A clinical trial* to establish the efficacy and safety of risdiplam for children and adults with SMA Types 2 and 3 (SUNFISH)

Date of preparation: January 2021
M-XX-00003979

*Referred to as a 'study' throughout this summary document. See the end of the document for the full title of the study.

About this summary

Thank you to those who took part in this clinical study. You have helped researchers to answer important questions about the study drug risdiplam and its impact on the progression of SMA in children and adults.

This document provides a summary of the 12-month results of Parts 1 and 2 of the SUNFISH study. The study started in October 2016 and met its key endpoints in September 2019, when the last person to take part had completed 12 months of treatment with risdiplam, the drug being investigated in this study. The study will continue up to 5 years after the last patient has enrolled in the study. This document has been written for members of the public, as well as the patients and families participating in the study.

Contents of the summary

Key information about this study

This study was carried out in two parts:

Part 1 (dose-finding part) had three purposes: to define the optimal dose of the drug to give to people with SMA Types 2 or 3, to identify any side effects; and to assess whether the drug has a positive impact on SMA.

Part 1 of the study began as **'double-blind and randomized'** which means that participants are randomly assigned to receive either the trial drug or a placebo. A placebo is a dummy drug with no active ingredient and which has no real physical effect on the individual. Neither the researchers nor the patient families knew which treatment was being given. For the first 12 weeks of the study, participants were given either risdiplam at various doses or **'placebo'**. At the end of 12 weeks all participants were given risdiplam for at least 12 months.

Part 2 (confirmatory part) was designed to find out more detailed information about the efficacy of the drug, any side effects and if the drug has a positive impact on quality of life for people with SMA Types 2 or 3. Part 2 uses the dose chosen from Part 1 of the study.

Part 2 of the study was also **'double-blind and randomized'**. Some participants were given risdiplam and some were given placebo. Neither the researchers nor the patient families knew which group received risdiplam and which group was given a placebo. This allowed for a fair comparison of the results. Those receiving placebo were switched to risdiplam after 12 months.

The study was described as a 'pivotal' trial, which means its aim was to demonstrate the efficacy and safety of risdiplam in order to support regulatory approval by health authorities to make the drug available to patients around the world.

1. General information about the study

Why was this study carried out and what is SMA?

When this study began, there were no available treatment options for people with SMA. SMA is a rare, inherited, neuromuscular disease, which destroys muscle-controlling nerve cells called motor neurons. It affects the central nervous system (brain and spinal cord), peripheral nervous system, and voluntary muscle movement (skeletal muscle). SMA causes progressive muscle weakness and loss of movement due to muscle wasting (atrophy).

SMA is caused by a change (mutation) in a specific motor neuron gene called ***SMN1 (survival of motor neuron 1).*** *SMN1* produces a protein called **survival motor neuron (SMN)** that is critical to the function of the nerves that control the muscles. Without SMN, those nerve cells cannot properly function and eventually die, leading to debilitating and sometimes fatal muscle weakness. People with SMA have low levels of SMN and are dependent on a related gene called ***SMN2*** as a 'back-up'. However, *SMN2* produces only approximately 10% of the working ('functional') SMN protein that the body needs. Without sufficient SMN protein, motor neurons degenerate and become non-functional. The more copies of the *SMN2* gene an individual has, the more SMN protein they can produce, which makes the symptoms of SMA less severe.

Individuals with SMA have difficulty performing the basic functions of life, including breathing and swallowing. SMA does not affect cognition (ability to understand), emotional development or learning ability. The severity of SMA varies among individuals and depends on a range of factors, including age of onset. There are **four primary types of SMA**, based on the age that symptoms begin and the highest physical milestone achieved. Some clinicians also refer to a Type 0 (also known as prenatal onset SMA). Type 0 is the most severe form of SMA and affects babies that are still in the womb.

The four primary types of SMA

SMA classification	Age of onset	Impact
Type 1	Birth – 6 months	Babies with this form of SMA will never sit independently
Type 2	6 –18 months	Babies are typically able to sit but not to stand
Type 3	18 months onwards	Children can typically stand and walk. However, many children lose the ability to walk in early life
Type 4	18 years onwards	Develops post adolescence. Causes mild motor impairment

The symptoms of **Type 2 SMA** start showing under the age of 18 months and include weakening of muscles, difficulty swallowing, difficulty breathing, curving spine, stiff joints, difficulty coughing and trembling hands. People with **Type 2 SMA** are able to sit, but are unable to walk independently.

Type 3 SMA starts to show after the age of 18 months but the actual age of onset is very variable and may not happen until late childhood or early adulthood. Symptoms include muscle aching, fatigue and difficulty in walking, trembling hands, weaker leg muscles compared to the arms and sometimes difficulty breathing during sleep. People with this form of SMA are able to stand and walk until late childhood and sometimes into adulthood, depending on how early their symptoms begin.

The impact of SMA on life expectancy varies according to the classification. Babies with the most severe types of SMA (Types 0 and 1) have a very short life expectancy: most would not live beyond two years without treatment. Individuals with Type 4 SMA usually have a normal life expectancy.

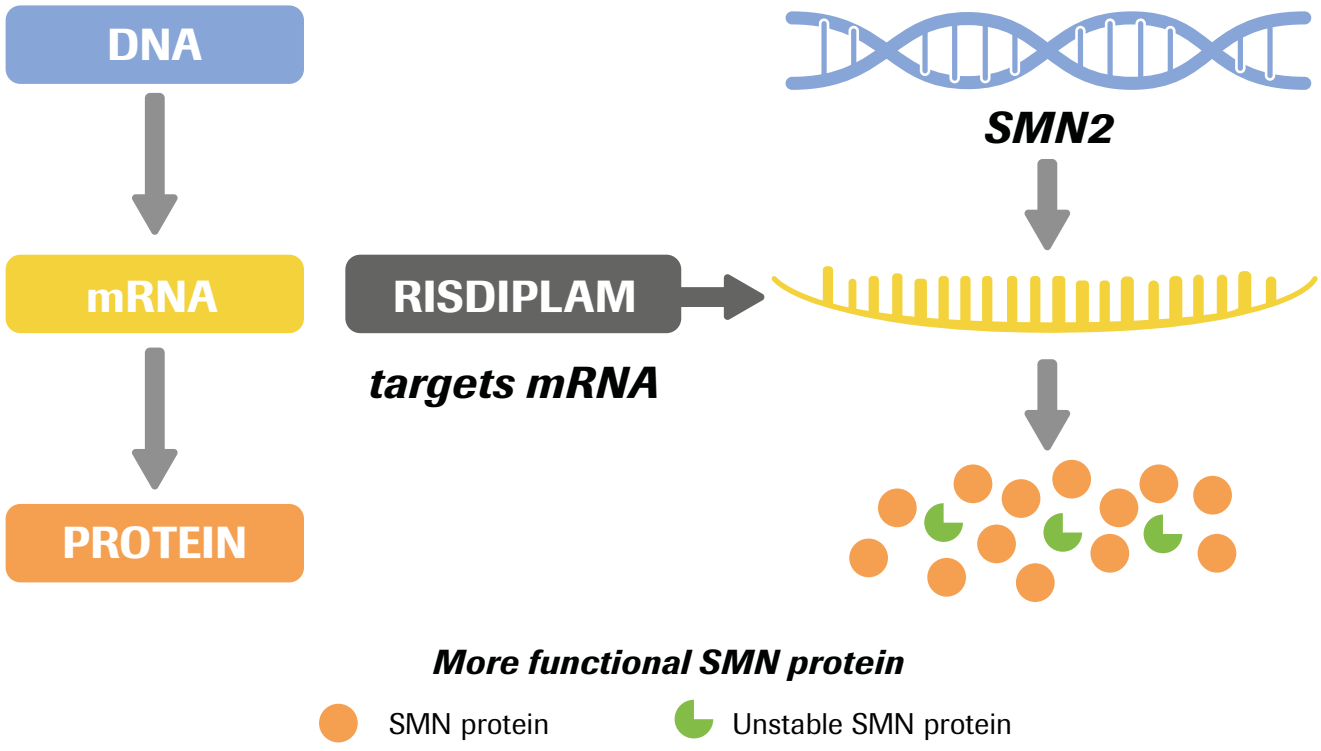
The goal of new treatments is to address the underlying cause of the disease, improve life expectancy, maintain vital motor functions, stabilize functionality and enhance quality of life. Even small changes such as a modest improvement in functionality or prevention of deterioration can have a meaningful effect on peoples' lives.

The SUNFISH study was carried out to understand the safety and efficacy of ridiplam in people with **Type 2 or Type 3 SMA**.

What is risdiplam and how does it work?

Risdiplam is the drug that is studied in SUNFISH. Risdiplam is a liquid taken once a day by mouth (orally) or, for people with difficulty swallowing, by feeding tube.

Risdiplam is designed to target the *SMN2* gene and help it to produce more functional SMN protein. The aim is to prevent motor neuron degeneration and preserve muscle function. Risdiplam is distributed throughout the body, raising the levels of SMN protein in various organs and not only the central nervous system (brain and spinal cord).



In individuals with SMA, the *SMN2* gene cannot produce enough functional SMN protein because of the abnormal 'splicing' of the gene. Splicing is a process where some parts of the gene called introns are removed and others, called exons, are joined together. Risdiplam is designed to control this abnormal splicing of the *SMN2* gene and to allow production of a functional SMN protein.

How was the study designed?

The study was designed in two parts:

- An **exploratory dose-finding part (Part 1)** and
- A **confirmatory part (Part 2)** to demonstrate the efficacy and safety of risdiplam at the dose selected in Part 1, compared to placebo

Both parts of the study were **'double blind and randomized'**. This means that the participants are randomly chosen by a computer to receive either the trial drug or a 'placebo'. A placebo is a dummy drug with no active ingredient and which has no real physical effect on the individual. Neither the researchers nor the patient families knew which treatment participants were given.

Part 1: The key objective was to assess the safety and efficacy of risdiplam in the body at different doses. For the first 12 weeks of the study, different groups of people received either different doses of risdiplam or placebo. After the first 12 weeks, the patients on placebo started to receive risdiplam.

Part 2: Two-thirds of those that took part in Part 2 of the study were chosen by a computer at random to receive risdiplam at the dose selected after Part 1 and the other third received placebo for 12 months. Neither the patient nor the study team knew whether each participant was receiving risdiplam or the placebo. A double blind and randomized trial reduces the possibility of any bias when comparing the results. In this trial the sponsoring company (Roche) only discovered which participants were receiving the active treatment at the end of 12 months for the last patient enrolled in the study. However, in case of emergency, the investigators always have the option to break the code and reveal what a specific participant is receiving.

Participants in both parts of the SUNFISH trial continued receiving risdiplam at the dose selected in Part 1 for 24 months. They then had the option to enter an 'open label' phase for a duration of three years, when both researchers and participants are aware of which treatment is being given. Both parts of the trial are ongoing and will complete after the last patient has received up to five years of treatment.

What were the aims of the study?

The SUNFISH study aimed to answer a number of different questions about risdiplam, as shown in the table on the next page.

In order to understand and evaluate the effects of risdiplam and help answer the different questions set by researchers, the study included a number of outcome measures. These take the form of primary outcome measures (**'primary endpoints'**), secondary outcome measures (**'secondary endpoints'**) and **'exploratory endpoints'**.

A **primary endpoint** is a specific measure that aims to address the main research question. If met or verified at the end of a pre-specified study duration, that will define the success of the clinical trial. **Secondary endpoints** are there to provide additional information to evaluate the effects of the intervention that is being investigated in a clinical study, in this case treatment with risdiplam. A clinical study may have more than one secondary outcome measure. Lastly, **exploratory endpoints**, which were also included in the study, are generally evaluated less formally (from a statistical point of view) than primary and secondary endpoints.

As part of these endpoints, specific scales were used to measure movement ability in the participants of this study. You can find a full description of the scales on page 17 of this document.

Summary of the primary and secondary endpoints for Parts 1 and 2

Part 1 Primary and Secondary Endpoints

The main question researchers wanted to answer (known as the 'primary endpoint')	Additional questions the researchers wanted to answer (known as 'secondary and exploratory endpoints')
What is the recommended dose of risdiplam for people with SMA Types 2 and 3, to take forward into Part 2 of the study?	What changes in blood levels of SMN protein were seen after taking risdiplam? What effects does risdiplam have on: ■ Change from baseline in MFM-32* total score ■ Percentage of participants who achieve stabilization (≥0) or improvement (≥3) according to the MFM-32* scale

Part 2 Primary and Secondary Endpoints

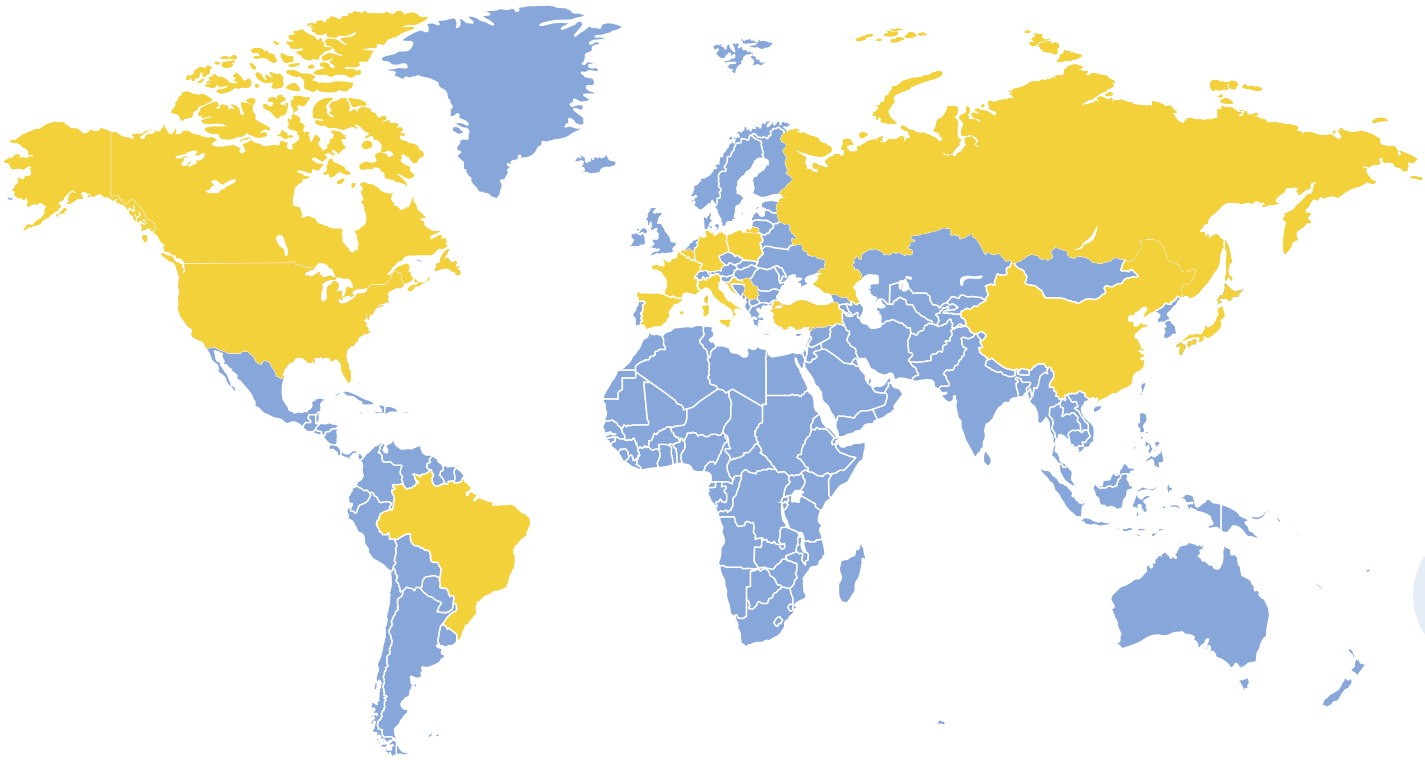
The main question researchers wanted to answer (known as the 'primary endpoint')	Additional questions the researchers wanted to answer (known as 'secondary and exploratory endpoints')
What is the change from baseline in participants according to the MFM-32* scale?	What effects does risdiplam have on: ■ Percentage of participants who achieve stabilization (≥0) or improvement (≥3) according to the MFM-32* scale ■ Change from baseline in RULM* total score ■ Change from baseline in HFMSE* total score ■ Change from baseline in SMAIS* total score

*Please see page 17 for a full description of the measurement scales used.

1. General information about the study (continued)

The SUNFISH study is a global, multicentre trial, involving 43 locations across 15 countries. The following map shows the countries where Parts 1 and 2 of the SUNFISH study has taken place. People enrolled in Part 2 were from a wider geographical area than people in Part 1.

Countries where the SUNFISH study has taken place



The countries that have taken part in the SUNFISH study are Belgium, Brazil, Canada, China, Croatia, France, Germany, Italy, Japan, Poland, Russia, Serbia, Spain, Turkey and the USA

2. Who took part in this study?

51 people aged between 2–25 years took part in **Part 1** of the study. 180 people aged between 2–25 years took part in Part 2 of the study. All had **Type 2 or 3 SMA**. See the **'baseline characteristics'** section for more information about the demographic and clinical data collected for each participant at the beginning of each part of the clinical trial. People were not allowed to participate in both parts of the trial.

People **could participate** ('inclusion criteria') in **Part 1** of the study if they:

- Had Type 2 or Type 3 ambulant or non-ambulant SMA (this means the trial was open to people who were able to walk unassisted for at least 10 meters and also to those who were unable to walk unassisted)

People **could participate** ('inclusion criteria') in **Part 2** of the study if they:

- Had Type 2 SMA or Type 3 non-ambulant SMA (they could not walk unassisted for at least 10 meters)
- Could sit independently

People **could <u>not</u> participate** ('exclusion criteria') in either part of the study if they:

- Had taken part in another clinical trial within the past 3 months
- Had previously received gene or cell therapy
- Could raise one or two hands to their mouth, but could not raise a 200g weight to their mouth
- Had experienced any recent emergencies requiring an overnight stay in hospital or major illnesses from which they had not fully recovered
- Had recently developed eye disease

Full details of the inclusion/exclusion criteria can be found by following the link in chapter 7.

The baseline characteristics of the people that took part

'Baseline characteristics' describe the demographic, clinical and other relevant information collected for each person at the beginning of a clinical trial, before they were given risdiplam or placebo.

This information allows researchers to measure the potential efficacy of risdiplam (seeing if someone's motor function improves or worsens, for example).

The baseline characteristics for **Part 1** and **Part 2** of the study are shown in the following table.

2. Who took part in this study? (continued)

	Part 1	Part 2		
	Risdiplam n = 51	Risdiplam n = 120	Placebo n = 60	All participants n = 180
Sex, number (%)				
Female	27 (53)	61 (51)	30 (50)	91 (51)
Male	24 (47)	59 (49)	30 (50)	89 (49)
Age (years)				
Age range of all participants	2–24	2–25	2–24	2–25
Average age at the time of screening	7	9	9	9
Type of SMA, number (%)				
Type 2 SMA	37 (73)	84 (70)	44 (73)	128 (71)
Type 3 SMA	14 (27)	36 (30)	16 (27)	52 (29)
Walking (ambulatory) status, number (%)				
Walkers	7 (14)	-	-	-
Sitters	33 (65)	-	-	-
Non-sitters	11 (22)	-	-	-
Scoliosis, number (%)				
People with scoliosis	29 (57)	76 (63)	44 (73)	120 (67)
People with >40 degrees curvature	-	34 (28)	23 (38)	57 (32)
Surgery for scoliosis before screening Yes No Not recorded	 - - -	 29 (24) 63 (53) 28 (23)	 17 (28) 33 (55) 10 (17)	 46 (26) 96 (53) 38 (21)
Movement ability according to measuring scales used in the study				
Average baseline MFM-32 score	42.9	45.48	47.35	46.11
Average baseline RULM score	-	19.65	20.91	20.06
Average baseline HFMSE score	-	16.10	16.62	16.27

3. What were the results of Part 1 of the study?

This summary provides an overview of the safety and efficacy results after participants had received **12 months of risdiplam** at the dose chosen for **Part 2** of the study.

Risdiplam successfully raised levels of SMN protein in people with **Type 2** or **3** SMA, aged between 2 to 24 years old, which was sustained throughout the whole 12-month period. All doses of risdiplam were well tolerated and no one left the trial due to any side effects from the drug.

Based on the concentration of risdiplam in the blood, an increase in SMN protein and safety data, the higher dose of risdiplam tested was chosen to be studied further in **Part 2** of the study. The higher dose of risdiplam also had more promising effects on the motor function of the participants in the trial, as detailed in the efficacy results section.

What were the safety results of Part 1 of the study?

All doses of risdiplam were well tolerated and no one left the trial due to any side effects from the drug.

A total number of 737 '**adverse events**' were reported during Part 1 of the study. The majority were considered to be events that are common in people with SMA, rather than side effects specifically related to risdiplam.

The percentage of people who had each of the most common adverse events reported over the course of the 12 months is included in brackets. The most common adverse events observed in Part 1 of the study included fever (41%), cough (33%), vomiting (29%), upper respiratory tract infections (26%), and a sore throat (22%).

At least one '**serious adverse event**'– one that is considered life-threatening or needs hospital care – was seen in 9 individuals. The most common one was pneumonia (4%) reported in 2 people. Everyone that had serious adverse events continued taking risdiplam without interruption.

What were the exploratory efficacy results of Part 1 of the study?

Research that tells us how SMA naturally progresses over time in people with SMA **Types 2 or 3** (natural history), shows us that improvements in mobility would not be possible without treatment. Instead, independence and mobility of people with SMA **Types 2 or 3**, as measured by a number of different scales, such as MFM-32 (see page 17 for more information), declines over time without treatment.

People achieving improvements in mobility

Proportion of individuals achieving a change of at least 3 points in the MFM-32 scale (compared with 8% in the Natural History study)

of people aged 2-11

of people aged 12-25

of all people

Without treatment, improvements in mobility would not be possible

4. What were the results of Part 2 of the study?

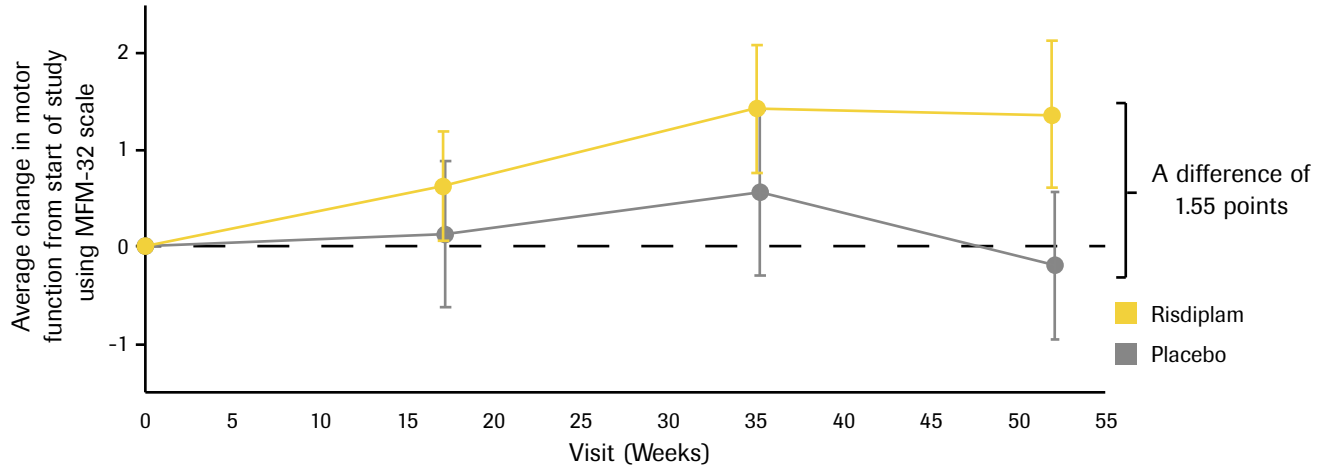
This summary provides an overview of the efficacy and safety results after the participants had received **12 months of treatment** with either risdiplam or placebo. Risdiplam was shown to successfully preserve and potentially enable independent movement for people with **Type 2** and **Type 3** SMA.

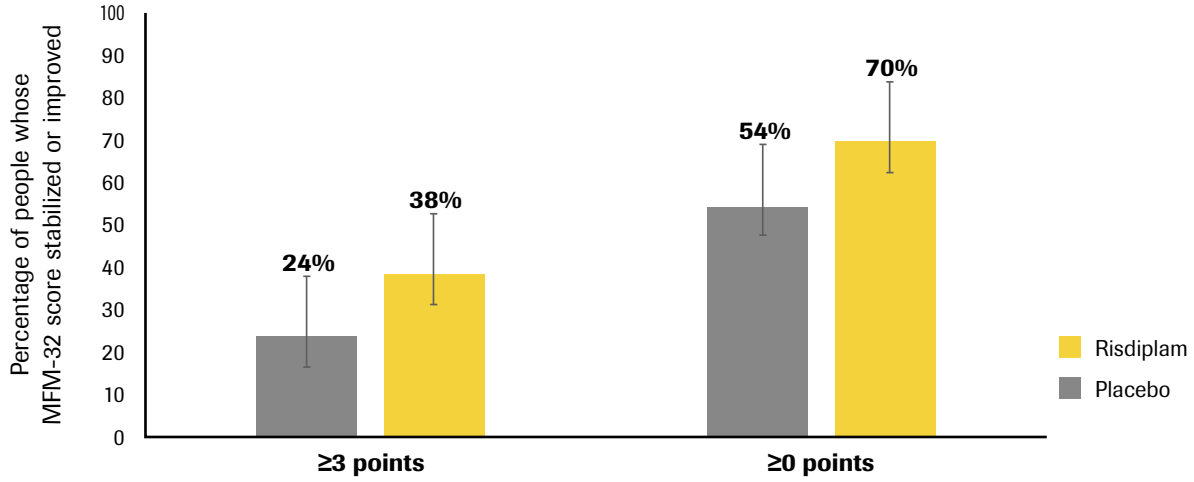
What were the efficacy results of Part 2 of the study?

As outlined previously, the outlook for people with **Type 2** or **Type 3** SMA who do not receive any treatment is declining mobility and independence.

People achieving improvements in mobility

Change in motor function measured

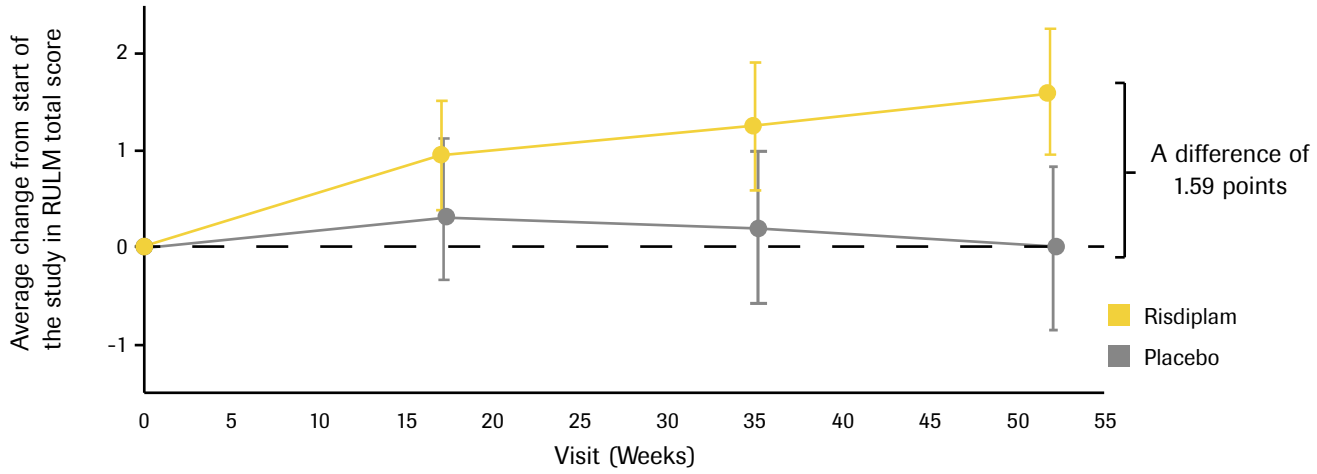




Those treated with risdiplam showed improved motor function compared with those not taking risdiplam

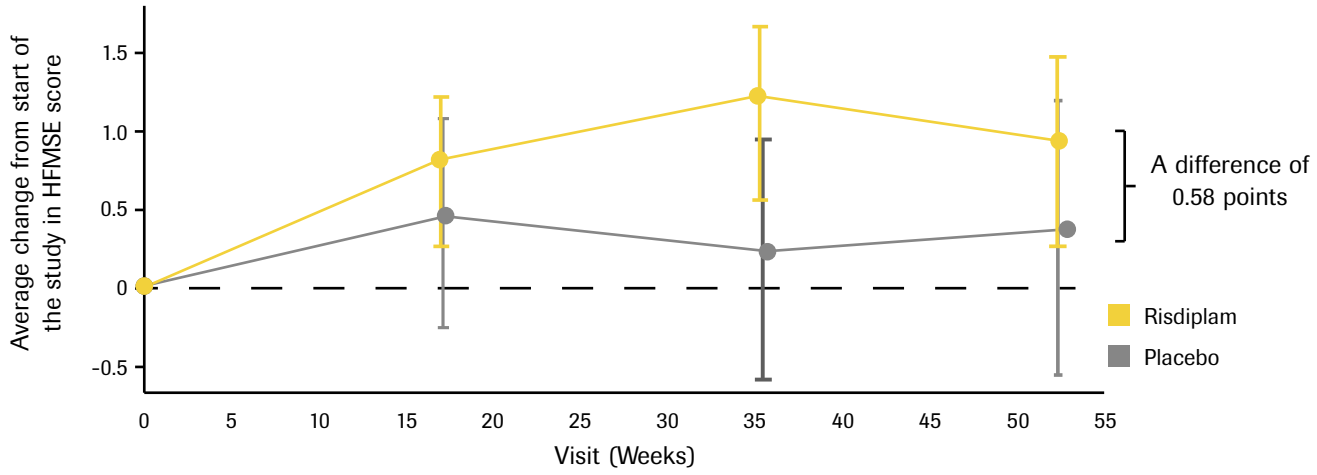
4. What were the results of Part 2 of the study? (continued)

People achieving improvements in upper limb function



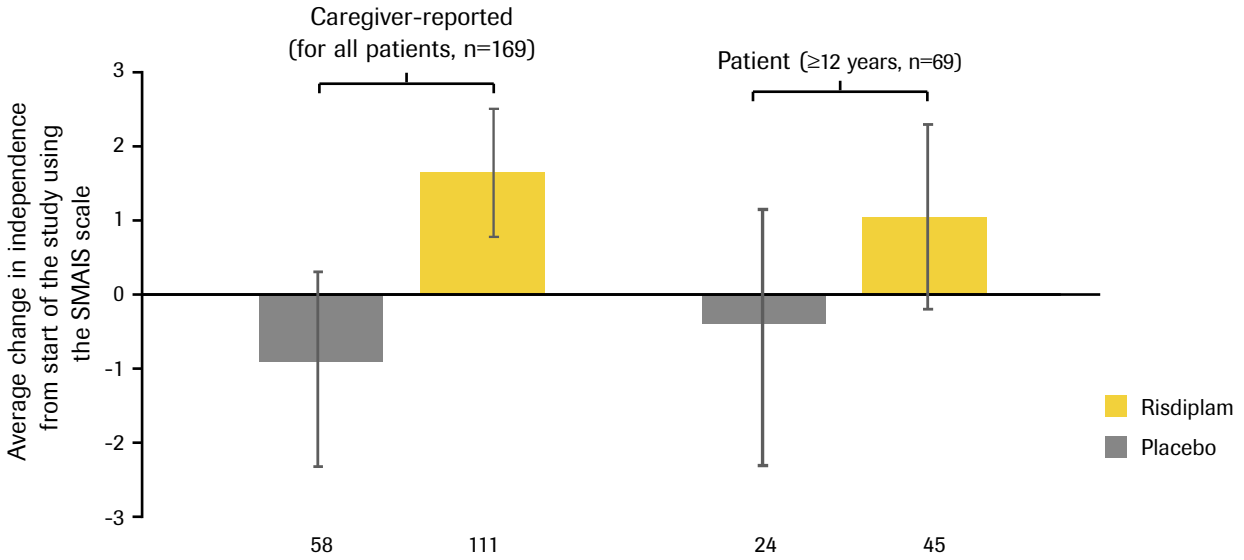
Those treated with risdiplam showed greater improvements in upper limb function compared with those not taking risdiplam

Comparable results between risdiplam and placebo according to the HFMSE scale



4. What were the results of Part 2 of the study? (continued)

Improvements in independence reported by caregivers and patients



Risdiplam improved independence in activities of daily life using the novel SMAIS measure, which measures activities such as brushing teeth, writing/using a pen and eating with a fork

What were the safety results of Part 2 of the study?

Risdiplam was well tolerated and no one left the trial due to any side effects from the drug.

A total number of 789 '**adverse events**' were reported during Part 2 of the study. The majority were considered to be events that are common in people with SMA, rather than side effects specifically related to risdiplam.

A table of the safety summary is shown on page 16. The percentage of people who had each of the most common adverse events reported over the course of the 12 months is included in brackets.

At least one **serious adverse event** – one that is considered life-threatening or needs hospital care – was seen in 24 individuals treated with risdiplam (20% of the participants), compared to 11 individuals treated with placebo (18% of the patients). Everyone that had serious adverse events still went on to continue taking risdiplam successfully without interruption.

4. What were the results of Part 2 of the study? (continued)

Side effects		Risdiplam n = 120	Placebo n = 60
Patients with at least 1 side effect, n (%)		111 (93)	55 (92)
Total number of side effects		789	354
Total number of patients with at least one side effects, n (%)	Related side effects leading to dose modification/interruption	0	0
	Side effects leading to dose modification/interruption	8 (7)	2 (3)
	Treatment-related side effects	16 (13)	6 (10)
	Serious side effects	24 (20)	6 (10)
	Serious side effects leading to dose modification/interruption	4 (3)	2 (3)
	Treatment-related serious side effects	0	0
Most common side effects, n (%)	Upper respiratory tract infection	38 (32)	18 (30)
	Common cold	31 (26)	15 (25)
	Fever	25 (21)	10 (17)
	Headache	24 (20)	10 (17)
	Diarrhea	20 (17)	5 (8)
	Vomiting	17 (14)	14 (23)
	Cough	17 (14)	12 (20)
Most common serious side effects, n (%)	Pneumonia	9 (8)	1 (2)
	Stomach virus	2 (2)	2 (3)
	Bacteria in the blood stream	2 (2)	0 (0)
	Flu	2 (2)	0 (0)
	Fever	2 (2)	0 (0)

Key difference between SUNFISH Part 1 and 2

Summary

- SUNFISH Part 2 (n = 180) has a larger patient population than Part 1 (n = 51)
- SUNFISH Part 1 includes patients with Types 2 and 3 SMA who were able or unable to walk. SUNFISH Part 2 is restricted to Type 2 and Type 3 patients who are unable to walk
- Patients enrolled in SUNFISH Part 2 are from a wider geographical area than patients in Part 1
- SUNFISH Part 1: patient data is compared to natural history data. SUNFISH Part 2: 12-month patient data is compared to the placebo group within the study

5. What scales were used to measure movement and independence in the study?

So that the effect of different drugs on SMA can be assessed, standard 'scales' are used by researchers. The following scales were used in the SUNFISH study to understand how risdiplam affects people's abilities to move and independence when completing daily activities.

The 32-item Motor Function Measure (MFM-32) scale

The MFM-32 is a scale that measures the movement of people affected by a neuromuscular disease, such as SMA. Individuals are scored from 0–3 on their ability to complete each of 32 tasks with a maximum total score of 96; higher scores reflect better function. The tasks are separated into three domains: D1, standing position and transfers (13 items); D2, head, trunk, legs and arms movement ability (12 items); and D3, hands and feet movement ability (7 items). In people with Type 2 or 3 SMA who don't receive treatment, these scores go down over time. The scale is more sensitive for patients with more advanced SMA.

The Hammersmith Functional Motor Scale–Extended (HFMSE)

The HFMSE assesses 33 tasks related to lying/rolling, crawling, kneeling, standing and walking/running/jumping. The ability to complete each exercise is scored on a scale of 0–2, with a maximum total score of 66. Higher scores reflect a better ability to complete the exercises. In people with Type 2 or 3 SMA who don't receive treatment, these scores go down over time, usually by half a point per year.

The Revised Upper Limb Module (RULM) scale

The RULM scale tests arm movement and coordination in people with SMA. People are scored on their ability to complete a series of exercises and tasks (e.g. lift a 200g weight, open ziplocked containers, trace a path using a pencil on a map). Higher scores reflect greater strength and ability to complete tasks.

SMA Independence Scale (SMAIS)

A novel scale to measure the relative independence of people living with SMA as assessed by their caregivers or the patient themselves if aged over 12 years. The SMAIS includes 29 questions assessing the level of independence when completing activities of daily living, including eating using hands, a fork or spoon, brushing teeth and writing/using a pen. The SMAIS was developed in collaboration with SMA patient groups and the support of patients and caregivers.

6. How has this study helped patients and researchers?

For a disease like SMA, where treatment options are limited, the study of possible new drugs and different modes of administration (such as risdiplam as the first oral treatment for SMA), is important to advance patient outcomes and care.

People who took part in the study have experienced improvements in their symptoms and continue to take risdiplam.

Building on previous research, the study results from SUNFISH have given researchers and patients a fuller understanding of the effects of risdiplam in people with Type 2 SMA and people with Type 3 SMA. The results have also enabled Roche to study risdiplam in a broader and older population than ever studied before.

It is the first SMA study to involve people beyond the age of 9 years old, including teenagers and young adults up to the age of 25. The results have enabled the sponsoring company (Roche) to submit the drug for regulatory approval by health authorities to make the drug available to patients with SMA Types 2 and 3 around the world. Risdiplam received first approval for use in the US for the treatment of SMA in patients 2 months of age and older, in August 2020. Since then, it continues to be reviewed and approved by national and regional health authorities on a global scale.

No single study can tell us everything about the risks and benefits of a medicine. Always speak to your doctor before making any decisions about your treatment.

7. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/study/NCT02908685
- https://forpatients.roche.com/en/trials/muscle-and-peripheral-nerve-disease/sma/a-study-to-investigate-the-safety--tolerability--pharmacokinetic1.html

If you or your child have took part in this study and have any questions about the results, please speak with your doctor or other medical staff at your study site.

If you have any further questions, please contact a representative at your local Roche office.

The full title of this study is: A Two Part Seamless, Multi-Center Randomized, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Type 2 and 3 Spinal Muscular Atrophy Patients

The study is known as 'SUNFISH'.

Address and telephone number for the sponsor of this trial:
F. Hoffmann-La Roche Grenzacherstrasse 124 CH-4070 Basel, Switzerland
+41-61-688-1111