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# CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on EVRYSDI

September 27, 2021

# Event Summary

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|---|---|
| **[Company Name]** | CHUGAI PHARMACEUTICAL CO., LTD. |
| **[Company ID]** | 4519-QCODE |
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| **[Event Type]** | Special Announcement |
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| **[Venue]** | Dial-in |
| **[Venue Size]** | |
| **[Participants]** | |

| | | |
|---|---|---|
| **[Number of Speakers]** | 2 | |
| | Hideto Kodaira | EVRYSDI Lifecycle Leader |
| | Dr. Kayoko Saito | Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University |
| **[Analyst Names]*** | Fumiyoshi Sakai | Credit Suisse Securities (Japan) Limited |
| | Seiji Wakao | JPMorgan Securities Japan Co., Ltd. |
| | Kazuaki Hashiguchi | Daiwa Securities Co. Ltd. |
| | George Zhou | Goldman Sachs Japan Ltd. |
| | Shinichiro Muraoka | Morgan Stanley MUFG Securities Co., Ltd. |

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

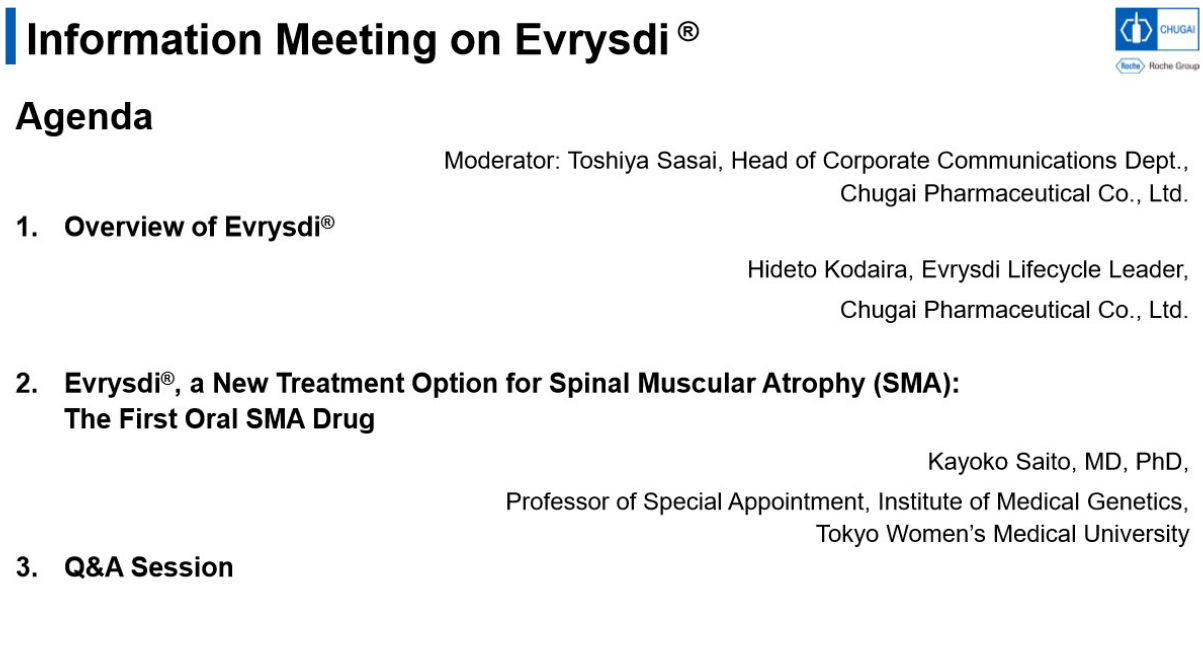
## Presentation

**Sasai:** Thank you very much for joining us for today's information meeting on Evrysdi, a new treatment for spinal muscular atrophy.

I am Sasai of Chugai's Corporate Communications Department, and I will be your host for today's session. Thank you.

Due to the ongoing coronavirus pandemic, today's session will be conducted in the form of a conference call. You can also view the materials and video of this presentation through the URL included in your email invitations.

The audio will come from the conference call system, so please do not disconnect your phones during the presentation.

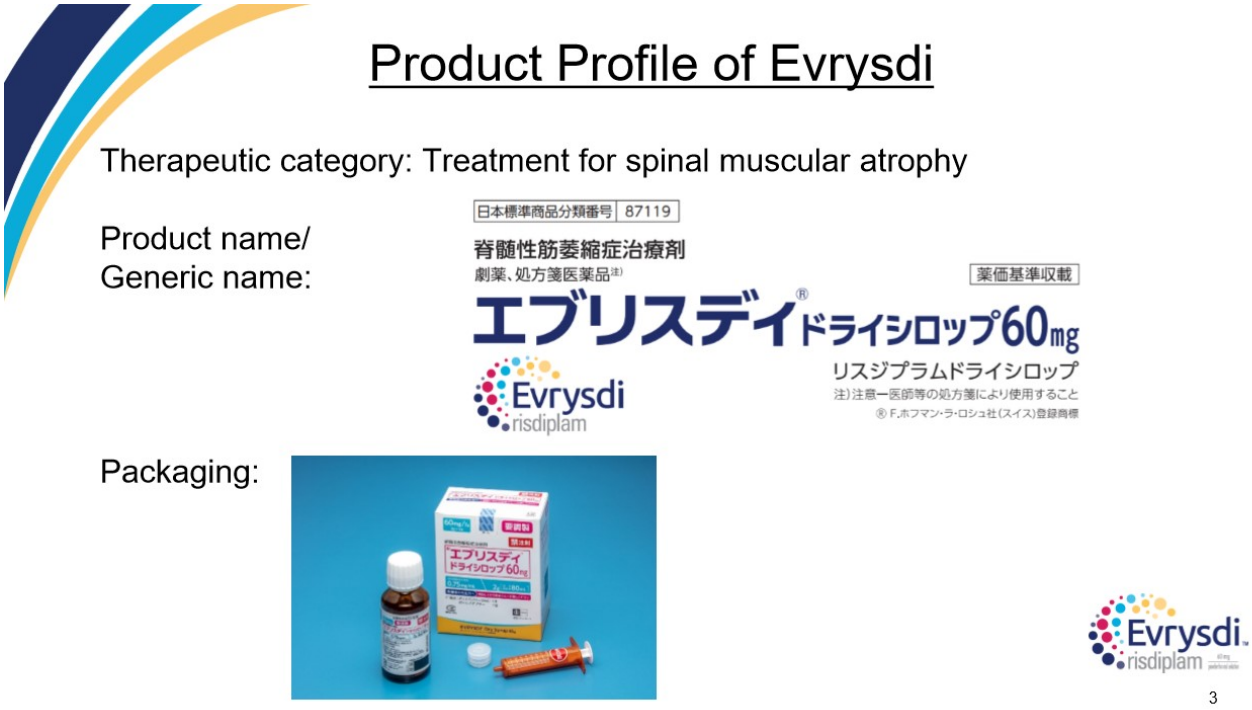



The agenda for today's meeting can be found on the web page and on the first page of the presentation materials. Today's presentation will follow that listed in the agenda.

Today, we have invited Professor Kayoko Saito, Professor of Special Appointment to the Institute of Medical Genetics, Tokyo Women's Medical University. An introduction to Professor Saito's work is included in today's presentation materials.

We will take your questions after the presentations have been completed.

First, I will hand over to Mr. Kodaira, Chugai's Lifecycle Leader for Evrysdi, who will give a summary of the treatment.




**Kodaira:** Hello everyone. My name is Kodaira, and I am the Evrysdi Life Cycle Leader at Chugai.

Today, I would like to give an outline about Evrysdi Dry Syrup 60 mg.

The indication for this drug is spinal muscular atrophy. The name of the product is Evrysdi Dry Syrup 60 mg. The drug is available in a white box as shown below.

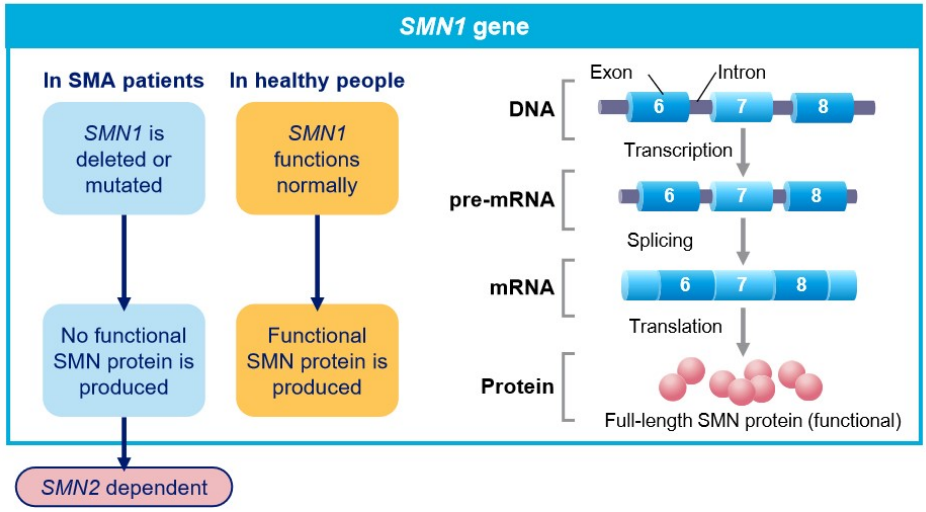
The product is delivered in the form of a dry syrup, in this brown bottle. The box includes an adapter and 2 syringes.

Evrysdi itself is a low molecular compound. It can be taken orally, and distributes throughout the body.

The drug can be mixed with water at pharmacies and medical institutions, dissolved, and then taken by patients.

## Mechanism of Onset of Spinal Muscular Atrophy (SMA) and Mechanism of Action of Evrysdi (risdiplam) (1)

(Illustrative example)




SMN: Survival Motor Neuron

Source: Evrysdi Appropriate Use Guide [Mechanism of Onset of SMA and Mechanism of Action of Risdiplam] Prepared on the basis of Swoboda KJ. J Clin Invest. 2011; 121: 2978-81.

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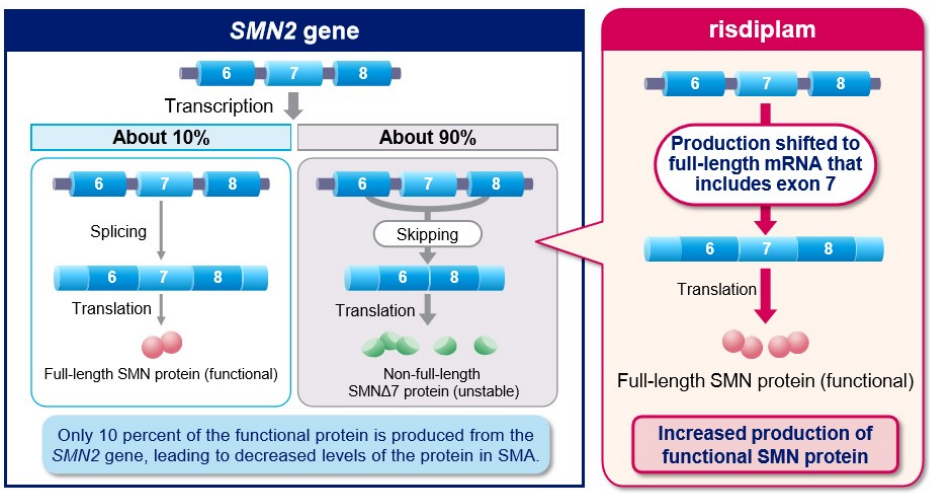
In the next few slides, I would like to explain the pathogenesis of SMA and the mechanism of action of Evrysdi.

SMA is a disease caused by a defect or mutation in the *SMN1* gene. In healthy individuals, this gene functions normally, resulting in the production of functional SMN protein. Unfortunately, in patients with SMA, malfunction of the *SMN1* gene means that this cascade does not work properly. As a result, patients with SMA need to depend on the *SMN2* gene.

## Mechanism of Onset of Spinal Muscular Atrophy (SMA) and Mechanism of Action of Evrysdi (risdiplam) (2)

(Illustrative example)




Source: Evrysdi Appropriate Use Guide [Mechanism of Onset of SMA and Mechanism of Action of Risdiplam] Prepared on the basis of Swoboda KJ. J Clin Invest. 2011; 121: 2978-81.

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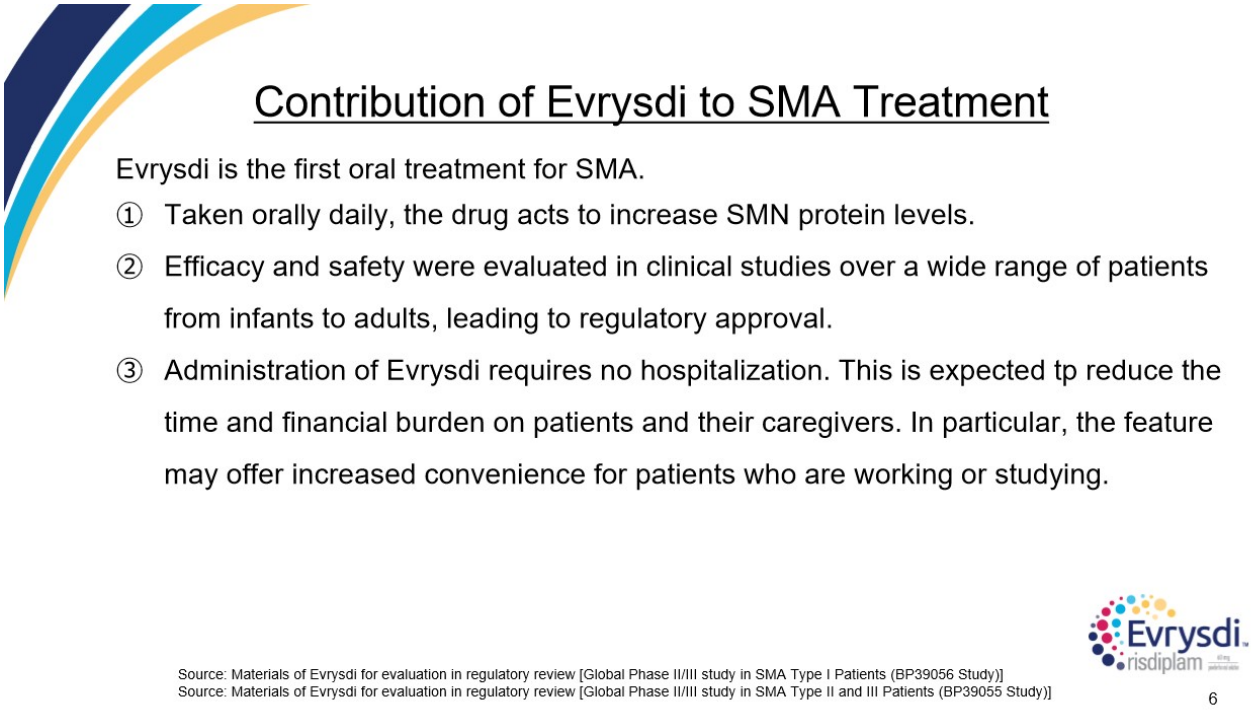
Humans have both the *SMN1* and *SMN2* gene. In the absence of treatment, the *SMN2* gene undergoes a phenomenon called 'skipping.' When skipping occurs, the pre-mRNA is skipped during the translation process.

For this reason, only non-full-lenrth proteins are produced. This drug has the effect of correcting this defective part. The mechanism of action of  this drug results in an increase in the number of full-length SMN proteins.




As I mentioned earlier, Evrysdi is  is the first oral treatment for SMA. Taking this drug orally every day results in an increase in the amount of SMN protein. In global clinical trials, the drug was evaluated its efficacy and safety in a wide range of patients, from infants to adults and obtained the regulatory approval.

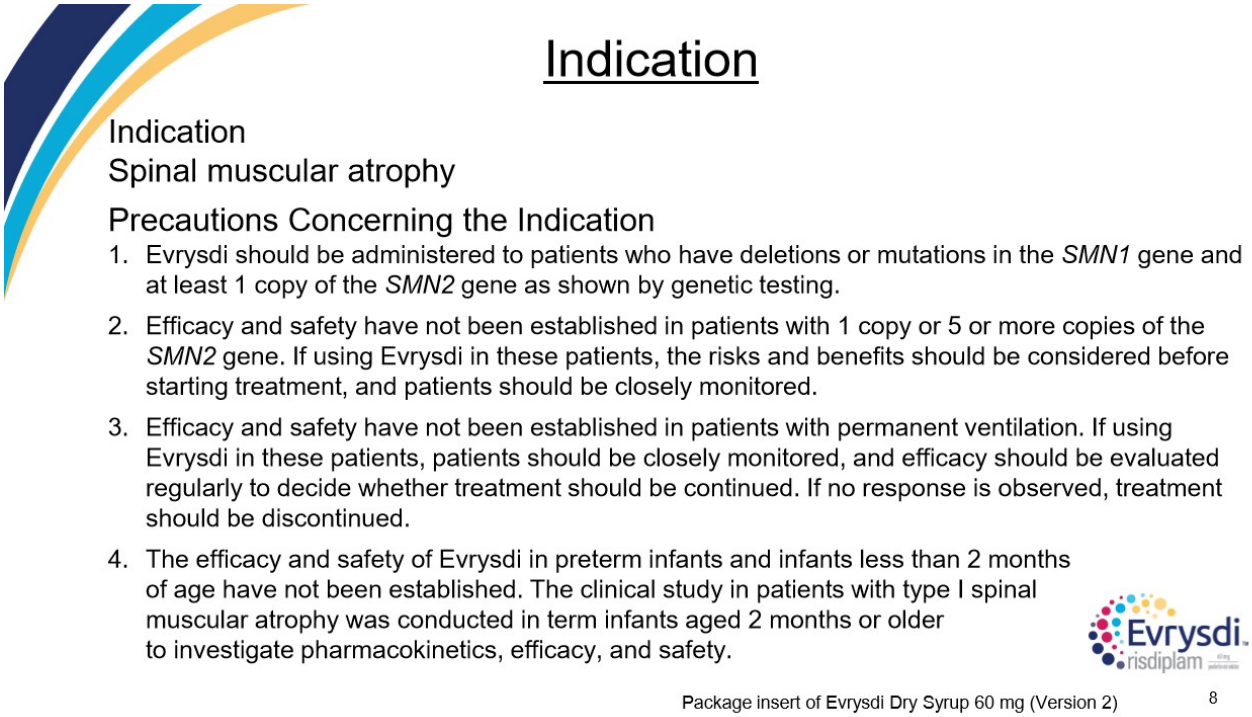
Because the drug is administered orally, patients don't have to be hospitalized to receive the medication. This is expected to reduce the time and financial burden on patients and care givers. We believe that this is especially convenient for SMA patients who are working or studying.


Here I would like to briefly talk about the background behind the development of Evrysdi.

The originator of this drug is not Roche, but PTC Therapeutics. PTC Therapeutics and the SMA Foundation have originally created Evrysdi, and Roche has joined from the clinical development phase.

Major clinical trials to date include the SUNFISH trial in adults, and another in infants called FIREFISH. This is back in 2016, and these were conducted to decide on dosage. In terms of trials conducted by our company, there is a Pphase I trial for Japanese people living in the United States taking place in parallel. After that, the dosage was decided, and as a part 2, we conducted phase III trials, and then the drug was approved.

In Europe, we have received the PRIME designation, and in Japan, we have received the orphan drug designation. The drug was approved in the US last year, and in Europe in March this year. In Japan, approval was obtained in June, and it was launched in August.




In this slide, I will explain the indication.

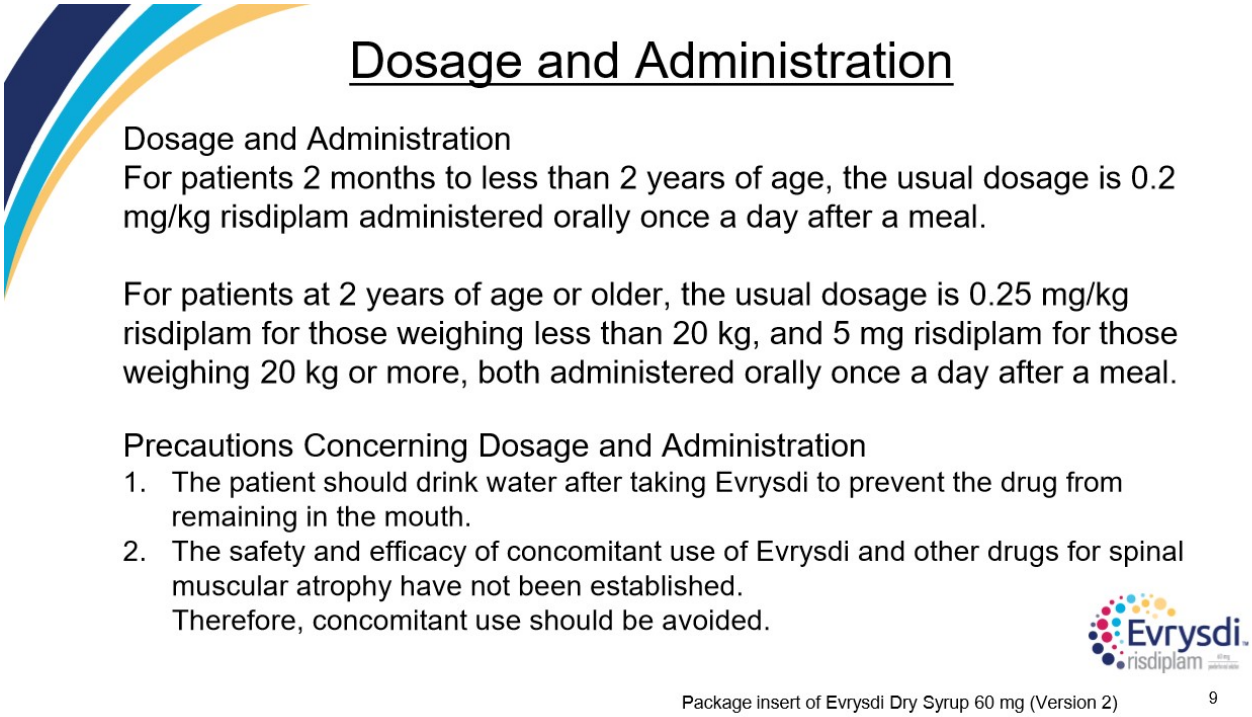
The indication is spinal muscular atrophy. In the section on precautions concerning the indicvation, the main focus is on patient groups in which clinical trials have not taken place.

The first is to make sure that there are 1 or more copies of the *SMN2* gene.

Second, efficacy and safety have not been established in patients with 1 copy , or 5 or more copies of the *SMN2* gene.

The third point is similar: there are no clinical trial data for patients on permanent ventilation, so the efficacy and safety have not been established. This is not necessarily meant that these patients cannot use Evrysdi. If using Evrysdi in the population, patients should be closely monitored.

The same applies to the fourth item. The efficacy and safety of the drug has not been confirmed for patients who were born prematurely or who are less than 2 months old, so the administration for these patients should be considered.




Next is the dosage and administration.

This medicine should be administered orally at a dose of 0.2 mg/kg once daily after a meal for patients who are 2 months to less than 2 years old. For patients over 2 years of age, the oral dosage should be 0.25 mg/kg for patients weighing less than 20 kg, and 5 mg for patients weighing 20 kg or more.

The medication is a dry syrup administered orally, so we advise to drink the water last so that it can be completely absorbed into the body. Also, although this is the third drug for SMA in Japan, the efficacy and safety of concomitant use of this drug with other drugs has not been established yet, so Evrysdi combination with the other drugs should be avoided.

## Approval Conditions

1. A risk management plan should be formulated and implemented appropriately.

2. Given the very limited sample sizes in clinical studies in Japanese patients, conduct a post-marketing all-patient drug use surveillance for a certain time to understand the background information of the patients using the product and to, in the near term, collect data on the safety and efficacy of the product, implementing necessary measures to ensure the appropriate use of the product.

Evrysdi risdiplam

Package insert of Evrysdi Dry Syrup 60 mg (Version 2) 10

Next are the approval conditions.

Approval was given on the condition that a risk management plan be formulated and properly implemented. Since SMA is a rare disease, and limited results are available, we have to conduct a survey of all cases. I would like to make a few final remarks about that.

## Summary of Risk Management Plan (RMP) of Evrysdi

**Safety Specification**

| Important identified risks | Important potential risks | Important missing information |
|---|---|---|
| • Not applicable | • Retinal toxicity<br>• Embryofetal toxicity<br>• Effects on male reproductive function<br>• Epithelial tissue disorders | • Safety in SMA type 4 patients and patients with 5 or more copies of the *SMN2* gene<br>• Effects on QT/QTc interval<br>• Safety in premature infants |

| Pharmacovigilance plan | | Risk minimization plan | |
|---|---|---|---|
| Routine | • Collection and evaluation of individual cases<br>• Research reports: Collection and evaluation of publications, etc.<br>• Reports of non-Japanese action plans: Collection and evaluation of information on measures taken outside Japan<br>• Signal detection and evaluation using approaches including data mining techniques for adverse events (including deaths) | Routine | • Create (revise) a package insert<br>• Medication guide for patients |
| Additional | • Early post-marketing phase vigilance<br>• General drug use surveillance (all-patient surveillance)<br>• Postmarketing clinical study: Postmarketing clinical study continuing from Phase II/III studies (BP39055 and BP39056)<br>• QTc study (BP42817) | Additional | • Provide information through early post-marketing phase vigilance |

Evrysdi risdiplam

Source: Risk Management Plan of Evrysdi 11

As detailed in the risk management plan, we have identified no significant risks. On the other hand, there are potential risks that have been identified in animal studies. These include retinal toxicity, embryofetal toxicity, effects on male reproductive function, and epithelial tissue disorders.

Other information not currently available is that relating to treatment for type IV patients and patients with 5 or more gene copies. In addition, there is a lack of information on the effects on the QT/QTc interval and safety in premature infants.

I will now detail our approach to this. This drug has been approved in patient groups not enrolled in clinical trials. The usual methods to address this are to collect information on individual cases, evaluate studies conducted overseas and scientific papers, evaluate information on the 4,000 patients who have already been treated overseas, and identify adverse events.

In addition, we are continuing post-marketing surveillance of patients involved in trials, including those in the SUNFISH and FIREFISH studies. In particular, it is possible that retinal toxicity may appear at a later stage, so we are monitoring this in these patients. As for QT/QTc studies, plans are underway overseas.

As for the risk minimization plan, we will revise the package insert in a timely manner, create a drug guide for patients, and provide information obtained from post-marketing surveillance.

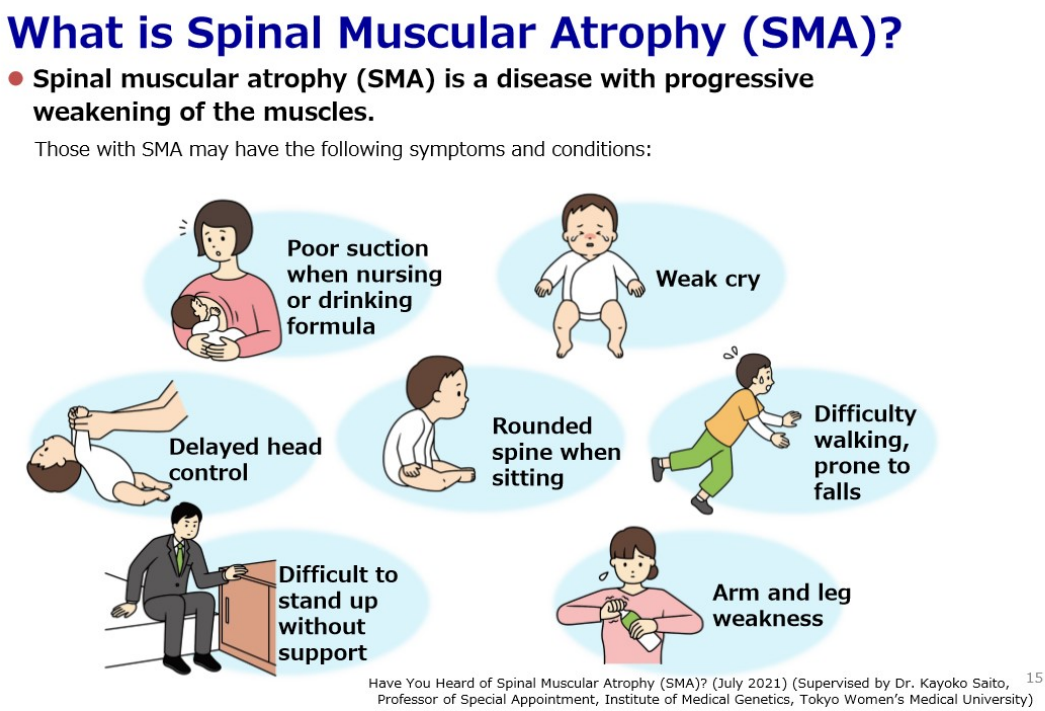
This concludes my presentation.

**Sasai:** Next, Professor Saito of Tokyo Women's Medical University will talk about a new treatment option for spinal muscular atrophy (SMA) - the first SMA oral drug, Evrysdi.

Thank you very much, Professor.


**Saito:** I am Saito from Tokyo Women's Medical University. The theme of my presentation is 'Evrysdi, the first oral treatment for spinal muscular atrophy (SMA).' I was involved inclinical trials at 10 sites as a principal investigator, and I would like to summarize them here. My COI is as shown here.


First, I would like to talk about spinal muscular atrophy.

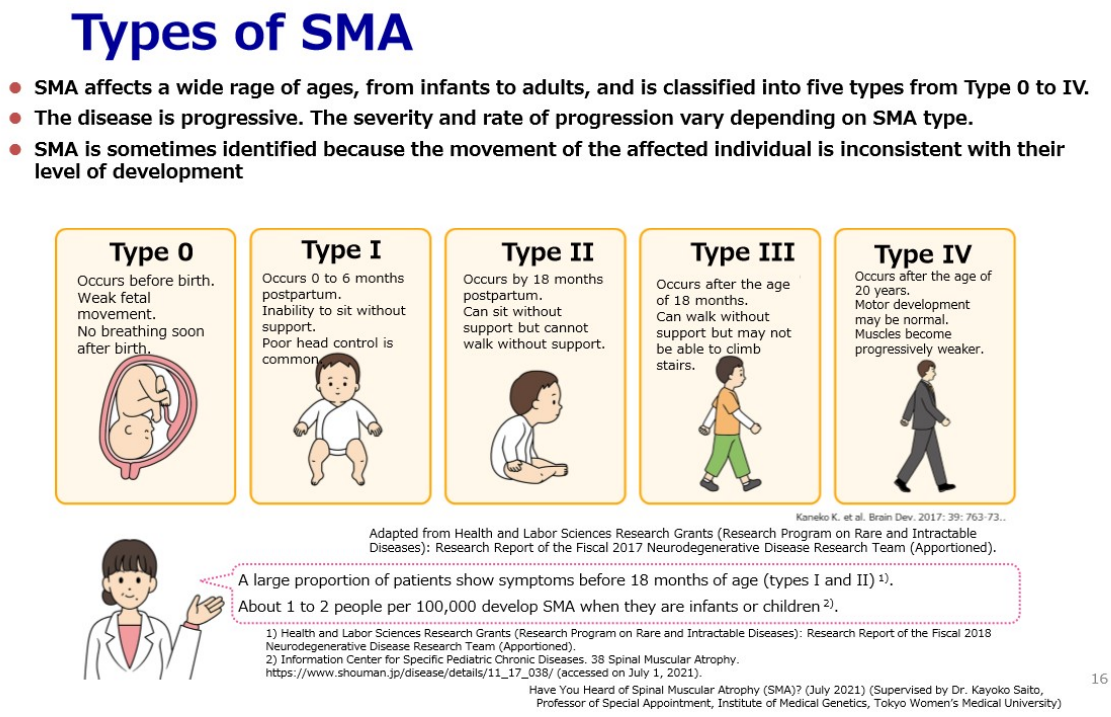



The cause of spinal muscular atrophy, a disease that causes muscle atrophy and muscle weakness, lies in the spinal cord. In this neurodegenerative disease, the anterior horn cells of the spinal cord, the motor nerve cells, degenerate and gradually disappear.

As you can see here, muscle weakness is a major symptom for these patients. For example, the baby here, from infancy, has a weak ability to suck breast milk or formula, has a weak cry, and cannot hold his or her head up. Even when the baby is able to sit up, his or her back is round, and the posture is not straight. Even

when toddlers with the condition can stand or walk, they may have a tendency to fall, have difficulty standing up, or have difficulty in using their legs.

The disabilities associated with these movementcan be very severe, especially in babies. Type I progresses very rapidly, while Type II, III, and IV progress slowly but constantly.




There are a total of 5 disease types of SMA. They are divided according to the age of onset and the highest level of motor function attained.

Type 0 is fetal onset. The condition manifests before birth, with poor fetal movement. The baby's general condition is poor at birth, with bent and stiff joints. In some cases, circulatory failure occurs in the limbs, which causes the tips of the limbs to turn black.

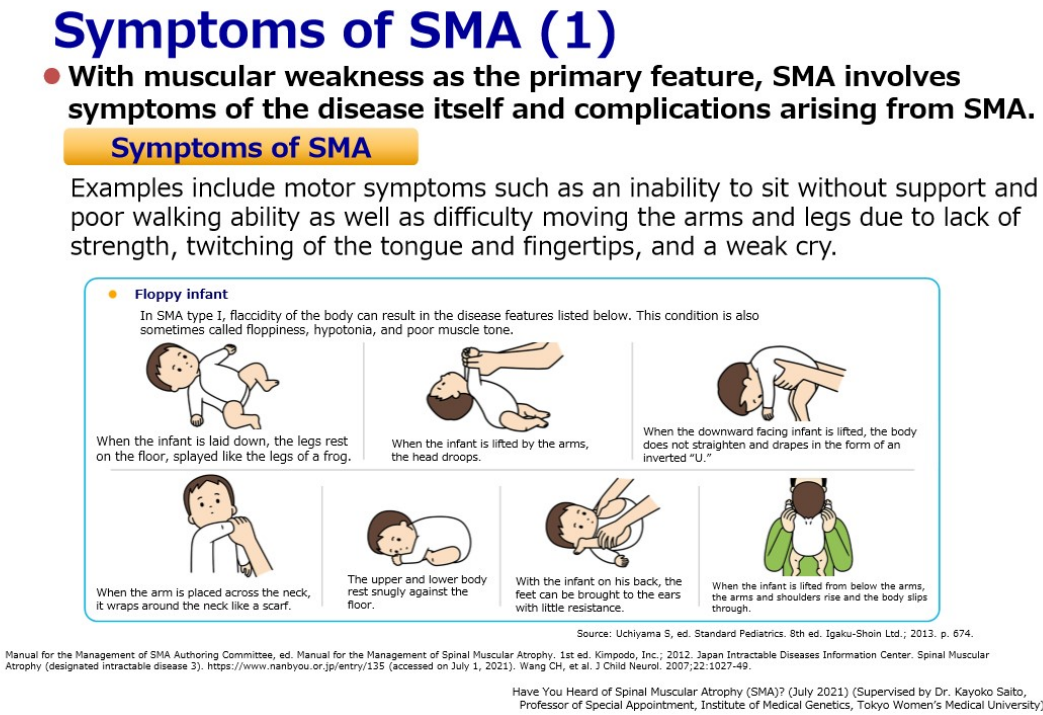
Type I is not so bad at birth, but it is very common to develop it around the 1-month checkup. It is a devastating disease that renders people bedridden and connected to a respirator for survival. In the past, we have seen parents who did not want respirator treatment for their child, only palliative care.

In type II, babies can sit up, but after that, cannot stand or walk. These patients are wheelchair-bound for life. The sitting posture is also like this, with a rounded back, and gradually deformity of the spinal column occurs due to the rounded posture. The disease progresses to the point where the joints become stiff.

In type III, patients are initially able to stand and walk, but gradually lose this ability as the disease progresses. Those who are in wheelchairs from before puberty experience the same spinal deformities as patients with type II disease. Then there are those who develop the disease after puberty, and then the condition progresses. For many people with type III disease, as they get older, they cannot move their arms or legs or turn over in bed.

Type IV develops in adulthood, but is often treated as ALS, as if it were a slightly milder form of ALS. Gradually, as the disease progresses, many people become wheelchair bound.

Types I, II, and III are childhood-onset, and we know that type I and type II are very numerous.




Now, the symptoms of SMA are divided into 2 main categories. I will divide my talk into 2 categories: symptoms of SMA itself and complications of SMA.

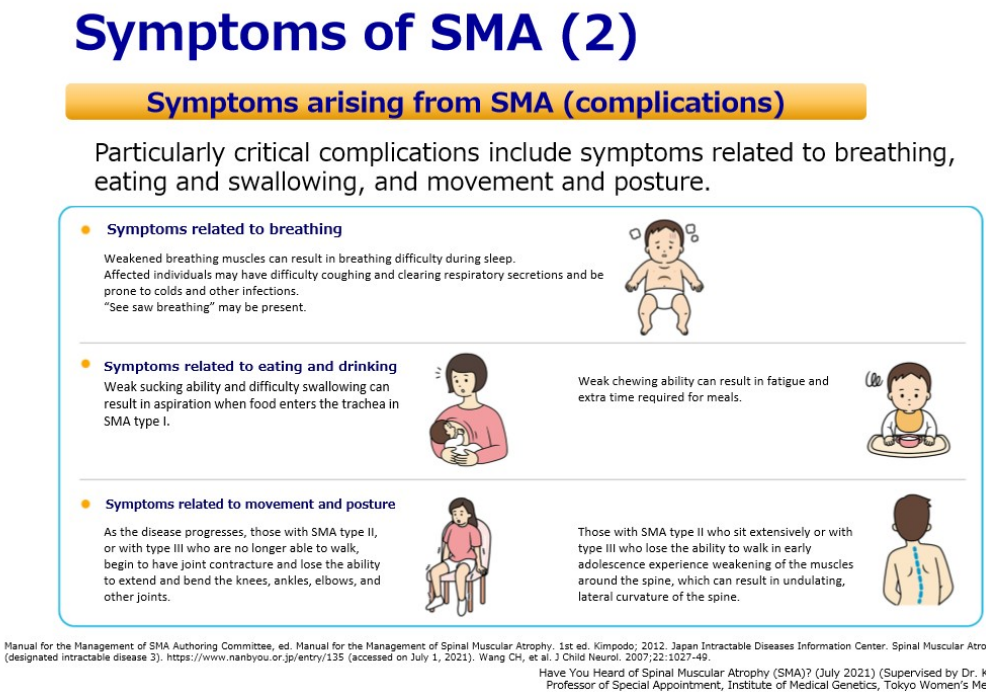
The symptoms of SMA itself include so-called muscle weakness, and fine tremor of the tongue and fingertips, which is due to spinal cord changes. This is a sign of nerve denervation. Therefore, we are thinking that as the medication takes effect, the tremors will decrease.

This is the floppy infant sign, a sign that pediatricians look for when they examine a patient. This is taken from a textbook. This is a sign of muscle weakness.

When a baby with the condition is lying down and its arms and legs are slouched, its legs look just like a frog spreading its legs. This is called the frog-leg posture. Also, when you hold the baby's hand and pull, the neck is slack. The hands are straight, and the legs are in the frog-leg posture I just mentioned. The body does not move in resistance to gravity at all. In addition, when you pick up a baby while he or she is prone, the body shape is like an inverted U. These are the kinds of posture we see.

Also, because of the softness of the joints, we see the scarf sign, where the hand wraps around the neck. Then there is the phenomenon of the double fold, where the body flattens into a double layer at the feet. It is possible to touch the heel to the ear, in the heel-to-ear sign. The shoulders are loose, with sagging if the baby is held up by the armpits. These are the kinds of signs we see.

Also, as I mentioned earlier, signs of tongue and fingertip trembling. In addition, the cry is very weak, and the coughing is also weak. These are direct symptoms of SMA.




Here are the complications that arise based on SMA.

The first is that the muscles of breathing are impaired. While the diaphragm is relatively intact, the intercostal muscles are impaired, resulting in seesaw breathing, where the movement of the stomach and chest is just like a seesaw. This is also called paradoxical breathing. Normally, when a baby breathes in, the baby's tummy and chest both expand, but on breathing out, it's more of a seesaw situation, with the tummy expanding but the chest not moving. This is the kind of breathing problem we see.

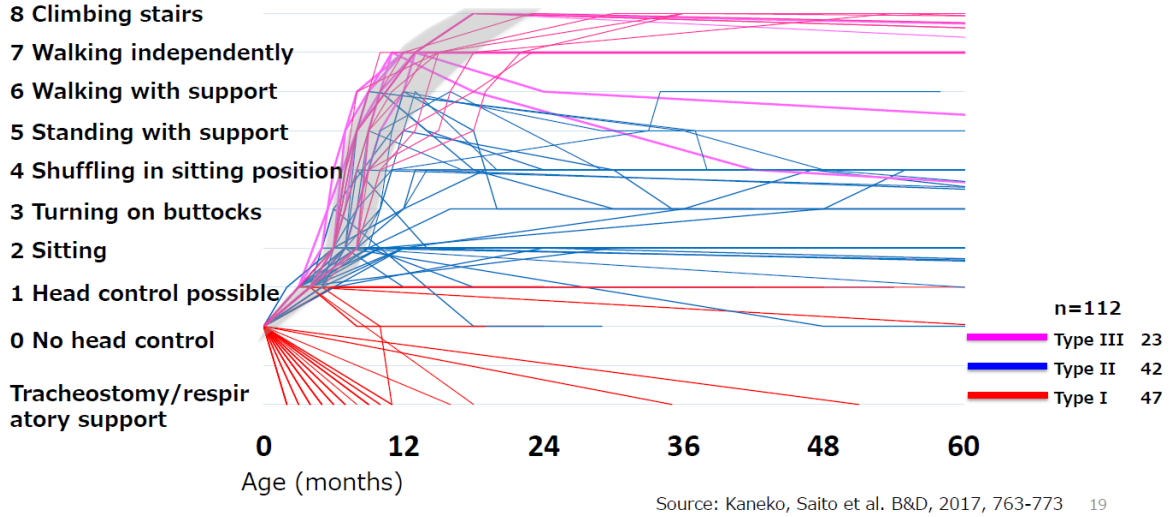
The combination of inability to cough and weak respiratory muscles gradually lead to respiratory failure and pneumonia. Even a slight cold can lead to pneumonia because of an inability to clear sputum. Then there's aspiration pneumonia.

Eating and drinking become weaker and weaker, which leads to dysphagia, a weakness in the ability to drink milk. Without tube feeding or gastrostomy, they will not be able to gain weight. These are the types of complications we see.

These are the main symptoms that occur in type I patients, but also in type II and III children and adults, joint contractures and scoliosis can cause complications.

## Time Course of Motor Function of Japanese SMA Patients by Type

Subjects: 112 patients with SMA 7 months to 57 years of age who consented and completed the questionnaire among 196 enrolled patients
Methodology: Questionnaire
Duration: July 2014 to July 2016



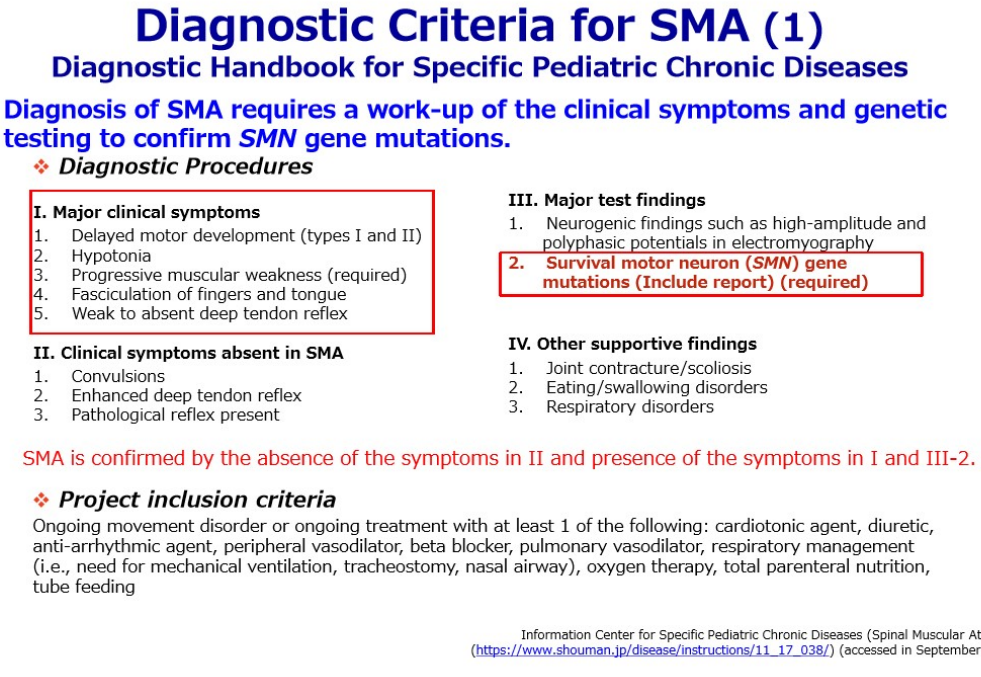

Source: Kaneko, Saito et al. B&D, 2017, 763-773 19

This is a graph of the lifetime natural history of SMA patients. We put this together before various treatments became available.

Type I is in red. Type I is divided into 2 groups: those with very severe breathing problems who require a tracheotomy or artificial respiration management immediately after birth, and those who are able to hold their head up for a while and then gradually lose their motor functions.

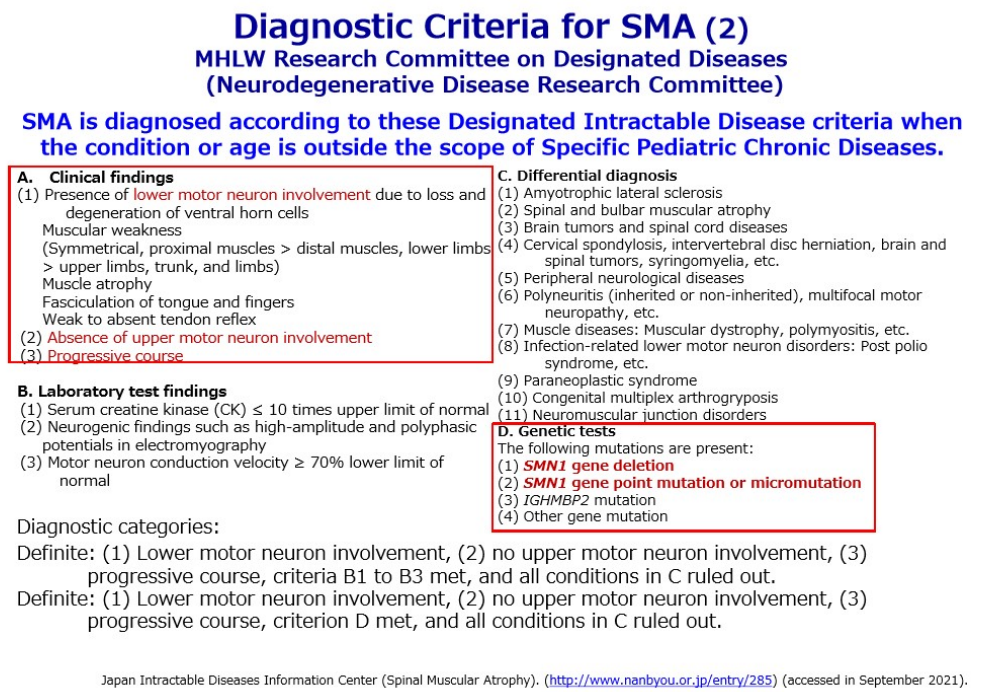
In the case of type II, this greyed-out area is the area of normal development. There are some type II patients who do not move within this shadow, suggesting that their motor development is delayed. In this case, those who are late in lifting their heads or sitting up will be type II. Then, even after some motor function is acquired, type II patients fall further and further behind as motor function declines.

Type III is this pink color. It includes patients who cannot go up and down stairs. Some of these patients can never walk up or down stairs. There are also people who can go up and down stairs, but gradually lose the ability to do so due to progressive motor dysfunction.

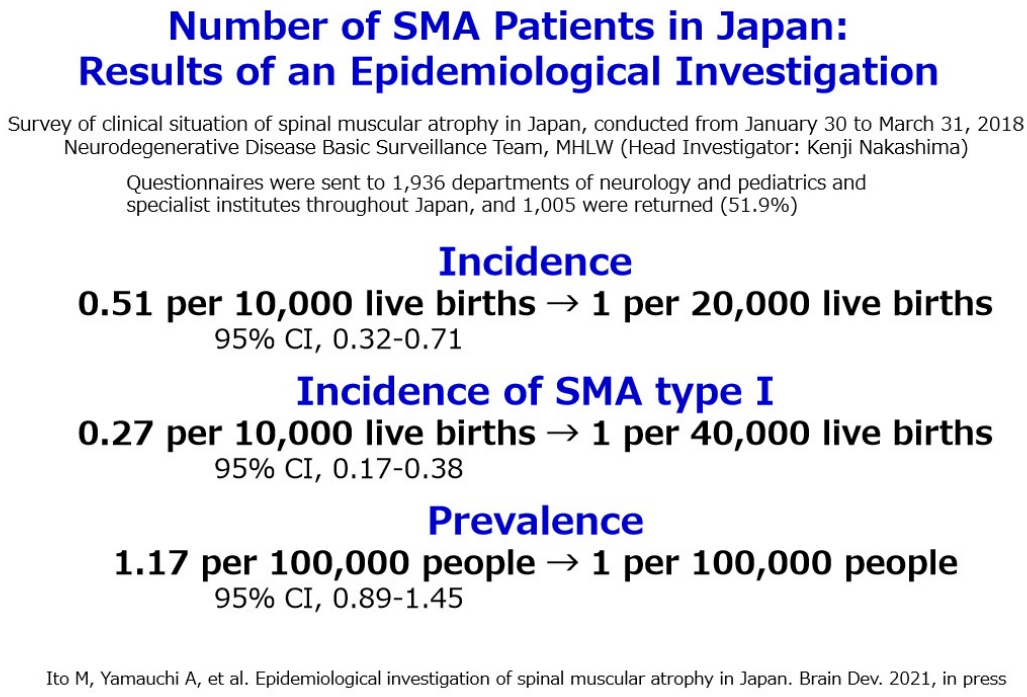



Now, since SMA is a childhood-onset disease, pediatric chronic specific diseases are mainly used as diagnostic criteria to guide the diagnosis. At present, a definitive diagnosis is made based on the main clinical symptoms, which are described here, and genetic tests.

Deletion or mutation of the *SMN*, or survival motor neuron gene, is a necessary condition of diagnosis.



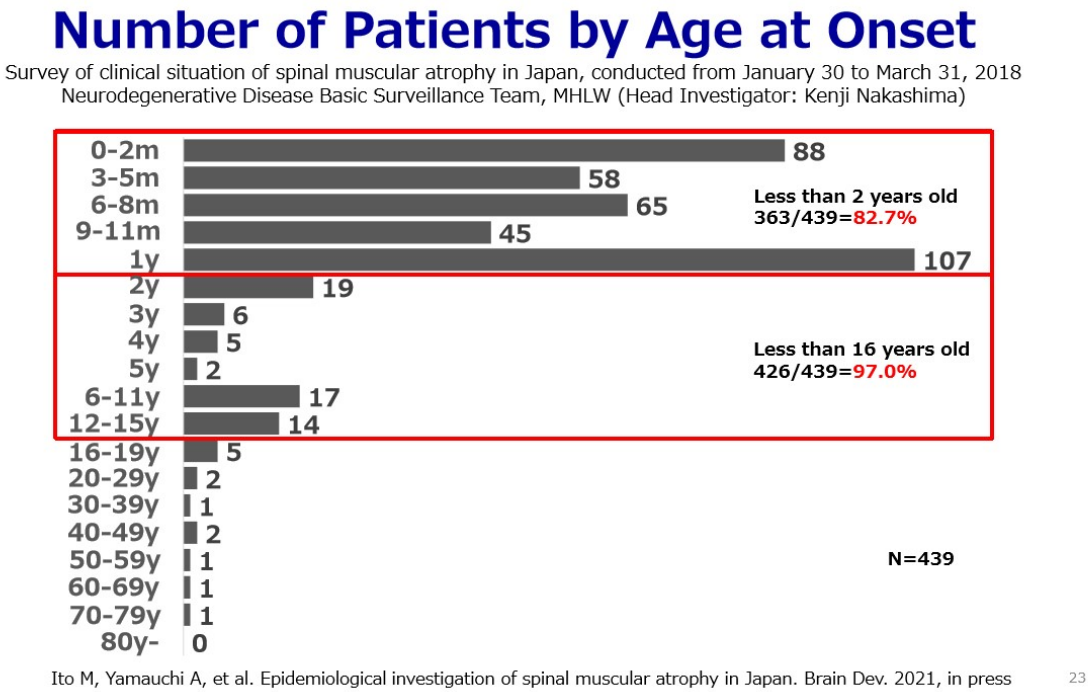

In addition, those who are beyond the scope of pediatric chronic specified diseases, that is, those who are older, are judged to meet the diagnostic criteria for designated intractable diseases. The diagnosis is also based on the clinical findings (circled in red) and the genetic findings relating to *SMN* (marked on the right).




Let's talk about the incidence and prevalence.

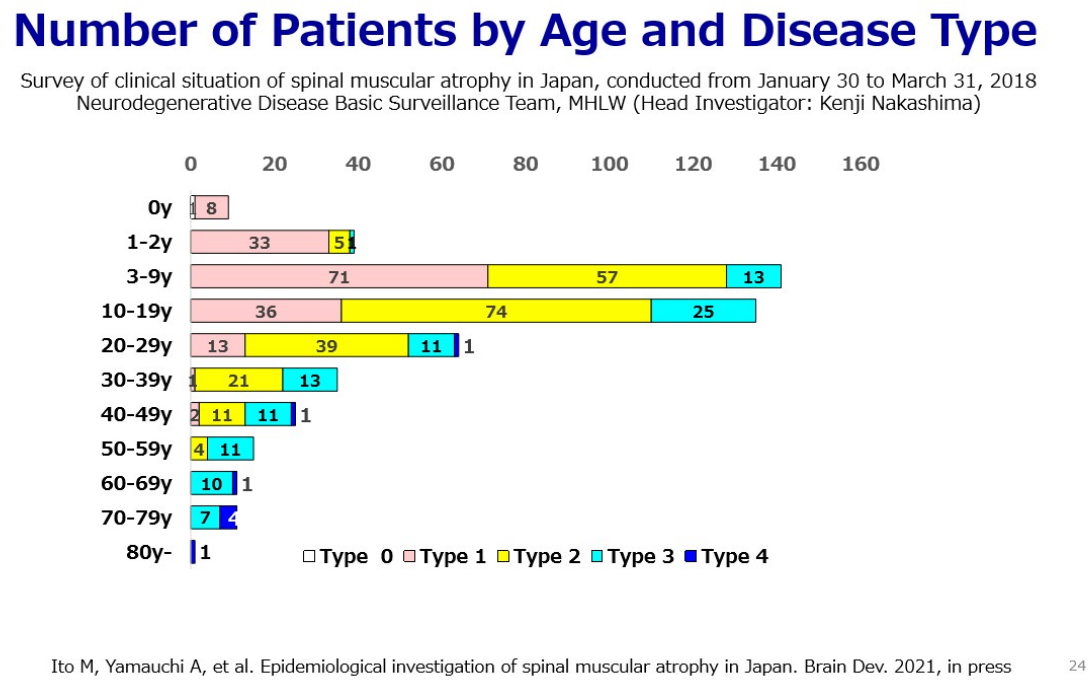
The incidence is thought to be roughly 1 in 20,000 births. Type I, in particular, occurs in about half of all cases, or about 1 in 40,000 people. This is the most severe form of the disease, and is thought to make up about half of all cases.

Next, prevalence. The number of people with the disease in Japan is about 1 in every 100,000 people. In other words, we estimate that there are about 1,400 to 1,500 patients in Japan.




Here is the number of patients by age of onset.

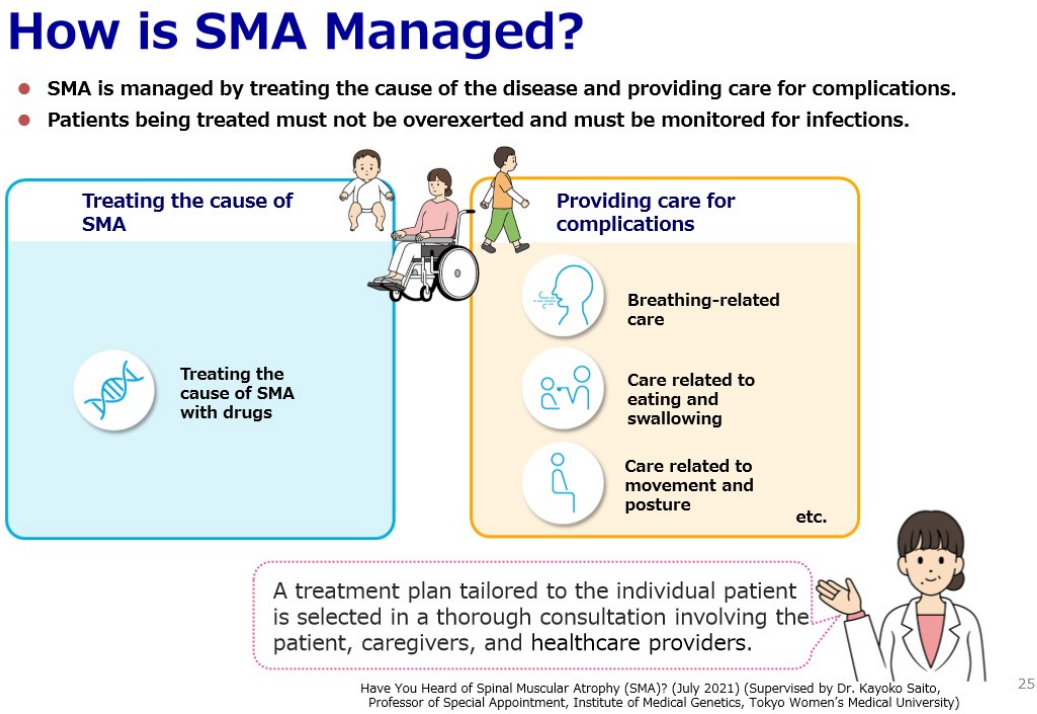
First of all, patients under the age of 2 account for 82.7% of the patients, as you can see here. Also, with childhood defined as age 15 or younger, 97% of patients are children, indicating that most of the patients have childhood onset. However, those with adult onset are also found at a frequency described here. This is from a 1-year survey in 2017.




Although it is a childhood-onset disease, patients receive excellent medical care in Japan. There are type I patients who are already in their 40s, who have had a tracheostomy and receive artificial respiration

management. In addition, some patients with type II disease are in their 50s. There are some with type III disease in their 70s.

Since pediatrics is for patients up to 15 years old, neurologists follow up a large number of patients. At present in Japan, doctors who are involved in home medical care follow up on patients at home and for motor dysfunction.



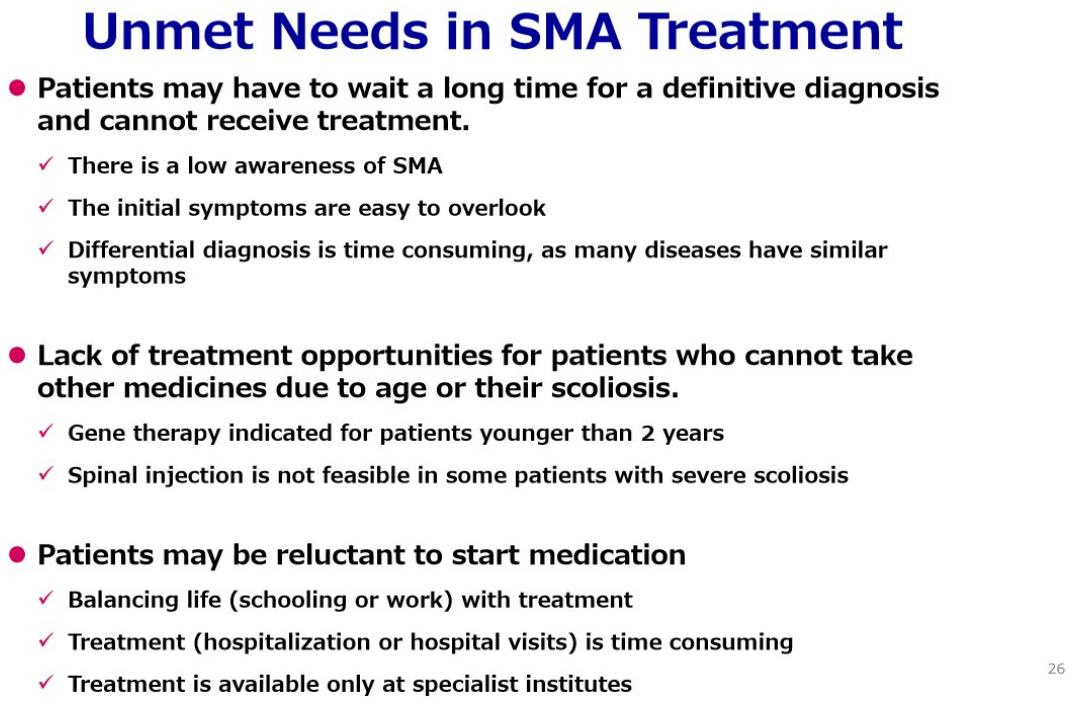

Now, let's talk about what kind of treatment is available.

First, there is treatment for SMA itself, which is called disease-modifying therapy. This is an area that's developing rapidly.

Next is care for complications. Traditionally, there has only been care for complications. Multidisciplinary professionals are involved in respiratory care, swallowing care, and physical therapy. However, due to the emergence of various disease-modifying therapies, we have this kind of treatment scheme.

However, that does not mean that management of complications has disappeared altogether. After all, physical therapy and other treatments are rather important. In this sense, multidisciplinary care is very important, so SMA is not only about therapeutic drugs, but also about care.

In addition, most SMA patients have only motor dysfunction and no intellectual disability. Many are very talented: there are many people who are active in society despite having the disease. I believe that it is an important form of social activity for these patients while receiving treatment.




Here is a summary of the unmet needs for SMA treatment.

It takes time before a definitive diagnosis of SMA is made. Treatment cannot be initiated until this has been done.

Awareness of SMA is low. With the release of this third drug, awareness of the disease is gradually increasing, but there is still a delay in diagnosis. Therefore, I think we have to recognize that there are many people with SMA who have been diagnosed with other diseases.

There is difficulty in recognizing early symptoms. The signs that I mentioned earlier appear rather gradually. Sometimes the family may notice, but the doctor would say, "let's see what happens," and leaves it at that. I think the important part from now on is to diagnose and treat the problem, not just wait and see. Therefore, I think it is important to notice the early symptoms.

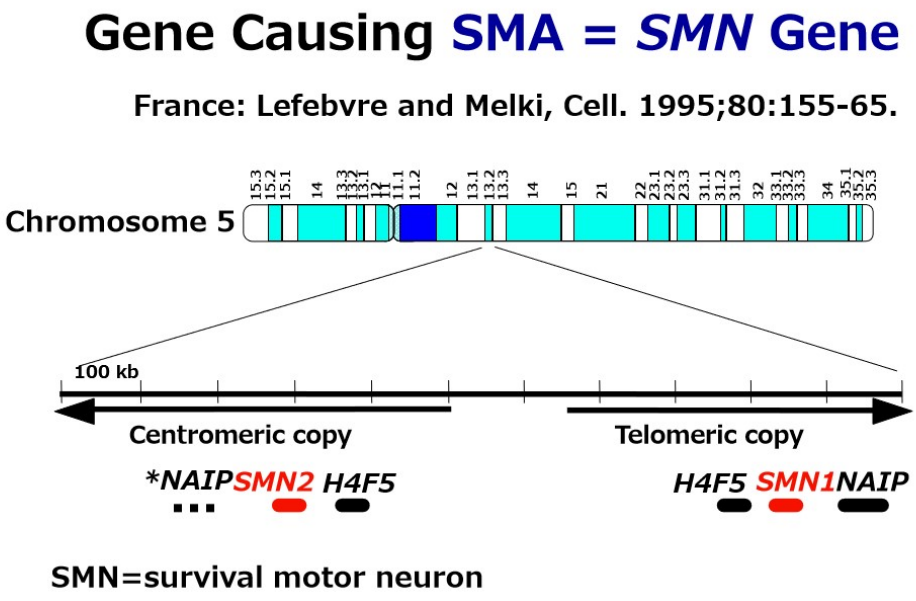
Another issue is that there are many diseases with similar symptoms. The differential diagnosis includes congenital myopathy, muscular dystrophy, or other such conditions. In particular, I think that type III or IV are often misdiagnosed because the creatine kinase levels found in muscular dystrophy can be high.

The result is that the patient's age and their scoliosis mean that they will no longer benefit from treatment with other drugs and have an opportunity for treatment.

These people are very common. They are happy that they finally have their own treatment, but because of their scoliosis, they can't receive intrathecal injections. In addition, gene therapy is only indicated for patients under 2 years old.

Then there are patients with SMA who are not able to receive treatment with existing drugs for other reasons. This includes those who are studying or working, and cannot be hospitalized easily. The possibility of treatment at home with oral medication is a fantastic development.

In the past, treatment could only be provided at specialized facilities. In this respect, we believe that we have the scope to provide community medicine in various new areas.




Source: Manual for the Management of SMA. Kimpodo, Inc., 2012.

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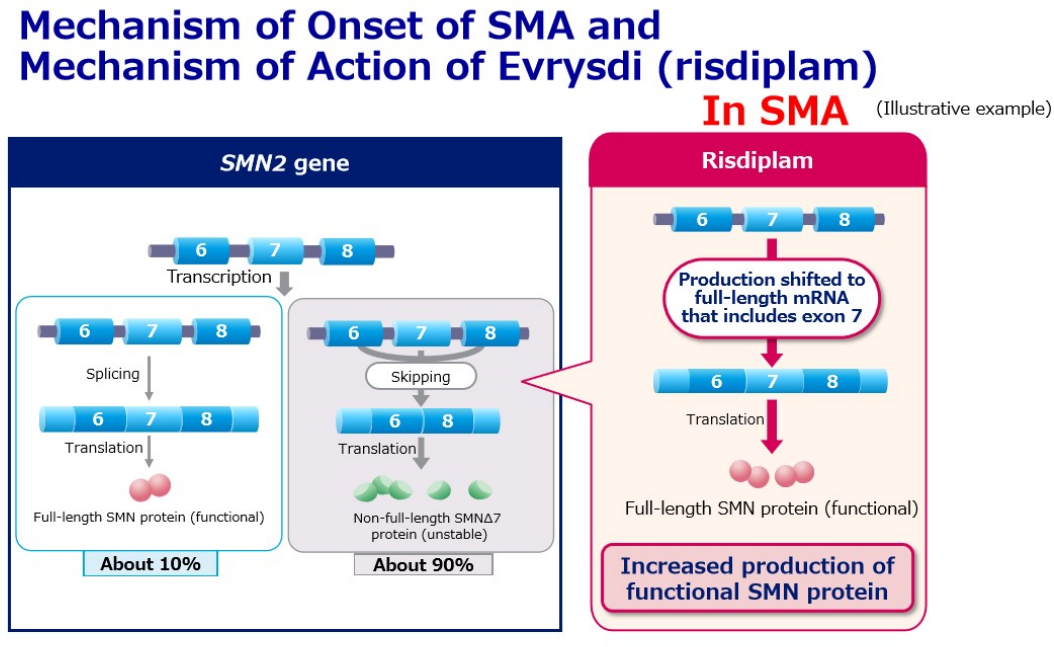
I will now talk about the mechanism of SMA. First, I will talk about the gene mutations that cause SMA. The gene is located on the long arm of chromosome 5. The chromosome is divided into 2 parts, and the *SMN1* gene is on the longer part. As mentioned earlier, mutations in this gene cause the disease. Then there is *SMN2*, which is a modifier gene, or you could call it a backup gene, a shadow gene.




Adapted from Swoboda KJ. J Clin Invest. 2011; 121: 2978-81.

Data for evaluation in regulatory review [SMN protein function and action of the *SMN2* splicing modifier risdiplam in spinal muscular atrophy]

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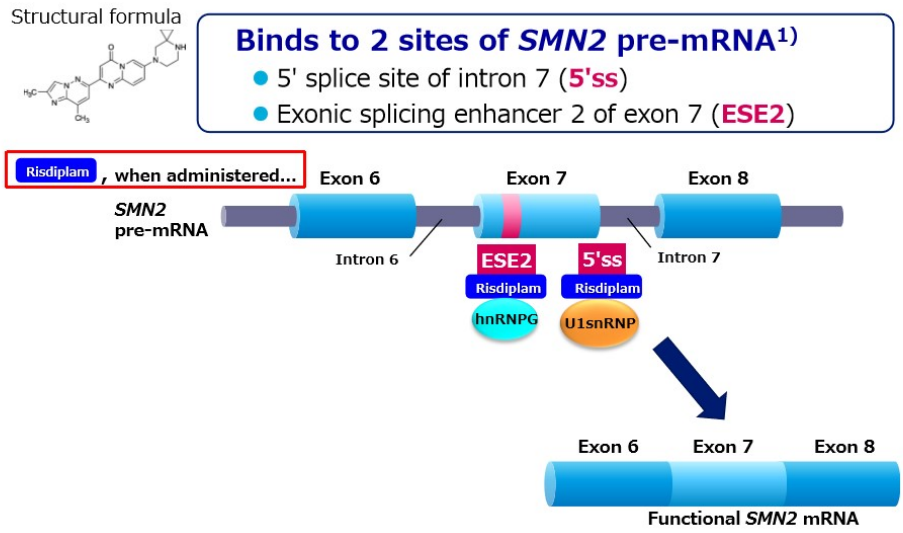
Source: Appropriate Use Guide for Evrysdi Dry Syrup 60 mg (August 2021 revision)

In SMA, the *SMN1* gene is not working. As a result, the *SMN1* gene does not produce the SMN protein, and there is no full-length protein. Therefore, I think the use of a disease-modifying drug such as risdiplam, which works by treating the skipping problem, is a very reasonable treatment. That is how *SMN2* is being converted to *SMN1*. This treatment works by causing the creation of SMN proteins.

# Site of Action of Risdiplam




ESE2: exonic splicing enhancer 2, mRNA: messenger ribonucleic acid, SMN: survival motor neuron, ss: splice site

1) Sivaramakrishnan M, et al. Nature Communications 2017; 8:1476.

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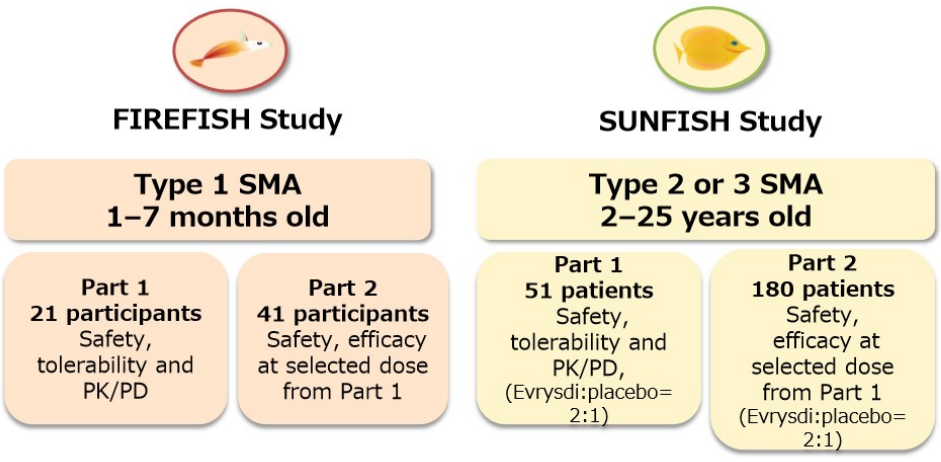
To be a little more specific, risdiplam splices here at Exon 7. There are 2 splicing sites at Exon 7, and this is where the protein binds. If risdiplam is not bound there, the protein doesn't bind, so it jumps from 6 to 8. Risdiplam acts like a glue, sticking these light-blue and orange protein sections together. This will induce Exon inclusion, giving a sequence of Exon 6, 7, and then 8.

# Clinical Trials of Evrysdi (Pivotal Trials)




Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

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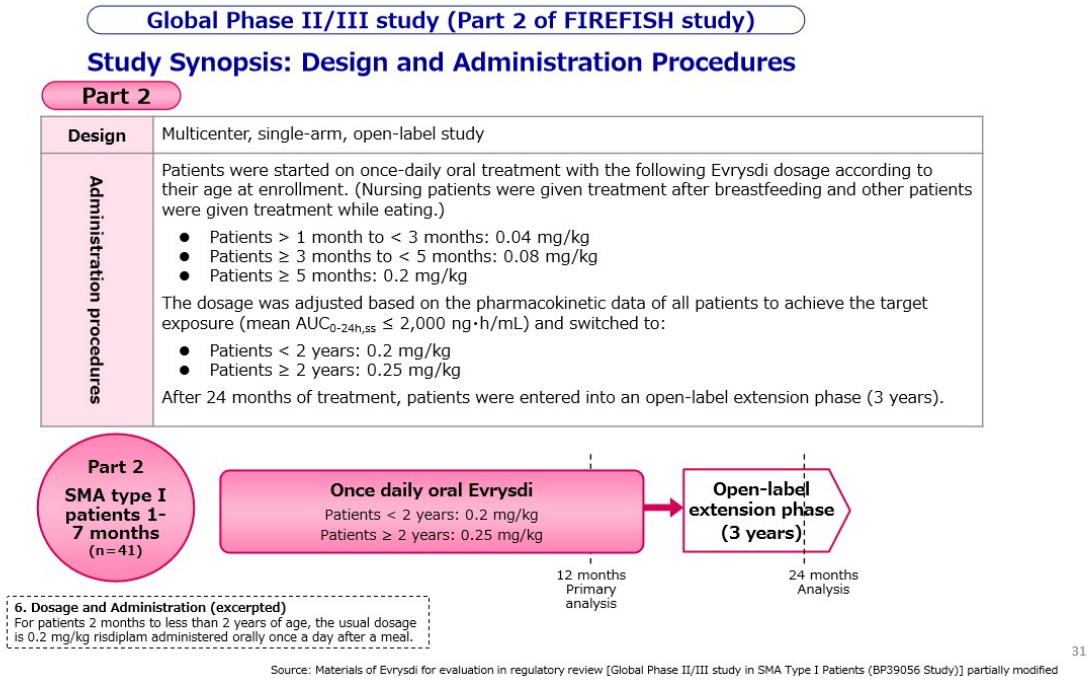
Now, let's talk about clinical trials.

2 main clinical trials have been conducted for Evrysdi: FIREFISH and SUNFISH. FIREFISH was conducted in patients with type I SMA up to 7 months old. SUNFISH was conducted in patients with type II and III disease from 2 to 25 years old.

Part 1 is for dose-finding and also for investigating safety. Efficacy was assessed in part 2. Of course, we also investigated safety. I would like to explain about part 2 in particular.




First, here is part 2 of FIREFISH.

41 patients up to 7 months old participated in the global trial. 1 patient from Japan took part. These are the results after about a year. The trial is a single-arm trial, and is still ongoing. Since the trial involved type I disease, blinds were considered unethical, so we went with a single-arm design. We will then observe changes over time.

Global Phase II/III study (Part 2 of FIREFISH Study)

## Patient Baseline Characteristics

| | | Evrysdi arm (n=41) |
|---|---|---|
| Age at enrollment (months) | Median (range) | 5.3 months (2.2-6.9) |
| | ≤ 5 months | 19 (46.3%) |
| | > 5 months | 22 (53.7%) |
| Sex | Female | 22 (53.7%) |
| | Male | 19 (46.3%) |
| Race | Asian | 14 [34.1%, 1 (2.4%) of whom was Japanese] |
| | Caucasian | 22 (53.7%) |
| | Unknown | 5 (12.2%) |
| Region | EU | 24 (58.5%) |
| | China | 11 (26.8%) |
| | Others | 6 (14.6%) |

Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified

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Next, the patients' background.

It says here that there was only 1 Japanese case, and the Japanese data is essential for approval in Japan. In that sense, the presence of a Japanese person made a very significant contribution to the launch of the drug for type I patients.

There were Asians, Caucasians, patients from a wide variety of backgrounds. The total number of cases was 41. The median time was 5.3 months.

Global Phase II/III study (Part 2 of FIREFISH study)

## Study Synopsis: Endpoints

| | |
|---|---|
| **Primary endpoint** | Percentage of patients sitting without support for 5 seconds at Month 12 (assessed per Item 22 of the BSID-III Gross Motor Scale)*1 *2 |
| **Secondary endpoints** | • Percentage of patients achieving a CHOP-INTEND total score of 40 points or more at Month 12<br>• Percentage of patients achieving an increase from baseline in CHOP-INTEND total score of 4 points or more at Month 12<br>• Percentage of motor milestone responders as assessed by HINE-2 at Month 12*3<br>• Percentage of patients achieving attainment levels of a subset of motor milestones as assessed by HINE-2 at Month 12*4<br>• Percentage of patients alive without permanent ventilation at Month 12*5<br>• Percentage of patients alive at Month 12<br>• Percentage of patients able to feed orally at Month 12<br>• Safety and tolerability<br>• Pharmacokinetics, pharmacodynamics, etc. |
| **Exploratory endpoints** | • Percentage of patients achieving an increase from baseline of at least 0.3 mV in CMAP (ulnar nerve) negative peak amplitude at Month 12<br>• Number of admissions per patient-year at Month 12*6<br>• Percentage of patients who had not been admitted at Month 12, etc. |

*1 The BSID-III Gross Motor Scale was used to make assessments in a modified order beginning with sitting assessment (the primary endpoint of Part 2).
*2 Patients not achieving sitting, patients not maintaining previously achieved sitting, study discontinuations, and deaths were considered non-responders.
*3 Responders were those who had a greater number of motor milestone improvements than worsening. Motor milestone improvement was defined as a ≥ 2 points increase [or maximum score] in ability to kick, or ≥ 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking. Motor milestone worsening was defined as a ≥ 2 points decrease [or minimum score] in ability to kick, or ≥ 1 point decrease in the motor milestones of head control, rolling, sitting, crawling, standing, or walking. Voluntary grasping was not included in the definitions.
*4 The 8 items of head control, sitting, voluntary grasping, kicking, rolling, crawling, standing, and walking were assessed.
*5 Permanent ventilation was defined as tracheostomy or ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event.
*6 This includes all hospitalizations of ≥ 2 days.
BSID-III : Bayley Scales of Infant and Toddler Development - Third Edition. CHOP-INTEND : Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
HINE-2 : Hammersmith Infant Neurological Examination 2
CMAP: Compound muscle action potential. The summated action potentials reaching individual muscle fibers when the nerve trunk is stimulated via the skin.

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

Here is a summary of the trial.

These are the primary endpoints, which should absolutely be achieved. The primary endpoint here is based on the BSID-III score, which we call the Bayley. This is a motor function assessment of babies with SMA. It is a gross motor scale, and it is very important and essential that this is achieved.

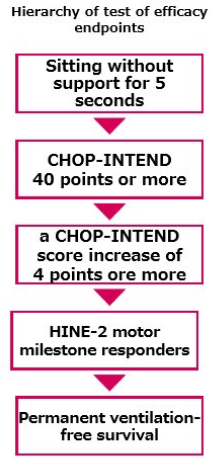
Other secondary and exploratory assessment items are listed as described here.

Global Phase II/III study (Part 2 of FIREFISH study)

## Study Synopsis: Analysis Plan

**Analysis plan**

- All 41 cases were included in the ITT and safety analysis populations, with key efficacy analysis performed in the ITT population and safety analysis performed in the safety analysis population.
- The data cutoff date (November 14, 2019) was defined as the time when the last enrolled patient completed the evaluation at Month 12.
- For some endpoints, natural history data was used to preset the success criteria for efficacy endpoints and compared the success criteria with the lower bounds of the 90% confidence intervals on both sides (corresponding to one-sided test with alpha=0.05).
- Confidence intervals calculated using the Clopper-Pearson method
- The Kaplan-Meier method was used for the time-to-event type endpoint.
- The p-value for long-term ventilator-free survival was calculated by the Z-test, and the p-values for other endpoints were calculated by the exact binomial test (one-sided p-value, one-sided, alpha=0.05)
- To control the multiplicity between endpoints, apply the hierarchical test procedure to the primary and four main secondary endpoints and a lower test were performed only if the upper test is significant (right figure)
- The hierarchical test included the evaluation items at Month 12, followed by the evaluation items at Month 24 (sitting without support for 30 seconds, standing without support, walking).
- A subpopulation analysis was performed based on the pre-specified age, gender, race, region, duration of illness (duration from onset to the start of Evrsydi treatment), and baseline motor function level (CHOP-INTEND total score). [Primary endpoint: percentage of patients sitting without support for 5 seconds at Month 12, secondary endpoint: Percentage of patients achieving an increase from baseline in CHOP-INTEND total score of 40 points or more at Month 12, Percentage of patients alive without permanent ventilation management at Month 12]

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ITT: Intent-to-treat

Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

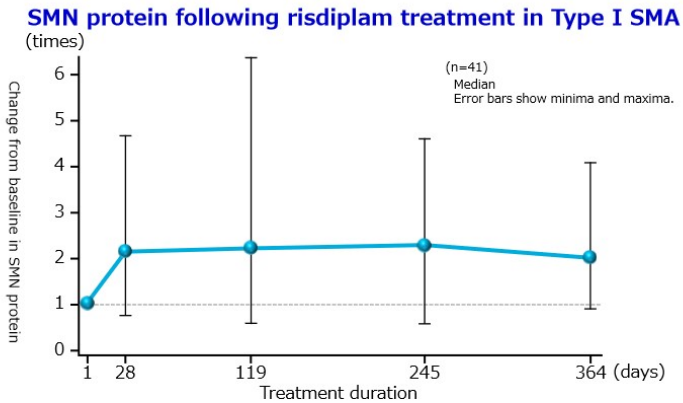
This is the analysis plan.

Since we have a wide variety of patients, we are taking a statistical approach to stratify and evaluate them in the form of 4 strata. First of all, it is a prerequisite that the patient has achieved the most basic primary endpoint of sitting for 5 seconds without support.

Global Phase II/III study (Part 2 of FIREFISH study) Clinical Pharmacology Data

## SMN Protein Production: Type I SMA (children, Japanese and non-Japanese data)

- **Blood SMN protein levels at baseline and the last observation [median (range)] were 2.93 ng/mL (0.423-5.8) and 5.37 ng/mL (0.761-9.39), and the change from baseline at the last observation [median (range)] was 2.01 fold (0.9-4.06).**




**Assessment methods:** Patients 2 to 7 months of age with Type I SMA were started on once daily oral risdiplam (0.04 mg/kg for patients > 2 to < 3 months, 0.08 mg/kg for patients ≥ 3 to < 5 months, and 0.2 mg/kg for patients > 5 months)*, and changes in SMN protein were assessed at baseline after escalation to a dose of 0.2 mg/kg and at the last observation.

*Nursing patients were given treatment after breastfeeding and other patients were given treatment while eating.

**6. Dosage and Administration (excerpted)**
For patients 2 months to less than 2 years of age, the usual dosage is 0.2 mg/kg risdiplam administered orally once a day after a meal.

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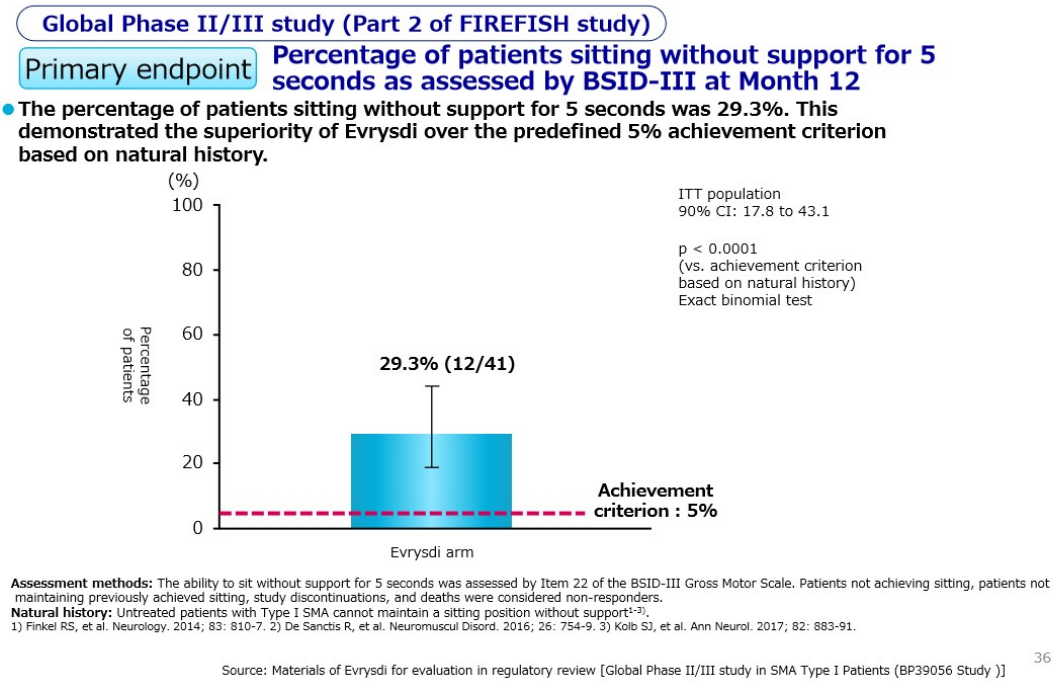
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

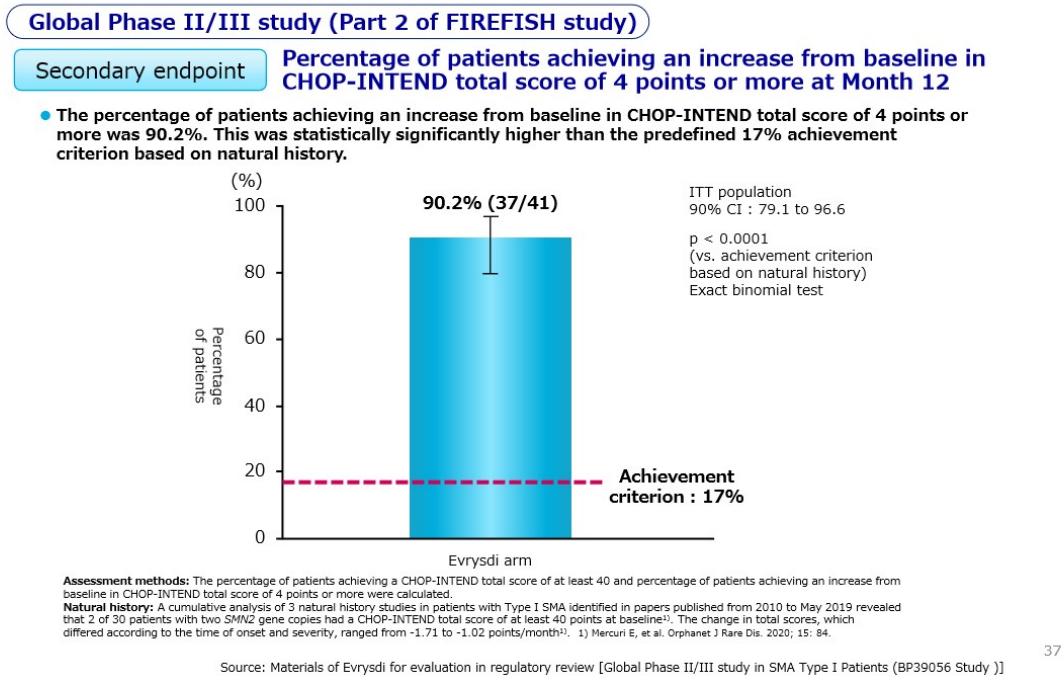
For this clinical trial, Roche has the technology to measure the SMN protein. There have been 3 trials so far, but this is the only 1 that is measuring SMN protein. I was very impressed by this, from a scientific point of view. The results show that SMN protein has increased about twofold from before administration.




Here are the main evaluation items.

The ability to hold a seated position for 5 seconds without support is a Bayley's III assessment item. This was expected to be achieved by 5%, but was actually achieved by 29.3%, far exceeding expectations.

Also, although the timing doesn't line up, this is a 1-year evaluation, so it will gradually go up a bit more.




Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

Here are the secondary endpoint.

The goal was to achieve at least 4 points from baseline on CHOP-INTEND, which is also a motor function assessment for babies with type I disease, after 12 months of treatment.

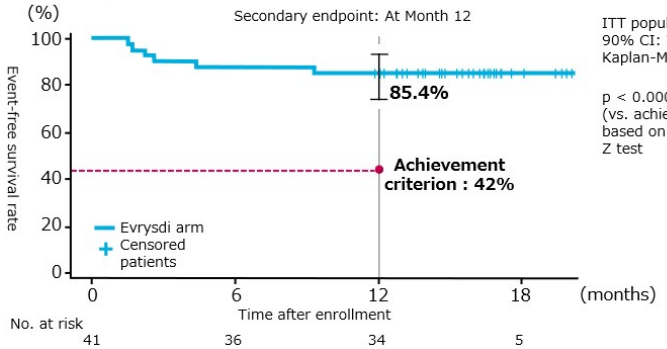
In general, CHOP-INTEND says that more than 3 points from the baseline is significant, but in this case, we set it to 4 points. While we set a target of 17% patients who achieved 4 points, the actual figure was very high, at 90.2%. The value was significantly higher than expected.

Global Phase II/III study (Part 2 of FIREFISH study)

Secondary endpoint

## Percentage of patients alive without permanent ventilation at Month 12

- **The percentage of patients alive without permanent ventilation was 85.4%. This was statistically significantly higher than the predefined 42% achievement criterion based on natural history.**




**Assessment methods:** Times to death or the initiation of permanent ventilation were plotted on a Kaplan-Meier curve, and the proportions of affected patients were estimated. Permanent ventilation was defined as tracheostomy or ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Patients for whom neither death nor initiation of permanent ventilation was reported by the data cutoff date were censored as of the final day before the cutoff date on which survival without permanent ventilation was confirmed.
**Natural history:** A prospective natural history study in 34 patients with Type I SMA registered with the United States Pediatric Neuromuscular Clinical Research Network for SMA from May 2005 to April 2009 revealed median event-free survival in the 23 patients with 2 *SMN2* gene copies to be 10.5 months (either death or requiring at least 16 hours/day of ventilation support)[1]. In a prospective natural history study of 34 patients with Type I SMA diagnosed from November 1996 to November 1999 in the Netherlands, 25 of the patients died by age 1 and 2 of the patients survived beyond age 2[2].

1) Finkel RS, et al. Neurology. 2014; 83: 810-7. 2)Cobben JM, et al. Neuromuscul Disord. 2008; 18: 541-4.



Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified

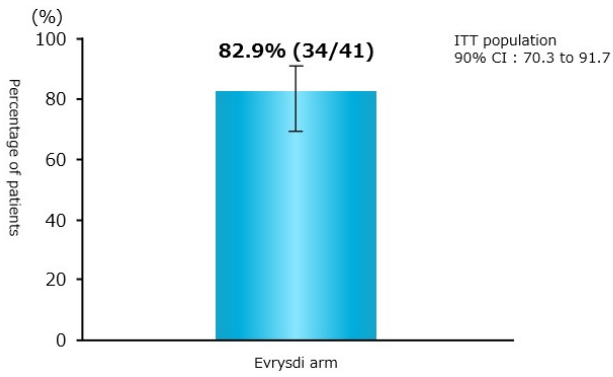
This is another secondary endpoint: the percentage of patients who survive without long-term ventilation management. The expected value was 42%, but it turned out to be 85.4%, which is also significantly high. The *P*-values are as described here.

Global Phase II/III study (Part 2 of FIREFISH study)

Secondary endpoint

## Percentage of patients able to feed orally at Month 12

- **82.9% of the patients were able to feed orally.**
  **(There were no natural history-based achievement criteria.)**




**Assessment methods:** The percentage of patients able to feed orally was calculated.
**Natural history:** A prospective natural history study in 34 patients with Type I SMA registered with the United States Pediatric Neuromuscular Clinical Research Network for SMA from May 2005 to April 2009 revealed that 24 patients required nutritional support (nasogastric tube or gastrostomy tube) at baseline and that 19 of the 20 patients at least 12 months of age at enrollment were initiated on nutritional support[1].

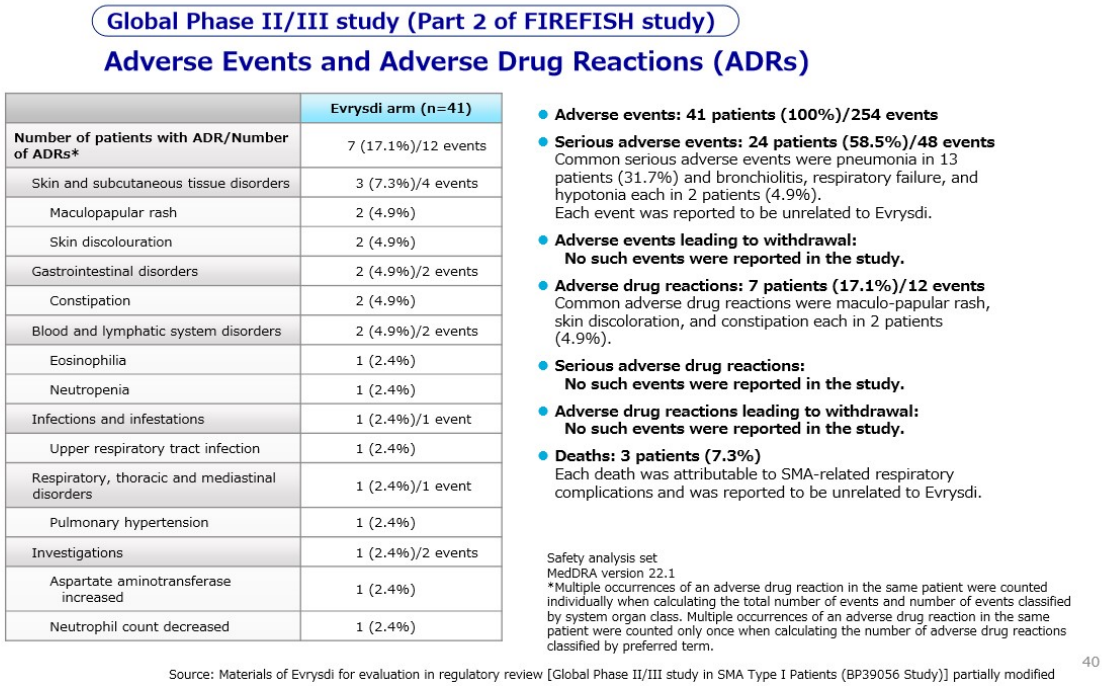
1) Finkel RS, et al. Neurology. 2014; 83: 810-7.

**6. Dosage and Administration (excerpted)**
For patients 2 months to less than 2 years of age, the usual dosage is 0.2 mg/kg risdiplam administered orally once a day after a meal.



Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

A very good efficacy for oral intake was also observed in this trial. The percentage of patients with the ability to take oral intake at month 12 was 82.9%. Babies who were tube fed or had a gastrostomy became able to eat food with a spoon, so this was a very good result.



Global Phase II/III study (Part 2 of FIREFISH study)

Adverse Events and Adverse Drug Reactions (ADRs)

| | Evrysdi arm (n=41) |
|---|---|
| Number of patients with ADR/Number of ADRs* | 7 (17.1%)/12 events |
| Skin and subcutaneous tissue disorders | 3 (7.3%)/4 events |
| Maculopapular rash | 2 (4.9%) |
| Skin discolouration | 2 (4.9%) |
| Gastrointestinal disorders | 2 (4.9%)/2 events |
| Constipation | 2 (4.9%) |
| Blood and lymphatic system disorders | 2 (4.9%)/2 events |
| Eosinophilia | 1 (2.4%) |
| Neutropenia | 1 (2.4%) |
| Infections and infestations | 1 (2.4%)/1 event |
| Upper respiratory tract infection | 1 (2.4%) |
| Respiratory, thoracic and mediastinal disorders | 1 (2.4%)/1 event |
| Pulmonary hypertension | 1 (2.4%) |
| Investigations | 1 (2.4%)/2 events |
| Aspartate aminotransferase increased | 1 (2.4%) |
| Neutrophil count decreased | 1 (2.4%) |

- **Adverse events: 41 patients (100%)/254 events**
- **Serious adverse events: 24 patients (58.5%)/48 events**
  Common serious adverse events were pneumonia in 13 patients (31.7%) and bronchiolitis, respiratory failure, and hypotonia each in 2 patients (4.9%).
  Each event was reported to be unrelated to Evrysdi.
- **Adverse events leading to withdrawal:**
  **No such events were reported in the study.**
- **Adverse drug reactions: 7 patients (17.1%)/12 events**
  Common adverse drug reactions were maculo-papular rash, skin discoloration, and constipation each in 2 patients (4.9%).
- **Serious adverse drug reactions:**
  **No such events were reported in the study.**
- **Adverse drug reactions leading to withdrawal:**
  **No such events were reported in the study.**
- **Deaths: 3 patients (7.3%)**
  Each death was attributable to SMA-related respiratory complications and was reported to be unrelated to Evrysdi.

Safety analysis set
MedDRA version 22.1
*Multiple occurrences of an adverse drug reaction in the same patient were counted individually when calculating the total number of events and number of events classified by system organ class. Multiple occurrences of an adverse drug reaction in the same patient were counted only once when calculating the number of adverse drug reactions classified by preferred term.

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified

This shows adverse events and side effects.

Serious adverse events have been reported in 24 cases. There were no adverse events that led to discontinuation of treatment.

There were 7 cases of side effects, and the main side effect was rash. Cases of constipation were also observed, but were not serious. There were no side effects serious enough to lead to the discontinuation of administration.

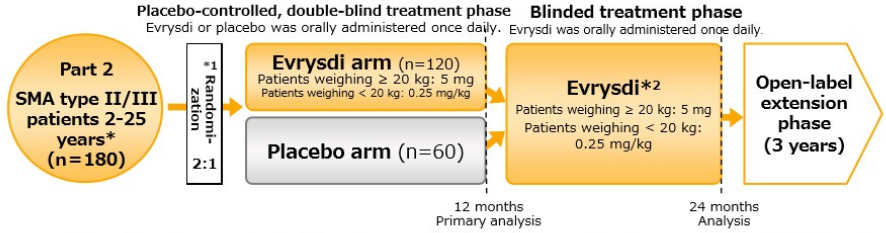
There were 3 deaths, but  all were due to the original disease, and not due to the medication. The patients in this study had the severe type I form of the disease and died from the disease.

Global Phase II/III study (Part 2 of SUNFISH Study)

## Study Synopsis: Design and Administration

**Part 2**

| | |
|---|---|
| **Design** | Multicenter, randomized, placebo-controlled, double-blind study |
| **Administration** | Evrysdi (at the dosage shown below) or placebo was orally administered once daily with a meal.<br>● Patients weighing ≥ 20 kg: 5 mg<br>● Patients weighing < 20 kg: 0.25 mg/kg<br>After 12 months of treatment in each arm, the placebo arm was switched to Evrysdi under blinded conditions and treated for another 12 months.<br>After 24 months of treatment, patients were entered into an open-label extension phase (3 years). |




***Type II and non-ambulant (unable to walk at least 10 m without support) type III SMA patients**

*1 Randomization factor: Age at randomization (2-5, 6-11, 12-17, 18-25 years)
*2 Unblinding for the primary analysis was conducted after the Month 12 assessment of the last subject was completed, but blinding in terms of the initially assigned arm was maintained for the subjects and investigators until the last subject completed the Month 24 assessment. Blinding was also maintained until this time at the study sites for all personnel in direct contact with the subjects (excluding the pharmacists handling the investigational medicinal product).

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

Next, I will talk about the SUNFISH trial of type II and type III patients.

This trial included patients who, even though they had type II or type III disease, were unable to walk. In total, 180 people around the world participated in this trial, including people who cannot walk more than 10 meters.

This is a double-blind study. The ratio is 2:1, with 120 people taking the actual drug and 60 people taking the placebo. This trial was double blind for 1 year, after which all subjects received the investigational drug. Clinical trials are still ongoing.

Global Phase II/III study (Part 2 of SUNFISH Study)

## Patient Baseline Characteristics (1)

Note: The clinical study results shown below represent the data of the primary analysis in Part 2.

| | | Evrysdi arm (n=120) | Placebo arm (n=60) |
|---|---|---|---|
| Age in years at screening | Median (range) | 9.0 years(2-25) | 9.0 years(2-24) |
| | 2-5 years | 37(30.8%) | 18(30.0%) |
| | 6-11 years | 39(32.5%) | 18(30.0%) |
| | 12-17 years | 30(25.0%) | 16(26.7%) |
| | 18-25 years | 14(11.7%) | 8(13.3%) |
| Sex | Female | 61(50.8%) | 30(50.0%) |
| | Male | 59(49.2%) | 30(50.0%) |
| Race | Caucasian | 80(66.7%) | 41(68.3%) |
| | Asian | 23 [19.2%, 10 (8.3%) of whom were Japanese] | 12 [20.0%, 5 (8.3%) of whom were Japanese] |
| | Others | 3(2.5%) | 0 |
| | Unknown | 14(11.7%) | 7(11.7%) |
| Region | EU | 81(67.5%) | 43(71.7%) |
| | North America | 16(13.3%) | 6(10.0%) |
| | Japan | 10(8.3%) | 5(8.3%) |
| | China | 11(9.2%) | 5(8.3%) |
| | Others | 2(1.7%) | 1(1.7%) |

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

Let's talk about the patients' backgrounds.

As you can see here, 15 patients from Japan participated in the study, 10 in the actual drug group and 5 in the placebo group. Their ages ranged from 2 to 25 years old, a very wide range.

Until now, clinical trials for such a wide range of age groups had not been conducted in Japan, but a number of older SMA patients participated in the trial. Various countries were involved, covering a variety of races.

Global Phase II/III study (Part 2 of SUNFISH Study)

## Patient Baseline Characteristics (2)

| | | Evrysdi arm (n=120) | Placebo arm (n=60) |
|---|---|---|---|
| Disease type | Type II | 84(70.0%) | 44(73.3%) |
| | Type III | 36(30.0%) | 16(26.7%) |
| *SMN2* copy number | 2 | 3(2.5%) | 1(1.7%) |
| | 3 | 107(89.2%) | 50(83.3%) |
| | 4 | 10(8.3%) | 8(13.3%) |
| | Unknown | 0 | 1(1.7%) |
| Age in months at onset: Median (range) | | 12.3 months(0-57) | 12.8 months(6-135) |
| Time in months from onset to start of study treatment: Median (range) | | 106.3 months(17-275) | 96.6 months(1-271) |
| Standing*1 | Able | 13(10.8%) | 6(10.0%) |
| | Unable | 107(89.2%) | 54(90.0%) |
| Walking*2 | Able | 3(2.5%) | 1(1.7%) |
| | Unable | 117(97.5%) | 59(98.3%) |
| Scoliosis | | 76(63.3%) | 44(73.3%) |
| | Severe (> 40°) | 34(28.3%) | 23(38.3%) |
| Hip subluxation or dislocation | | 26(21.7%) | 11(18.3%) |

*1 The ability to stand was defined as having an MFM item 25 score of ≥ 1 at baseline.
*2 The ability to walk was defined as having an HFMSE item 20 score of ≥ 2 at baseline.

**5. PRECAUTIONS CONCERNING INDICATIONS (excerpted)**
**5.1** EVRYSDI should be administered to patients who have deletions or mutations in the *SMN1* gene and at least 1 copy of the *SMN2* gene as shown by genetic testing.
**5.2** Efficacy and safety have not been established in patients with 1 copy or 5 or more copies of the *SMN2* gene. If using EVRYSDI in these patients, the risks and benefits should be considered before starting treatment, and patients should be closely monitored.

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

1 of the unique features of this trial was the participation of patients with scoliosis or hip dislocation, who had signs or complications that could influence assessment of motor function. The number of copies of *SMN2* correlates with the severity of the disease, and 3 copies were the most common.

Global Phase II/III study (Part 2 of SUNFISH Study)

## Study Synopsis: Endpoints

| | |
|---|---|
| **Primary endpoint** | Change from baseline in MFM32 total score at Month 12 |
| **Secondary endpoints** | ● Percentage of patients with an improvement from baseline in MFM32 total score of 3 points or more at Month 12*<br>● Change from baseline in RULM total score at Month 12<br>● Change from baseline in HFMSE total score at Month 12<br>● Change from baseline in best percent predicted forced vital capacity (FVC) value at Month 12<br>● Percentage of patients with general health improved versus baseline as assessed with CGI-C at Month 12<br>● Change from baseline in caregiver-reported SMAIS total score at Month 12 (supportive information)<br>● Safety and tolerability<br>● Pharmacokinetics, pharmacodynamics, etc. |
| **Exploratory secondary endpoints** | ● Percentage of patients who achieve stability or improvement (change from baseline of ≥ 0 points) in MFM32 total score at Month 12<br>● Change from baseline in patient-reported SMAIS total score at Month 12 (supportive information), etc. |

*Early dropouts and patients with missing data were handled as non-responders.

MFM : Motor Function Measure、RULM : Revised Upper Limb Module、HFMSE : Hammersmith Functional Motor Scale-Expanded
CGI-C : Clinical Global Impression of Change、SMAIS : SMA Independence Scale

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)]

Here are the evaluation items.

The primary endpoint, as you can see here, is the motor function assessment called MFM32, and this score is used as the baseline. This is a motor function assessment that evaluates 32 items, including peripheral

movements, upper limb movements, body axial movements, and lower limb movements. This test incorporates all of these factors.

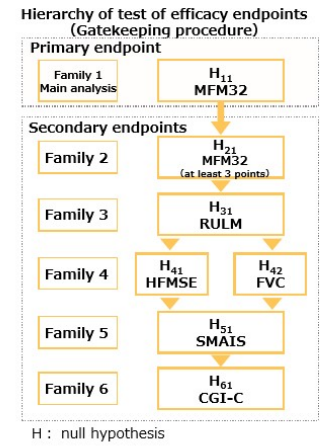
Next, here are the secondary endpoints. Here we have the upper limb module, which is an assessment item specific to the upper limb, and Hammersmith, which is an assessment item used in other assessment tests. These things were also used for evaluation.

Global Phase II/III study (Part 2 of SUNFISH Study)

## Study Synopsis: Analysis Plan

**Analysis plan**

- All 180 cases were included in the ITT and safety analysis populations, efficacy analysis was performed in the ITT population, and safety analysis was performed in the safety analysis population (4 of 180 cases, the study was discontinued to switch to other treatments and the double-blind administration period was not completed.)
- The data cutoff date (September 6, 2019) was defined as the time when the last enrolled patient completed the evaluation 12 months after administration (last visit date).
- MMRM was used to analyze the amount of change in the efficacy endpoint, and logistic regression model was used to analyze the proportion of patients.
- A gatekeeping procedure was applied to the primary endpoint and the six main secondary endpoints to control the multiplicity of tests (right figure).
- The adjusted p-value was calculated so that the p-values of all evaluation items above the evaluation hierarchy were taken into consideration and the significance level could be compared at 0.05 on both sides.
- For Family 4, the truncated Hochberg method with a truncation parameter of 0.95 was used.
- A subpopulation analysis was performed by pre-defined randomized age group, region, severity (baseline MFM32 total score), disease type, and *SMN2* gene copy number [primary endpoint: change from baseline in MFM32 total score at Month 12, secondary endpoints: percentage of participants with marked improvement (defined as ≥ 3) in the total MFM32 score at month 12, change from baseline in RULM total score, exploratory secondary endpoint: percentage of participants who achieve stabilization or improvement (change from baseline defined as ≥ 0) in the total MFM32 score at month 12]

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Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

This is the analysis plan. Because of multiplicity, we are using this method of hierarchical evaluation.

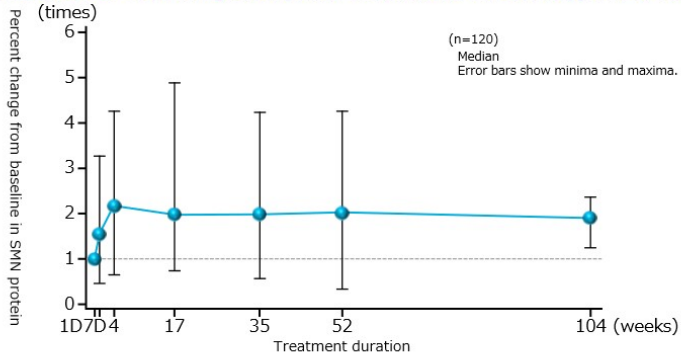
Global Phase II/III study (Part 2 of SUNFISH) Clinical Pharmacology Data

## SMN Protein Production: SMA type II / III patients

### (Japanese and non-Japanese data)

- **SMN protein levels in blood at baseline and the last observation [median (range)] were 3.58 ng/mL (1.54-11.4) and 7.04 ng/mL (0.786-13.8), and the change from baseline at the last observation [median (range)] was 1.98-fold (0.359-4.25).**

**SMN protein level following risdiplam treatment in SMA type II / III patients**




**Assessment methods:** SMA type II / III patients 2 to 25 years of age were started on once daily oral risdiplam (0.25 mg/kg for patients weighing < 20 kg and 5 mg for patients weighing ≥ 20 kg), and changes in SMN protein level were assessed at baseline and at the last observation.

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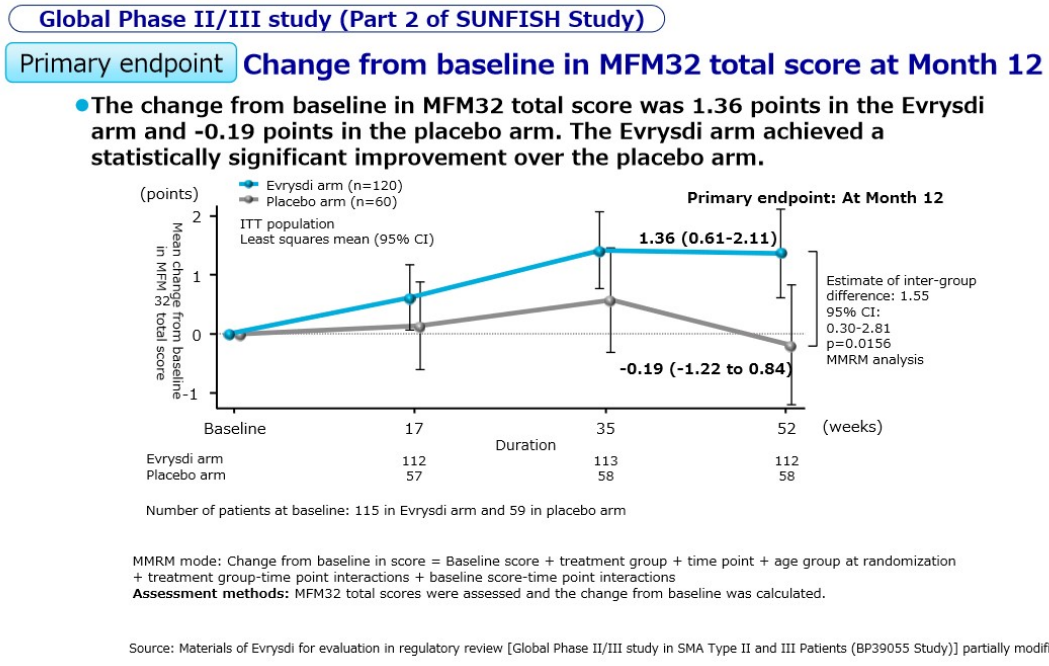
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

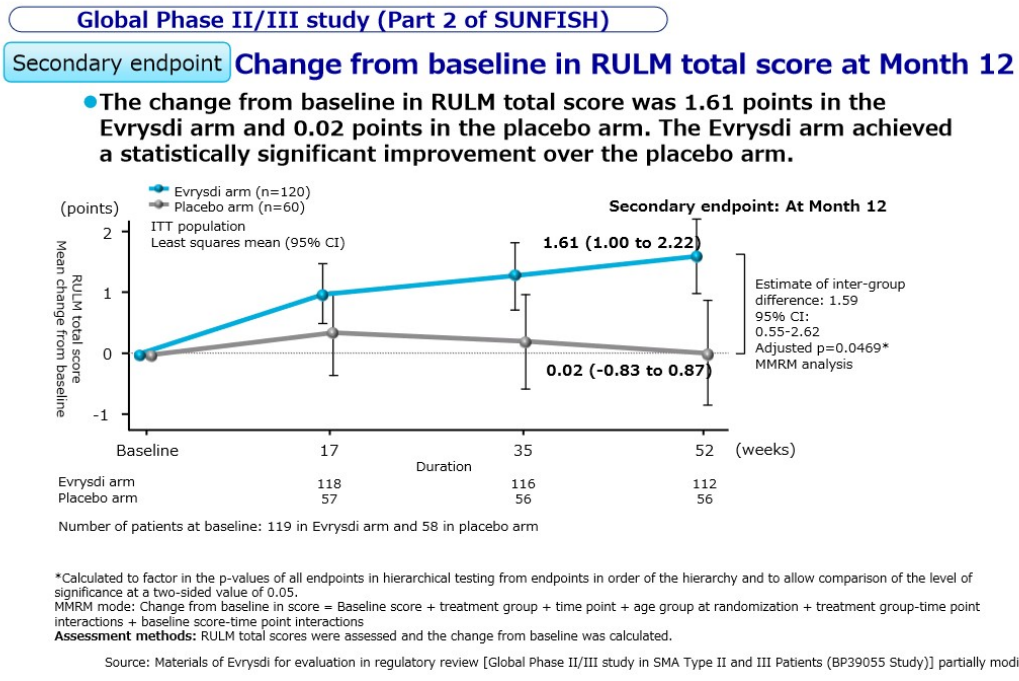
This is protein level. This shows the level of SMN proteins.

My impression is that it goes up relatively quickly. It took about 2 weeks to reach maximum, so I think it effect very quickly. It is an orally administered drug, but I had impression that it responds very rapidly. We can see that the value was maintained an approximate doubling of the baseline figure.




Here is primary endpoint.

The primary endpoints have been met. This is the MFM32. The placebo group is represented by the gray line. The light-blue line is the investigational drug group. The results showed efficacy, with highly significant differences. The *P*-value was 0.0156.

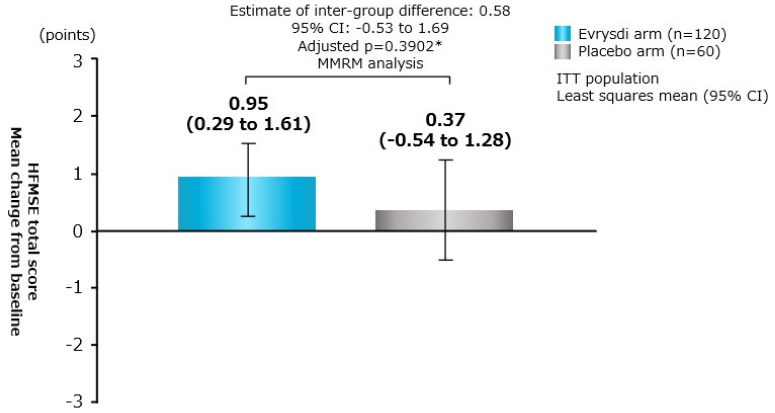



This is RULM, the upper limb module. We are looking at the motor function of the upper limbs. This is a group of people who are unable to walk (type II and type III), so many of them have quite advanced disease. It shows a large significant difference in those aspects where patients could keep their grip strength and improve.

Global Phase II/III study (Part 2 of SUNFISH study)

Secondary endpoint **Change from baseline in HFMSE total score at Month 12**

- **The change from baseline in HFMSE total score was 0.95 points in the Evrysdi arm and 0.37 points in the placebo arm. The intergroup difference was not statistically significant.**




*Calculated to factor in the p-values of all endpoints in hierarchical testing from endpoints in order of the hierarchy and to allow comparison of the level of significance at a two-sided value of 0.05.
MMRM mode: Change from baseline in score = Baseline score + treatment group + time point + age group at randomization + treatment group-time point interactions + baseline score-time point interactions
**Assessment methods:** HFMSE total scores were assessed and the change from baseline was calculated.
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)]

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This is Hammersmith.

This was not significantly different. Since we evaluate people who have progressed, Hammersmith often evaluates at people who are relatively young and not very advanced in age, but I think the fact that the age limit is 25 may have had an effect. While there was a difference between the 2 groups, the value was not statistically significant. The *P*-values are as described here.

Global Phase II/III study (Part 2 of SUNFISH study)

## Adverse Events and Adverse Drug Reactions

| | Evrysdi arm (n=120) | Placebo arm (n=60) |
|---|---|---|
| **Number of patients with ADR/Number of ADRs*1** | 16 (13.3%)/21 | 6 (10.0%)/9 |
| Gastrointestinal disorders | 6 (5.0%)/6 | 1 (1.7%)/1 |
| Nausea | 2 (1.7%) | 0 |
| Mouth ulceration | 2 (1.7%) | 0 |
| Abdominal pain upper | 1 (0.8%) | 1 (1.7%) |
| Loose stool | 1 (0.8%) | 0 |
| Skin and subcutaneous tissue disorders | 6 (5.0%)/6 | 1 (1.7%)/1 |
| Dermatitis acneiform | 1 (0.8%) | 0 |
| Eczema | 1 (0.8%) | 0 |
| Rash | 1 (0.8%) | 0 |
| Rash maculo-papular | 1 (0.8%) | 0 |
| Dry skin | 1 (0.8%) | 0 |
| Skin discolouration | 1 (0.8%) | 0 |
| Dermatitis herpetiformis | 0 | 1 (1.7%) |
| Infections and infestations | 3 (2.5%)/3 | 1 (1.7%)/2 |
| Upper respiratory tract infection | 2 (1.7%) | 0 |
| Gastroenteritis viral | 1 (0.8%) | 0 |
| Bronchitis | 0 | 1 (1.7%) |
| Respiratory tract infection | 0 | 1 (1.7%) |

| | Evrysdi arm (n=120) | Placebo arm (n=60) |
|---|---|---|
| Nervous system disorders | 2 (1.7%)/2 | 1 (1.7%)/1 |
| Headache | 2 (1.7%) | 1 (1.7%) |
| Eye disorders | 1 (0.8%)/2 | 0 |
| Posterior capsule opacification*2 | 1 (0.8%) | 0 |
| Cataract subcapsular*2 | 1 (0.8%) | 0 |
| Blood and lymphatic system disorders | 0 | 1 (1.7%)/3 |
| Thrombocytopenia | 0 | 1 (1.7%) |
| Neutropenia | 0 | 1 (1.7%) |
| Leukopenia | 0 | 1 (1.7%) |
| Cardiac disorders | 1 (0.8%)/1 | 0 |
| Palpitations | 1 (0.8%) | 0 |
| Psychiatric disorders | 0 | 1 (1.7%)/1 |
| Sleep disorder | 0 | 1 (1.7%) |
| Metabolism and nutrition disorders | 1 (0.8%)/1 | 0 |
| Hypercholesterolaemia | 1 (0.8%) | 0 |

Safety analysis set
MedDRA version 22.0
*1 Multiple occurrences of an adverse drug reaction in the same patient were counted individually when calculating the total number of events and number of events classified by system organ class. Multiple occurrences of an adverse drug reaction in the same patient were counted only once when calculating the number of adverse drug reactions classified by preferred term.
*2 The occurrences of posterior capsule opacification and subcapsular cataract noted in the same patient were not handled as adverse events in the January 2020 cutoff data because they were absent in reevaluation that included additional red reflex evaluation.

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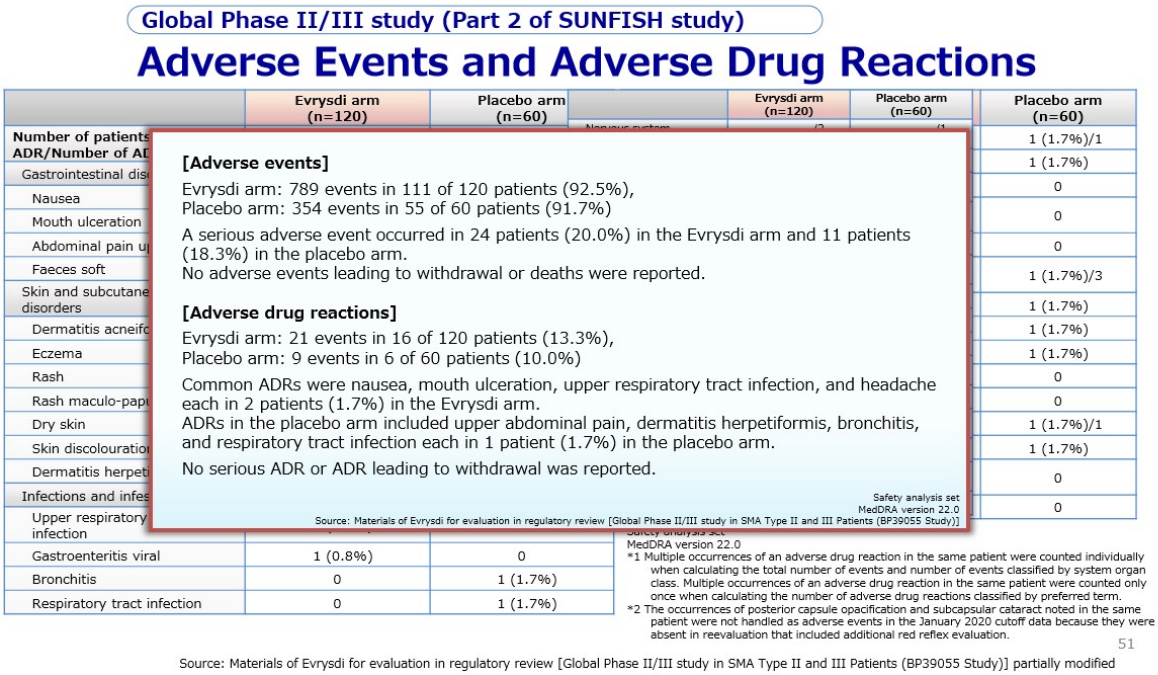
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

Next, adverse events and side effects.



Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

This slide shows a lot of information, so I'll just sum it up in a few words.

In the Evrysdi group, there were 789 adverse events, occurring in 92.5% of the 120 patients. Adverse events were also observed in the placebo group (91.7%, 55 of 60 patients). The number of serious adverse events was 24 in the Evrysdi group and 21 in the placebo group. There were deaths, and no adverse events that led to discontinuation of treatment.

As for the side effects, the third line from the bottom shows that in the Evrysdi group, side effects included nausea and oral ulcers. These are thought to have been caused by the medication, as it is thought that Evrysdi may have a stimulating effect on the mucous membranes. It is very important to gargle the throat not to leave the drug in the mouth.

These changes were also observed in the placebo group. No serious side effects or side effects that led to discontinuation of administration were observed.

## Evrysdi Dry Syrup 60 mg
## Generic name: Risdiplam dry syrup

**Indication**

**Spinal muscular atrophy**

**Dosage and administration**

| | |
|---|---|
| ≥ 2 months to < 2 years of age: | 0.2mg/kg |
| ≥ 2 years of age: | < 20 kg: 0.25mg/kg |
| | ≥ 20 kg: 5mg |

Orally administer after meal once daily

Source: Package insert revised in Aug, 2021 (Version 2) and Patient Medication Guide of Evrysdi Dry Syrup 60 mg

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The dose of Evrysdi dry syrup is 60 mg, but it does vary by age group.

The dose is 0.2 mg/kg for children between 2 months and 2 years of age, and 0.25 mg/kg for children over 2 years of age and weighing less than 20 kg. If you exceed 20 kg, you will need 5 mg, which is equivalent to 6.6 mL. 1 bottle is about 80 mL. If you factor in some loss, it will take about 11 days to consume 1 bottle. That's an idea of the dosing.

It's a strawberry-flavored syrup. You might think it would be difficult for older adults to take strawberry-flavored syrup, but we have already started administering it to them, and they say they have gotten used to it, so I don't think the flavor is a particular problem. The people who participated in the clinical trial have been taking it for years now.

# Precautions concerning Patients With Specific Backgrounds

**Patients with Hepatic Impairment: Patients with severe hepatic Impairment**

No clinical studies have been conducted in patients with severe hepatic impairment, and they may have increased risdiplam exposure.

**Females of reproductive potential**

The pregnancy status of females of reproductive potential should be verified prior to initiating Evrysdi therapy. Instruct female patients of childbearing potential to use appropriate contraception during treatment with Evrysdi and for a certain period after the last dose. Embryo-fetal toxicity has been observed in animal studies.

**Male patients who have a partner of childbearing potential**

Suspend treatment if the partner wishes to become pregnant. Instruct these patients to use appropriate contraception during treatment with Evrysdi and for a certain period after his last dose.
In animal studies (rat and cynomolgus monkey), reversible findings on male reproductive organs (sperm degeneration, reduced sperm numbers and decreased sperm motility) were observed. A micronucleus-inducing effect has been observed in a genotoxicity study.

Evrysdi Dry Syrup 60 mg (pmda.go.jp) (accessed in September 2021)

Package insert revised in Aug, 2021 (Version 2) and Patient Medication Guide of Evrysdi Dry Syrup 60 mg 53

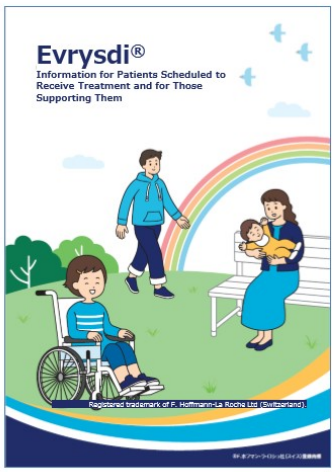
Here is a note of caution regarding patients with specific backgrounds.

As Mr. Kodaira explained earlier, the first caution relates to severe liver dysfunction. Where this is very severe, to the point of cirrhosis, I think it would be best avoided, as the blood level rises. The main excretion route is hepatic. There is a little bit of urinary excretion, but it is mostly hepatic, so we have to be careful in case of severe liver damage.

Another caution is women of childbearing potential. It has been shown to be teratogenic in animal studies. In terms of embryo-fetal toxicity in animal studies, I think it is important to use contraception or take a break from the medication during pregnancy.

In addition, for men, sperm degeneration, decreased sperm count, and decreased sperm motility can occur. If a man's partner has the potential to become pregnant, he should take precautions, such as using contraception.

## Warnings for Pregnancy and Breastfeeding




**Information for women**

As studies with animals showed that Evrysdi affects fetal and breast milk, breastfeeding could result in transfer of the active ingredient of the drug to the baby.

- Appropriate birth control is required during treatment and after treatment for a certain period (at least 1 month).
- **Tell your doctor if you are or may be pregnant or are breastfeeding.**

**Information for men**

Studies with animals showed that Evrysdi affects sperm changes and low sperm counts.

- Appropriate birth control is required during treatment and after treatment for a certain period (at least 4 months).
- **Tell your doctor if you are a male patient with a partner of childbearing potential.** If you and your partner wish to have a baby, appropriate birth control is required for a certain period (at least 4 months) after treatment discontinues.

For those who receive treatment with Evrysdi and those who support treatment (July 2021)
(Supervised by Dr. Kayoko Saito, Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University)

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This is a very important point for adults, so we have created an explanation sheet for Evrysdi. In this sheet, there is an easy-to-understand explanation for patients. The term of contraception is 1 month for women, and 4 months for men.

## Expectations for Evrysdi

- Patients will be able to receive treatment regardless of their conditions* (e.g., age, scoliosis).
- Since Evrysdi is an oral drug that does not require hospitalization for administration, home treatment can be provided.
- Evrysdi may reduce patients' time burden and opportunity loss (schooling, work)
- As SMA is a rare disease with limited data on the drug's efficacy and safety, it is hoped that data will be accumulated in the future. Until then, it is necessary to carefully observe the course of treatment.

**Based on these features, Evrysdi may help improve the QoL of all those living with SMA.**

* Efficacy and safety have not been established for patients with permanent mechanical ventilation and for preterm infants and infants <2 months of age.

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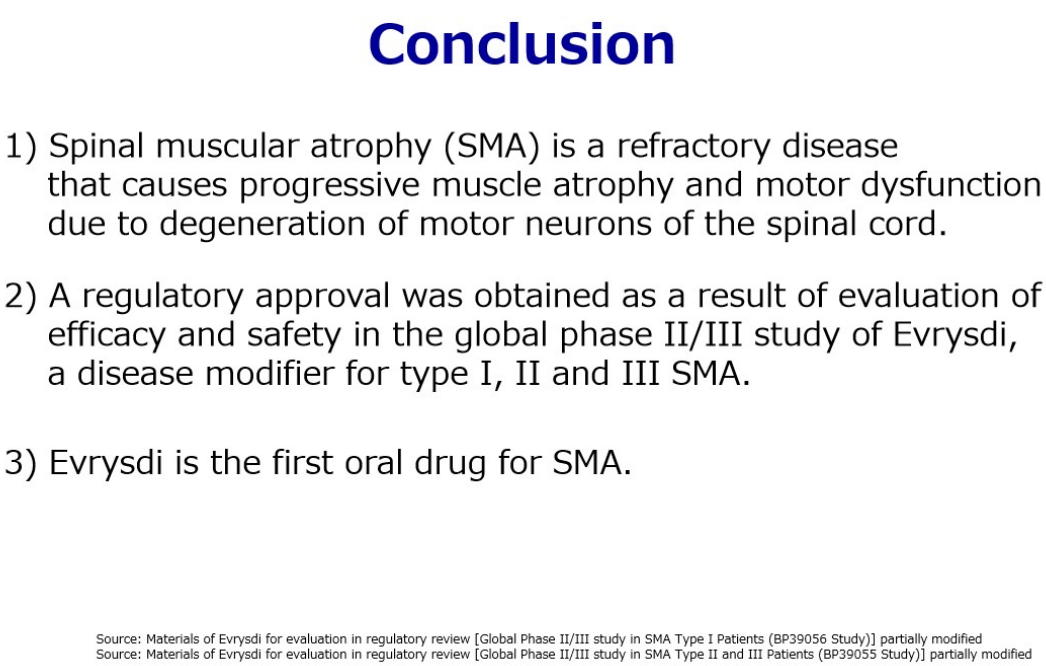
We think that Evrysdi will be able to treat patients regardless of their disease condition, whether they have scoliosis or not, or their age.

Treatment doesn't require hospitalization. Treatment can be done at home. That means that you don't have to go to a large hospital to be treated.

That can reduce the burden on the patient's time, schooling and employment.

Since SMA is a rare disease and there are very little data on the efficacy and safety of this drug, we need to accumulate a lot of data from now on. I think it is also necessary to carefully monitor patients' progress with medication.

We believe that we can contribute to improving the QoL of SMA patients while they are taking these medications.




Finally, a summary.

SMA is an intractable disease that causes progressive muscle atrophy and motor dysfunction due to degeneration of motor neurons in the spinal cord.

Approval has been obtained for Evrysdi, a disease-modifying drug, for SMA types I, II, and III, based on the evaluation of its efficacy and safety through international clinical trials and Phase II/III studies.

Evrysdi is the first oral drug for SMA.

This concludes my presentation. Thank you for your attention.

**Sasai:** Thank you very much, Professor Saito.

## Question & Answer

**Sasai:** We will now move on to the question-and-answer session.

In order to allow as many people as possible to ask questions, we would like to limit the number of questions to 2 per person. Please note that the audio of your questions, along with the presentation, will be posted on our website at a later date.

When it is your turn to ask a question, we will call your name. If you have any questions, please let us know your company name and your name.

Now I would like to move on to the first question.

First of all, Mr. Sakai of Credit Suisse Securities, please go ahead.

**Sakai:** My name is Sakai from Credit Suisse. Thank you very much for your time today.

I also had a chance to look at your SMA website. I believe that you are also involved in Novartis' Zolgensma, but now that this oral drug has come out, what do you think about the place of Zolgensma and Spinraza as drug choices for this disease? That's my first question.

**Saito:** Thank you for your question.

There have not yet been any comparative tests to determine which one to choose. Since the conditions of each clinical trial are different, they are not at the same starting line, but at different stages. Therefore, it is difficult to say which one to choose.

In terms of criteria, 1 of the first things to consider when choosing is age. Novartis' onasemnogene is indicated in patients under 2 years old. This is especially significant in the case of very small babies, since it is gradually being discovered that the younger the age of treatment, the less side effects occur. Especially for Evrysdi, which is for patients over 2 months old, I think this is a situation where comparisons have not been made yet.

Also, as for Spinraza, I felt that almost all people diagnosed with SMA in Japan are using it, since it has been out for a little while. Since the release of Evrysdi, my outpatient clinic has become extremely crowded, and I'm getting a lot of patients with scoliosis, patients who can't use previous medications due to work, and so on. In that sense, I think there will be some changes.

However, in terms of efficacy, we are still at the clinical trial stage, so we do not have the data to compare each of them. I'm afraid that's the most specific I can be in my answer.

**Sakai:** No, not at all. Thank you very much.

The second question is a simple one: you yourself commented that you do not have enough clinical trial data for Evrysdi yet. It was mentioned that after starting oral administration, the drug should be withdrawn during breast feeding or pregnancy. Apart from that, is this basically a drug that you take for life? If you stop, will the expression of protein become abnormal again?

**Saito:** Indeed. At the moment, there are only these 3 drugs. There may be many more drugs coming out in the future, but as of now, after starting the clinical trials, I have only presented data for the first year or so. In the second year, we actually have data that show an increase. For example, the upper limb module has

improved even more in the second year than in the first, so we will not give up so easily, and we are hoping that it will get better.

From a clinician's point of view, while other medications may come out in the future, at the moment, we are starting this drug with the intention of it being continued long term.

**Sakai:** Understood. Thank you very much for your presentation today.

**Sasai:** Thank you very much.

Next, Mr. Wakao from JP Morgan Securities Japan, please join us.

**Wakao:** This is Wakao from JP Morgan. Thank you very much for your time today, Professor Saito. I learned a lot.

I was wondering if you could tell us a little more about the difference in usage between the 3 drugs. Now that Evrysdi, an oral medication, is available, I think that more people will use this drug for its convenience.

As for the factors for switching from Spinraza to Evrysdi, is the convenience and dosing method the main difference, and will that be the key factor for switching? In addition, although the data are not yet completed, is there a possibility that there will be differences in efficacy and safety that will lead to different uses of the drugs? That's my first question.

**Saito:** I think you are right. I think we are still in the process of accumulating data on the efficacy and safety of these drugs, but it's not just about convenience. For example, if you are administering intrathecal drugs many times, it may become difficult to administer them. Then there is the case of scoliosis progressing or other such changes.

In addition, there are patients who have headaches and so-called post-lumbar puncture syndrome when intrathecal administration is used. To date, they have had no choice but to continue those treatments, but now they are wondering what to do.

There are people who are unable to use other medications, and there are also people who use these medications for side effects that they can tolerate to a certain extent, although the safety of the medication is ensured. That is what we hear from our patients.

Is that all right?

**Wakao:** Yes. I understand now. Thank you.

Also, Spinraza has a wider range of indications than Zolgensma, so I wonder if this is also a big factor. How is Zolgensma being used in actual clinical practice? Is this kind of drug very widespread in patients under 2 years of age with type I and type II? Zolgensma is only used once in a lifetime, so if that is indeed the case, I was wondering whether Evrysdi would be used after that. Could you please tell me about that possibility as well?

**Saito:** The Japanese Society of Pediatric Neurology has issued guidelines about this type of add-ons, or additions, to a drug. It's called the Guideline for Appropriate Use.

If the patient is in a state where motor function is declining, we can change to another medication. Since we only give Zolgensma once, I think we will end up adding to it. We have those guidelines in place supporting that. Therefore, I think the principle is to follow the guidelines for the use of so-called insurance-listed drugs.

**Wakao:** Understood. Thank you. That's all.

**Sasai:** Thank you very much.

Next, Mr. Ebisawa of Jiho, please go ahead.

**Ebisawa:** Now that the 3 drugs are available, since Evrysdi is administered orally, will there be any problems in terms of medication management? Please let me know if you have any thoughts about that.

**Saito:** In terms of medication management, when I talk with and explain to patients, the first important thing is to remind them not to forget to take their medication once a day because some of them are a bit older. Patients are encouraged to decide if they're going to take it every morning or every evening after dinner. In the leaflet I mentioned earlier, there's a calendar to help patients keep track of whether they've taken their medication. I think this is a very important point. I tell them, "don't forget to take it."

Also, the medication itself should be stored at 2 to 8 degrees Celsius. You can't freeze it. Then, as was explained earlier, it comes in a brown bottle, because it is light shielded. In this respect, it is very important that medication management is properly followed. To avoid freezing, for example, if the temperature in the refrigerator is lowered, the food will freeze even though it was intended to be refrigerated. Also, if the medication is left out, it will warm up. We give patients a thorough warning to prevent these situations from happening.

As for the actual medication to take home after receiving it at the pharmacy, Chugai Pharmaceutical has made a very stylish bag with ice pouches that can hold 6 bottles at a time. We tell patients that if their refrigerator stops working, they should transfer the medication to a cool bag with some ice pouches to keep them cool. It is a very important point.

Is that all right?

**Ebisawa:** Thank you very much.

I'm not sure who should take my second question, but regarding pregnancy, in order to prevent embryo-fetal toxicity from occurring in patients, is there anything in particular that can be done clinically or as a manufacturer, or is there any system to cover this?

**Kodaira:** Thank you for your question.

As you mentioned earlier, in the section on precautions for pregnancy and breastfeeding, those who wish to become pregnant are asked to stop taking the drug for 1 month. Men are asked to stop taking it for 4 months. Once that period is over, there are various concerns, but we believe that the drug will not have any effect on the pregnancy, so the patient can become pregnant during that period.

At the moment, we can only provide information, but we would like to ask those who actually wish to become pregnant to be very careful and consider the best way to use this drug in combination with other drugs.

**Ebisawa:** Is this the case not only in Japan, but also in other countries, where manufacturers are providing information and asking people to be careful?

**Kodaira:** Yes. The system differs from country to country, so, in some cases, the information is included in the package insert, and in other cases, like in Japan, the information is provided in this form.

**Ebisawa:** Thank you very much.

**Sasai:** Thank you very much.

Ms. Mitsutake of the Nihon Keizai Shimbun, please go ahead.

**Mitsutake:** Thank you very much.

I would like to ask Professor Saito, what kind of questions do you receive from patients and doctors you advise now that these 3 drugs are available?

**Saito:** Many patients ask me if they can take the new orally available medication. When that happens, I try to explain the points that I mentioned earlier about Evrysdi in a more patient-oriented way.

**Mitsutake:** This may be a duplicate of your previous answer, but I think that patients and doctors are often troubled by the question of which one is better than the other.

**Saito:** For example, I sometimes get consultations over the phone. A patient has type I disease, and has been taking Spinraza, and whether they should change. It's very difficult to say over the phone, "Let's change that," or "Let's continue," and the coronavirus pandemic makes that very difficult.

In fact, I think it should be done on a case-by-case basis. I don't have enough experience at the moment, but I would like to consult with the parents directly and continuing to observe while making these decisions.

There are a lot of different feelings among parents, some of whom think there is no particular need to change, and others who really want to change. Nowadays, information can be found on the Internet, so I think a lot of parents are wringing their hands over this. That's very much what I've been hearing.

In Kyushu and other distant areas, we are approached in a variety of ways, so we do our best to consult with them by listening to their actual voices over the phone or through other means. In fact, there are people who say they are coming to Tokyo from Kyushu, for a consultation.

**Mitsutake:** I see. Indeed. Do you think that general practitioners also have the same problems?

**Saito:** Actually, I think general practitioners know the patients much better than we do, but I don't think they have much experience in using these medicines. In this sense, I think it is necessary for specialists in university hospitals to receive referrals from general practitioners for so-called second opinions, and to give advice and suggestions. That way, patients can receive treatment at the home physician's office.

Even if you are actually involved in a lot of clinical trials, it is difficult to come to a conclusion right away. In that sense, I think that medical professionals need to communicate better with each other.

**Mitsutake:** Understood.

I'd also like to ask about the guidelines. I'm sorry if you mentioned this during your presentation. I thought I heard somewhere that new guidelines would be issued soon. Could you tell us anything about this?

**Saito:** The problem here is that treatment is advancing as the guidelines are being written. They have to be updated before they can even be published. We are now in the final stages, and the peer-review process for external conferences has been completed. We are almost at the final stage, and since we have given it the title of Guideline 2021, we are planning to release it in FY2021, so it will be published soon.

**Mitsutake:** Understood. Within this year, understood. Thank you.

**Sasai:** Thank you very much.

The next speaker is Mr. Hashiguchi from Daiwa Securities.

**Hashiguchi:** My name is Hashiguchi from Daiwa Securities. Thank you.

Earlier, it was mentioned about taking this medication for life. However, there is also the possibility of other medications being launched in the future.

Among the new treatment methods that are being developed and researched now, what kind of approaches are you paying attention to now? Do you think there is a possibility that the treatment system will change when these new methods come out?

**Saito:** Thank you very much.

I think this is a very important point. In the end, these disease-modifying therapies all have 1 thing in common: they are designed to treat diseases at the level of genes, DNA sequences, mRNA sequences, and so on.

In that sense, I really believe that SMA is a disease that is very well suited to this treatment concept. Since we have already cured the root of the problem, such as the DNA and RNA of the SMA, we can manipulate the muscles at the same time. I think it is possible that we can make the treatment more effective. In that sense, I think there is still room for development.

**Hashiguchi:** In terms of muscle, I think that several myostatin activation inhibitors have been developed, but is it safe to assume that these approaches can be used in combination with drugs such as Evrysdi?

**Saito:** I think that's a very good point. I think you're talking about a very specialized area now, but I personally think it could be a very good treatment.

For muscle diseases, anti-myostatin antibodies may not be as effective. I think it would be difficult to do this without curing the fundamental genetic disorder. While SMA isn't a muscle disease, the idea of curing the gene defect while making the muscles strong is a very good one.

Also, in the future, I think that there will be potential for the development of cell transplantation for the spinal cord and muscle transplantation using iPS cells. Still, that's a long way off at the moment. I think that there are many different stages of treatment and development that can be considered.

**Hashiguchi:** Thank you very much. That's all.

**Sasai:** Thank you very much.

The next speaker is Mr. Zhou  from Goldman Sachs Japan.

**Zhou:** Thank you very much for your time.

I have a question for Professor Saito. I think there was an interview article in a professional journal the other day. It was mentioned that patients who have a gastrostomy may choose Evrysdi, or that patients who have scoliosis and cannot receive Spinraza may choose Evrysdi.

How many SMA patients actually have scoliosis as well? Also, how many patients have a gastrostomy as well?

**Saito:** First of all, in terms of gastrostomy, type I patients receive tube feeding, or rather, as the disease develops, all patients receive tube feeding or gastrostomy. The number of patients with type I disease who can eat food is almost zero.

In terms of scoliosis, in type II and type III, it is almost always seen in type II. In short, it's already a common feature of SMA to be in a wheelchair before puberty and to have scoliosis. In the case of type III, scoliosis is still present when the child is in a wheelchair before puberty.

As for the mechanism, I mentioned earlier that the intercostal muscles are weak, and while the intercostal muscles do not grow and the rib cage does not enlarge, as the person grows taller, only the spine grows vertically. When that happens, the spine will have nowhere to go. The result is curvature.

Since adolescence is a time when people are growing taller, scoliosis becomes much worse during this time, and the so-called scoliotic angle can exceed 100 degrees, so it's really like being folded in 2. Scoliosis is always accompanied by twisting, so when some people decide to take Spinraza, to their surprise, the place they can administer to is on the side of their abdomen. There were people who said they didn't have a place where they could actually inject it, and those people had given up on administering Spinraza.

Almost 100 percent of type II patients are those types of patients, and more than half of type III patients are prepubescent.

In terms of gastrostomy, most of the type I patients have tube feeding or gastrostomy, so the frequency of such complications is quite high.

**Zhou:** Thank you very much.

The second question is about Zolgensma, but I think it is difficult to comment on it because it is another company's drug.

First of all, we think that Zolgensma is quite difficult to use because it takes 2 to 3 weeks from the time it is ordered to the time it is administered, and also because it needs to be handled according to the Cartagena Act.

In that case, I think that Spinraza may be the first choice rather than Zolgensma in Japan. Is that correct?

**Saito:** Regarding Zolgensma, as you pointed out, it is indeed Cartagena Act, and imported, and it is essentially custom made. It is true that it takes a bit of time to order when there is a patient.

However, it is difficult to say how many hospitals actually want to use it, because there are many hospitals that do not want to use it, but there are also hospitals that actively want to use it. Some hospitals are saying that they want to give more and more Zolgensma, especially for babies who have undergone newborn screening, so that part is still not clearly assessable by me.

**Zhou:** I understand. Thank you very much.

**Sasai:** Thank you very much.

The next speaker is Mr. Muraoka from Morgan Stanley MUFG Securities.

**Muraoka:** Hello. My name is Muraoka and I am with Morgan Stanley. Thank you. I also have a question for Professor Saito.

First of all, it's been 4 years since the first treatment came out, that is, Spinraza, so I guess it's been a while. I think you mentioned earlier that when a good drug is released for a common treatment, patients are more likely to be diagnosed as SMA and to become aware of it.

With Spinraza, for example, could you estimate what proportion of patients have newly diagnosed as SMA having found information about the drug for themselves? Was it 50 percent or something like that?

**Saito:** Actually, it's hard for me to feel the difference because I'm recently communicating on the web, and when I give lectures, I feel that there is a lot of information in big cities, but it's rather difficult to find out by the doctors in rural areas.

Strangely enough, there are more cases of SMA in the south and west, and fewer cases in the east and north. Tokyo is a place where everyone gathers and there is a large population, so there are many patients in Tokyo, and Kanagawa is also very populated. There are many patients in Tokyo and Kanagawa, but the number is gradually decreasing in Tohoku and Hokkaido. That's what we've seen as a result of epidemiological surveys. In my paper, I tried to explain the reason for this, and whether it was a difference between the Jomon and the Yayoi, but in fact there is a difference in frequency between eastern and western Japan.

In that sense, I gave a web lecture to people in Tohoku the other day, and when they asked me questions like, "No, we might have thought it was muscular dystrophy or myositis," I have recognized that there is still a lot to be discovered.

As I mentioned earlier, the results of epidemiological studies show that as of 2017, there should be 1,400 to 1,500 patients in Japan. However, the number of people who have received Spinraza has not yet reached that level, and there are still many people who have not received treatment, or who have not been diagnosed.

Particularly with types III and IV, people who are a little slow at sports events in junior high school eventually show symptoms at the age of 30 or 40. It's more like a slowly developing symptom. These people may not even go to the hospital because they just feel that they are not good at sports, or that it is because of the shape of their feet, or something like that.

That is why I am recommending that orthopedic surgeons pick it up at elementary, junior high, and high school checkups, and I believe that there are still many people who have not been diagnosed.

**Muraoka:** Thank you very much.

Also, in your current patient population, how many patients do you see now, and how many of them do you think will be using Evrysdi?

**Saito:** Some patients come from all over Japan for consultations, and some SMA patients visit about 3 hospitals by themselves. The epidemiological survey revealed that some people had visited 5 different locations. After all, if the specialist has something good to say, they will come even if they are far away. If I were to do that, I would have to see so many people that I would lose count.

I haven't really counted the number of patients I see regularly, but I think I've just started to see about 10 patients a month on Evrysdi. To be a bit more precise, I would say that about 10 people have started in the past month.

**Muraoka:** How many other drugs were administered or newly started in that 1 month?

**Saito:** For the rest of the patients, we are an outpatient department called the Department of Genomic Medicine, so we don't do Spinraza or Zolgensma at our clinic. There are times when I request a shot of Spinraza elsewhere and see the patient every 3 months, or I see a patient after a shot of Zolgensma and monitor their progress.

There are quite a few people like that. The people who come twice a year, for example, we haven't talked about that at all yet. Sorry, I don't have an exact count.

**Muraoka:** No, I got a sense of the situation on the ground, which was very helpful. That's all. Thank you.

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**Sasai:** Thank you very much.

We've run out of time, so we will now conclude today's briefing session on Evrysdi.

If you have any additional questions, please contact the Investor Relations Department. Phone numbers and email addresses can be found on the last page of the presentation materials.

Once again, thank you very much for taking time out of your busy schedule to join us today. Thank you.

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