, because the muscle is constantly moving and there is no support from the back, it eventually becomes unable to withstand the stress, leading to a situation where muscle cells are prone to damage or actually break down.

As a result, the membrane breaks down, allowing an excessive influx of calcium ions. This could contribute to further damage. This can lead to inflammation. Therefore, muscles are among the organs with the most active regenerative capacity. Even if they break down, new muscles will form again after a while. Even if it breaks, it will be restored. Therefore, not all cases of muscular dystrophy are necessarily progressive. In fact, some relatively mild forms of the disease may take several decades to finally begin progressing. That means there's a general balance between destruction and regeneration, isn't it?

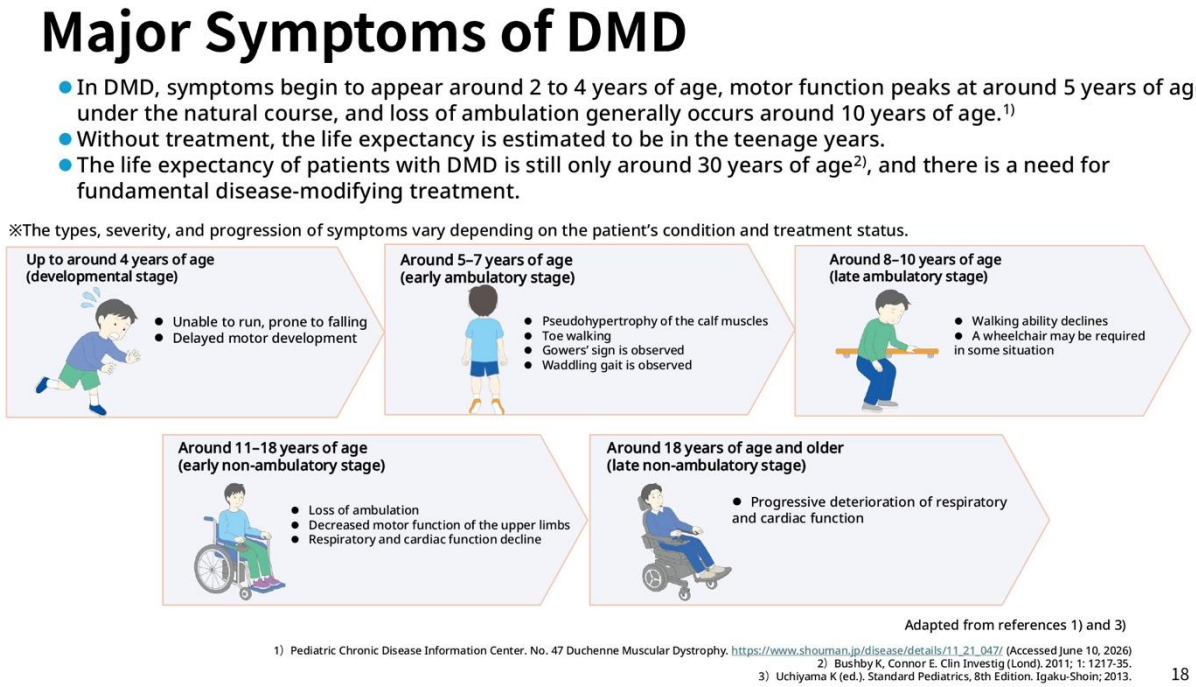
Duchenne muscular dystrophy is a very fragile condition resulting from a complete lack of dystrophin protein. In that case, the body's ability to regenerate can't keep up. For example, even if 100 are broken, as long as 100 are regenerated, the net result is zero. However, even if the number is slightly lower, say, 95 or 90, the balance is always negative. So, while you might not see any major changes over the course of one or two years, if you look at it in five-year increments, muscle mass will steadily decrease.

Therefore, in terms of the natural course of the disease, patients are initially able to walk, but they lose the ability to walk before the age of 10.

In this illustration, the parts shown in red are muscles. The areas highlighted in yellow indicate necrosis, regeneration, and the process of tissue breakdown and regeneration, with adipose tissue infiltrating these

areas. What appears to be a mesh-like structure is actually called fibrosis, which is characterized by an increase in fibrous tissue. This results in muscle tissue being replaced by something other than normal muscle tissue. This leads to a decrease in muscle mass.

If you bundle a lot of rubber bands together, they create resistance, but if you use just one, it stretches out, doesn't it? The number of bands is very important. As the number decreases, muscle strength declines. It is progressing steadily. I'd like you to start by getting a general idea of what this disease is like.



Although I mentioned the major symptoms, the condition is often first noticed between the ages of two and four. However, the disease does not present with a sudden, clearly identifiable onset on a specific date. Parents may gradually begin to notice things such as, “This child seems physically weak,” or “Their motor development appears delayed.” Even so, this does not necessarily lead them to seek medical attention. And even when they do visit a doctor, they often first see a general pediatrician, or if the child seems to have problems with the legs, they may visit an orthopedic specialist. In many cases, they are simply told, “There doesn’t appear to be any major problem.” As a result, diagnosis is often further delayed.

In Japan, medical care for children is often free of charge, so many parents today tend to take their children to a pediatrician even for relatively minor concerns. Physicians also frequently perform blood tests as a precaution.

As a result, blood tests conducted for unrelated reasons sometimes reveal abnormalities. There are substances in the blood whose levels rise when muscle tissue breaks down, such as creatine kinase (CK). In addition, AST and ALT, which are commonly used as liver function markers, are also present in muscle tissue. Therefore, elevated levels may prompt further examination, ultimately leading to the diagnosis.

One characteristic feature in Japan, which is relatively uncommon in other countries, is that approximately two-thirds of children with DMD are diagnosed around one year of age, often before they experience significant symptoms. In many cases, the disease is discovered incidentally through blood tests performed for other purposes.

In any case, around the ages of three or four, it is often noticed that the child has markedly poor motor function and tends to fall easily. Motor function is generally said to peak around the ages of five to six. At that stage, many children are just barely able to run. They can usually still walk reasonably well, but they are unable to run properly and may only appear to shuffle or jog slowly. They may climb stairs only one step at a time and often require the use of a handrail. Difficulties are often first noticed during movements against gravity, such as climbing stairs or running.

Without treatment, most patients lose the ability to walk before the age of 10. Regarding life expectancy, natural history data from more than 40 years ago suggested survival only into the teenage years. Muscles are not limited to skeletal muscles; respiratory muscles and cardiac muscle are also affected. Duchenne muscular dystrophy impacts all of these muscle groups. Therefore, in the era before effective treatment, life expectancy was generally considered to be in the late teens.

As for the current situation, as I will show later, treatments now available have improved life expectancy considerably. Patients receiving care at specialized centers are now surviving into their late 30s. However, some patients still develop severe cardiac complications at an early age and may pass away even during their teenage years. There is no doubt that this remains a very severe disease. Nevertheless, it is true that prognosis has gradually improved over time.

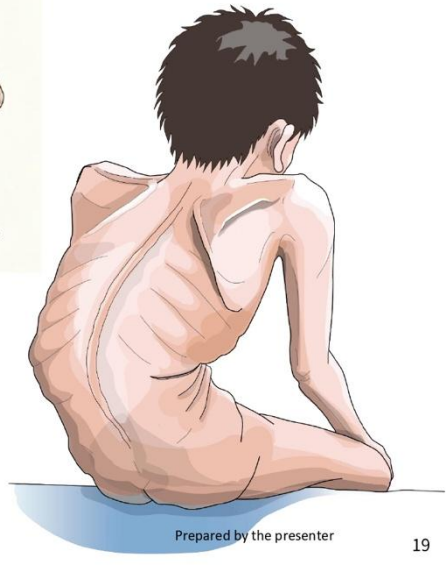
In the past, it was difficult even to envision adult life for these patients. Attending university itself used to be extremely rare, but today many patients attend university as a matter of course. This is partly because medical conditions have improved and partly because society's understanding and support systems have advanced.

Employment is another important aspect. I sometimes describe this as an unintended positive consequence of the pandemic. As remote work has become more widespread, it is no longer unusual for people with disabilities such as these to work online. In other words, the number of economically independent individuals contributing to society through employment is steadily increasing.

< Illustration >

Gowers sign

Scoliosis, muscle atrophy



Prepared by the presenter

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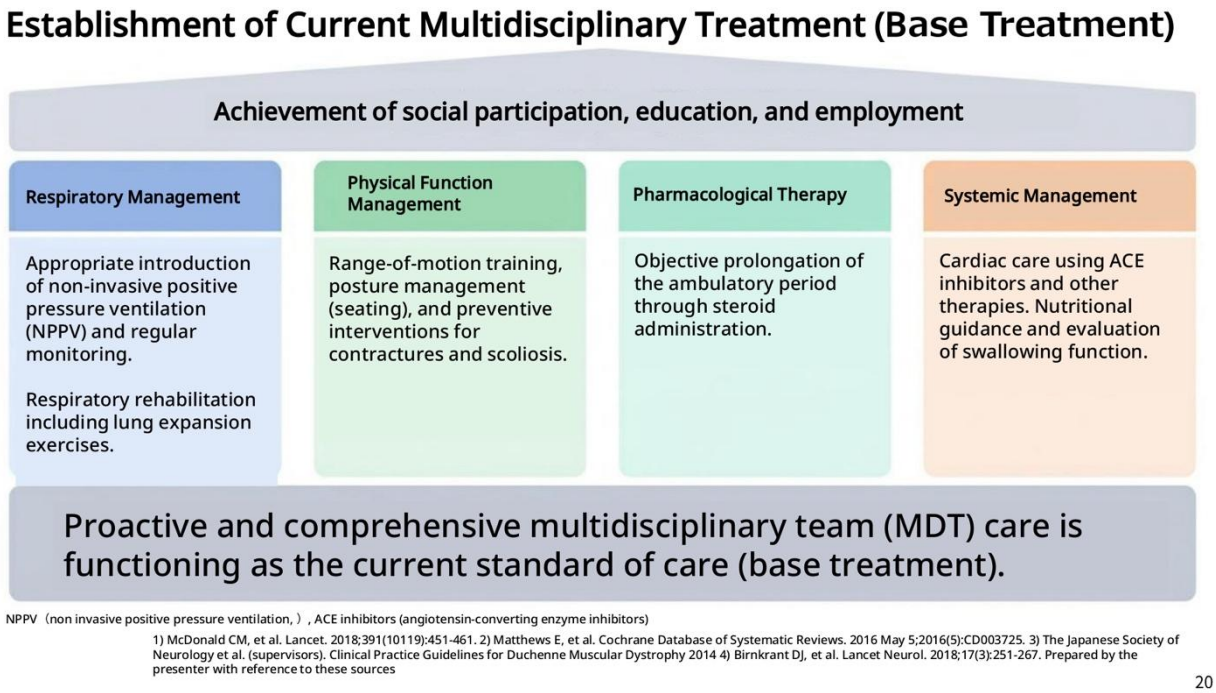
This is a representative illustration. The image in the upper left shows what is called Gowers' sign, which is a characteristic finding that appears when the trunk and pelvic girdle muscles become weakened. Standing up requires considerable effort. Patients may first lift their hips slightly and use momentum to stand up. They may also place their hands on their knees or thighs and climb up their own body in order to stand. To give you an idea, it is similar to the effort required to stand up after running for a while or quickly climbing a flight of stairs. It feels like standing up always requires extra effort.

Nowadays, it has become less common to see patients progress to this stage because of advances in treatment. However, without sufficient treatment, the muscles supporting the trunk become severely weakened, causing the spine to gradually curve visibly. Patients may develop severe scoliosis. In addition, muscle wasting can become so advanced that the ribs become visibly prominent. In the past, this was the typical image of patients reaching their late teens.



I'll talk more about treatments later, but as you can see, these are the treatments we currently offer.

As for respiratory management, we're talking about mechanical ventilation. Mechanical ventilation, which includes tracheostomy, mask ventilation, or NPPV, is the primary method used. Since people with DMD tend to have relatively good cognitive function, a tracheostomy would cause them to lose their ability to speak or become unable to speak at all, so NPPV is often the treatment of choice. It is not uncommon for people to use NPPV for the rest of their lives. Management has been improving significantly. Thanks to technological innovations, both the machines and the masks themselves, including their designs, have become much easier to use.

Also, as I mentioned earlier, it's a condition that causes the body to stiffen or become deformed. Once it gets to that point, there aren't many options left, but since this is a condition that can lead to that, we can focus on prevention. Since posture is prone to becoming distorted, it's important to manage it starting from childhood. Take various measures to ensure you sit with good posture. Those things are important, too.

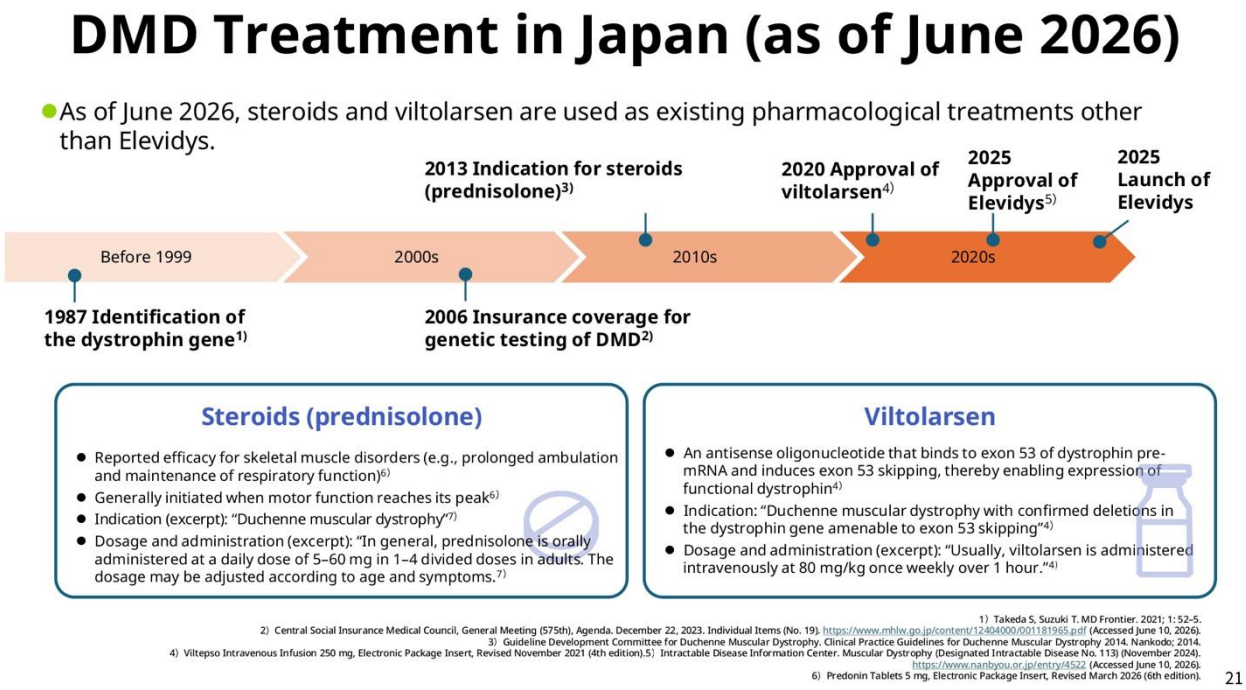
It's called proactive care, which means taking preventive measures in advance based on an understanding of the natural history and progression of this disease. This approach is particularly important for this condition.

I'll discuss pharmacological therapy later, but one treatment that can be used for all forms of DMD is steroid therapy. Although prednisolone is the most well-known example, steroid therapy has been documented for over 40 years, and it has now been established that it is effective in preventing the loss of ambulation, prolonging the period of walking, maintaining respiratory function, and preventing scoliosis.

As you may already know, steroids can have very serious side effects. However, since there are no other options at this time, it is extremely important to continue taking steroids while effectively managing the side effects.

Then, the systematic management. Since issues related to the heart, breathing, and swallowing are becoming increasingly significant as life expectancy continues to improve, measures to address these issues will also be necessary.

It says here that MDT is key, but the concept of multidisciplinary collaboration, where professionals from various fields work together as a team to provide the best possible care, is becoming increasingly important. Making this available in various regions is quite challenging, and this has become one of the issues we face.

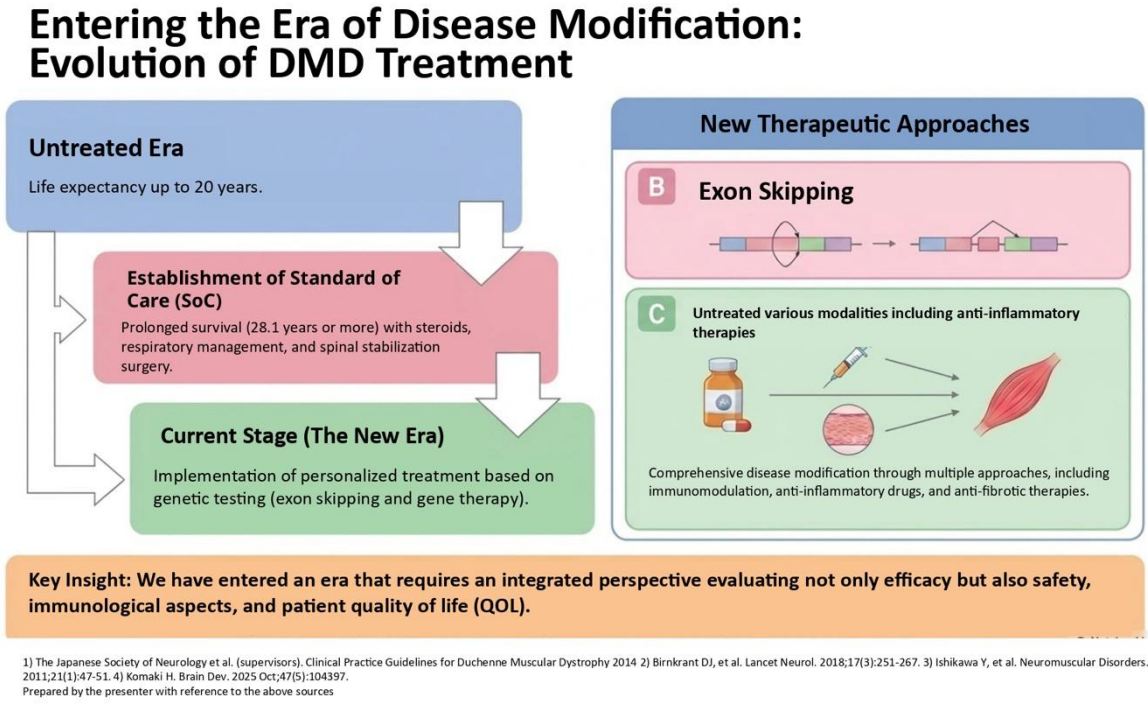


As you can see, there are currently two drug treatments for DMD available in Japan.

One is steroids, as I mentioned earlier. This is generally taken orally. There are various methods, but you will need to continue taking the medication, either in tablet or powder form.

As for viltolarsen, which is a drug developed in Japan, it is a treatment known as exon skipping. Although it is different from gene therapy, it has been used in Japan for about six to seven years as a drug that acts on genes.

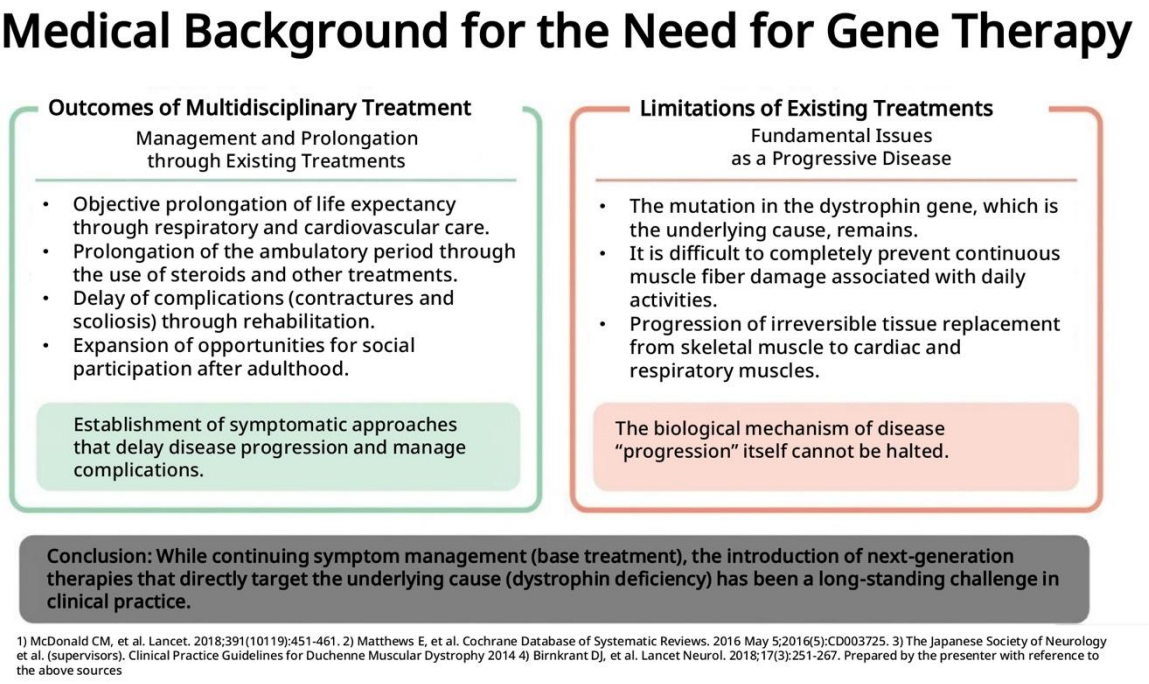
One challenge is continuous intravenous administration. Since this medication generally requires weekly intravenous infusions, it places a significant burden on patients etc. Another point is that it is only indicated for a specific genetic mutation. Since only about 10% of DMD patients have the specific genetic mutation eligible for this treatment, a major challenge with viltolarsen is that not all patients are eligible for treatment.



In the days before treatment, nearly 40 years ago, the patients rarely lived past their teens. It's been over 30 years since I graduated from college and became a doctor, but I happened to spend a short time at a specialized facility during my second year, and at that time, the patients really did have a life expectancy of only up to age 20. It's true that things were like that back in the day.

As the standard of care has become established, the prognosis has gradually improved. Over the past 10 years, a wide variety of clinical development projects have been under way, and new drugs have been gradually coming to market. Since several other drugs have likely demonstrated efficacy overseas, it is reasonable to expect that a number of new drugs will become available in the future.

Therefore, given that various approaches, including drugs that act at the genetic level and anti-inflammatory therapies, are promising options, I think it's becoming a realistic possibility that these different modalities will emerge and, depending on the situation, such drugs may be used in combination.



We're gradually moving on to gene therapy, but the question is, why is gene therapy necessary for this disease? As I have explained so far, existing treatments are also extremely effective. However, it does not guarantee that the progression will be stopped. Slowing the progression is a realistic goal. Although viltolarsen has received conditional approval based on evidence of some efficacy, slowing disease progression is also a realistic goal for this drug.

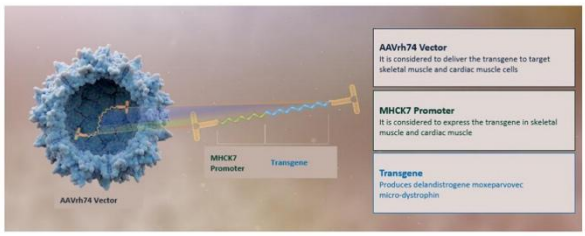
Therefore, it's only natural for people to want more and more, and that's why there is such a high demand for new drugs to meet that need. I think it's fair to say that the level of unmet need remains high.

As for existing treatments, such as viltolarsen, which I mentioned earlier, their mechanism of action is based on acting at the genetic level, which brings them closer to the root cause. That's because the root cause lies at the genetic level. While we can certainly expect anti-inflammatory effects, we believe that by acting at the genetic level, we are likely moving closer, step by step, to a fundamental cure.

As I mentioned earlier, exon skipping is indicated only for patients with a specific genetic mutation and requires multiple, ongoing treatment sessions. Given that, I believe it's fair to say that there are very high expectations for gene therapy, which is expected to be effective for a certain period of time with a single treatment.

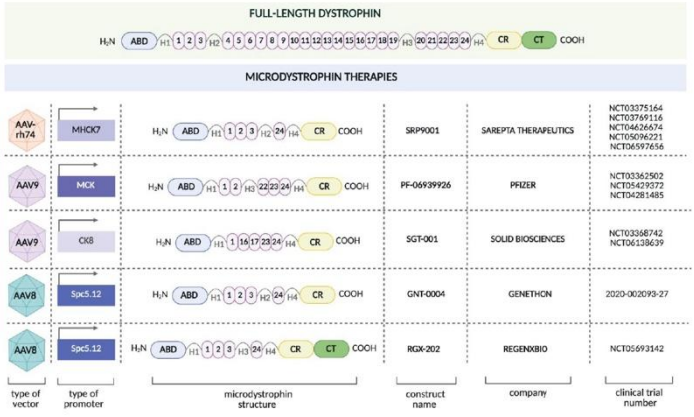
Structure of Elevidys and Micro-dystrophin

(Illustration)



Adapted from references 1) and 2)

1) Review data at the time of approval [Structure of delandistrogene moxeparvovec]
2) Review data at the time of approval [Overview of delandistrogene moxeparvovec]



Loboda A, et al. Genetic strategies for therapy of Duchenne muscular dystrophy. Mol Ther Nucleic Acids. 2025;36(4):102759

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As Ms. Sano mentioned earlier regarding Elevidys, the dystrophin gene is known to be a giant gene, so the fact that it does not fit within the size of an adeno-associated virus, AAV, which is primarily used in gene therapy, has long been a challenge.

If you make it shorter, it'll fit. Normally, if a gene is shortened, it should lose its function. However, some time ago, there happened to be a patient with a genetic mutation involving many deletions, and that patient happened to have Becker type, a milder form of the disease caused by the same gene, and even within that group, the patient's condition was milder still. So, there are reports like that from several decades ago.

So, there was someone who came up with the idea that, even if cutting it here might not be 100% effective, it would probably work reasonably well. That is why, in the sense of making it shorter, terms like mini and micro are used. The micro-dystrophin approach has been proposed, and clinical development is currently under way at a very active pace.

The figures on the right are small, so I think it might be a little hard to see, but the basic concept is the same, which vector should we choose? Since there are various serotypes of AAV, adeno-associated virus, their characteristics may differ slightly depending on the serotype.

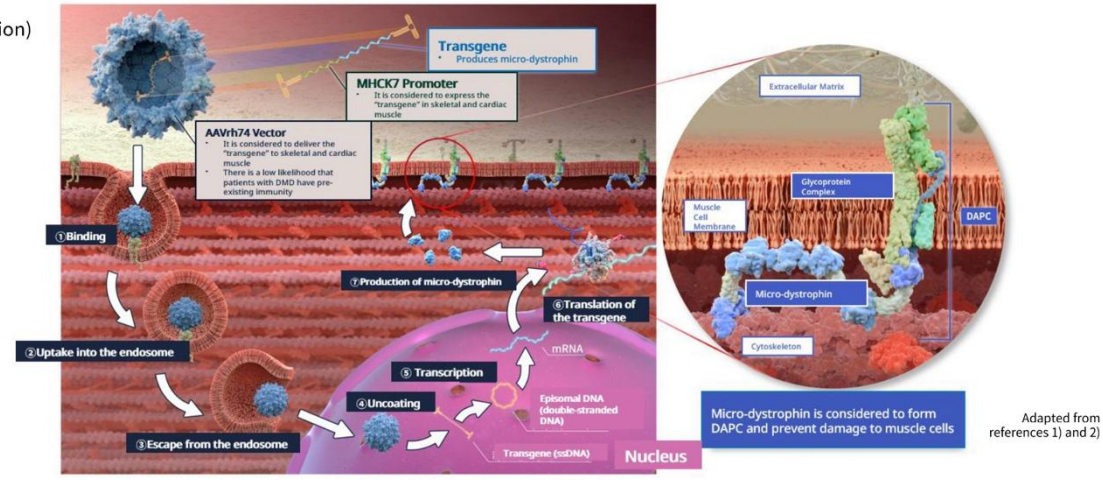
A promoter has an organ preference. The organ preference varies depending on the type of vector used. The orientation of the organs changes depending on the vector. It is said that eight and nine are relatively more focused on the muscles. A promoter is like a switch that controls the specific expression of a gene in a particular organ. This is the structure of micro-dystrophin. Various companies and research groups are working on their own versions, and while the concept is the same, the structure of this gene differs slightly.

There are currently a great many companies and research groups working on the development of DMD-related genes. As I mentioned earlier, this involves using the infectivity of a specific virus to introduce genes.

Mechanism of Action of Elevidys

- The micro-dystrophin gene carried by Elevidys is considered to be expressed in skeletal and cardiac muscle.[1)]
- It is considered that expression of micro-dystrophin in muscle cells improves muscle function and prevents the loss of muscle strength.[2)]

(Illustration)



Adapted from references 1) and 2)

1) Review data at the time of approval [Structure of delandistrogene moxeparvovec]
2) Review data at the time of approval [Overview of delandistrogene moxeparvovec]

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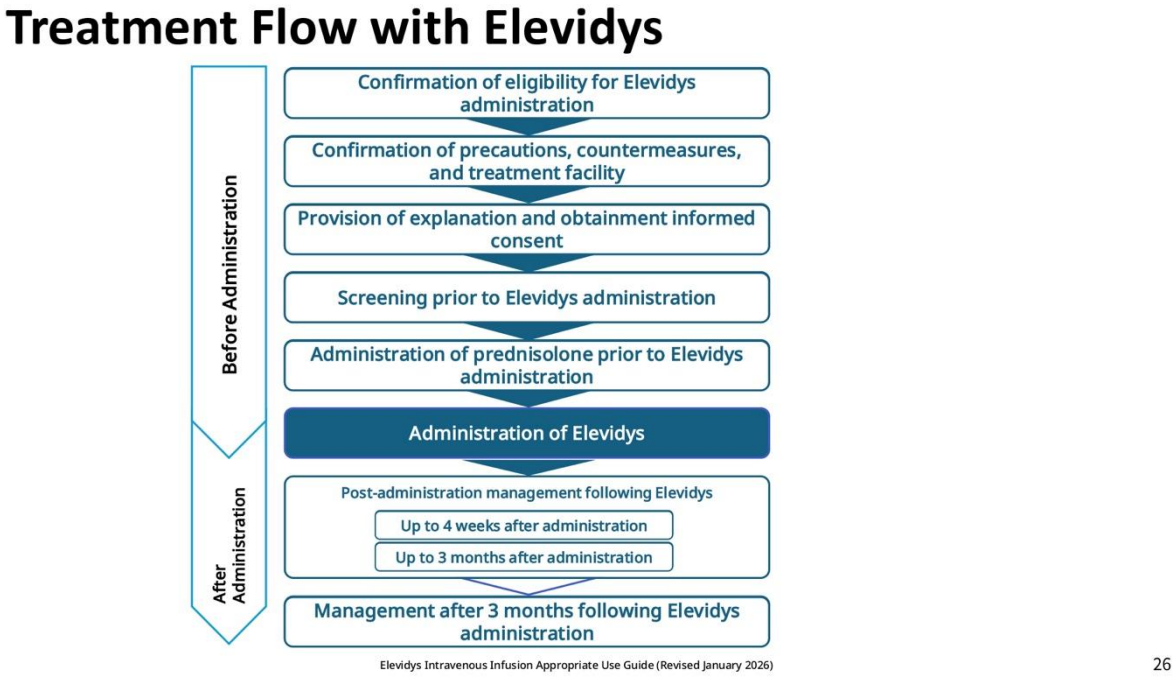
Another key point is that insertion into the patient's own nuclear DNA almost never occurs. I understand that in similar cases several decades ago, vectors were integrated into the cell's nucleus, which led to conditions such as leukemia and resulted in the termination of development. In theory, however, AAV-based vectors exist as episomes, meaning that they do not integrate into the nuclear genome but instead remain outside it.

The advantage is that, because the vector does not interfere with the patient's own nuclear genes, the risk of cancer is either nonexistent or extremely low. The challenge, on the other hand, is that because it is not integrated into the nuclear genome, it does not replicate when the cell divides. Since muscle cells are a type of tissue that undergoes division, the vector becomes diluted as the cells divide. The question, therefore, is how long the therapeutic effect will last, and at present there is no definitive answer.

While follow-up data covering three- and five-year periods are now available from patients in the Elevidys clinical trials, we recognize that determining how long the efficacy persists beyond these time frames remains a challenge for the future.



Here is the treatment flow.

This slide outlines various standard procedures, such as confirming eligibility for administration. However, since each step in gene therapy involves significant risks and requires careful identification of eligible patients, we must ensure that no mistakes are made.

In theory, gene therapy is indicated for all patients with DMD. However, as will be discussed later, several serious adverse events have occurred during clinical trials. In particular, since myositis has been reported as a side effect, it has been suggested that patients with certain genetic mutations may be at higher risk. As a result, the labeling includes a precaution stating that the drug is contraindicated in patients with these specific genetic mutations, or that administration should be considered with caution. We must ensure that these points are strictly observed.

In addition, the eligible age range is currently clearly defined as three years of age or older but under eight years of age. This means that administration becomes difficult even if the child is just one day past their eighth birthday. For this reason, schedule management is extremely important. If preparations begin at seven years and eleven months, there is simply no way to be ready in time. We need to plan well in advance.

Next is the explanation and consent process. This may seem obvious, but it is essential that families fully understand that very serious complications, which I will discuss later, may occur. Since this treatment is indicated for children aged three to under eight, it is difficult to fully convey such information to the children themselves, so the decision is generally made by the parents or legal guardians. That said, children at this age can understand certain things to some extent, so we make a point of regularly talking with them—within the limits of their understanding—about the significance of the treatment, the burdens involved, and the importance of working through it together.

This slide shows the screening process. Through blood tests and imaging examinations, we check for any complications other than DMD. For example, since liver failure has been reported, the risk increases if pre-existing liver complications are present, so we confirm in advance whether any such conditions exist.

After obtaining final confirmation, we proceed with preparations. As I mentioned earlier, prednisolone is administered the day before. In this context, prednisolone is used to prevent side effects of the gene therapy, and its use is only temporary.

However, since prednisolone is also used as a standard treatment for DMD, patients who are already taking it will have their dose temporarily increased. For those who are not yet taking it, prednisolone is administered for a limited period—approximately two months—and discontinued once it is confirmed that no issues have arisen.

Next is the administration itself. The first three months following administration are designated as the intensive monitoring period. In principle, patients are required to undergo blood tests and clinical visits at least once a week. We check their condition, perform blood tests, and review the data to make sure there are no issues. If there are any concerns, we may ask the patient to return again later in the same week. This places a considerable burden on patients and their families.

In particular, we pay close attention to two key time points: one peak within one week of administration and another peak approximately one month later. During this period, the prednisolone dose is increased and then gradually tapered if no problems arise.

As mentioned earlier regarding the Cartagena Protocol, measures to prevent the spread of the viral vector are explicitly stipulated by law. For this drug, the Cartagena compliance period is generally about one month, during which patients are required to remain socially isolated. Children who attend school must take a leave of absence during this period.

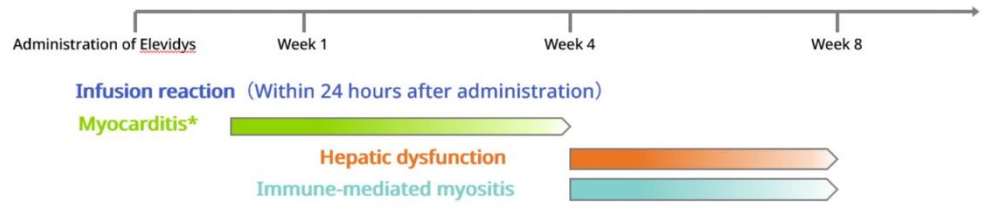
Another consideration is that increasing the prednisolone dose carries a risk of immunosuppression as a side effect, which could lead to serious complications if the patient contracts another infection. For both of these reasons, patients are required to rest at home for at least one month. Once the three-month intensive

monitoring period ends, we transition back to the standard care regimen.

Adverse Reactions and Issues Requiring Attention and Their Countermeasures
Serious Adverse Reactions

- The general timing of onset is as follows.[1)–3)] Among early adverse reactions, myocarditis occurring within several days after administration is suggested to be associated with innate immune responses to the viral vector. On the other hand, immune-mediated myositis occurring 4 to 8 weeks after administration is considered to be the result of acquired immune responses to micro-dystrophin.[3)]

<Timing of onset of each adverse reaction (schematic)>



*In cases of delayed myocarditis, treatment as immune-mediated myositis may be required.[4)]

Adapted from references 1) - 4)

1) Review data at the time of approval [Multinational Phase III clinical study in patients with DMD (SRP-9001-301)]
2) Review data at the time of approval [Pooled analysis of safety studies]
3) Zaidman CM, et al. J Neuromuscul Dis. 2024; 11: 687-99.
Conflict of interest: This study was supported by Sarepta Therapeutics.
The authors include employees of Sarepta Therapeutics and individuals who have received research funding, consulting fees, and other compensation from Sarepta Therapeutics, F. Hoffmann-La Roche Ltd., and Genentech.
4) Kaufman BD, et al. J Neuromuscul Dis. 2024: 22143602241303357.
Conflict of interest: The authors include individuals who have received consulting fees from Sarepta Therapeutics.

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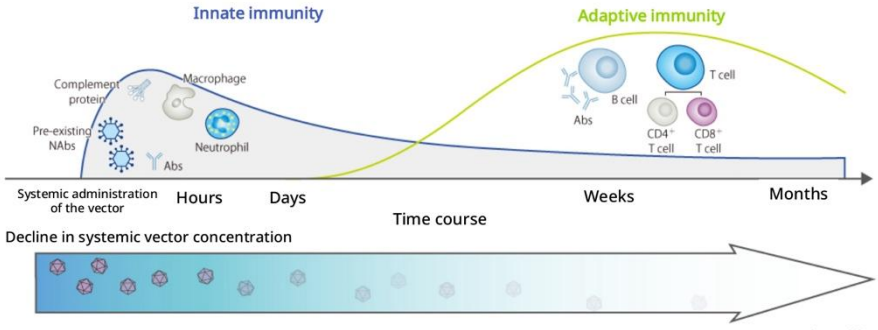
As I mentioned earlier, there are two peaks, and based on the results of clinical trials to date, we now have a fairly good understanding of which types of adverse events tend to occur at which time points. In the early phase, infusion reactions—essentially similar to anaphylactic shock—may occur. These typically arise within 24 hours of administration, and in most countries, patients are hospitalized for at least one day for observation and management.

From a few days to about one month after administration, there is a risk of myocarditis, an inflammation of the heart muscle. In addition, it is generally understood that immune-mediated myositis and liver injury tend to occur around one month after administration. Based on this knowledge, we carefully monitor each patient's clinical course with these risks in mind.

Adverse Reactions and Issues Requiring Attention and Their Countermeasures
Serious Adverse Reactions

- Following AAV-mediated gene transfer, innate immune responses are activated within hours to several days, while acquired immune responses are observed after several weeks. Along with these immunological responses, the systemic vector concentration is considered to decrease.[1)]

<Course of immunological responses after AAV gene transfer (schematic)>



Adapted from 1)
Reprinted from Mol Ther Methods Clin Dev., 25, Mendell JR, et al., Testing preexisting antibodies prior to AAV gene transfer therapy: rationale, lessons and future considerations, 74-83, Copyright (2022), with permission from Elsevier.

1) Mendell JR, et al. Mol Ther Methods Clin Dev. 2022; 25: 74-83.
Conflict of interest: This study was supported by Sarepta Therapeutics. The authors include employees of Sarepta Therapeutics and individuals who have received research funding, consulting fees, and other compensation from Sarepta Therapeutics and Genentech.

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As for why this happens, we are beginning to gain some understanding of the mechanisms underlying these adverse events. The reactions that occur around one week after administration are thought to be mediated by an immune response triggered by the direct introduction of the viral vector. As for those occurring approximately one month later, antibodies are produced in response to the exposure—specifically, antibodies against the introduced dystrophin. There is a concern that these antibodies may cause adverse effects. This is why we see a biphasic pattern with two distinct peaks, each associated with different types of adverse events.

Adverse Reactions and Issues Requiring Attention and Their Countermeasures
Implementation of Tests Before and After Administration of This Product

- Please perform the tests shown in the figure below both before initiation and after administration of this product.
- If the patient is followed up at another facility after the administration of this product, please ensure that the same tests are performed and confirm the patient's condition.
- For monitoring items and frequency beyond 3 months after administration of this product, please confirm the patient's condition and consult with the appropriate specialist. After 1 year, perform monitoring in conjunction with routine DMD examinations.

Test Schedule

		Baseline※1	After administration: Day 2–3	Week 1	Week 2	Week 3	Week 4	Weekly up to 3 months thereafter	Month 3	Month 4	Month 5	Month 6	Month 9	1 year
Liver (including partial TMA)	AST、ALT	●		●	●	●	●	●	●	○	○	●	○	●
	γ-GTP	●		●	●	●	●	●	●	○	○	●	○	●
	Albumin	●		●	●	●	●	●	●	○	○	●	○	●
	APTT	●		●	●	●	●	●	●	○	○	●	○	●
	PT%／PT-INR	●		●	●	●	●	●	●	○	○	●	○	●
	Total bilirubin / Direct bilirubin	●		●	●	●	●	●	●	○	○	●	○	●
	CK※2	●		●	●	●	●	●	●	○	○	●	○	●

● Required ○ Recommended

※1：For baseline cardiac examinations, use results obtained within 6 months prior to administration of this product.
※2：Although CK levels are not clinical laboratory values directly related to hepatic dysfunction, AST and ALT are often elevated in DMD patients due to muscle breakdown, making it difficult to assess hepatic dysfunction. In such cases, CK levels are useful in differentiating hepatic disease from muscle-derived enzyme elevation. Fluctuation patterns of CK levels and their divergence from AST and ALT levels suggest the complication of hepatic disease, leading to an appropriate evaluation.
TMA：Thrombotic Microangiopathy、APTT：Activated Partial Thromboplastin Time、PT：Prothrombin Time、PT-INR：Prothrombin Time-International Normalized Ratio

Excerpt from Elevidys Intravenous Infusion Appropriate Use Guide (Revised January 2026)

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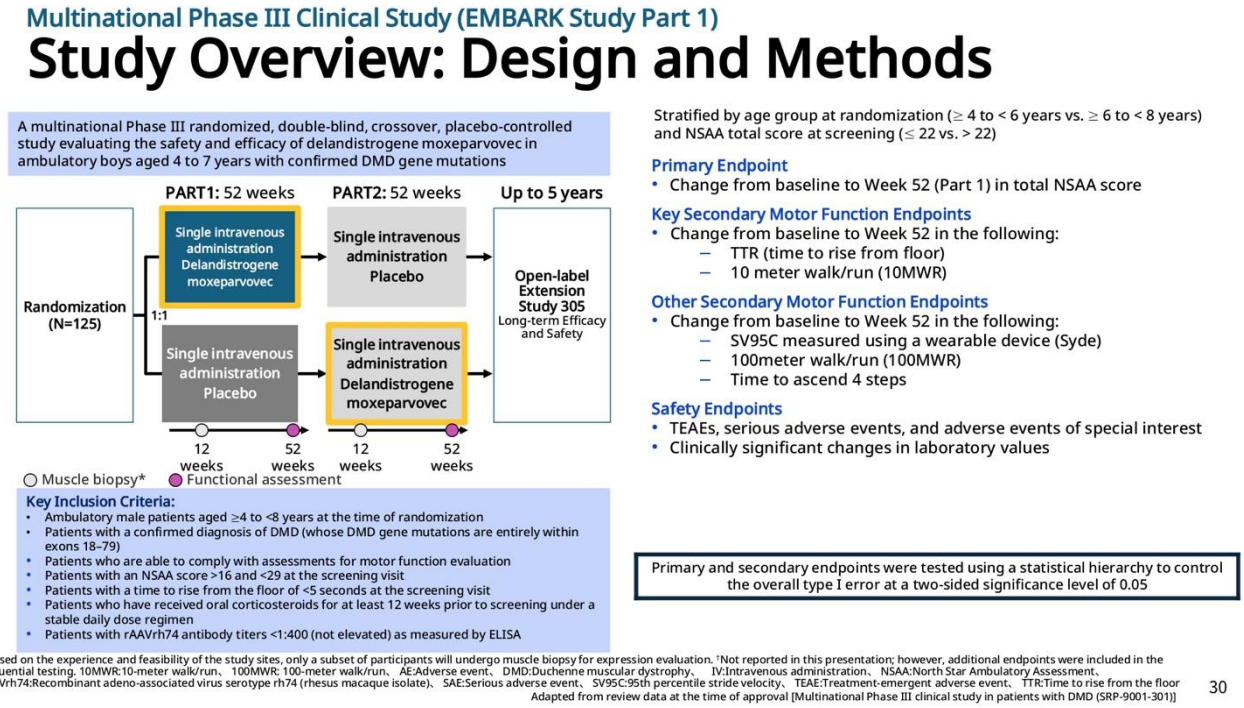
This is an excerpt from the Appropriate Use Guide created by Chugai Pharmaceutical. It outlines the minimum required procedures that must be followed. The items listed here are blood test parameters. Testing is required at baseline (before administration), then weekly at weeks one, two, three, and four, and every week thereafter up to three months. After that, testing should continue at extended intervals. The blue marks indicate mandatory tests, while the white circles indicate recommended tests. In other words, the blue-marked weekly blood tests during the first three months are obligatory. This is one of the key approaches used to ensure patient safety.



I'd like to briefly introduce the results of the clinical trial that was recently approved.

It's called the EMBARK trial, and children between the ages of four and under eight are participating in this clinical trial. There are also a few Japanese participants.

The 125 patients were divided into two groups. In the first year, half of the patients were administered the actual Elevidys. As for the other group, they receive a placebo. They undergo the medical procedure but are given a solution that does not contain the virus, so that the comparison can be made without anyone knowing. We'll compare these blinded.

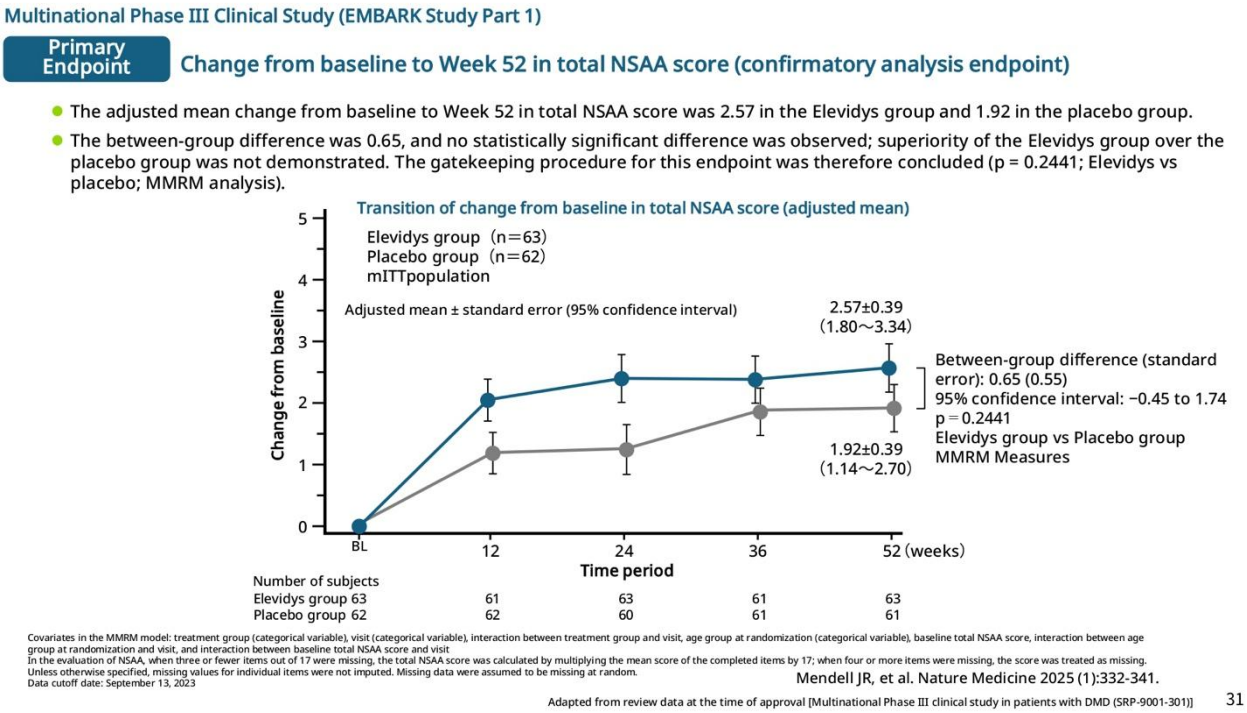
In part two, the groups switch after one year, those who received Elevidys in the first year are given a placebo, and those who received a placebo in the first year are given the actual drug in the second year. The study is designed so that by the end of the second year, each group will have received the actual drug at some point.

I'd like to briefly present some data from the clinical trials that led to this approval, primarily from the first half, the placebo-controlled study, evaluating safety and efficacy by comparing these two groups.

They're generally between four and just under eight years old, so seven years old. Certain requirements regarding motor function have been established.

The primary endpoint, the first item we'll evaluate, is the NSAA, or North Star Ambulatory Assessment score, which I'll introduce later. In addition to that, there are several other tests, such as the time it takes to stand

up from a lying position on the count of “Ready, set, go!” and how quickly one can move 10 meters, measured in seconds. The study is designed to collect information on side effects as well.

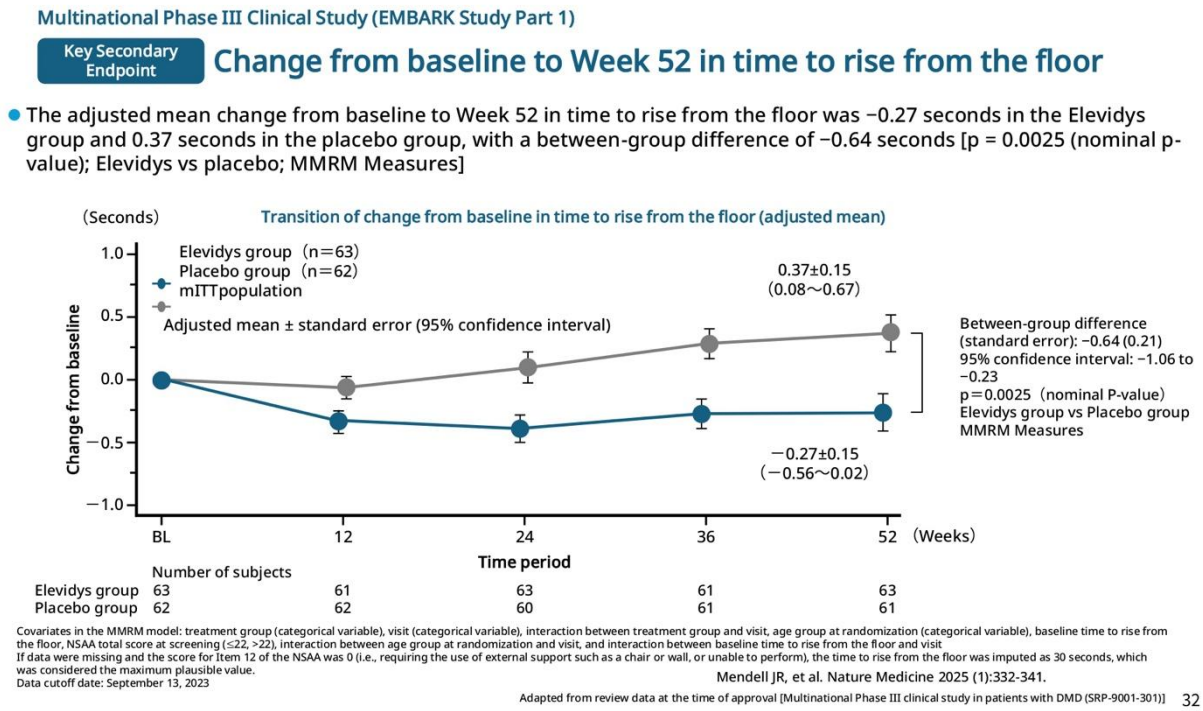


This is the primary endpoint, known as the NSAA.

In this case, a higher score is better, so moving up the scale means improvement. The blue group is the actual medication, this one here in that group. This group is blue. The gray one is the placebo. It's empty.

When compared, the Elevidys treatment group shows slightly better results, so there is a trend toward improvement. However, based on a sample size of just over 60 participants, the results do not indicate a clear difference.

One conclusion is that the primary endpoint was not met.



The following are secondary endpoints, which are the evaluation items set after the primary one.

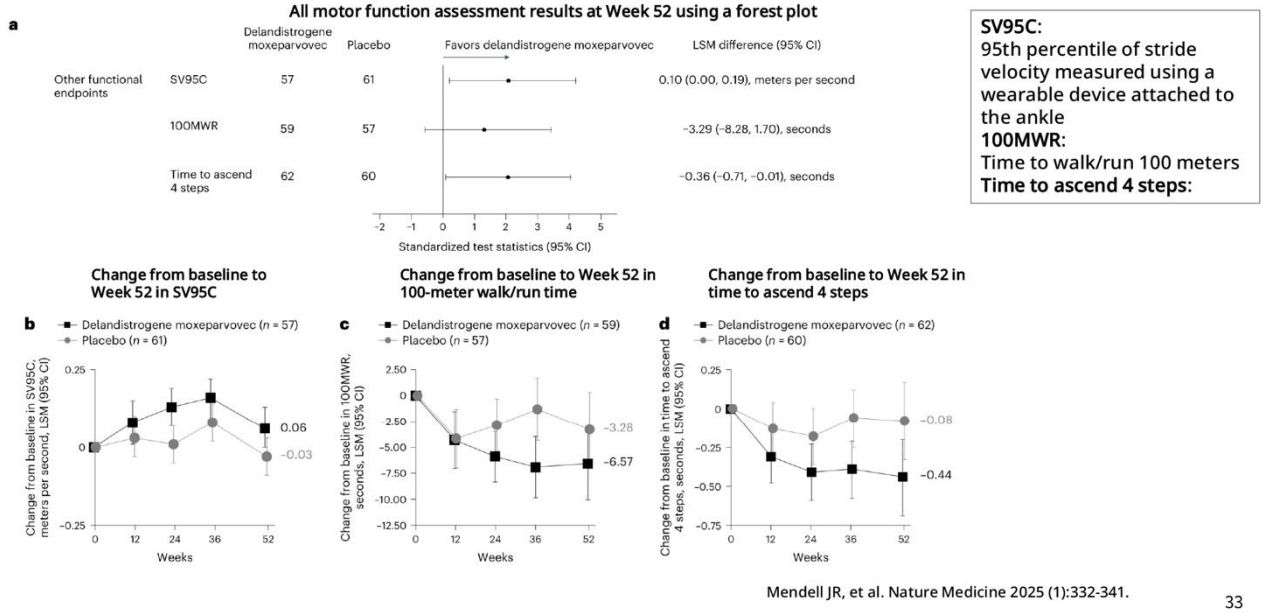
It's an easy-to-visualize test, like lying on your back, waiting for the "Ready, set, go!" signal, being timed with a stopwatch while standing up. Since it's measured in seconds, faster is better, so a lower number is actually better. At one year, the results show that there is a statistically significant difference.

Looking at the various other items, it seems that, with the exception of the North Star Ambulatory Assessment, the results generally show some degree of difference. How we interpret the fact that there was no difference in the primary endpoint is actually a pretty important point.

The other items are in seconds. That's why we evaluate based on the number of seconds. A difference of 0.1 seconds results in a 0.1-second difference, but since NSAA uses a scoring system, it assigns scores to 17 items, rating them on a scale of zero, one, or two points. To put it simply, when you jump, for example, you get two points if you are completely off the ground. If it is just a little bit off the ground, that's one point, and if you aren't off the ground, that's zero points. I think that gives you a general idea of how even a one-point difference can make quite a difference.

Therefore, among experts, there is also debate as to whether setting the NSAA for this one-year evaluation was a mistake. Since this is a primary endpoint, the fact that it was not met is certainly significant. However, I would like to highlight that there are various perspectives on this matter.

Secondary Endpoints for Motor Function Assessment



SV95C:
95th percentile of stride velocity measured using a wearable device attached to the ankle
100MWR:
Time to walk/run 100 meters
Time to ascend 4 steps:

Mendell JR, et al. Nature Medicine 2025 (1):332-341.

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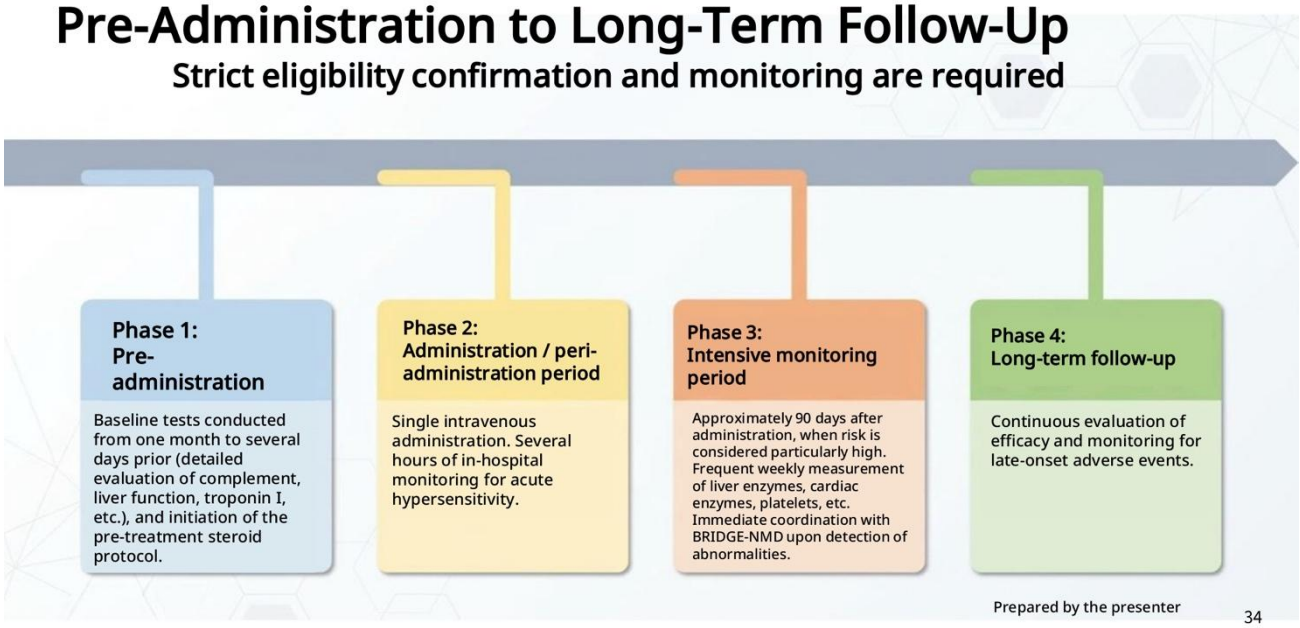
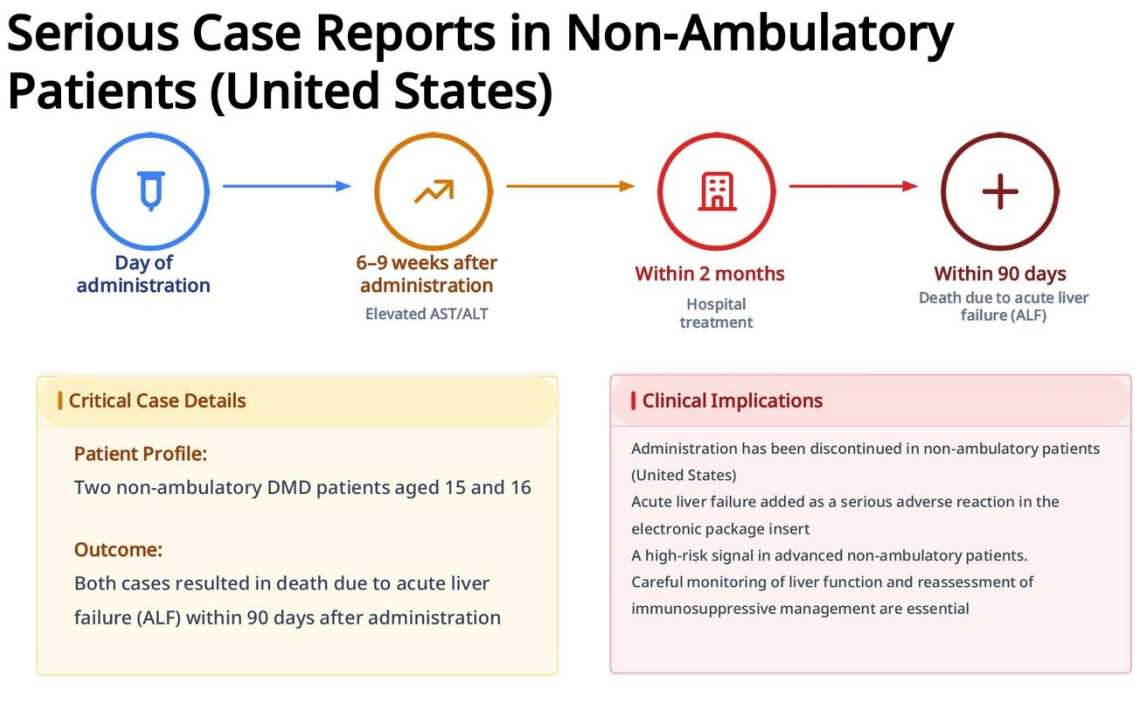
Most of the items in this section are checked at the hospital, in a designated area, under the supervision of a physical therapist, but there's one I'd like to highlight, the SV95C.

People often wear something like a pedometer, don't they? Just like the Apple Watch, it can track various metrics like activity levels, and this metric monitors your stride speed.

In that case, the patients are asked to take the device, put it on, and their daily routines are observed. So, while the other items are generally measured when patients come to the hospital, this one represents numbers from their actual daily lives. I think the fact that there was a difference with the SV95C is actually a pretty important point. I think the fact that physical activity levels have improved in everyday life is a very significant finding.



To sum up, pre-administration preparations, ensuring safety during administration, and thorough weekly checks during the intensive monitoring period, followed by long-term follow-up. I haven't mentioned this yet, but we don't know what will happen in the long run. It is not yet clear how long the effectiveness will last. Also, we still don't fully understand what long-term side effects, if any, might occur. There is no doubt that the situation remains extremely challenging, so ongoing monitoring is crucial.



As mentioned earlier, it was approved last May, and sales began in February. Although there's something like an unwritten rule known as the 90-day rule, this is exactly why the release was delayed so significantly beyond that timeframe.

Around the time of approval, two cases of death due to liver failure were reported in the United States. I've heard that even after it was approved, there were various discussions on the matter within the Central Social Insurance Medical Council. Since deaths were involved, I think it's a fact that there was a debate about whether such a drug should be released onto the market in the first place.

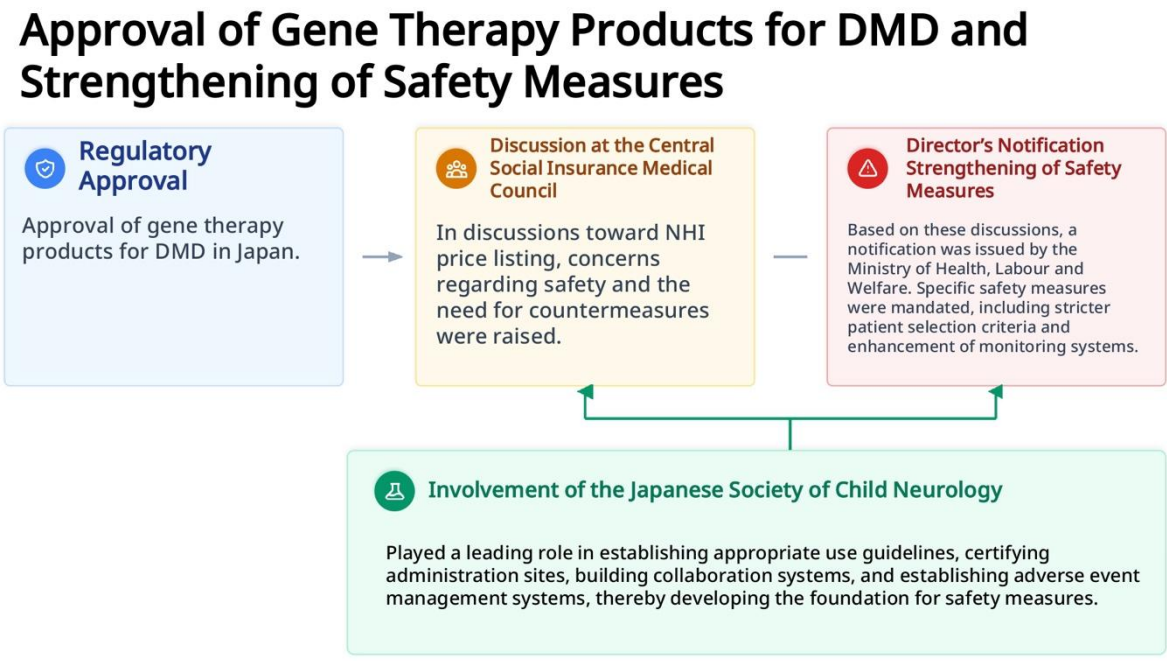
So, as for what to do, I imagine the Ministry of Health, Labor and Welfare and the pharmaceutical companies took the lead in considering this, but from our perspective as the Japanese Society of Child Neurology, we have been holding various discussions on how to proceed.

In this case, the fatal cases in the US involved patients aged 15 and 16, respectively. By the age of 15, they are generally unable to walk, so they are non-ambulatory. Americans are quite a bit bigger than Japanese people. The viral dose is set based on body weight, so the more you weigh, the higher the dose you'll receive. Also, when patients are in a situation where they can no longer walk, their muscle mass decreases significantly, and that, in turn, changes how their bodies metabolize nutrients. It has long been known that fatty liver is relatively common.

There are various debates like these, but it's not entirely clear what the problem is. However, the situation for 15- and 16-year-olds differs significantly from that of the three- to eight-year-olds who have now been approved, and based on data from younger patients, such as those from the EMBARK trial I mentioned earlier, there are currently no major safety concerns regarding liver failure. I believe many clinicians share the view that, while we are fully aware of the risks, we want to provide this medication to patients who, after we have implemented appropriate management measures and ensured that they and their families fully understand the risks, still wish to proceed with treatment.

As I've been explaining, this is a progressive disease, step by step. Some people may believe that not undergoing treatment also carries risks. So, while I am fully aware that there is a debate over whether it is appropriate to release medications that could, in some cases, be life-threatening, as the attending physicians actually managing these patients, we do not believe everyone is a suitable candidate for this treatment, and naturally, there are patients who choose not to undergo treatment because they perceive the risks.

However, for those who wish to take on such a challenge, I believe it is our role to provide the medication only after ensuring that adequate measures are in place.

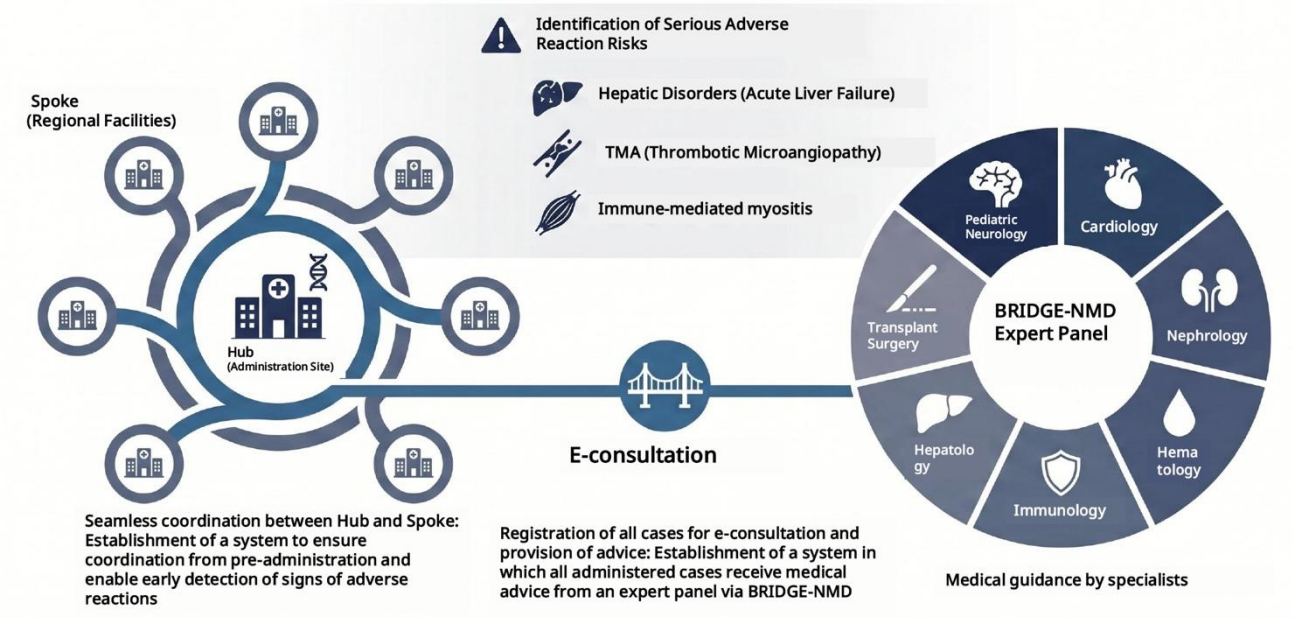


The drug was approved last May following discussions by the Central Social Insurance Medical Council, and sales actually began this February. Following discussions at the Central Social Insurance Medical Council and various deliberations by the Ministry of Health, Labor, and Welfare, a section chief's notice was issued at the end of last year. We have been asked to establish a certain system regarding this drug within academic society. I would like to introduce them now.

The society revised its guidelines for appropriate use, the guidelines it had established. After discussing the issue of where to administer the treatment, we decided on a policy to limit administration sites. In fact, there are currently 13 facilities nationwide that have been certified to administer the treatment.

Conversely, that means there are some patients who have difficult access. Since there isn't one in every prefecture, and people living far away would have to spend several hours traveling each week, as stated in the notice, we were asked to establish a solid system of cooperation in place. We have also been considering what to do about this system.

Also, side effects. DMD is a very rare disease, and the side effects of gene therapy are also very specific, so it's not as though we can simply ask specialists in each organ system to step in and handle the situation right away. We've been thinking about how to handle situations that require highly specialized approaches and knowledge. That's how we've built the system.



Japanese Society of Child Neurology website https://www.childneuro.jp/general/8664/ (accessed June 2026)

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Here is an overview.

First, the treatment facilities, as I mentioned earlier, there are 13 of them. This is available on the Japanese Society of Child Neurology's website, so please feel free to refer to it if you'd like.

For this model, we are developing a hub-and-spoke model. The hub facility will take the lead and bear ultimate responsibility. When we talk about spoke facilities, you can think of these as local university hospitals, local children's hospitals, or general hospitals.

This varies somewhat depending on the hospital, but in Japan, patients are generally hospitalized for about a week, or in some cases, depending on local circumstances, for up to about a month for monitoring. Given that the evaluation monitoring period is three months and weekly examinations are required, spending three or four hours every week just traveling back and forth is quite exhausting, so we are currently asking these spoke facilities to handle some of that. Through this close collaboration, we are currently implementing measures to reduce the burden on our patients.

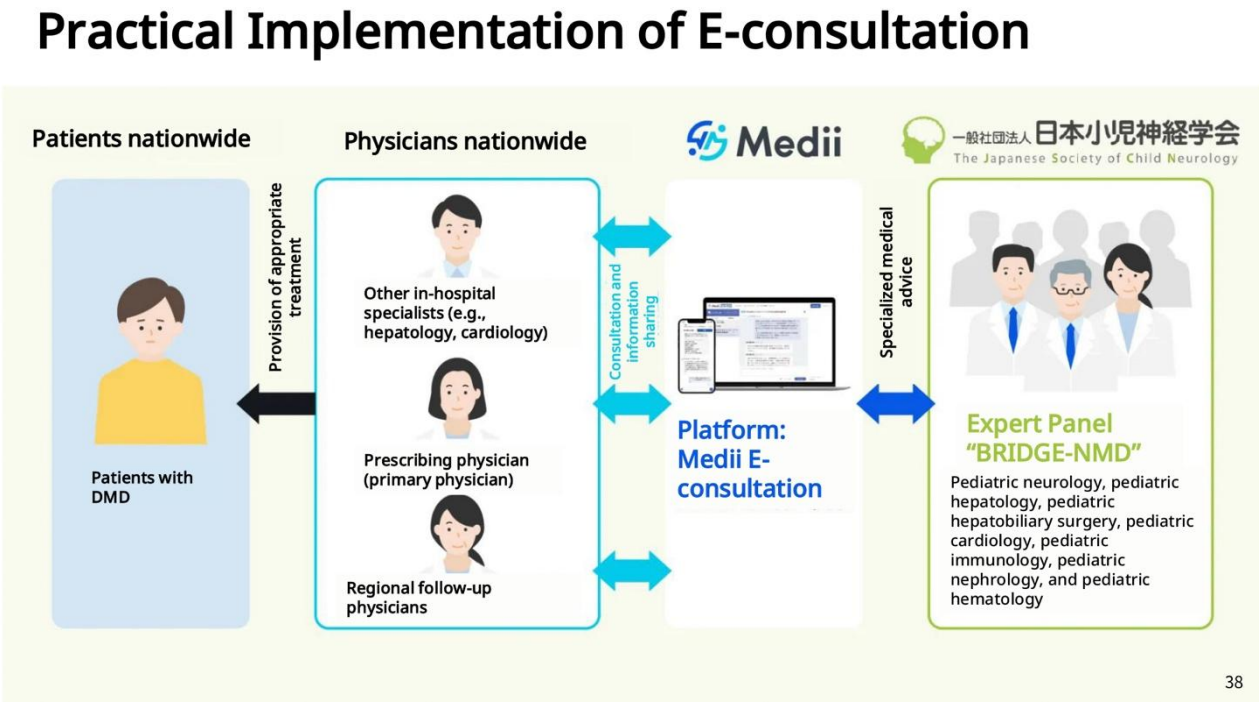
We've established a system that ensures seamless coordination between the hub and spokes. For example, based on where a patient lives, we decide from the outset—even before administration—to collaborate with the team at University A in that region. We report this to the academic conference, and announce that we will proceed under this framework.

Another factor is that, while some universities may have pediatric hepatologists or cardiologists on staff, as I mentioned earlier, both the disease itself and the side effects of gene therapy are quite unique. Given that it's not always possible to simply ask any doctor to handle the case and expect them to respond appropriately right away, we established an expert panel based on that premise.

In fact, we had already decided to create this before the liver failure occurred. We were fully aware from the start that this was a high-risk treatment, so while we had decided to move forward with it, ultimately the entire project is being carried out as an initiative of the Japanese Society of Child Neurology.

All of these specialties are labeled pediatric, including pediatric cardiology, pediatric nephrology, pediatric hematology, pediatric immunology, pediatric hepatology, and transplant surgery, we have established a system in which a panel consisting of roughly one to two experts from each specialty is formed to provide consultations.

As for the consultation method, we generally use E-consultation. This is a system for conducting consultations online. You might wonder why transplant surgery is included, but when liver failure occurs, a liver transplant is ultimately the only way to save the patient. While I certainly hope it doesn't come to that, we are currently working with doctors who perform liver transplants.



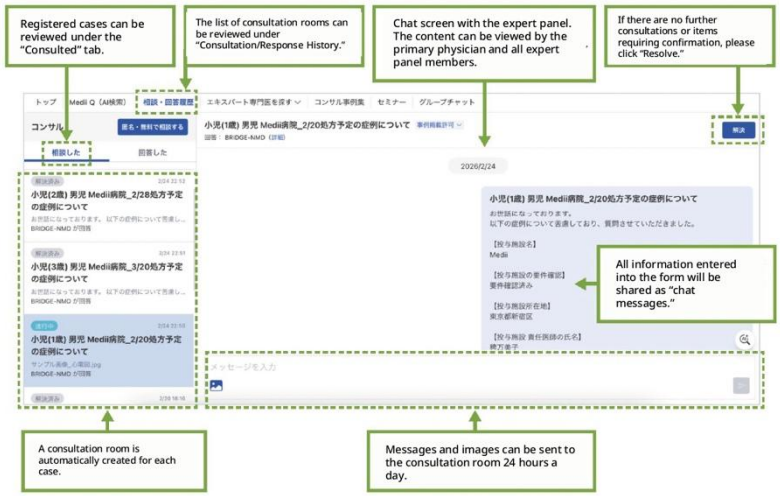
The company Medii has already established a system for case consultations called E-consultation, and we use their platform to manage side effects. We have individual patients, the hub-and-spoke team of doctors I mentioned earlier, and we use Medii's e-consultation service as the infrastructure that connects them with experts.

Basically, all patients are registered for this e-consultation service, and they are asked to upload all their weekly data to this platform. Through this system, they receive advice from expert physicians, such as confirmation that their data has been reviewed, or specific instructions like, "This is a bit concerning, so please be careful to do this," and so on. This is a workflow that is already in place.

Overview of the Adverse Event Management System in DMD Gene Therapy

Workflow of Adverse Event Management in DMD Therapeutics

Through a consultation platform established via case registration, it is possible to seek advice at any time, 24 hours a day, when there is uncertainty in clinical decision-making, including in the management of adverse events.



It's similar to LINE. It's like a chat app. We've set up a system that's designed to feel like a chat, allowing for casual, back-and-forth exchanges. Since the standard Medii E-consultation service alone isn't quite sufficient in some areas, we've had the system modified slightly to create a framework that supports these consultations.

It's a task that takes quite a bit of time and effort, entering data and getting everyone to respond, but so far, things seem to be going smoothly.

Overview of the Adverse Event Management System in DMD Gene Therapy

Workflow of Adverse Event Management in DMD Therapeutics

Through a consultation platform established via case registration, it is possible to seek advice at any time, 24 hours a day, when there is uncertainty in clinical decision-making, including in the management of adverse events.

<Prescribing Facility Information>		
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投与施設所在地	*	
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フォローアップ施設名		
フォローアップ施設の所在地	*	
フォローアップ施設の窓口医師 氏名	*	
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定期予防接種の接種状況	*	
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遺伝学的検査結果（画像）	*	＊＊

＊Required selection item
＊＊Attach image

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ALT（IU/L）	*	
γ-GTP（IU/L）	*	
アルブミン（g/dL）	*	
APTT（秒）	*	
PT%	*	
PT-INR	*	
総ビリルビン（mg/dL）	*	
直接ビリルビン（mg/dL）	*	
CK（IU/L）		
アンモニア（μg/dL）		
Dダイマー（μg/mL）		
ALP（U/L）		
C3（mg/dL）		
C4（mg/dL）		
CH50（CH50/mL）		
LDH（U/L）		
K（mEq/L）		
血液検査における破砕赤血球の所見	*	
実施したウイルス検査値	*	
BNP（pg/mL）		
NT-proBNP（pg/mL）		
心筋トロポニンI（cTnI）（ng/mL）	*	
抗AAVrh74抗体価	*	

<Liver Function / Imaging Findings>		
腹部エコー画像	*	＊＊
腹部CT画像		
腹部MRI画像		
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肝腫大の有無	*	
胸腺の有無	*	
肝性脳症の有無	*	
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12誘導心電図画像	*	＊＊
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壁運動異常の有無	*	
心嚢液貯留の有無	*	
心臓MRIでの左室駆出率（LVEF）（%）		
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遅延造影MRI		
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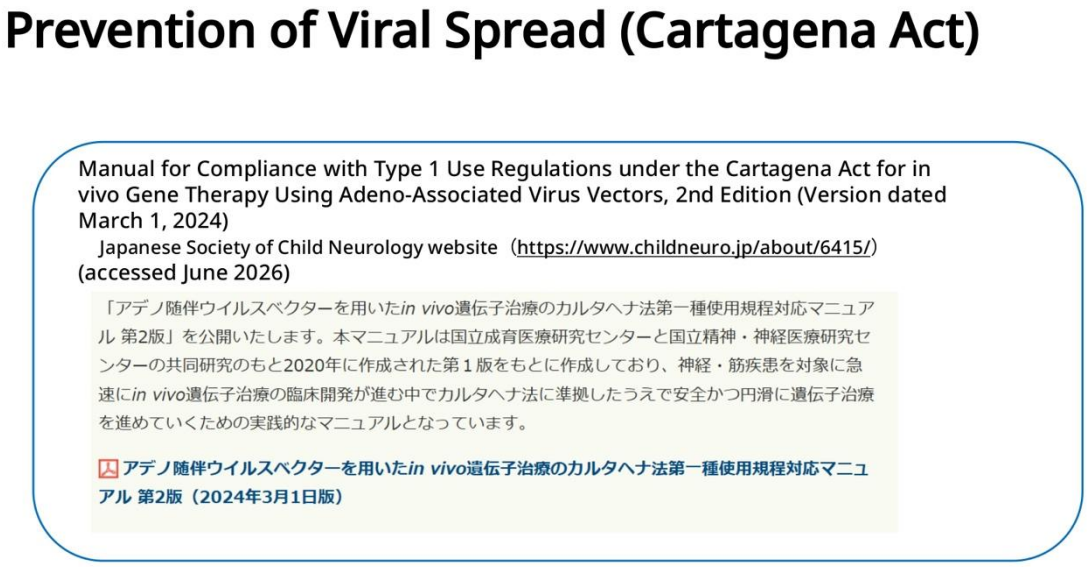
プレドニゾロン投与開始日	*	
プレドニゾロン投与量（mg/kg/日）	*	

This is just to give you an idea of how we enter all these data. Since this is an e-consultation service, the system is set up so that you can post messages anytime, including weekends and evenings.



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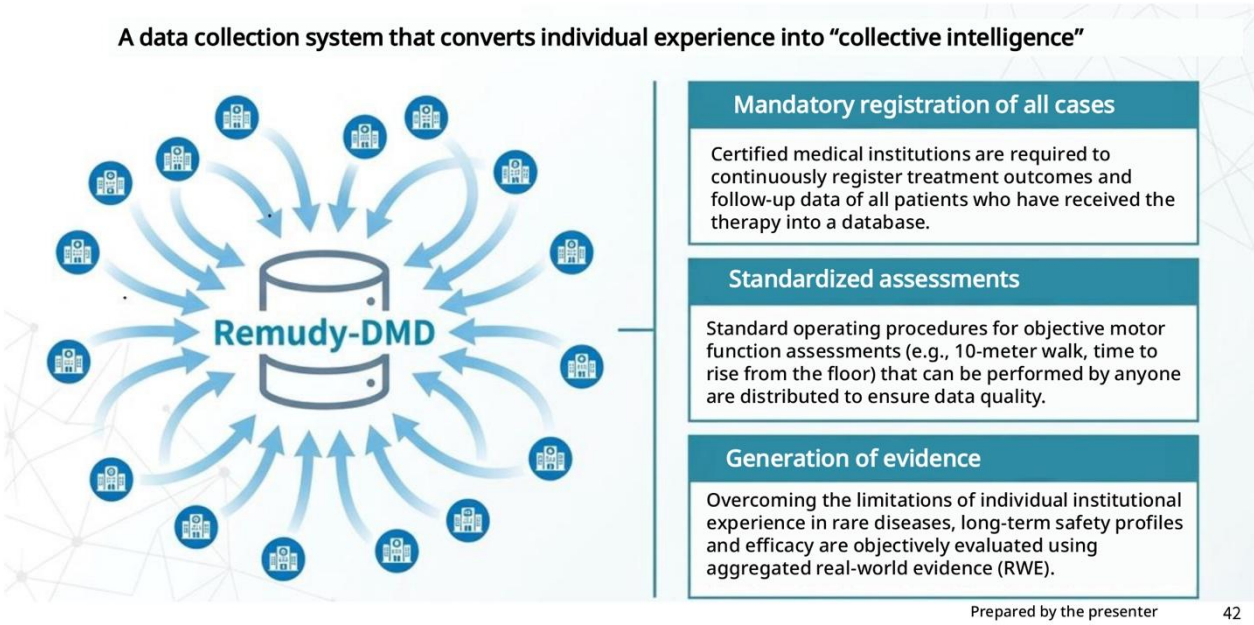
Another challenge for hospitals and patients is the need to comply with the Cartagena Act.

For several days after administration, large amounts of the virus are shed in the stool. So, I think you probably saw people on TV wearing full PPE during the COVID pandemic. It’s kind of like that. Every time a nurse comes in, they put on PPE and then take it off and dispose of it. That happens. It’s a burden on the hospital, too. This applies to manpower as well. Since PPE is disposable, the cost of putting it on and taking it off can be quite a burden. As is the case in any field, hospitals don’t make much profit despite offering these advanced treatments. I suppose the fact that they're operating at a loss is a bit of a tough situation for us.

However, since adeno-associated virus (AAV) is a very important virus, if people become infected and develop antibodies, an increase in antibody-positive individuals would limit the number of patients who can benefit from these treatments. Therefore, the current reality is that we have no choice but to take certain precautions.

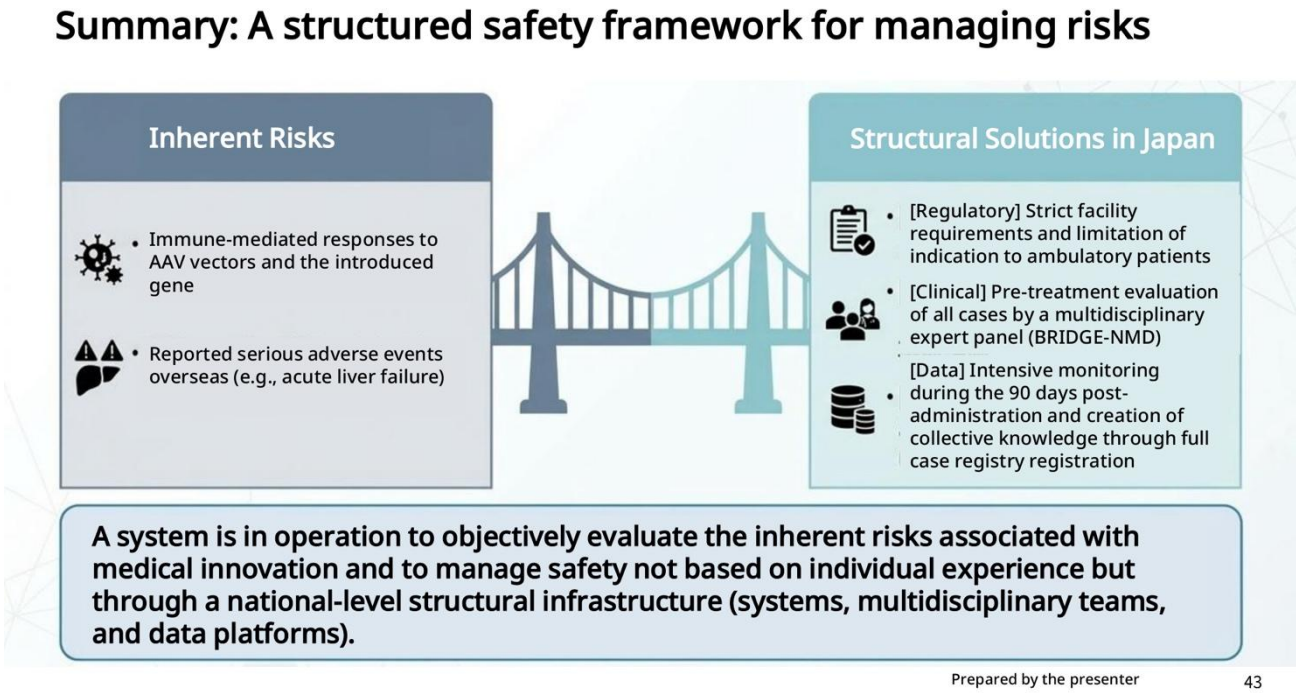
Data Infrastructure: Building Long-term Evidence Using Registries



So far, we've only discussed safety measures, but efficacy remains just as important. Unlike clinical trials, it's not that easy to figure out how to accumulate data.

This is a database that we at the National Center of Neurology and Psychiatry created in conjunction with the approval of Viltepso. We are currently using it as a database that ensures data quality capable of withstanding post-marketing surveillance requirements.

We are proposing to include specific efficacy endpoints, and to evaluate all future new drugs within this database. In case of DMD, this database can be used for long-term follow-up and follow-up on efficacy. We are currently considering whether we can provide safety and efficacy data using a system like this.



The last slide. I think the issue of risk is receiving a lot of attention right now, but there is no doubt that it is a serious matter, so we are currently implementing all possible measures and doing our utmost to administer the treatment.

Treatment has already begun starting in February, and I believe more than 10 patients nationwide have now received the treatment. So far, the treatment has been administered, and everything is proceeding smoothly.

One thing that went particularly well this time is that I think the collaboration between industry, government, and academia is going well so far. I believe we have reached this point thanks to the excellent collaboration between the Ministry of Health, Labor, and Welfare, CHUGAI PHARMACEUTICAL, and we physicians and medical societies.

Since we don’t know what the future holds, we intend to maintain this system while paying close attention to the situation. However, because this is a system that places a very heavy burden on our resources, we also have significant concerns about how to ensure its sustainability.

That's all from me. Thank you very much for listening.

Question & Answer

Ozaki [Q]: My name is Ozaki from the Nikkei. Thank you very much for your presentation. As was mentioned earlier, about 10 patients have already received the treatment, are they at the NCNP?

Komaki [A]: No, it's nationwide. Although there are 13 administration sites, we are coordinating closely via email and other means, so we are able to monitor the situation in real time.

Ozaki [Q]: Thank you very much. Also, there was a discussion that administration places a heavy burden, and you need to ensure sustainability. If the system is such that medical institutions incur a loss with every administration, what is the approximate scale of that financial burden, for example, how much does it amount to for each case treated? I would like to know in detail.

Komaki [A]: Previously, when we estimated the costs for another drug and for gene therapy, we found that the expenses would likely range from several hundred thousand to about 1 million JPY, and we've been using that as a basis for discussion.

In this case, the target age group is a little different, so things might turn out a bit differently, and while we might not end up with a deficit in the millions, I don't think we'll be in the black, at least.

In terms of content, this refers to the disposable PPE supplies I mentioned earlier, as well as the hidden labor costs. It's not just a matter of two or three doctors. We'd have to allocate a significant amount of resources to this, so when you factor in the labor costs, the way that estimate is calculated is a bit difficult for me to grasp. So, I can't really say for sure, but at the very least, it won't turn out a profit. Ultimately, what we're hoping for is a system that ensures we can earn a fair income when providing these kinds of pioneering treatments.

One point. There's something called the Cartagena Law premium, and we became able to apply such an addition starting this month in the current fiscal year. However, to be honest, the amount isn't really enough.

Ozaki [M]: Thank you very much.

Kozaki [Q]: This is Kozaki from International Pharmaceutical Information. Thank you very much for today. I'd like to ask Dr. Komaki a question. You mentioned that no statistically significant differences were observed in the primary outcome measures of the NSAA score. Are you hoping that statistically significant differences will emerge as the number of cases increases in the future? Even though no statistically significant differences are found, these approaches are still being approved and introduced into clinical practice. I'd like to hear your thoughts on that.

Komaki [A]: I suppose one approach would be to increase the number of cases, but that's not something we can do at this point.

The other thing is that this is a progressive disease, and it progresses slowly. Therefore, if the placebo-controlled phase of the trial were extended to a year and a half or two years, the difference might become a little more apparent.

However, there is also debate over whether it is ethically acceptable to make people in the placebo group wait for a year and a half or two years with a placebo, so while the details of how to handle that period are planned quite meticulously, this is the outcome we ended up with.

As for the data on the second and third years, while we can't directly compare it to a placebo, there is data on the natural history of the disease that has been accumulated worldwide to date. The data based on that research has already been published in a paper covering the second year. As for the third year, I understand that the findings have already been presented at academic conferences and the like, and that work is currently under way to prepare a paper based on them. While this is a comparison with the natural history, data has now emerged showing clear differences from the natural history in terms of motor function assessment, including the NSAA.

Kozaki [Q]: If we evaluate this by comparing it to what's known as a historical control group, would that be considered a statistically significant difference?

Komaki [A]: There is a difference compared to the historical control. Of course, there is some debate about whether using historical controls is the right approach, but that's certainly true.

Kozaki [Q]: This overlaps a bit with my previous question, but I think we can't just ignore the fact that doing this places a financial burden on the facilities. Is there any possibility this might change in the future?

Komaki [A]: We've been discussing that we need to make such arguments through academic societies and other channels. However, from what I've heard, even surgical departments are performing highly advanced treatments, and I've heard they're doing so while operating at a loss, so this may not be a problem that we alone can solve just by making our case.

Kozaki [M]: Thank you very much.

Innami [Q]: My name is Innami from Toyo Keizai. I'd like to ask Dr. Komaki a question.

What I'm wondering is when to administer Elevidys. Considering what was mentioned earlier about how it works and the fact that it's a progressive disease, I wonder if it might be better to get the shot sooner rather than later, but there's the issue of how long the effects last, as discussed earlier. Given the current situation, what is your opinion on whether the treatment should be administered immediately at age three upon diagnosis or whether it would be better to take a more conservative approach regarding the duration of efficacy?

Komaki [A]: That is a very sharp observation. Since we have a strict policy, at least at this point, limiting administration to children up to age eight. The situation is the same nationwide. The treatment is being administered almost exclusively to seven-year-olds. This isn't for medical reasons but for social ones. We're doing this because, as things stand, once your birthday has passed, you'll no longer have the opportunity.

As for the next step, if the situation stabilizes around the end of the year or the beginning of the new year, I think we'll consider expanding the age range to include children from three to eight years old. As you pointed out, I do believe there is a good chance that retaining muscle mass can lead to better results. At this point, we lack that kind of data. I understand that there is no clear answer. Theoretically, you're right. It might be better to do it sooner rather than later.

And there's one more thing. As you pointed out, there's the issue of duration. So, I think we need to weigh those factors carefully. There's no doubt that time is of the essence, and it's becoming increasingly difficult, in a good way, to envision what the situation will be like five or ten years from now.

So, personally, I think there's a possibility that things might gradually speed up because of that. However, to reiterate, I understand that there is not yet sufficient evidence to support the view that it should be done sooner rather than later. This is a very important issue.

Innami [Q]: Thank you very much. Just one more point. You briefly mentioned this earlier in your explanation, but I'd like to ask about the possibility of using this medication in combination with other drugs.

For example, Viltepso, and also the anti-inflammatory drug currently being developed by Capricor. In this case, regarding cardiomyopathy, there are proteins in the heart muscle associated with Elevidys.

Komaki [A]: Yes, we can expect Elevidys to also express the protein in the heart muscle to some extent.

Innami [Q]: Is it possible to consider using this medication in combination with other drugs in the future?

Komaki [A]: This is also an important issue, but aside from medical costs, I think it makes sense to use treatments with different mechanisms of action in combination, for example. So, as I mentioned earlier, steroid treatments and Elevidys are generally used together. Combination therapy has already begun.

However, as you know, prednisolone is incredibly cheap, so its cost is negligible. That said, I think we'll start seeing more cases of combining new drugs with other new drugs in practice going forward.

In terms of the mechanism, I think it makes sense to combine a method for restoring the dystrophin protein with measures to suppress inflammation and fibrosis.

As for the other points you raised, gene therapy and exon-skipping drugs would be possible, I would say. Since this would involve different proteins coexisting, I personally have some reservations about whether this is medically feasible and safe.

In essence, while there are full-length dystrophins, both the protein derived from Elevidys and the one derived from Viltepso are short proteins, so their structures differ from one another. I think we need to investigate whether it's okay for such conditions to coexist in a single patient.

Saga [Q]: I'm Saga, a freelance writer. Thank you very much. Just one thing, doctor, this is sort of a follow-up to what we were just discussing, but if that's the case, do you present this option to nearly all of your patients during your daily practice? Or are you, to some extent, selecting specific targets to share, similar to what you've been doing so far? I would like to know in detail.

Komaki [A]: Since, in principle, people have a right to know, we will generally share this information with everyone. At least for those who are within the recommended age range, we'll explain the situation and discuss what to do.

As for genetic mutations specifically, although I didn't go into much detail about them this time, for example, administration is contraindicated for patients with deletions in exons eight and nine. So, for those parents, even if a treatment like this becomes available, we explain that, unfortunately, your child would not be eligible for it. Please assume that, as a general rule, we won't select anyone to explain.

Saga [Q]: So, you just mentioned the number of cases nationwide. How many of those cases were treated at your institution?

Komaki [A]: I can't give specific examples, but we've handled several cases.

Saga [Q]: This is the last one. So, for patients who have a history of using viltolarsen, this Elevidys, that's a possibility.

Komaki [A]: That's possible. However, I think that, for the time being at least, the administration of viltolarsen will be put on hold.

Saga [M]: Thank you very much.

Shimomura [Q]: My name is Shimomura from Jihou. I'd like to ask Dr. Komaki a question.

Regarding regenerative medicine products, I believe conditional and time-limited approvals are currently the mainstream or at least account for about half of them. Since Elevidys has received conditional approval this time, I'd like to hear your thoughts on what you, as a clinician, consider important for transitioning this to full approval.

Komaki [A]: From a very personal perspective, I do not believe that presenting real-world data on efficacy over a period of three years or so can yield data that is more robust than that from clinical trials.

On the other hand, when it comes to safety, I believe that as the number increases, so does the amount of information available, and I don't think the quality will decline significantly. As for priorities, in this case, the top priority is to properly compile the safety data. Also, what are the mechanisms and timing of side effects, and how should we manage them? I believe that clearly communicating these kinds of information is our mission.

So, when it comes to this medication, I'm thinking we might need to place a lot more emphasis on that aspect.

Shimomura [M]: Thank you very much.

Tomioka [Q]: My name is Tomioka from Yakuji Nippo. This might sound a little rude, but the drug price for Elevidys is about JPY300 million, and on top of that, the hospital also incurs costs in the form of a financial loss, as well as in terms of the human resources required.

On the other hand, based on the results of this clinical trial and other data, how much do doctors and experts expect the life expectancy of DMD patients, which has traditionally been around 30 years, to increase with the administration of Elevidys? I would like to know specifically how much the cost to society and the benefits to Elevidys patients actually amount to in terms of how much longer life expectancy is extended.

Komaki [A]: I think this is a very important and difficult issue. Although it's not about age, and while it's difficult to assess life expectancy and quality of life, I think these metrics are steadily improving. I happened to come across this field in my second year as a doctor, and the truth is, they had all passed away by the time they turned 20. Of course, they couldn't go to school. It is true that even these people are becoming much better able to envision their lives as adults.

If that happens, then unlike in the past, the number of people contributing to society may steadily increase going forward. While health economics is certainly important, I personally believe we need to consider not only the cost savings resulting from a reduction in the severity of their conditions, which facilitates their social participation, but also the broader social value, including their participation in and contribution to society.

As for whether JPY300 million is a reasonable figure, I'm afraid I can't really answer that, since I'm not an expert in health economics. On the other hand, we recognize that as the number of different drugs increases and expensive medications become available for similar conditions, society is likely to raise various concerns, and we acknowledge that this is an issue our community must gradually take more seriously.

I understand that we must demonstrate not just in the short term but over the long term as well that this drug has value, including its efficacy, and that it is effective enough to withstand that situation.

The only data available for this clinical trial is from a one-year study or something like that. So, I guess I just don't know how much value it has right now. We will carefully consider the long-term data available to determine the value of this drug. In that sense, we are currently building a database, as I mentioned earlier, to verify various aspects, including efficacy, after the product is released, and we are certainly keeping that in mind as we do so.

Taking into account these various combination therapies, I personally recognize that the challenges we'll face as new issues arise will gradually become more serious, and to be honest, it will be difficult to address them solely within the healthcare setting. For example, when a patient says, "There's this medication," or "I'd like to try another one," if it's allowed under the system, it's difficult for us to say no.

In such cases, it's important to establish clear guidelines. Since this field often requires highly specialized knowledge and experience, there may be a case for limiting the facilities authorized to administer such treatments. I think this is an issue that we need to address not just on our own but by working together with our stakeholders.

Sorry, that wasn't really an answer. Is that all right?

Tomioka [Q]: I left out a bit of what I wanted to say earlier. Even for these patients themselves, although the age at which the drug is administered differs in the US, there is a possibility they might die, so there are situations where they must accept that risk. The question is whether, even when considering the risks these patients themselves might face, Elevidys is still considered to offer benefits that outweigh those risks.

Komaki [A]: Since there are only two cases, I can't say anything definitive. However, the fact is, they were 15 and 16 years old. Considering the progression of this disease, these patients are at very different stages of the disease. That is one key difference. As I mentioned briefly earlier, the important Phase III EMBARK trial, which has now been approved, has, as I noted, including the crossover phase, a total of just over 120 patients are currently receiving this drug. Looking at the safety data, I believe that, at least for patients aged three to eight, the risk-benefit profile remains favorable at this point.

To be honest, this really depends on how things unfold going forward, so with that in mind, we are proceeding very cautiously and with a sense of unease. I'm not sure if we should say this, but to be honest, this is our first time taking on a challenge like this, too. So, the treatment facilities have come together, and when various problems arise, we all discuss how to handle them. That sort of thing hasn't really happened much before. We're currently working on this as a nation, holding timely discussions and exploring possibilities, so I hope you'll understand our situation.

Tanaka [Q]: I am Tanaka from Mizuho Securities. Dr. Komaki, thank you very much for today.

First, regarding the conditional, time-limited approval, which is for three years, I'd like to know what kind of information you can expect to gather during those three years. I believe there was one more trial that included patients who were unable to walk. Do you think the results of that trial will be significant? Or will real-world data become more important?

Komaki [A]: As I mentioned earlier, I personally believe it would be difficult to produce new post-marketing data on efficacy within those three years. I think that after three years, we can expect to have reached a certain number of cases, so- and I realize I'm repeating myself here, I believe we'll be able to present some

data regarding safety, as well as what kind of management approach would be appropriate. I think that's the most crucial point.

Unfortunately, the trial involving data on patients who are unable to walk is currently on hold, and as far as I know, there is still no timeline for its resumption. So, I don't know myself yet how this will turn out.

Since the current indication is limited to patients aged three to eight and haven't yet resumed the study including patients who are unable to walk, I don't think this will make much of a difference.

Tanaka [Q]: Even if this is fully approved, since the age limit is under eight, is your impression that the majority of patients will want to receive the treatment before they turn eight?

Komaki [A]: Given that clinical trials have not yet resumed, I personally feel that the timeline for expanding the approved age range beyond the current limit at that time appears rather challenging.

Tanaka [M]: I see. Thank you very much.

Miyata [M]: The first question, Ms. Murakawa from Kyodo News. Please go ahead.

Murakawa [Q]: My name is Murakawa. Thank you very much. I'd like to ask Dr. Komaki a question.

Since this drug is administered as a single dose, I imagine that even with close monitoring of liver function, there would be no way to reverse the administration if such a signal were to emerge along the way. Is there actually anything that can be done once that signal appears to prevent acute liver failure from setting in? How is care handled in that area?

Komaki [A]: Due to the nature of clinical treatment, it is a one-time procedure that is completed in a single day or within a few hours, and there is no going back because it infects cells throughout the entire body. Therefore, there is virtually no chance of turning back.

Before that, though, what I'm really focusing on right now is identifying the signals that indicate when a problem will occur. How do we determine the cause of liver damage? In addition, while relatively mild liver damage occurs with some frequency, a major challenge right now is determining when to identify signs that a situation may be developing that carries a risk of leading to acute liver failure. Various proposals have been put forward, including at international conferences, suggesting that this is the approach we should take, but nothing has been finalized yet. I think that's a very important issue.

To get into the details, we often check for liver damage using AST and ALT during health checkups, but these enzymes are also found in muscle tissue. Consequently, diseases that cause muscle breakdown are characterized by inherently high AST/ALT levels. So, while it's relatively easy to determine when AST levels indicate liver damage, that's not clear when it comes to DMD.

Normally, the reference range is around 40, but for the DMD patients, their AST/ALT base levels are around 200. There is a general guideline that suggests liver damage may be present if the level exceeds a certain multiple of the reference range, but since these values naturally fluctuate quite a bit, it's very difficult to determine with certainty. So, taking that into account, there are still major challenges ahead. Right now, the areas we're focusing on the most, or rather, the challenges we're facing are things like how to make decisions and what criteria to use.

Once it actually occurs, there is still no established treatment. For example, there are methods such as pulse therapy, which involves administering large doses of steroids via IV drip, immunosuppressive therapy,

plasmapheresis, or adding different immunosuppressants, but the question of which option is best at what stage is currently the subject of international debate, it hasn't been fully decided yet.

Murakawa [M]: Thank you very much.

Wakao [Q]: Thank you very much. I'm Wakao from JP Morgan. Thank you. I believe there was some discussion about this in the Q&A session, but I'd like to ask you to elaborate a bit more on your thoughts regarding how to distinguish with the use of viltolarsen.

You mentioned earlier that this medication can be used by people who have a history of treatment with viltolarsen. Are you anticipating that patients currently undergoing treatment with viltolarsen will switch to this medication? I'd like to know if you're referring to people who were taking viltolarsen but stopped treatment because their condition progressed.

Another question is whether, for patients who may be eligible for Exon 53 skipping and have not yet received treatment, it is better to start with viltolarsen or with Elevidys. I'd also like to know your current thoughts on this matter, if there are any.

Komaki [A]: The easiest way for us to make a choice would be if there were clinical trial data comparing the two, but unfortunately, that data isn't available. First of all, effectiveness is a very important factor, but the data is still unclear at this point.

One thing I'd like to point out about Viltepso is that, as far as I know, there's no evidence that its effectiveness diminishes with repeated use. However, the fact remains that this is a drug designed to slow the progression of the disease, not to stop it. I think Elevidys takes essentially the same approach, while it may be effective and lead to improvements in the short term, I believe that slowing the rate of progression is a realistic goal when viewed from a long-term perspective.

The burden of administration is quite different. Their characteristics are also completely different. For example, viltolarsen is administered via IV drip for one hour every week. A one-hour IV for a child is quite a burden. In that sense, it's really tough on them. We are currently administering viltolarsen to several dozen patients, nearly 30 people, at our hospital, but generally speaking, few patients receive the treatment here. In most cases, we refer them to local hospitals. To minimize the burden as much as possible, we are currently arranging for the treatment to be administered at a relatively nearby hospital.

So, once it's up and running, since everything's going smoothly, even though Elevidys is only a short-term program, it actually places a pretty heavy burden on families. Given that it's difficult to implement the kind of regimen I mentioned earlier, such as weekly sessions for three months or a month of home therapy, some people are currently opting to proceed with Viltepso.

On the other hand, even if there's no difference in efficacy, some patients may be considering switching because a single dose provides protection for a certain period since administering the medication repeatedly can be burdensome. So, there isn't a single objective criterion that dictates, "This is the case, so that's the answer." I think it depends quite a bit on the individual patient's and family's circumstances. I don't think this is good, but given the nature of this drug, that's just the way it is at the moment.

To be honest, our approach is to share as many facts as possible, including the liver failure I mentioned earlier, and to avoid reaching a conclusion after just one discussion. Instead, we're taking the stance of having multiple conversations so we can think things through carefully.

Wakao [M]: Thank you very much. I understand very well.

[END]

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