# Information Meeting on Evrysdi®

## Agenda

Moderator: Toshiya Sasai, Head of Corporate Communications Dept.,
Chugai Pharmaceutical Co., Ltd.

1. **Overview of Evrysdi®**

Hideto Kodaira, Evrysdi Lifecycle Leader,
Chugai Pharmaceutical Co., Ltd.

2. **Evrysdi®, a New Treatment Option for Spinal Muscular Atrophy (SMA): The First Oral SMA Drug**

Kayoko Saito, MD, PhD,
Professor of Special Appointment, Institute of Medical Genetics,
Tokyo Women's Medical University

3. **Q&A Session**

# Overview of Evrysdi®

September 27, 2021

Hideto Kodaira
Evrysdi Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

# Product Profile of Evrysdi

Therapeutic category: Treatment for spinal muscular atrophy

Product name/
Generic name:

日本標準商品分類番号 87119

脊髄性筋萎縮症治療剤

劇薬、処方箋医薬品注)

薬価基準収載

エブリスディ®ドライシロップ60mg

Evrysdi
risdiplam

リスジプラムドライシロップ

注)注意－医師等の処方箋により使用すること

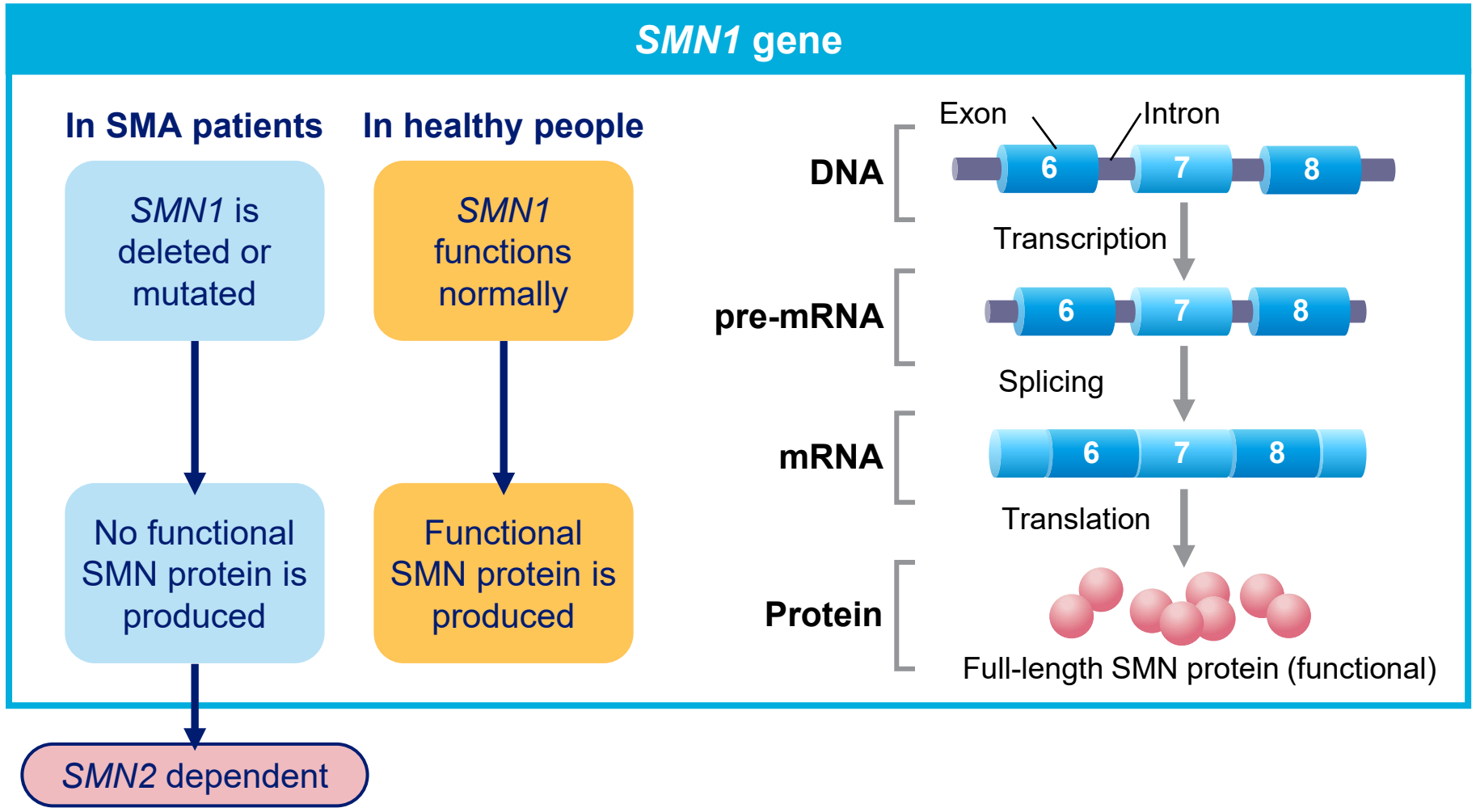
® F.ホフマン・ラ・ロシュ社(スイス)登録商標

Packaging:


Evrysdi™
risdiplam
60 mg
powder for oral solution

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

(Illustrative example)

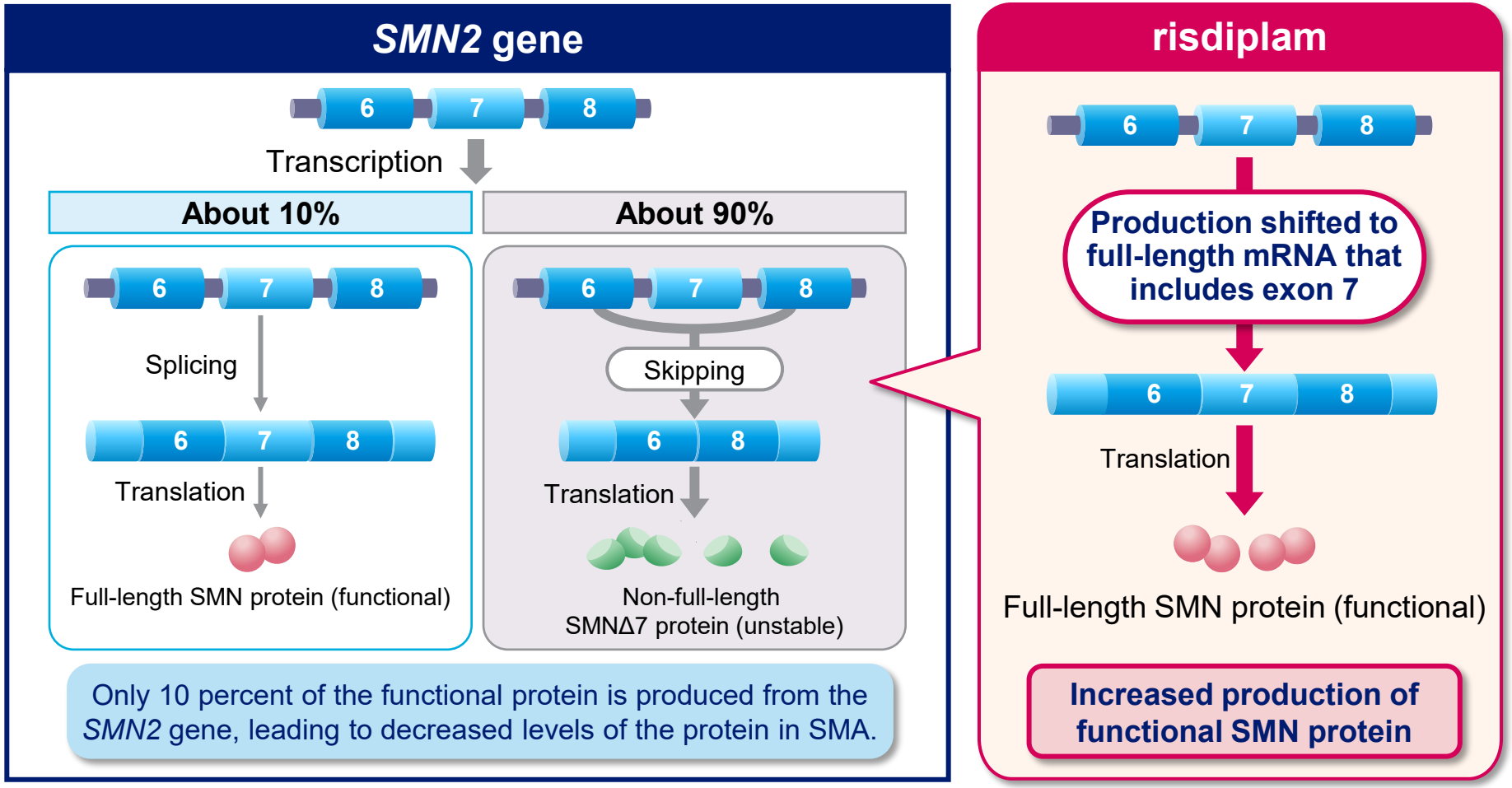



SMN: Survival Motor Neuron

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.

# 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.

# Contribution of Evrysdi to SMA Treatment

Evrysdi is the first oral treatment for SMA.

① Taken orally daily, the drug acts to increase SMN protein levels.

② Efficacy and safety were evaluated in clinical studies over a wide range of patients from infants to adults, leading to regulatory approval.

③ Administration of Evrysdi requires no hospitalization. This is expected tp reduce the time and financial burden on patients and their caregivers. In particular, the feature may offer increased convenience for patients who are working or studying.

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

# History of Evrysdi Development

| | |
|---|---|
| November 2011 | Roche enters into license agreement with PTC Therapeutics |
| January 2016 | Roche begins a Phase I clinical study |
| October | Part 1 of SUNFISH study (Phase II portion) begins |
| December | Part 1 of FIREFISH study (Phase II portion) begins |
| February 2017 | Phase I clinical study in Japanese patients (residing in the United States) begins |
| October | Part 2 of SUNFISH study (Phase III portion) begins |
| March 2018 | Part 2 of FIREFISH study (Phase III portion) begins |
| December | PRIME (PRIority MedicinEs) designation in the EU |
| March 2019 | Orphan drug designation in Japan |
| August 2020 | US Approval |
| March 2021 | EU Approval |
| June | Japan Approval |

Evrysdi™ risdiplam 60 mg powder for oral solution

# Indication

## Indication
Spinal muscular atrophy

## Precautions Concerning the Indication

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.
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.
3. Efficacy and safety have not been established in patients with permanent ventilation. If using Evrysdi in these patients, patients should be closely monitored, and efficacy should be evaluated regularly to decide whether treatment should be continued. If no response is observed, treatment should be discontinued.
4. The efficacy and safety of Evrysdi in preterm infants and infants less than 2 months of age have not been established. The clinical study in patients with type I spinal muscular atrophy was conducted in term infants aged 2 months or older to investigate pharmacokinetics, efficacy, and safety.

Evrysdi™ risdiplam 60 mg powder for oral solution

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

# Dosage and Administration

Dosage and Administration
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.

For patients at 2 years of age or older, the usual dosage is 0.25 mg/kg risdiplam for those weighing less than 20 kg, and 5 mg risdiplam for those weighing 20 kg or more, both administered orally once a day after a meal.

Precautions Concerning Dosage and Administration

1. The patient should drink water after taking Evrysdi to prevent the drug from remaining in the mouth.
2. The safety and efficacy of concomitant use of Evrysdi and other drugs for spinal muscular atrophy have not been established.
   Therefore, concomitant use should be avoided.

Evrysdi™ risdiplam 60 mg powder for oral solution

# 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 60 mg powder for oral solution

# 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 | |
|---|---|
| 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) |
| 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) |

| Risk minimization plan | |
|---|---|
| Routine | • Create (revise) a package insert<br>• Medication guide for patients |
| Additional | • Provide information through early post-marketing phase vigilance |

Evrysdi™ risdiplam 60 mg powder for oral solution

Source: Risk Management Plan of Evrysdi

# Evrysdi®, a New Treatment Option for Spinal Muscular Atrophy (SMA): The First Oral SMA Drug


**Kayoko Saito, MD, PhD**
**Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University**

# COI Disclosure

**Kayoko Saito, MD, PhD**

**Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University**

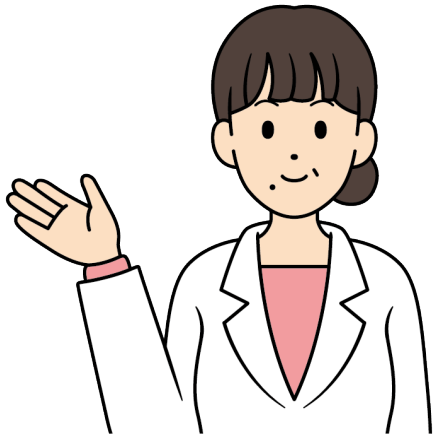
**Companies with which I have an interest warranting disclosure in relation to this presentation:**

| | |
|---|---|
| **(1) Consultant:** | **None** |
| **(2) Shareholding/profits:** | **None** |
| **(3) Patent royalties:** | **None** |
| **(4) Speaker fees:** | **Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Biogen Japan Ltd.** |
| **(5) Manuscript fees:** | **Novartis Pharma K.K., Biogen Japan Ltd.** |
| **(6) Contract research/joint research:** | **Biogen Japan Ltd.** |
| **(7) Scholarship donations:** | **None** |
| **(8) Posting in funded department:** | **None** |
| **(9) Recipient of other forms of remuneration:** | **None** |

**A disease with progressive weakening of the muscles**

# Have You Heard of Spinal Muscular Atrophy (SMA)?

＊Spinal Muscular Atrophy



Have You Heard of Spinal Muscular Atrophy (SMA)? (July 2021) (Supervised by Dr. Kayoko Saito, Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University)

# What is Spinal Muscular Atrophy (SMA)?

- **Spinal muscular atrophy (SMA) is a disease with progressive weakening of the muscles.**

  Those with SMA may have the following symptoms and conditions:

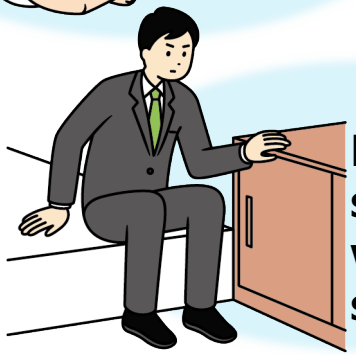
**Poor suction when nursing or drinking formula**

**Weak cry**

**Delayed head control**

**Rounded spine when sitting**

**Difficulty walking, prone to falls**



**Difficult to stand up without support**

**Arm and leg weakness**

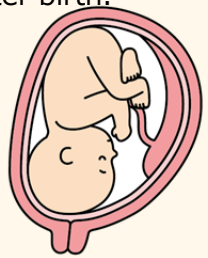
Have You Heard of Spinal Muscular Atrophy (SMA)? (July 2021) (Supervised by Dr. Kayoko Saito, Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University)

# Types of SMA

- **SMA affects a wide rage of ages, from infants to adults, and is classified into five types from Type 0 to IV.**
- **The disease is progressive. The severity and rate of progression vary depending on SMA type.**
- **SMA is sometimes identified because the movement of the affected individual is inconsistent with their level of development**

## Type 0

Occurs before birth.
Weak fetal movement.
No breathing soon after birth.



## Type I

Occurs 0 to 6 months postpartum.
Inability to sit without support.
Poor head control is common.

## Type II

Occurs by 18 months postpartum.
Can sit without support but cannot walk without support.

## Type III

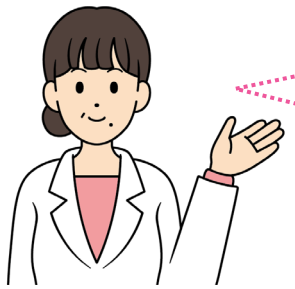
Occurs after the age of 18 months.
Can walk without support but may not be able to climb stairs.

## Type IV

Occurs after the age of 20 years.
Motor development may be normal.
Muscles become progressively weaker.

Kaneko K. et al. Brain Dev. 2017: 39: 763-73..

Adapted from Health and Labor Sciences Research Grants (Research Program on Rare and Intractable Diseases): Research Report of the Fiscal 2017 Neurodegenerative Disease Research Team (Apportioned).



A large proportion of patients show symptoms before 18 months of age (types I and II) [1].

About 1 to 2 people per 100,000 develop SMA when they are infants or children [2].

1) Health and Labor Sciences Research Grants (Research Program on Rare and Intractable Diseases): Research Report of the Fiscal 2018 Neurodegenerative Disease Research Team (Apportioned).
2) Information Center for Specific Pediatric Chronic Diseases. 38 Spinal Muscular Atrophy. https://www.shouman.jp/disease/details/11_17_038/ (accessed on July 1, 2021).



Have You Heard of Spinal Muscular Atrophy (SMA)? (July 2021) (Supervised by Dr. Kayoko Saito, Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University)

# Symptoms of SMA (1)

- **With muscular weakness as the primary feature, SMA involves symptoms of the disease itself and complications arising from SMA.**

## Symptoms of SMA

Examples include motor symptoms such as an inability to sit without support and poor walking ability as well as difficulty moving the arms and legs due to lack of strength, twitching of the tongue and fingertips, and a weak cry.

- **Floppy infant**

In SMA type I, flaccidity of the body can result in the disease features listed below. This condition is also sometimes called floppiness, hypotonia, and poor muscle tone.

When the infant is laid down, the legs rest on the floor, splayed like the legs of a frog.

When the infant is lifted by the arms, the head droops.

When the downward facing infant is lifted, the body does not straighten and drapes in the form of an inverted "U."

When the arm is placed across the neck, it wraps around the neck like a scarf.

The upper and lower body rest snugly against the floor.

With the infant on his back, the feet can be brought to the ears with little resistance.

When the infant is lifted from below the arms, the arms and shoulders rise and the body slips through.

Source: Uchiyama S, ed. Standard Pediatrics. 8th ed. Igaku-Shoin Ltd.; 2013. p. 674.

Manual for the Management of SMA Authoring Committee, ed. Manual for the Management of Spinal Muscular Atrophy. 1st ed. Kimpodo, Inc.; 2012. Japan Intractable Diseases Information Center. Spinal Muscular Atrophy (designated intractable disease 3). https://www.nanbyou.or.jp/entry/135 (accessed on July 1, 2021). Wang CH, et al. J Child Neurol. 2007;22:1027-49.

# Symptoms of SMA (2)

## Symptoms arising from SMA (complications)

Particularly critical complications include symptoms related to breathing, eating and swallowing, and movement and posture.

- **Symptoms related to breathing**

  Weakened breathing muscles can result in breathing difficulty during sleep.
  Affected individuals may have difficulty coughing and clearing respiratory secretions and be prone to colds and other infections.
  “See saw breathing” may be present.

- **Symptoms related to eating and drinking**

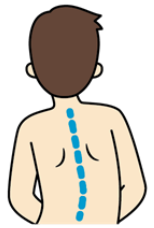
  Weak sucking ability and difficulty swallowing can result in aspiration when food enters the trachea in SMA type I.

  Weak chewing ability can result in fatigue and extra time required for meals.

- **Symptoms related to movement and posture**

  As the disease progresses, those with SMA type II, or with type III who are no longer able to walk, begin to have joint contracture and lose the ability to extend and bend the knees, ankles, elbows, and other joints.

  Those with SMA type II who sit extensively or with type III who lose the ability to walk in early adolescence experience weakening of the muscles around the spine, which can result in undulating, lateral curvature of the spine.



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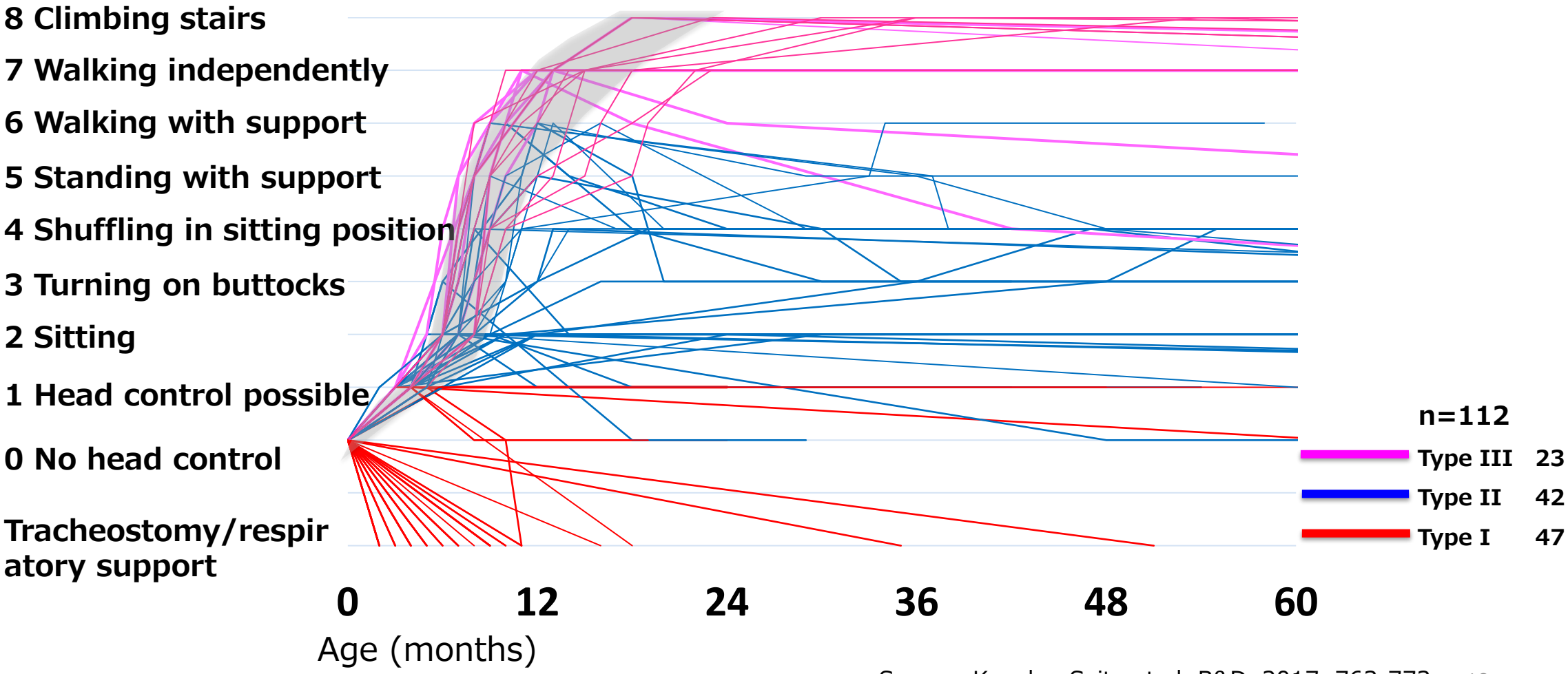
# Time Course of Motor Function of Japanese SMA Patients by Type

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

# Diagnostic Criteria for SMA (1)

## Diagnostic Handbook for Specific Pediatric Chronic Diseases

**Diagnosis of SMA requires a work-up of the clinical symptoms and genetic testing to confirm *SMN* gene mutations.**

### ❖ *Diagnostic Procedures*

**I. Major clinical symptoms**

1. Delayed motor development (types I and II)
2. Hypotonia
3. Progressive muscular weakness (required)
4. Fasciculation of fingers and tongue
5. Weak to absent deep tendon reflex

**II. Clinical symptoms absent in SMA**

1. Convulsions
2. Enhanced deep tendon reflex
3. Pathological reflex present

**III. Major test findings**

1. Neurogenic findings such as high-amplitude and polyphasic potentials in electromyography
2. **Survival motor neuron (*SMN*) gene mutations (Include report) (required)**

**IV. Other supportive findings**

1. Joint contracture/scoliosis
2. Eating/swallowing disorders
3. Respiratory disorders

SMA is confirmed by the absence of the symptoms in II and presence of the symptoms in I and III-2.

### ❖ *Project inclusion criteria*

Ongoing movement disorder or ongoing treatment with at least 1 of the following: cardiotonic agent, diuretic, anti-arrhythmic agent, peripheral vasodilator, beta blocker, pulmonary vasodilator, respiratory management (i.e., need for mechanical ventilation, tracheostomy, nasal airway), oxygen therapy, total parenteral nutrition, tube feeding

Information Center for Specific Pediatric Chronic Diseases (Spinal Muscular Atrophy). (https://www.shouman.jp/disease/instructions/11_17_038/) (accessed in September 2021).

# Diagnostic Criteria for SMA (2)

## MHLW Research Committee on Designated Diseases (Neurodegenerative Disease Research Committee)

**SMA is diagnosed according to these Designated Intractable Disease criteria when the condition or age is outside the scope of Specific Pediatric Chronic Diseases.**

**A. Clinical findings**

(1) Presence of lower motor neuron involvement due to loss and degeneration of ventral horn cells
- Muscular weakness
- (Symmetrical, proximal muscles > distal muscles, lower limbs > upper limbs, trunk, and limbs)
- Muscle atrophy
- Fasciculation of tongue and fingers
- Weak to absent tendon reflex

(2) Absence of upper motor neuron involvement

(3) Progressive course

**B. Laboratory test findings**

(1) Serum creatine kinase (CK) ≤ 10 times upper limit of normal

(2) Neurogenic findings such as high-amplitude and polyphasic potentials in electromyography

(3) Motor neuron conduction velocity ≥ 70% lower limit of normal

**C. Differential diagnosis**

(1) Amyotrophic lateral sclerosis
(2) Spinal and bulbar muscular atrophy
(3) Brain tumors and spinal cord diseases
(4) Cervical spondylosis, intervertebral disc herniation, brain and spinal tumors, syringomyelia, etc.
(5) Peripheral neurological diseases
(6) Polyneuritis (inherited or non-inherited), multifocal motor neuropathy, etc.
(7) Muscle diseases: Muscular dystrophy, polymyositis, etc.
(8) Infection-related lower motor neuron disorders: Post polio syndrome, etc.
(9) Paraneoplastic syndrome
(10) Congenital multiplex arthrogryposis
(11) Neuromuscular junction disorders

**D. Genetic tests**

The following mutations are present:
(1) ***SMN1* gene deletion**
(2) ***SMN1* gene point mutation or micromutation**
(3) *IGHMBP2* mutation
(4) Other gene mutation

Diagnostic categories:

Definite: (1) Lower motor neuron involvement, (2) no upper motor neuron involvement, (3) progressive course, criteria B1 to B3 met, and all conditions in C ruled out.

Definite: (1) Lower motor neuron involvement, (2) no upper motor neuron involvement, (3) progressive course, criterion D met, and all conditions in C ruled out.

Japan Intractable Diseases Information Center (Spinal Muscular Atrophy). (http://www.nanbyou.or.jp/entry/285) (accessed in September 2021).

# Number of SMA Patients in Japan: Results of an Epidemiological Investigation

Survey of clinical situation of spinal muscular atrophy in Japan, conducted from January 30 to March 31, 2018
Neurodegenerative Disease Basic Surveillance Team, MHLW (Head Investigator: Kenji Nakashima)

Questionnaires were sent to 1,936 departments of neurology and pediatrics and specialist institutes throughout Japan, and 1,005 were returned (51.9%)

## Incidence

**0.51 per 10,000 live births → 1 per 20,000 live births**

95% CI, 0.32-0.71

## Incidence of SMA type I

**0.27 per 10,000 live births → 1 per 40,000 live births**

95% CI, 0.17-0.38

## Prevalence

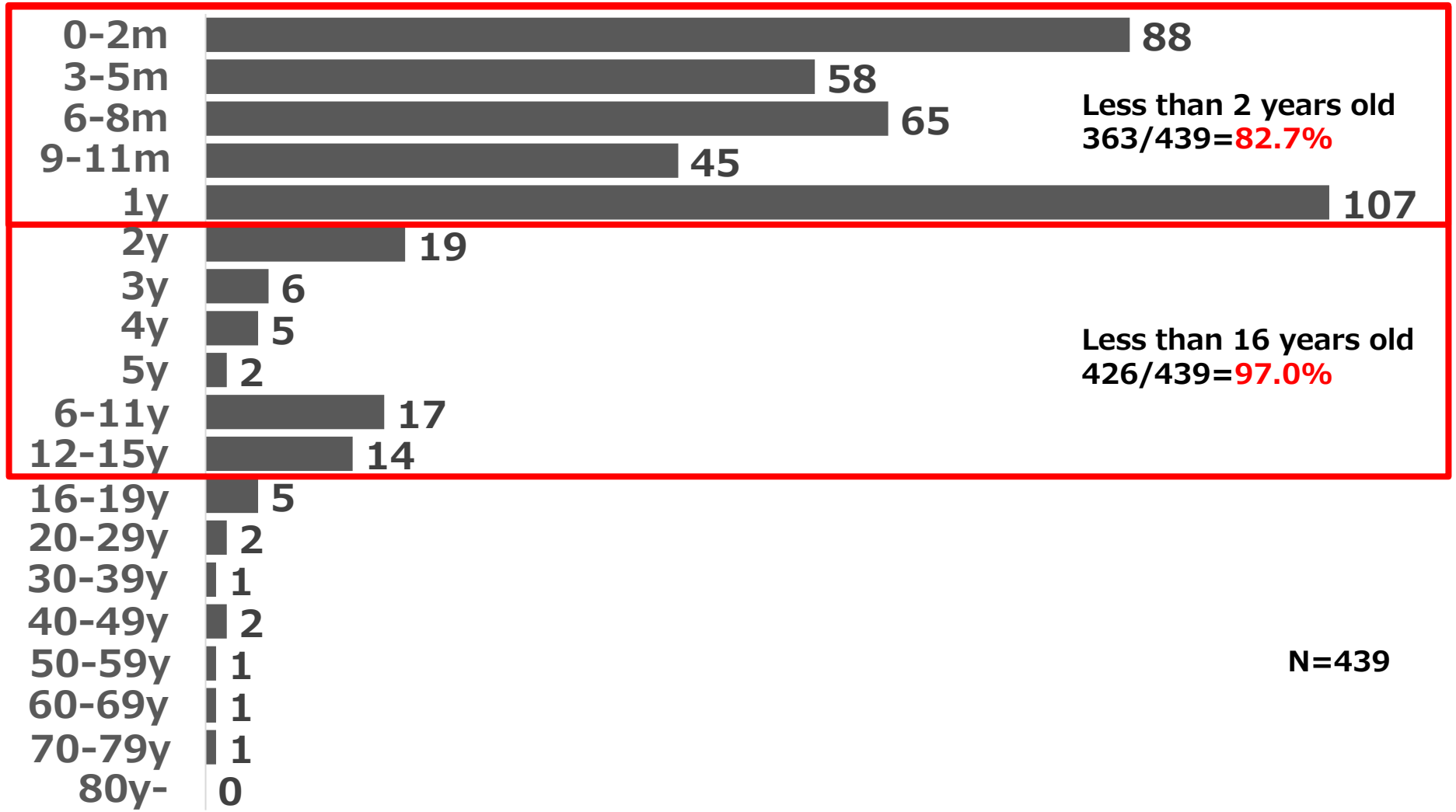
**1.17 per 100,000 people → 1 per 100,000 people**

95% CI, 0.89-1.45

Ito M, Yamauchi A, et al. Epidemiological investigation of spinal muscular atrophy in Japan. Brain Dev. 2021, in press

# Number of Patients by Age at Onset

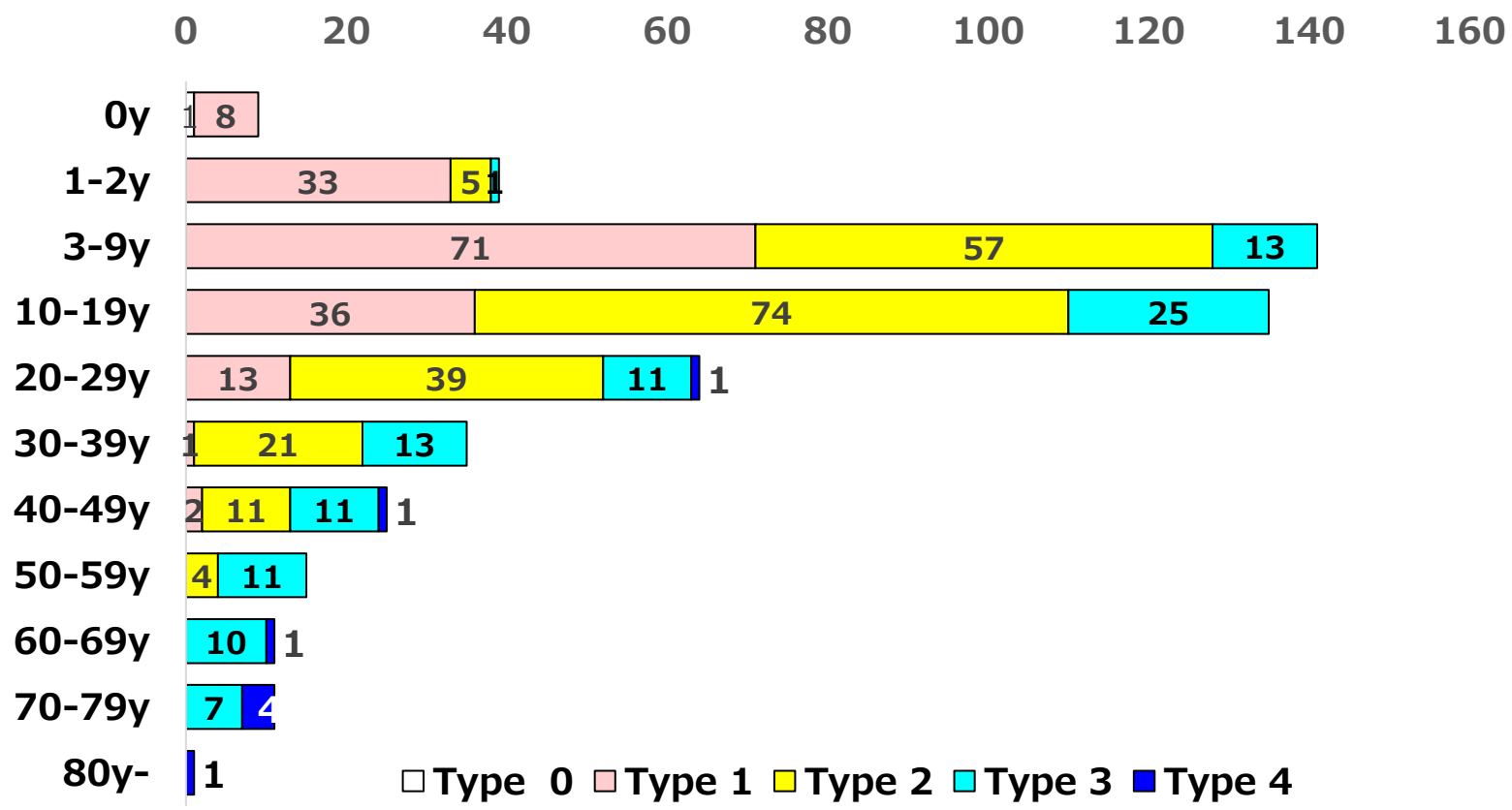
Survey of clinical situation of spinal muscular atrophy in Japan, conducted from January 30 to March 31, 2018
Neurodegenerative Disease Basic Surveillance Team, MHLW (Head Investigator: Kenji Nakashima)




Ito M, Yamauchi A, et al. Epidemiological investigation of spinal muscular atrophy in Japan. Brain Dev. 2021, in press

# Number of Patients by Age and Disease Type

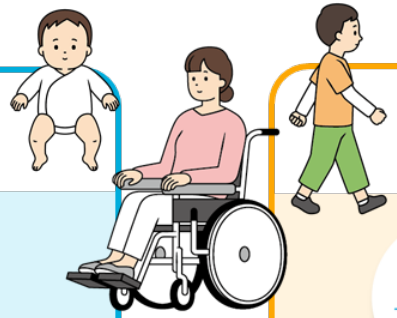
Survey of clinical situation of spinal muscular atrophy in Japan, conducted from January 30 to March 31, 2018
Neurodegenerative Disease Basic Surveillance Team, MHLW (Head Investigator: Kenji Nakashima)




Ito M, Yamauchi A, et al. Epidemiological investigation of spinal muscular atrophy in Japan. Brain Dev. 2021, in press

# How is SMA Managed?

- **SMA is managed by treating the cause of the disease and providing care for complications.**
- **Patients being treated must not be overexerted and must be monitored for infections.**



## Treating the cause of SMA

**Treating the cause of SMA with drugs**

## Providing care for complications

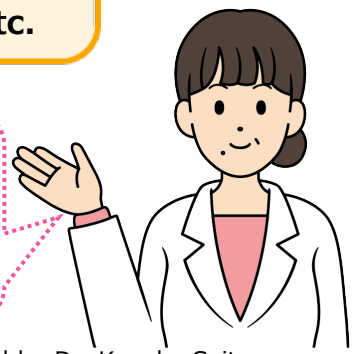
**Breathing-related care**

**Care related to eating and swallowing**

**Care related to movement and posture**

**etc.**

A treatment plan tailored to the individual patient is selected in a thorough consultation involving the patient, caregivers, and healthcare providers.



Have You Heard of Spinal Muscular Atrophy (SMA)? (July 2021) (Supervised by Dr. Kayoko Saito, Professor of Special Appointment, Institute of Medical Genetics, Tokyo Women's Medical University)

# Unmet Needs in SMA Treatment

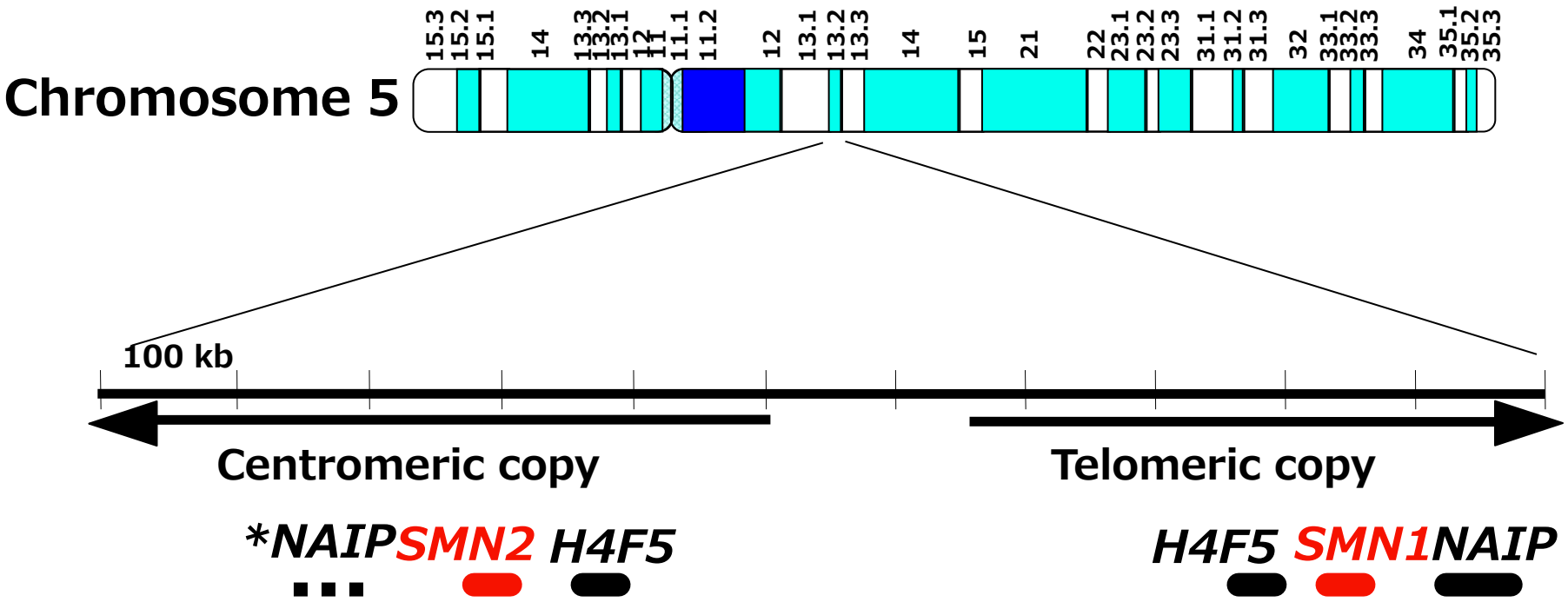
- **Patients may have to wait a long time for a definitive diagnosis and cannot receive treatment.**
  - ✓ There is a low awareness of SMA
  - ✓ The initial symptoms are easy to overlook
  - ✓ Differential diagnosis is time consuming, as many diseases have similar symptoms

- **Lack of treatment opportunities for patients who cannot take other medicines due to age or their scoliosis.**
  - ✓ Gene therapy indicated for patients younger than 2 years
  - ✓ Spinal injection is not feasible in some patients with severe scoliosis

- **Patients may be reluctant to start medication**
  - ✓ Balancing life (schooling or work) with treatment
  - ✓ Treatment (hospitalization or hospital visits) is time consuming
  - ✓ Treatment is available only at specialist institutes

# Gene Causing SMA = *SMN* Gene

**France: Lefebvre and Melki, Cell. 1995;80:155-65.**

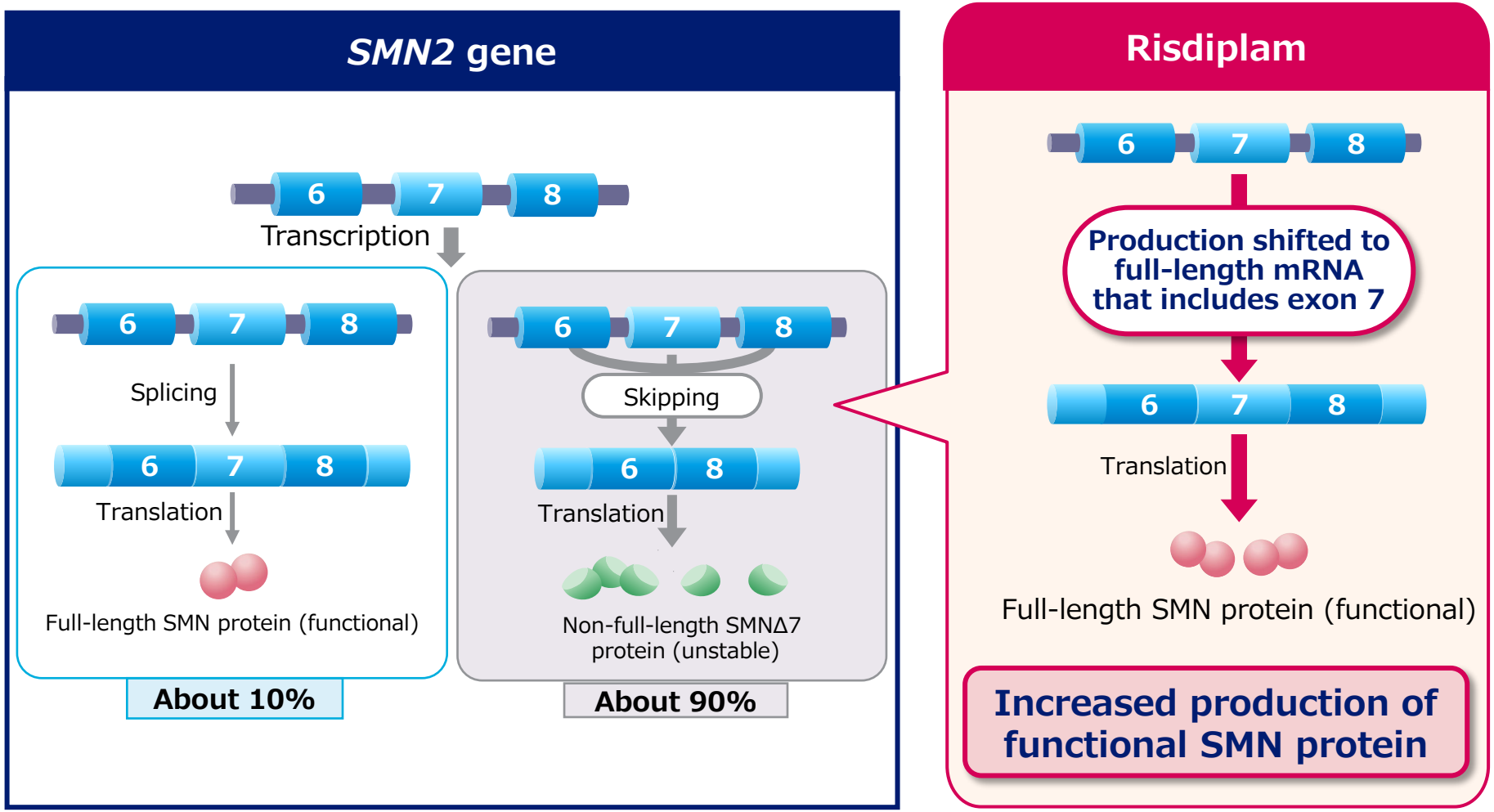



**SMN=survival motor neuron**

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

# Mechanism of Onset of SMA and Mechanism of Action of Evrysdi (risdiplam)

## In SMA (Illustrative example)




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

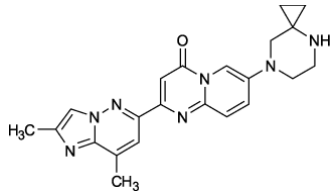
Data for evaluation in regulatory review [SMN protein function and action of the *SMN2* splicing modifier risdiplam in spinal muscular atrophy]



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

# Site of Action of Risdiplam

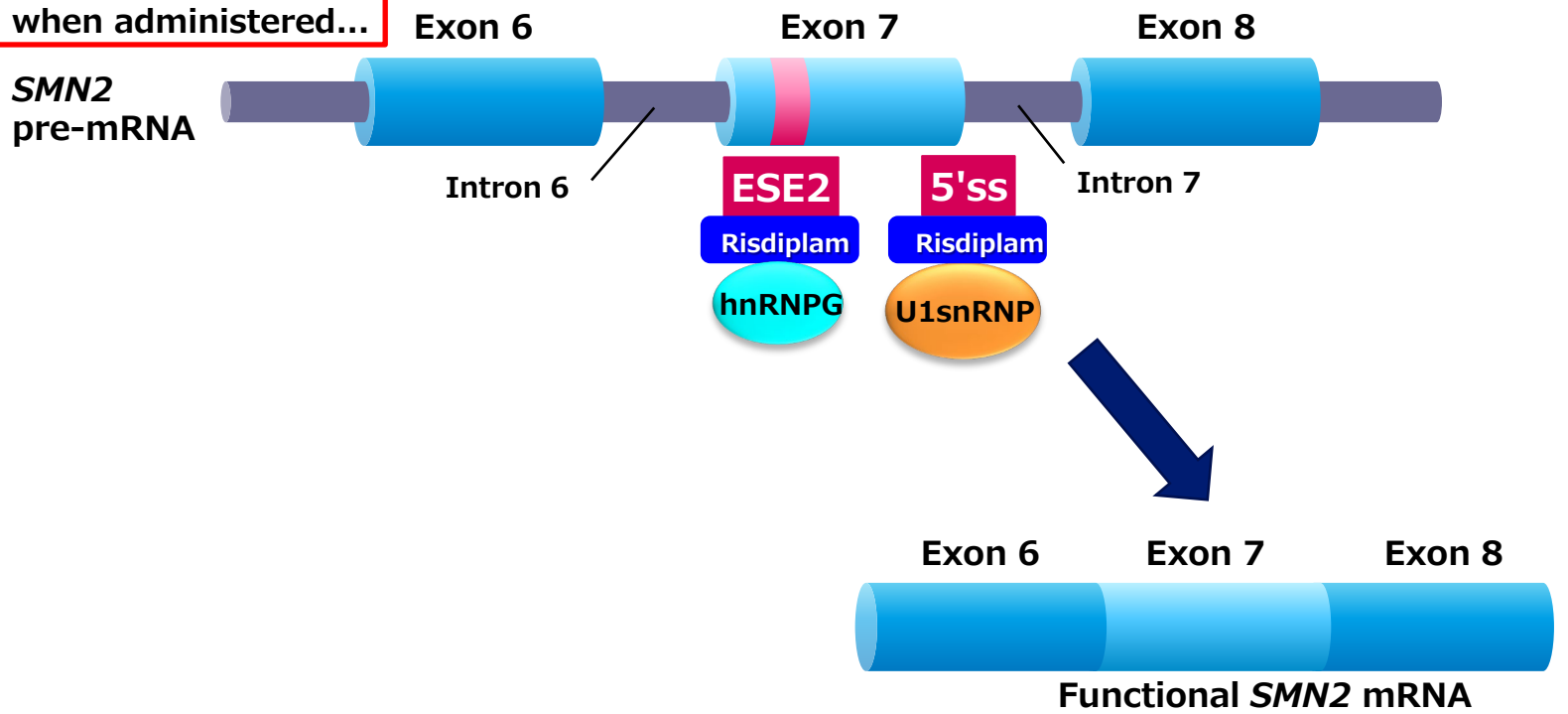
Structural formula



## Binds to 2 sites of *SMN2* pre-mRNA[1)]

- 5' splice site of intron 7 (**5'ss**)
- Exonic splicing enhancer 2 of exon 7 (**ESE2**)

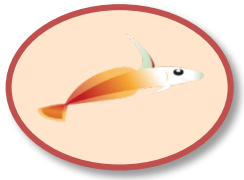
**Risdiplam**, when administered...




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.

# Clinical Trials of Evrysdi（Pivotal Trials）

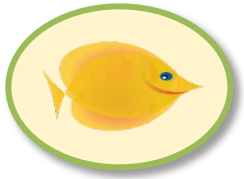


## FIREFISH Study

**Type 1 SMA**
**1–7 months old**

**Part 1**
**21 participants**
Safety, tolerability and PK/PD

**Part 2**
**41 participants**
Safety, efficacy at selected dose from Part 1



## SUNFISH Study

**Type 2 or 3 SMA**
**2–25 years old**

**Part 1**
**51 patients**
Safety, tolerability and PK/PD, (Evrysdi:placebo= 2:1)

**Part 2**
**180 patients**
Safety, efficacy at selected dose from Part 1 (Evrysdi:placebo= 2:1)

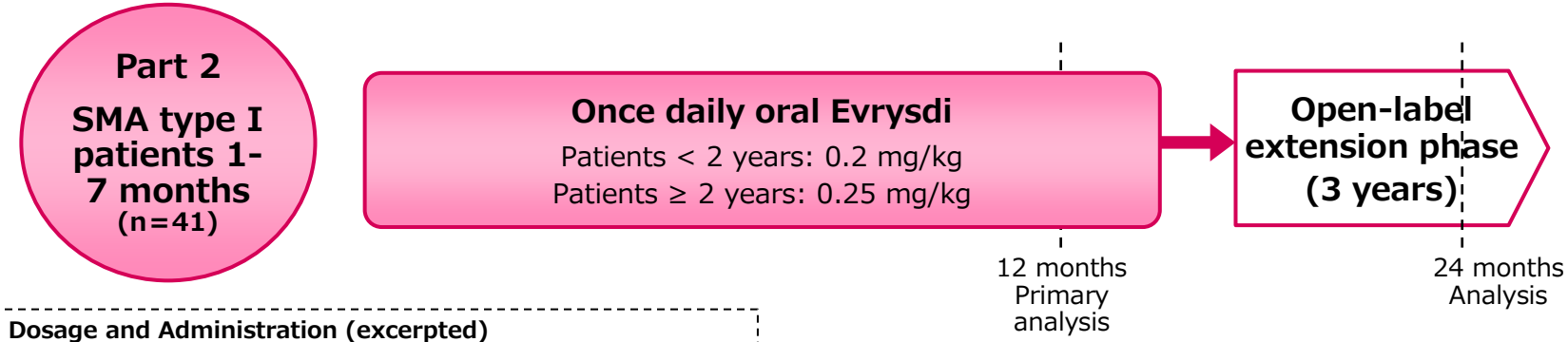
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially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

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

# Study Synopsis: Design and Administration Procedures

## Part 2

| | |
|---|---|
| **Design** | Multicenter, single-arm, open-label study |
| **Administration procedures** | Patients were started on once-daily oral treatment with the following Evrysdi dosage according to their age at enrollment. (Nursing patients were given treatment after breastfeeding and other patients were given treatment while eating.)<br>● Patients > 1 month to < 3 months: 0.04 mg/kg<br>● Patients ≥ 3 months to < 5 months: 0.08 mg/kg<br>● Patients ≥ 5 months: 0.2 mg/kg<br>The dosage was adjusted based on the pharmacokinetic data of all patients to achieve the target exposure (mean $AUC_{0\text{-}24h,ss}$ ≤ 2,000 ng･h/mL) and switched to:<br>● Patients < 2 years: 0.2 mg/kg<br>● Patients ≥ 2 years: 0.25 mg/kg<br>After 24 months of treatment, patients were entered into an open-label extension phase (3 years). |




**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)] partially modified

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

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.



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

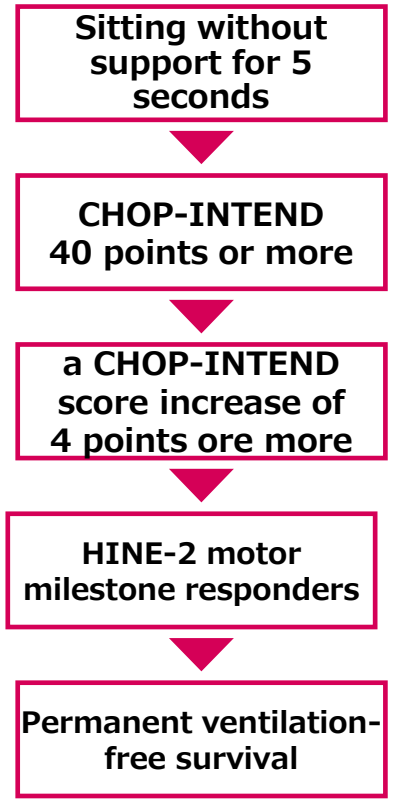
Global Phase II/III study (Part 2 of FIREFISH study)

# 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]

**Hierarchy of test of efficacy endpoints**





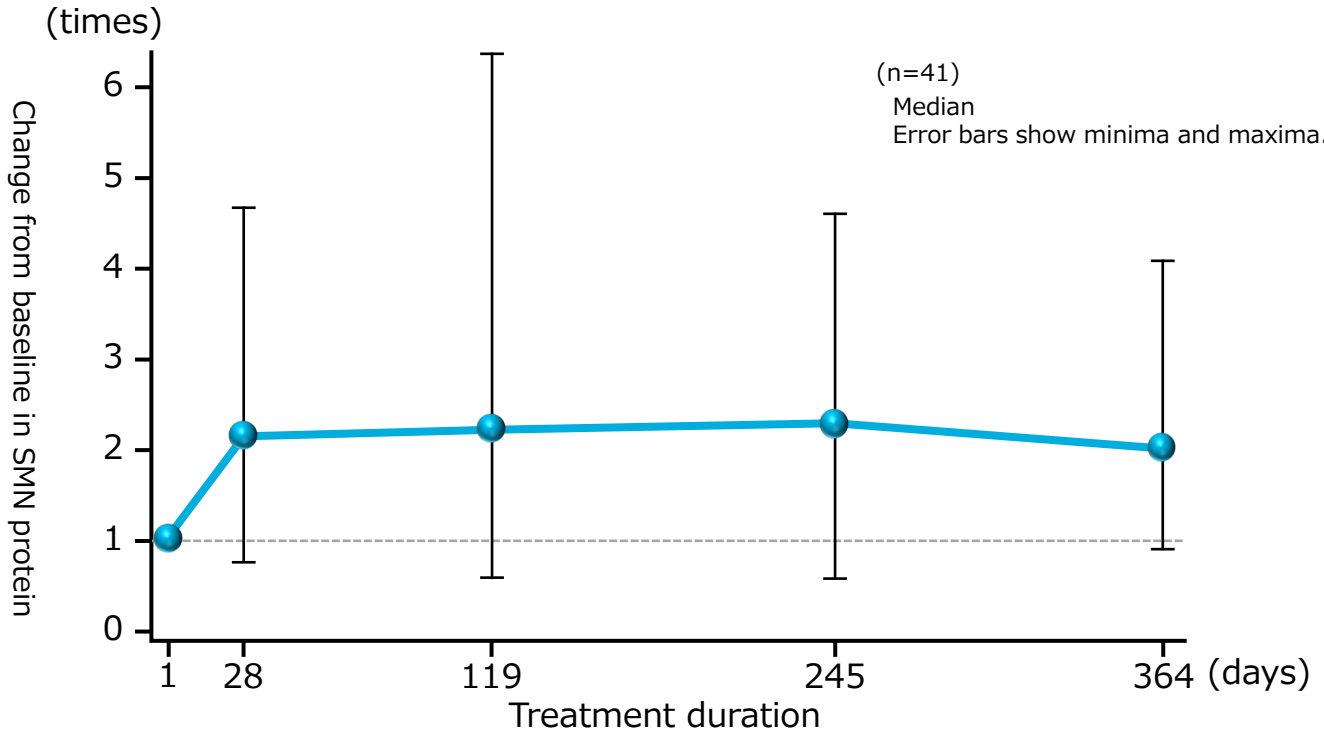

ITT: Intent-to-treat

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

# 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).**

## SMN protein following risdiplam treatment in Type I SMA




**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.



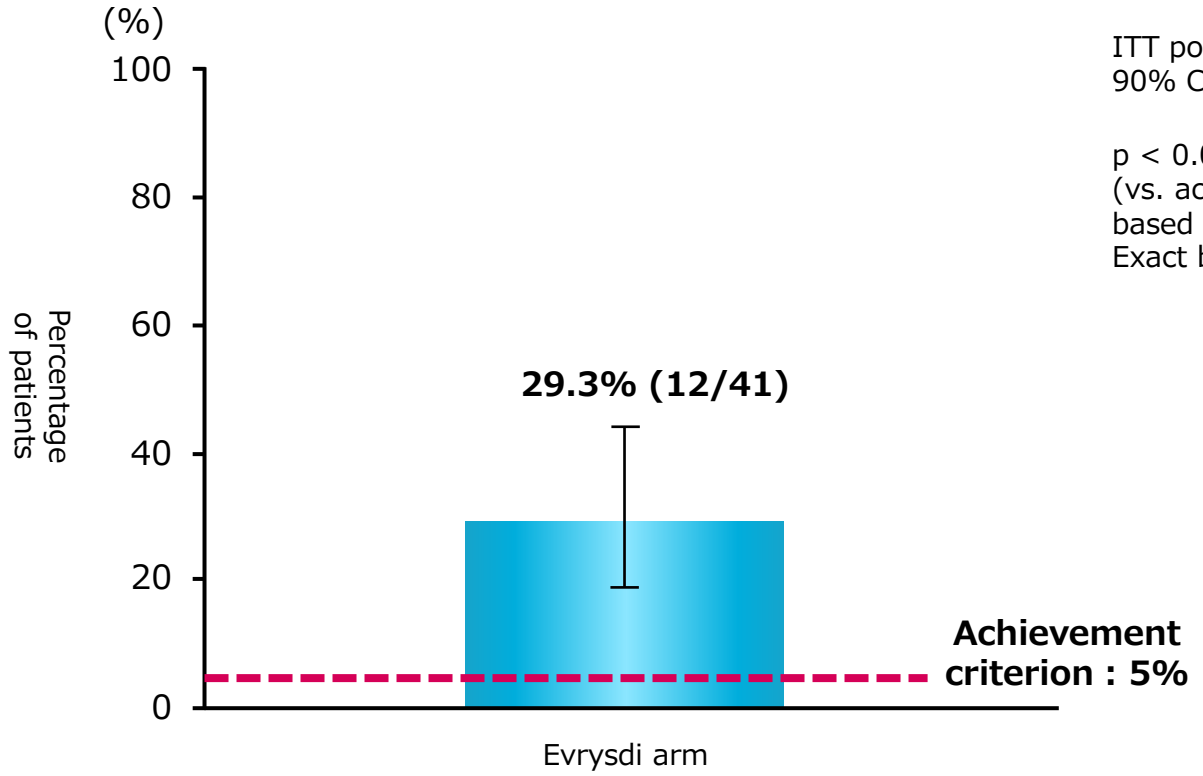
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

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

Primary endpoint

# Percentage of patients sitting without support for 5 seconds as assessed by BSID-III at Month 12

- **The percentage of patients sitting without support for 5 seconds was 29.3%. This demonstrated the superiority of Evrysdi over the predefined 5% achievement criterion based on natural history.**




ITT population
90% CI: 17.8 to 43.1

p < 0.0001
(vs. achievement criterion based on natural history)
Exact binomial test

**Assessment methods:** The ability to sit without support for 5 seconds was assessed by Item 22 of the BSID-III Gross Motor Scale. Patients not achieving sitting, patients not maintaining previously achieved sitting, study discontinuations, and deaths were considered non-responders.
**Natural history:** Untreated patients with Type I SMA cannot maintain a sitting position without support[1-3].
1) Finkel RS, et al. Neurology. 2014; 83: 810-7. 2) De Sanctis R, et al. Neuromuscul Disord. 2016; 26: 754-9. 3) Kolb SJ, et al. Ann Neurol. 2017; 82: 883-91.



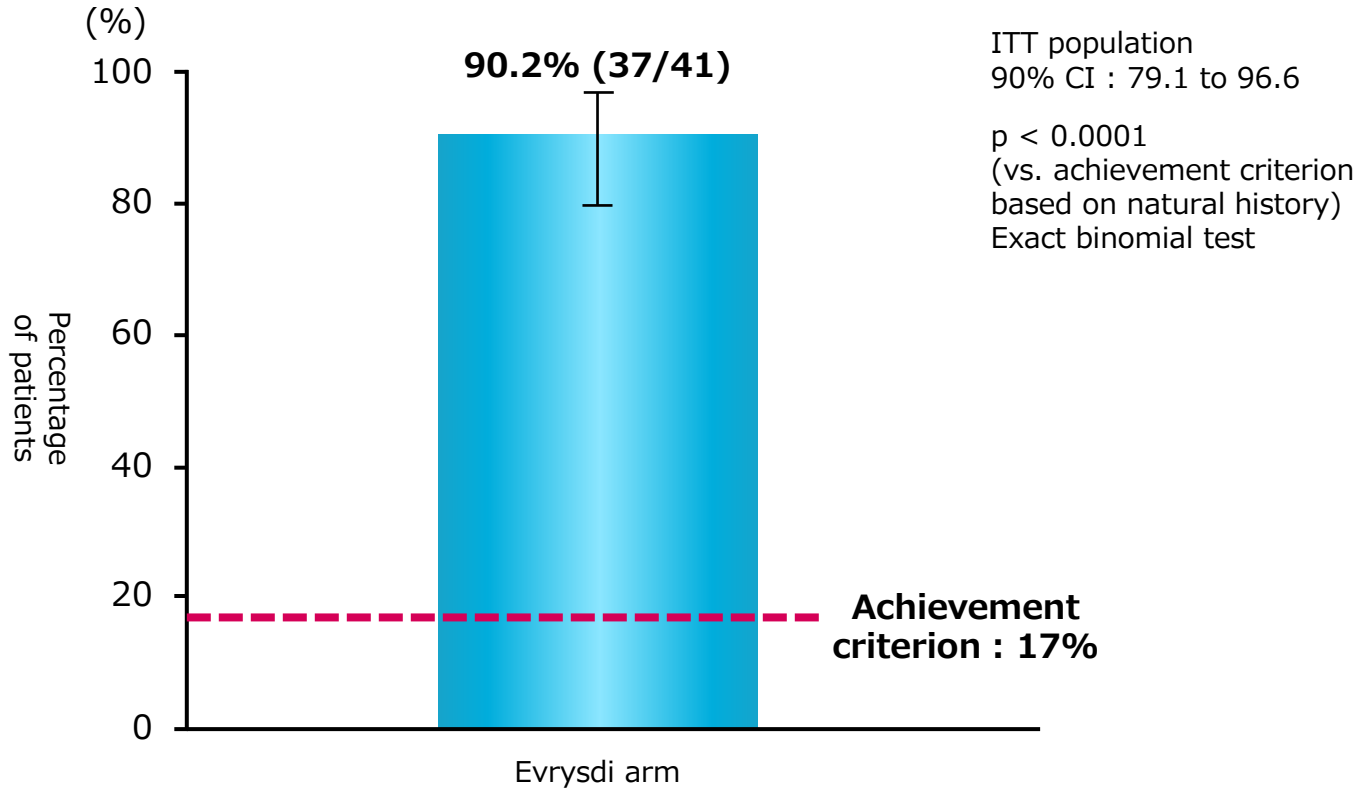
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

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

Secondary endpoint

# Percentage of patients achieving an increase from baseline in CHOP-INTEND total score of 4 points or more at Month 12

- **The percentage of patients achieving an increase from baseline in CHOP-INTEND total score of 4 points or more was 90.2%. This was statistically significantly higher than the predefined 17% achievement criterion based on natural history.**




ITT population
90% CI : 79.1 to 96.6

p < 0.0001
(vs. achievement criterion based on natural history)
Exact binomial test

**Assessment methods:** The percentage of patients achieving a CHOP-INTEND total score of at least 40 and percentage of patients achieving an increase from baseline in CHOP-INTEND total score of 4 points or more were calculated.
**Natural history:** A cumulative analysis of 3 natural history studies in patients with Type I SMA identified in papers published from 2010 to May 2019 revealed that 2 of 30 patients with two *SMN2* gene copies had a CHOP-INTEND total score of at least 40 points at baseline[1]. The change in total scores, which differed according to the time of onset and severity, ranged from -1.71 to -1.02 points/month[1]. 1) Mercuri E, et al. Orphanet J Rare Dis. 2020; 15: 84.



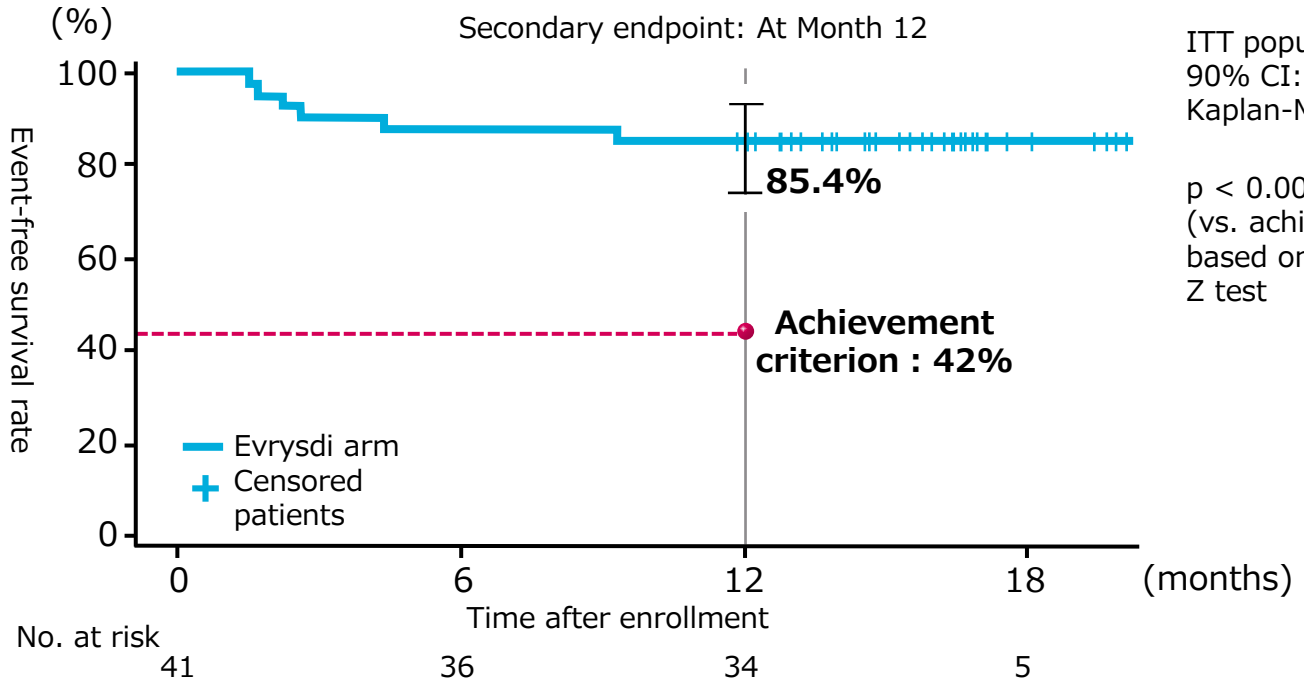
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study )]

## 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.**




ITT population
90% CI: 73.4 to 92.2
Kaplan-Meier methodology

$p < 0.0001$
(vs. achievement criterion based on natural history)
Z test

**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.



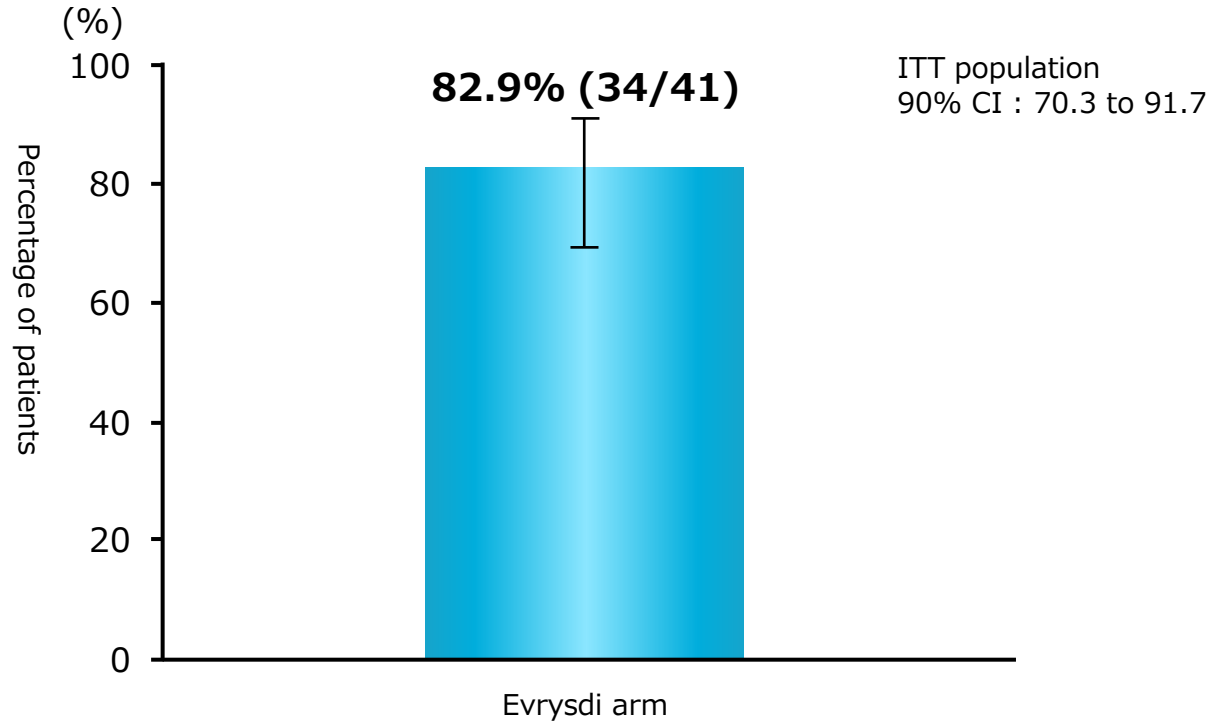
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified

## 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.)**




ITT population
90% CI : 70.3 to 91.7

**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 )]

## 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.



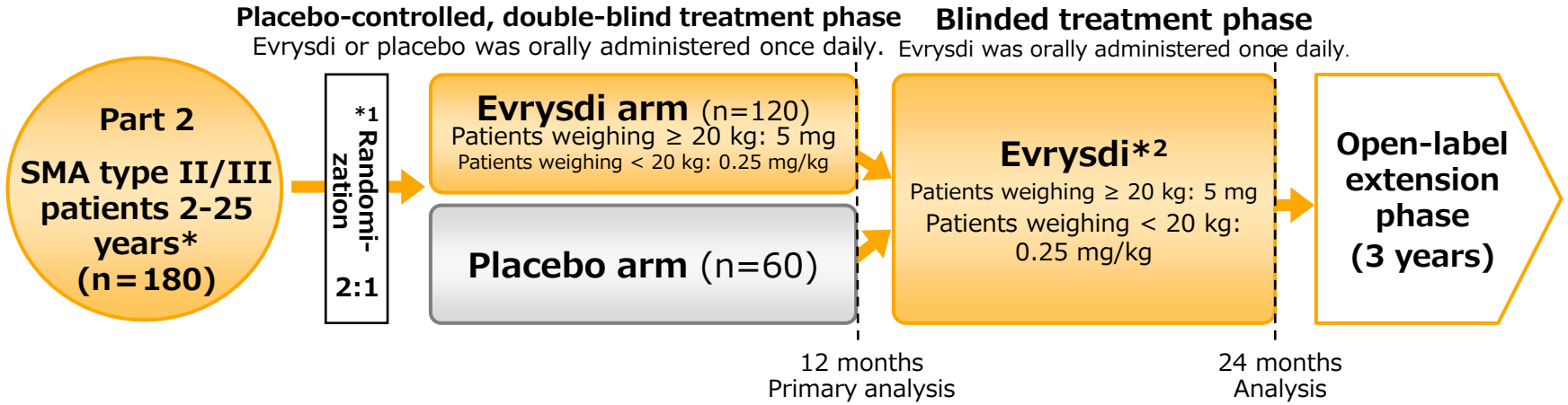
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type I Patients (BP39056 Study)] partially modified

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).



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

## 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%) |



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

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 (> 40º) | 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.



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

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

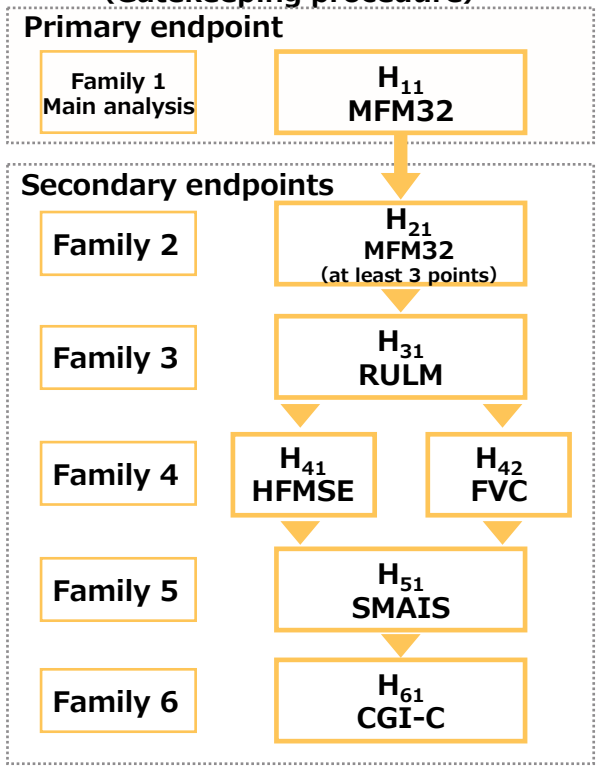
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)]

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.)<br>● 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).<br>● 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.<br>● A gatekeeping procedure was applied to the primary endpoint and the six main secondary endpoints to control the multiplicity of tests (right figure).<br>● 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.<br>● For Family 4, the truncated Hochberg method with a truncation parameter of 0.95 was used.<br>● 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] |

**Hierarchy of test of efficacy endpoints (Gatekeeping procedure)**




H : null hypothesis

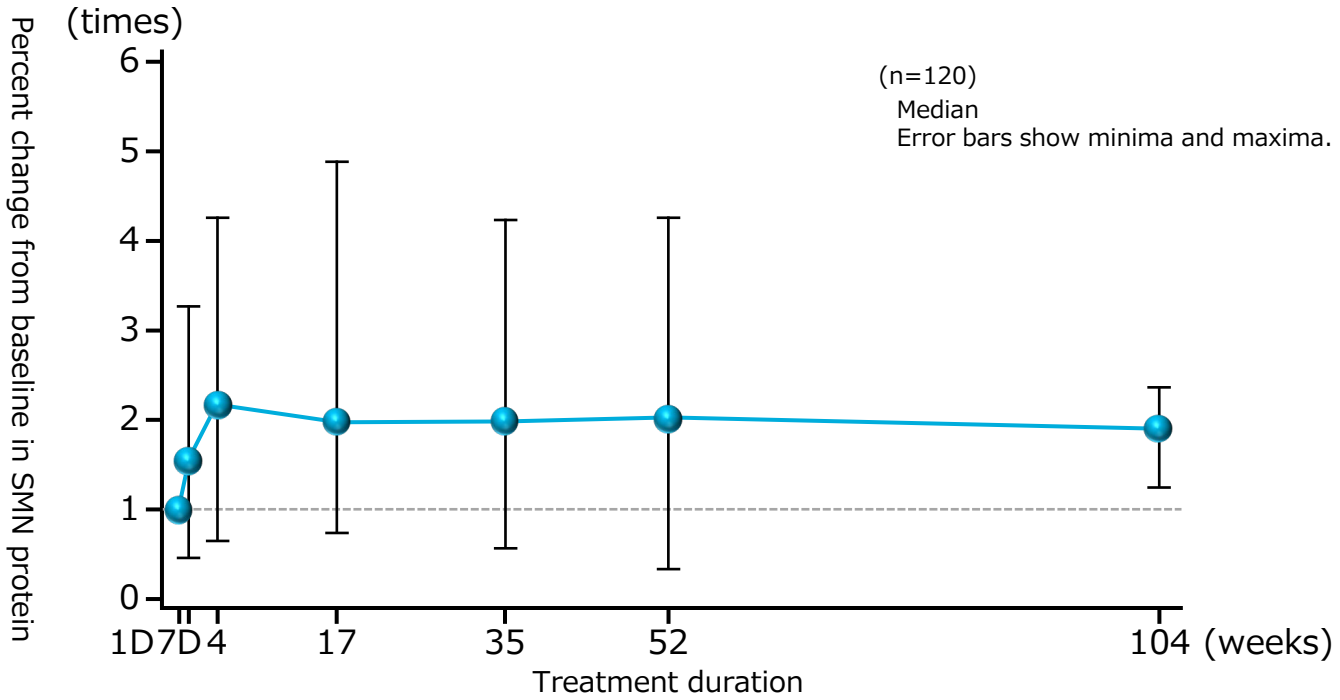


Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

# 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.



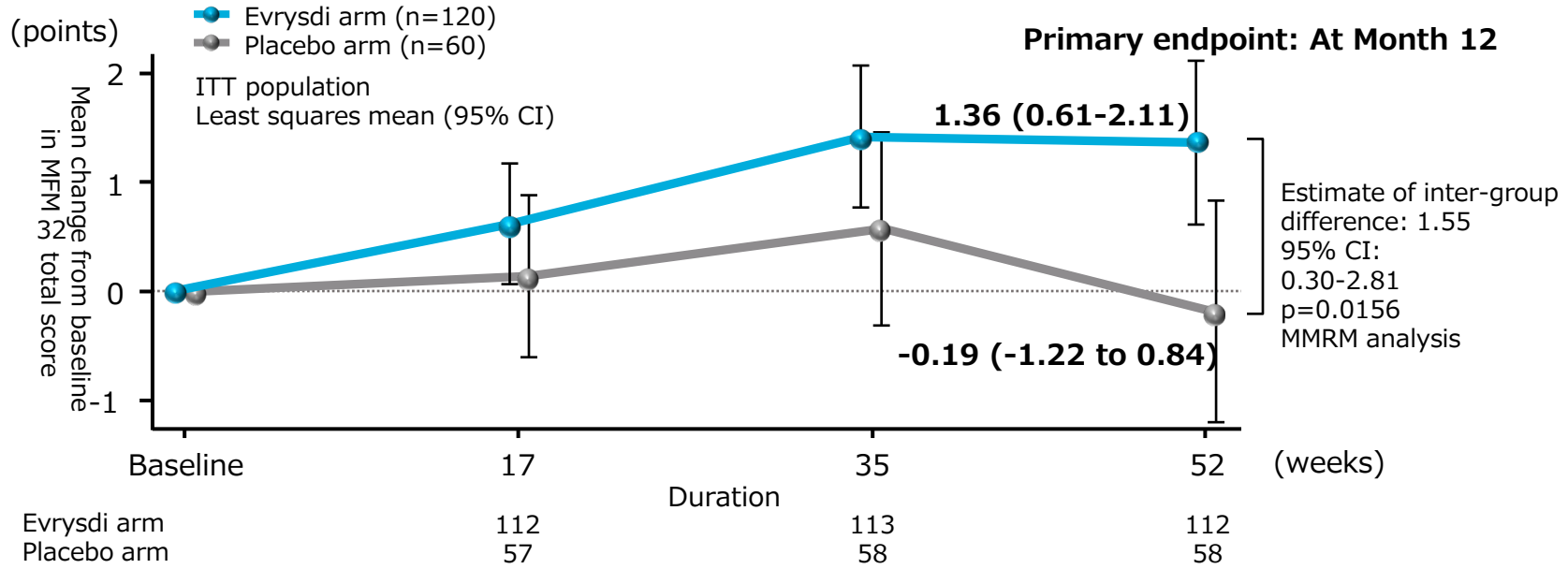
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

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

Primary endpoint

# Change from baseline in MFM32 total score at Month 12

- **The change from baseline in MFM32 total score was 1.36 points in the Evrysdi arm and -0.19 points in the placebo arm. The Evrysdi arm achieved a statistically significant improvement over the placebo arm.**




Number of patients at baseline: 115 in Evrysdi arm and 59 in placebo arm

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

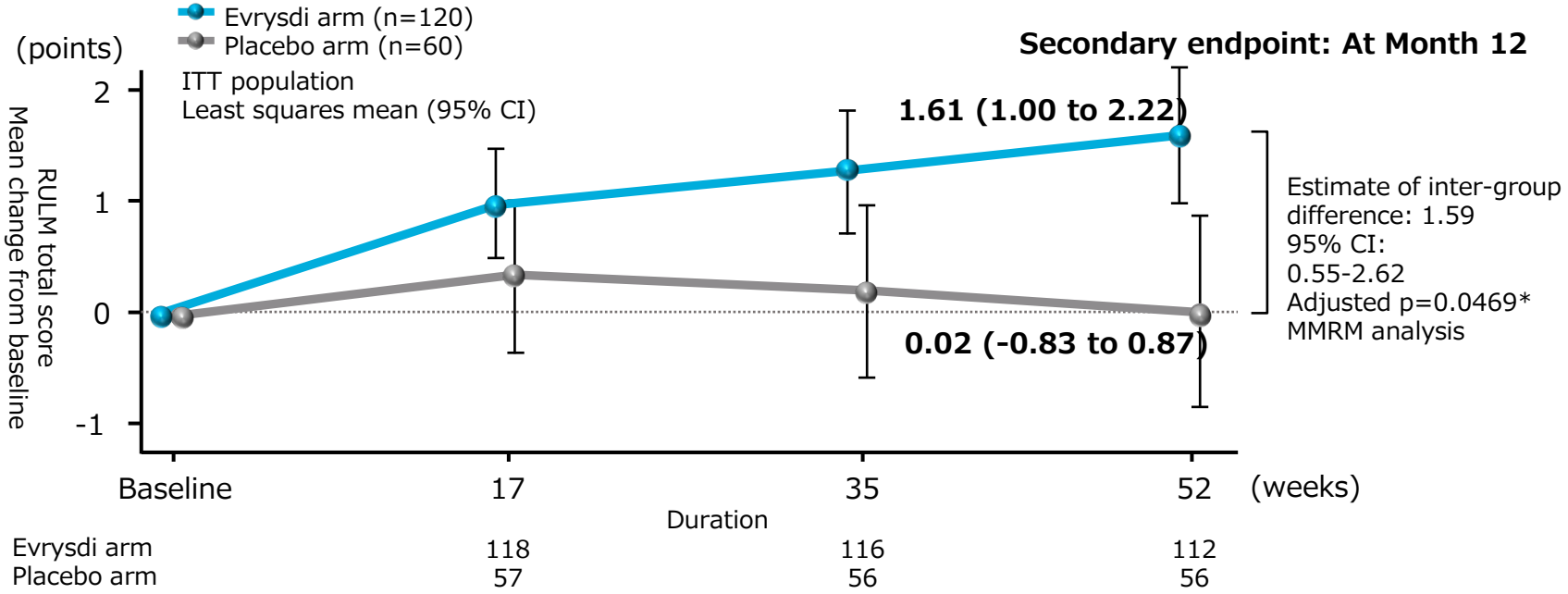
**Assessment methods:** MFM32 total scores were assessed and the change from baseline was calculated.

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

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

# Secondary endpoint Change from baseline in RULM total score at Month 12

- **The change from baseline in RULM total score was 1.61 points in the Evrysdi arm and 0.02 points in the placebo arm. The Evrysdi arm achieved a statistically significant improvement over the placebo arm.**




Number of patients at baseline: 119 in Evrysdi arm and 58 in placebo arm

*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:** RULM total scores were assessed and the change from baseline was calculated.



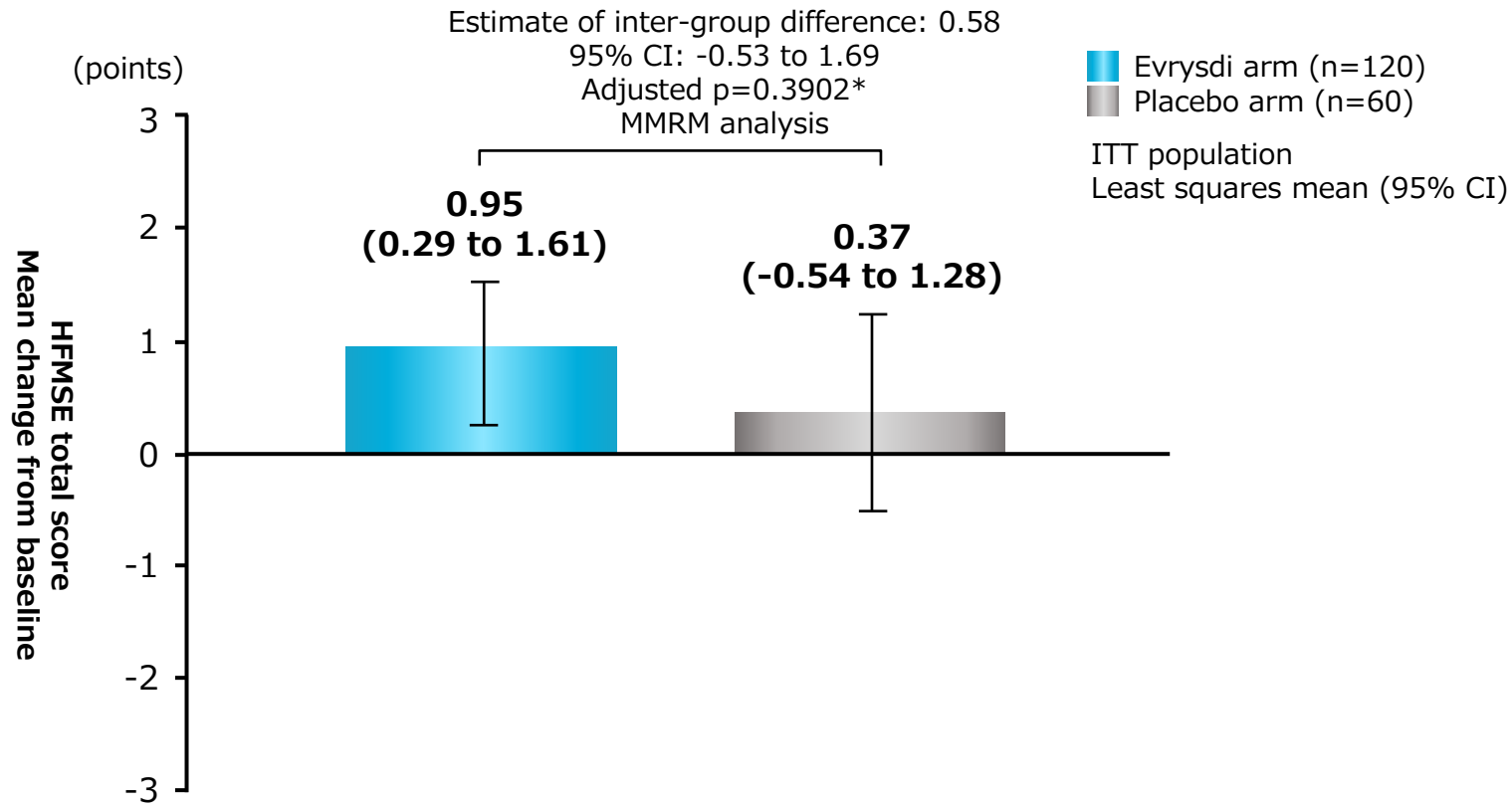
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)] partially modified

## 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)]

## 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.



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

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 ADR/Number of AD** | | |
| Gastrointestinal dis | | |
| Nausea | | |
| Mouth ulceration | | |
| Abdominal pain u | | |
| Faeces soft | | |
| Skin and subcutane disorders | | |
| Dermatitis acneifc | | |
| Eczema | | |
| Rash | | |
| Rash maculo-papu | | |
| Dry skin | | |
| Skin discolouratio | | |
| Dermatitis herpeti | | |
| Infections and infes | | |
| Upper respiratory infection | | |
| 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) | Placebo arm (n=60) |
|---|---|---|---|
| Nervous system | /2 | /1 | 1 (1.7%)/1 |
| | | | 1 (1.7%) |
| | | | 0 |
| | | | 0 |
| | | | 0 |
| | | | 1 (1.7%)/3 |
| | | | 1 (1.7%) |
| | | | 1 (1.7%) |
| | | | 1 (1.7%) |
| | | | 0 |
| | | | 0 |
| | | | 1 (1.7%)/1 |
| | | | 1 (1.7%) |
| | | | 0 |
| | | | 0 |

**[Adverse events]**

Evrysdi arm: 789 events in 111 of 120 patients (92.5%),
Placebo arm: 354 events in 55 of 60 patients (91.7%)

A serious adverse event occurred in 24 patients (20.0%) in the Evrysdi arm and 11 patients (18.3%) in the placebo arm.
No adverse events leading to withdrawal or deaths were reported.

**[Adverse drug reactions]**

Evrysdi arm: 21 events in 16 of 120 patients (13.3%),
Placebo arm: 9 events in 6 of 60 patients (10.0%)

Common ADRs were nausea, mouth ulceration, upper respiratory tract infection, and headache each in 2 patients (1.7%) in the Evrysdi arm.
ADRs in the placebo arm included upper abdominal pain, dermatitis herpetiformis, bronchitis, and respiratory tract infection each in 1 patient (1.7%) in the placebo arm.

No serious ADR or ADR leading to withdrawal was reported.

Safety analysis set
MedDRA version 22.0
Source: Materials of Evrysdi for evaluation in regulatory review [Global Phase II/III study in SMA Type II and III Patients (BP39055 Study)]

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.



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

# 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

# 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.

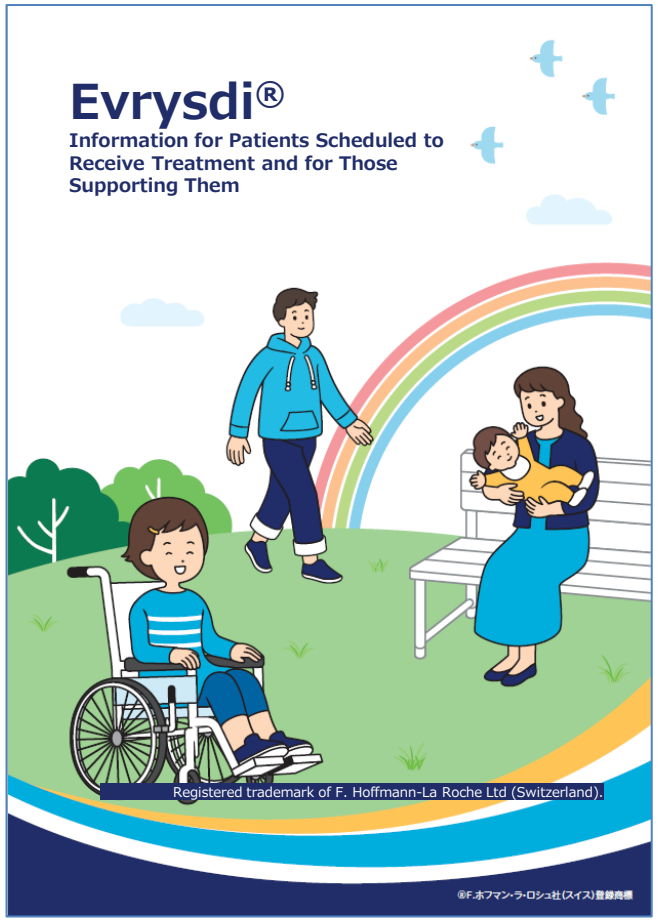
## Male patients who have a partner of childbearing potential

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

# 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)

# 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.

# Conclusion

1) Spinal muscular atrophy (SMA) is a refractory disease that causes progressive muscle atrophy and motor dysfunction due to degeneration of motor neurons of the spinal cord.

2) A regulatory approval was obtained as a result of evaluation of efficacy and safety in the global phase II/III study of Evrysdi, a disease modifier for type I, II and III SMA.

3) Evrysdi is the first oral drug for SMA.

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

# Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.
Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

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# INNOVATION BEYOND IMAGINATION