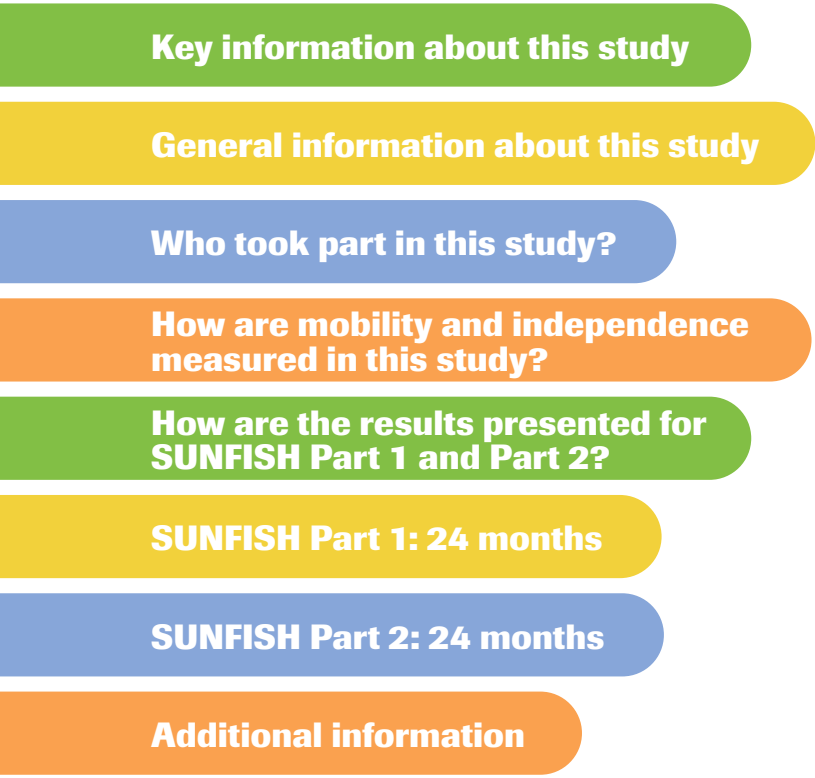
An updated summary of long-term (2-year) data from SUNFISH, a clinical trial to establish the efficacy and safety of risdiplam for children, adolescents and adults with Type 2 or 3 SMA

Date of preparation: January 2022 | M-XX-00007890

About this summary

Thank you to those who took part in this clinical study. You have helped researchers to answer important questions about the outlook for individuals with spinal muscular atrophy (SMA) and about the study drug risdiplam.

Figure 1: An overview of the information that can be found in this summary



A document was made in 2020 that provided 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 main aims (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 individual has enrolled in the study. Please see **Figure 1** for an overview of the information that can be found in this summary. Please click **here** to view the 2020 summary.

This document provides a summary of the 24-month results of Part 1 of the SUNFISH study and the 24-month results of Part 2 of the SUNFISH study.

This document has been written for members of the public, as well as the individuals with SMA and families taking part in the study.

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Key information about this study

The SUNFISH study included children, adolescents and adults with Type 2 or Type 3 SMA, aged between 2 and 25 years at the time they entered the study.

This study was designed in two parts, both were '**double-blind, placebo-controlled and randomised**'. This means that the individuals taking part were randomly assigned to either the study drug (risdiplam) or a '**placebo**'. A placebo is a 'dummy drug' with no active ingredient which has no physical effect on an individual. Neither the researchers nor the individuals taking part in the study knew which treatment individuals were given.

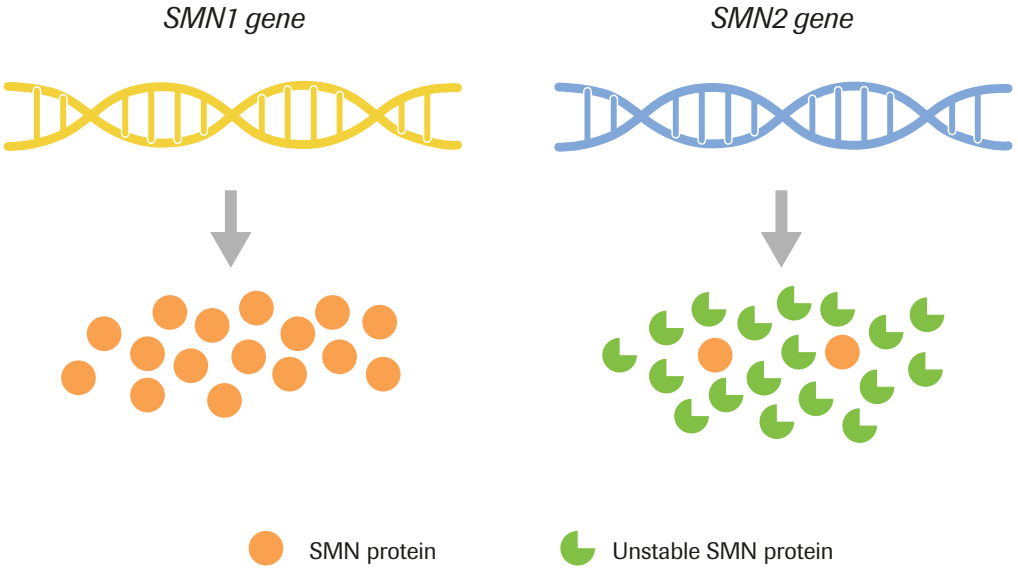
General information about this study

What is SMA?

When this study began, there were no approved treatment options for individuals with SMA. SMA is a rare, inherited, neuromuscular disease, which destroys muscle-controlling nerve cells called motor neurons. It affects the brain and spinal cord (central nervous system), the other parts of the nervous system outside of the 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 gene called *SMN1* (survival of motor neuron 1). *SMN1* produces a protein called survival of motor neuron (SMN) that is critical to the function of the nerves that control the muscles. Without SMN protein, those nerve cells cannot properly function and eventually die, leading to debilitating and sometimes fatal muscle weakness. Individuals with SMA have low levels of SMN protein 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 (**Figure 2**). 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.

Figure 2: How the *SMN1* gene and the *SMN2* gene work



SMN, survival of motor neuron.

General information about this study

What is SMA?

Individuals with SMA have difficulty performing the basic functions of life, including breathing and swallowing. SMA does not affect 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 (**Table 1**), 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 who are still in the womb.

Table 1: The four primary types of SMA

SMA Type	Age of onset	Impact
1	Birth–6 months	Children with this form of SMA will never sit independently
2	>6–18 months	Children are typically able to sit but not stand
3	18 months onwards	Children can typically stand and walk. However, many children lose the ability to walk in early life
4	18 years onwards	This form of SMA develops after adolescence and causes a mild decline in mobility

The symptoms of Type 2 SMA start showing in infants younger than 18 months of age and include weakening of the muscles, difficulty swallowing, difficulty breathing, curving spine, stiff joints, difficulty coughing and trembling hands. Untreated individuals 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 walking, trembling hands, weaker leg muscles compared with the arms and sometimes difficulty breathing during sleep. Untreated individuals 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.

General information about this study

What is the goal of treatments for SMA?

The impact of SMA on life expectancy varies according to the type of SMA. Children with the most severe types of SMA (Types 0 and 1) have a very short life expectancy: most would not live beyond 2 years or would need permanent breathing support without treatment. Individuals with Type 4 SMA usually have a normal life expectancy.

The goals of new treatments are generally to address the underlying cause of the disease, improve life expectancy, maintain essential motor functions, reduce overall symptoms and improve quality of life.

The SUNFISH study was carried out to understand the safety and efficacy of risdiplam in individuals with Type 2 or Type 3 SMA, aged between 2 years and 25 years when they entered the study.

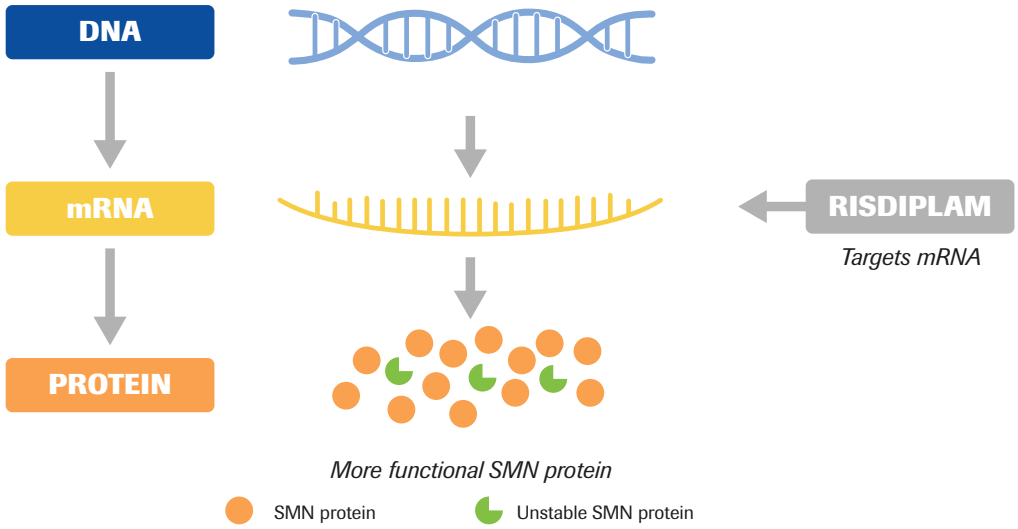
General information about this study

What is risdiplam and how does it work?

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

As shown in **Figure 2**, the *SMN2* gene only produces approximately 10% of the working ('functional') SMN protein that the body needs. However, risdiplam is designed to help the *SMN2* gene to produce more working SMN protein, which maintains and improves muscle function. Risdiplam does this by targeting the molecule (mRNA) that carries instructions from the *SMN2* gene to make SMN protein (**Figure 3**). In individuals with SMA, the instructions from the *SMN2* gene are faulty, and most of the SMN protein that the mRNA makes does not work. Risdiplam is designed to fix these instructions so that more of the SMN protein works.

Figure 3: How risdiplam works



DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; SMN, survival of motor neuron.

The aim is to prevent the loss of motor neurons and maintain muscle function. Risdiplam is distributed throughout the body, raising the levels of SMN protein in the brain, spinal cord (central nervous system) and other organs.

General information about this study

How was the study designed?

The study was designed in two parts (**Figure 4**):

- An **exploratory, dose-finding part (Part 1)** to find the optimal dose of risdiplam to give to the study population, identify any side effects of risdiplam and provide an initial assessment of the efficacy of risdiplam in treating children, adolescents and adults with Type 2 or Type 3 SMA
- A **confirmatory part (Part 2)** to measure the efficacy and safety of risdiplam in treating children, adolescents and adults with Type 2 or Type 3 SMA at the dose selected in Part 1

Both parts of the study were '**double-blind, placebo-controlled and randomised**'. This means that the individuals taking part in the study 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 physical effect on the individual. Neither the researchers nor the individuals taking part in the study knew which treatment individuals were given.

Part 1: For the first 12 weeks of the study, individuals received either risdiplam, at varying doses, or placebo. After the first 12 weeks, the individuals receiving placebo were given risdiplam. All individuals then continued to receive risdiplam for 24 months.

Part 2: For the first 12 months of this part of the study, two-thirds of the participants received risdiplam at the dose selected from Part 1 and the other third received placebo. After 12 months, the individuals receiving placebo were given risdiplam so that all individuals received risdiplam from 12 to 24 months.

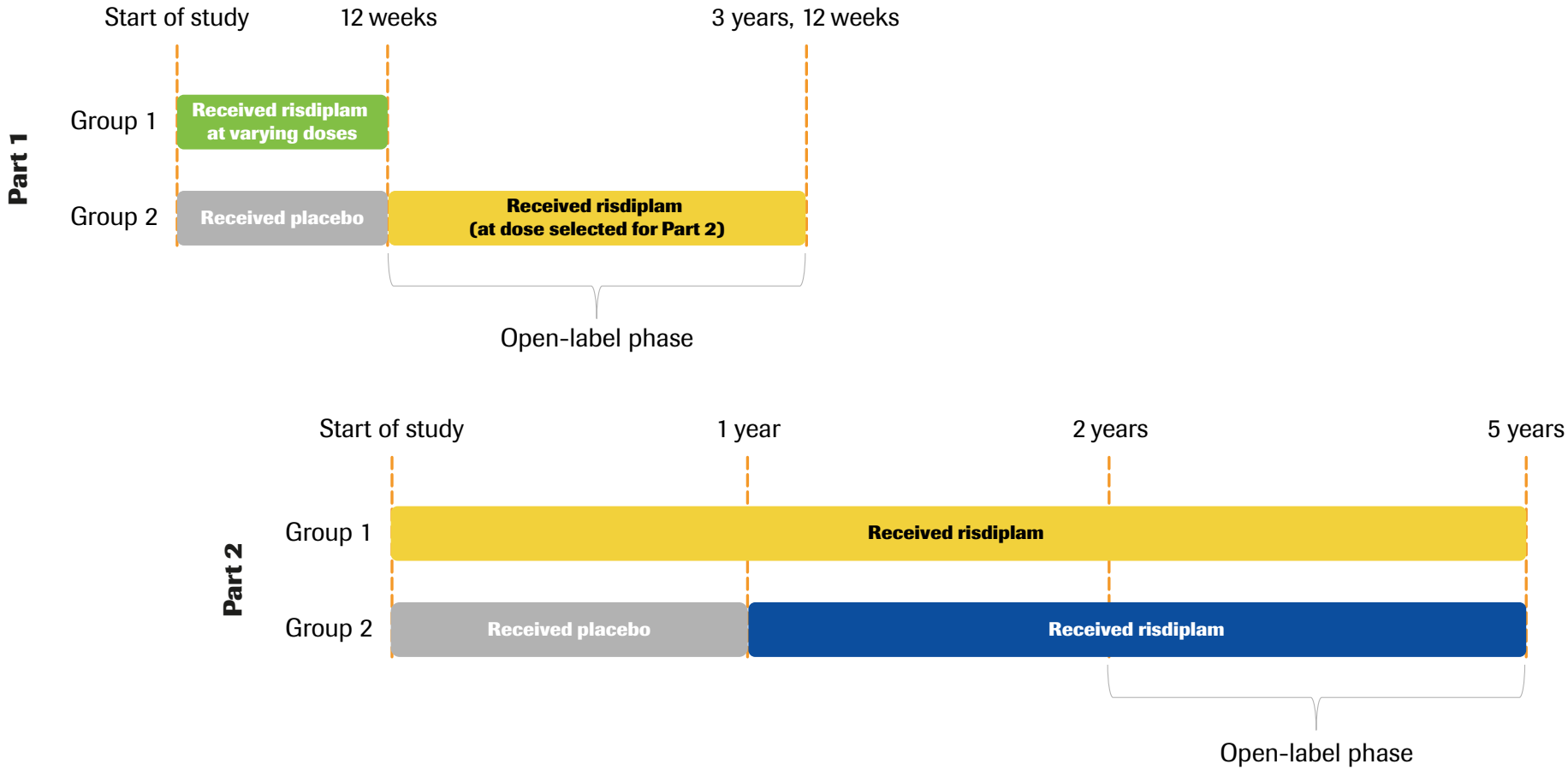
A double-blind, randomised trial reduces the possibility of any bias when comparing the results. In this study, the sponsoring company (Roche) only discovered which individuals were receiving risdiplam when the group receiving placebo were switched to risdiplam (at the end of 12 weeks in Part 1 and at the end of 12 months in Part 2).

After 24 months, individuals in both parts of the SUNFISH study had the option to enter an '**open-label**' phase for 3 years, during which all participants would be given risdiplam. Both parts of the trial are ongoing and will be completed after the last individual has received up to 5 years of treatment (**Figure 4**).

General information about this study

How was the study designed?

Figure 4: The design of the SUNFISH study



General information about this study

What were the aims of the study?

The SUNFISH study aimed to answer a number of different questions about risdiplam, as shown in **Table 2** and **Table 3**.

In order to understand the effects of risdiplam and help answer the different questions set by researchers, the study includes a number of measures (endpoints).

- **Primary endpoints** are specific measures that aim to address the main research question. The study is considered successful if these measures are met at a certain point in the study
- **Secondary endpoints** provide additional information to help understand the effects of the treatment that is being studied
- **Exploratory endpoints** include events that are not expected to occur frequently and thought to be less likely to show a treatment effect but are included in order to explore new questions. They are generally assessed less formally than primary and secondary endpoints

Each part of the SUNFISH study includes one main measure (primary endpoint) as well as other measures (secondary and exploratory endpoints).

To take these measurements, assessment scales were used to evaluate mobility and independence in the individuals taking part in the study. You can find a full description of the scales in the section '**How are mobility and independence measured in this study?**' later in this document.

General information about this study

What were the primary, secondary and exploratory endpoints for Parts 1 and 2?

Table 2: Primary, secondary and exploratory endpoints for Part 1

The main questions the researchers wanted to answer (primary endpoints)	Other important questions the researchers wanted to answer (secondary endpoints)
What is the recommended dose of risdiplam for the treatment of individuals with Type 2 or Type 3 SMA to be used in Part 2 of the study?	How does risdiplam affect the amount of SMN protein in the blood?
	Any additional questions the researchers wanted to answer (exploratory endpoints)
	What is the efficacy of risdiplam, as assessed by the following? • Change in mobility (as measured by change in MFM-32* total score from the start of the study) • Percentage of individuals who achieve stabilisation or improvement in mobility (measured by a change of either ≥0 points or ≥3 points on the MFM-32* scale, respectively)

*Please see the section '**How are mobility and independence measured in this study?**' for a full description of the assessment scales used.
MFM, Motor Function Measure; SMN, survival of motor neuron.

General information about this study

What were the primary, secondary and exploratory endpoints for Parts 1 and 2?

Table 3: Primary and secondary efficacy endpoints for Part 2

The main questions the researchers wanted to answer (primary endpoints)	Other important questions the researchers wanted to answer (secondary endpoints)
What is the efficacy of risdiplam, as assessed by change in mobility (as measured by change in MFM-32* total score from the start of the study)?	What is the efficacy of risdiplam, as assessed by the following? • Percentage of individuals who achieve stabilisation or improvement in mobility (as measured by a change from the start of the study of either ≥0 points or ≥3 points on the MFM-32* scale, respectively) • Change in mobility (as measured by the change in RULM* total score from the start of the study) • Change in mobility (as measured by the change in HFMSE* total score from the start of the study) • Change in the ability to perform everyday tasks independently (as measured by the change in SMAIS* total score from the start of the study)

*Please see the section 'How are mobility and independence measured in this study?' for a full description of the assessment scales used.
HFMSE, Hammersmith Functional Motor Scale Expanded; MFM, Motor Function Measure; RULM, Revised Upper Limb Module; SMAIS, Spinal Muscular Atrophy Independence Scale.

General information about this study

In which countries did the SUNFISH study take place?

The SUNFISH study is a global, multicentre trial taking place in 43 centres across 15 countries. The below map (**Figure 5**) shows the countries where Parts 1 and 2 of the SUNFISH study are taking 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.

Figure 5: The countries in which the SUNFISH study is taking place

Who took part in this study?

In total, 51 individuals aged between 2 years and 25 years took part in Part 1 of the study. Overall, 180 individuals aged between 2 years and 25 years took part in Part 2 of the study. All had Type 2 or Type 3 SMA. See **Table 4** for more information about the characteristics of the individuals (e.g. age, sex, SMA type, level of mobility) at the beginning of each part of the study. Individuals were not allowed to take part in both parts of the trial.

If an individual met the following requirements (inclusion criteria), they could take part in Part 1 of the study:

- Had Type 2 SMA, or ambulant or non-ambulant Type 3 SMA (individuals who were able to walk unassisted for at least 10 metres and those who were unable to walk unassisted)

If an individual met the following requirements (inclusion criteria), they could take part in Part 2 of the study:

- Had Type 2 SMA, or non-ambulant Type 3 SMA (individuals who were unable to walk unassisted)
- Could sit independently

If a person met the following requirements (exclusion criteria), they could not take part in either Part 1 or Part 2 of the study:

- Had taken part in another clinical trial within the past 3 months
- Had previously received gene or cell therapy
- Could not lift a 200 gram 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 at: **https://clinicaltrials.gov/ct2/show/NCT02908685**.

Who took part in this study?

The baseline characteristics of the individuals who took part

'**Baseline characteristics**' are data that describe the characteristics of each individual at the beginning of the study. These data include the individual's age and sex, as well as clinical and other relevant information from before they were given risdiplam. By comparing these baseline data with the data collected after the individuals received risdiplam, researchers can determine whether the treatment is working.

The baseline characteristics of the individuals who took part in Part 1 and Part 2 of the study are shown in the table on the following page (**Table 4**).

Who took part in this study?

The baseline characteristics of the individuals who took part

Table 4: Baseline characteristics of the individuals who took part in the study

Characteristic		Part 1 Risdiplam group (51 individuals)	Part 2 Risdiplam group (120 individuals)	Part 2 Placebo group (60 individuals)	Part 2 All participants (180 individuals)
Number of men (%)		24 (47)	59 (49)	30 (50)	89 (49)
Age range in years at enrolment		2–24	2–25	2–24	2–25
Average age in years at enrolment		7	9	9	9
Number of individuals with each SMA type (%)	Type 2 Type 3	37 (73) 14 (27)	84 (70) 36 (30)	44 (73) 16 (27)	128 (71) 52 (29)
Number of individuals with each level of mobility (motor function) (%)	Non-sitters Sitters Walkers	11 (22) 33 (65) 7 (14)	– – –	– – –	– – –
Scoliosis					
Number of individuals with scoliosis (%)		29 (57)	76 (63)	44 (73)	120 (67)
Number of individuals with scoliosis with >40 degrees curvature (%)		–	34 (28)	23 (38)	57 (32)
Number of individuals with/without surgery for scoliosis before screening, or for whom this was not recorded (%)	Surgery No surgery Not recorded	– – –	29 (24) 63 (53) 2 (23)	17 (28) 33 (55) 10 (17)	46 (26) 96 (53) 38 (21)
Mobility					
Average MFM-32 score		42.9	45.48	47.35	46.11
Average RULM score		–	19.65	20.91	20.06
Average HFMSE score		–	16.10	16.62	16.27

HFMSE, Hammersmith Functional Motor Scale Expanded; MFM, Motor Function Measure; RULM, Revised Upper Limb Module.

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How are mobility and independence measured in this study?

How is mobility (motor function) measured in this study?

Mobility can be measured by assessing how well a person can use different parts of their body to perform certain tasks.

Fine motor function measures how well a person can use their wrists, hands and fingers; this could be measured by assessing whether the person can hold an object or press a button.

Gross motor function measures how well a person can use their larger muscles (arms, legs and torso); this could be measured by assessing whether a person can move from their bed to their wheelchair or stand up from sitting.

Upper limb function measures how well a person can use the muscles in their arms and hands; this could be measured by seeing whether a person can lift a cup to their mouth or draw on a piece of paper.

When measuring the effectiveness of a drug such as risdiplam on mobility, it is important to compare with the mobility that can be expected from individuals with SMA who have not been treated with any drug. This information is available in a '**natural history study**', which is a study that measures mobility and other results, such as breathing ability, in individuals who have never been treated.

Motor function assessment scales are used by doctors in clinical trials and in the clinic to assess mobility. In SUNFISH, the following scales were used:

- The 32-item Motor Function Measure (MFM-32), which measures both **fine** and **gross motor function**
  - The MFM is an assessment scale that measures the movement of individuals affected by neuromuscular diseases, such as SMA, across a range of disease severities and ages
  - The MFM can be used to measure how SMA is changing over time by assessing three functions:

Standing position and transfers (i.e. how well a person can perform activities that involve standing)

Axial and proximal limb motor function (i.e. how well a person can perform activities involving the trunk and the head [axial function], and the shoulders and the upper arms [proximal function])

Distal limb motor function (i.e. how well a person can perform activities involving their forearms, hands, fingers and feet)

  - An increase in the MFM-32 total score over time shows that an individual has improved in overall mobility over time

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How are mobility and independence measured in this study?

How is mobility (motor function) measured in this study?

- The Hammersmith Functional Motor Scale Expanded (HFMSE), which measures **gross motor function**
  - The HFMSE is an assessment scale that was developed specifically for SMA
  - The HFMSE is useful to assess gross motor skills in stronger individuals who are able to sit or walk

- The Revised Upper Limb Module (RULM), which measures **upper limb function**
  - The RULM is an SMA-specific scale used to assess motor function of the arm, forearm and hand
  - This scale was designed to complement the HFMSE, as individuals who have very limited mobility may not be able to complete many items of the HFMSE
  - The items of the RULM have been designed to assess abilities that are needed to perform activities of daily living, such as drinking from a cup

How are mobility and independence measured in this study?

How is independence measured in this study?

Independence can be measured by testing how much help a person needs to perform certain daily activities, such as brushing their teeth, getting dressed or drinking from a cup.

The SMA Independence Scale (SMAIS) was used in SUNFISH to measure independence. This scale was completed by both the individuals taking part in SUNFISH (if they are at least 12 years old) and by their caregivers.

For more detail on these scales, please see the brochure '**Understanding the MFM and the SMAIS in the context of outcome measurements in SMA**'.

How are the results presented for SUNFISH Part 1 and Part 2?

How are the results presented for SUNFISH Part 1?

It is important to understand how the results of individuals with Type 2 or Type 3 SMA who were treated with risdiplam in the SUNFISH study compare with individuals who have never received treatment for SMA. By making this comparison, we can understand whether the changes seen in individuals treated with risdiplam are likely to be due to the efficacy of risdiplam. As such, the results from Part 1 were compared with results from a group of untreated individuals (called the '**external comparator**' group) from two studies:

- Individuals with Type 2 or Type 3 SMA from the NatHis-SMA natural history study who had never been treated for SMA
- Individuals with Type 2 or Type 3 SMA who received placebo in a Phase 2 trial of olesoxime

The individuals in the external comparator group had similar characteristics (such as age and mobility levels) to the individuals included in the SUNFISH study.

How are the results presented for SUNFISH Part 1 and Part 2?

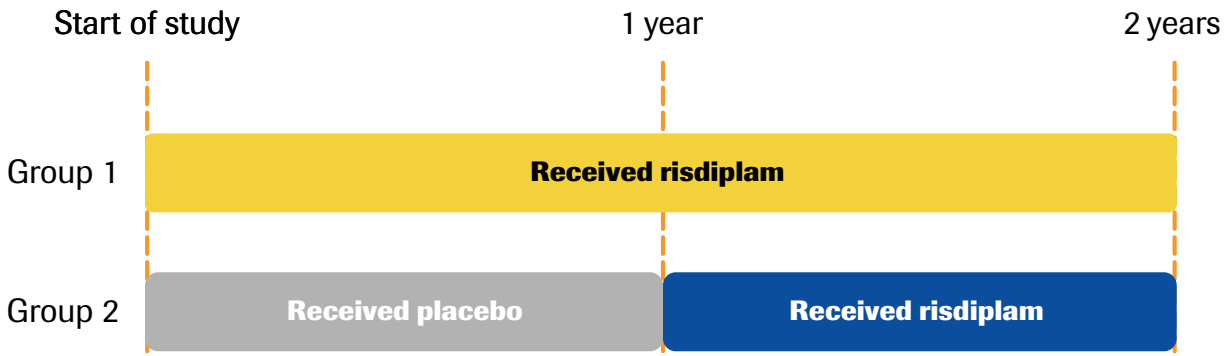
How are the results presented for SUNFISH Part 2?

In Part 2, some individuals were given risdiplam and some were given placebo for the first 12 months. After the first 12 months, the group that was given placebo was switched to risdiplam so that all individuals in the study received risdiplam from 12 to 24 months (**Figure 6**).

The results from Part 2 are presented for one of the following:

- Group 1 (receiving risdiplam treatment) over 24 months
- Group 1 (receiving risdiplam treatment) over 24 months, compared with Group 2 (receiving placebo) over 12 months
- Group 2 (receiving risdiplam treatment) over 12 months

Figure 6: Overview of groups in Part 2 of the SUNFISH study



SUNFISH Part 1: 24 months

What were the results of Part 1 of the study after 24 months?

This summary provides an overview of the safety and efficacy results from Part 1 of the SUNFISH study, after the individuals with Type 2 or Type 3 SMA had received treatment with risdiplam for 24 months.

A 2020 summary of the SUNFISH study included an overview of the 12-month results of Part 1 of the SUNFISH study. The 2020 summary can be found **here**.

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SUNFISH Part 1: 24 months

Safety results of Part 1 of the study (after 24 months of treatment)

No individuals left the study due to side effects from risdiplam.

A table summarising the safety results is shown below (**Table 5**). The percentage of individuals who had each of the most common side effects, or serious side effects, during the 24 months of treatment with risdiplam is included in brackets.

Serious side effects – those that are considered life-threatening or that need hospital care – were seen in 15 individuals (29%). Three individuals (6%) who experienced serious side effects had a change in dose or an interruption of treatment with risdiplam.

Table 5: Side effects of individuals who took part in Part 1 of the SUNFISH study, after 24 months of treatment with risdiplam

Side effects, number of individuals (% of individuals)		Total (51 individuals)
Individuals with at least one side effect		49 (96)
Individuals with at least one serious side effect		15 (29)
Most common side effects	Fever	28 (55)
	Cough	18 (35)
	Vomiting	17 (33)
	Upper respiratory tract infection	16 (31)
	Cold	12 (24)
	Sore throat	11 (22)
Most common serious side effects	Pneumonia	3 (6)
	Femur fracture	2 (4)

The reported side effects and serious side effects were in line with those expected in untreated individuals with SMA of the same age. None of the serious side effects were considered related to treatment with risdiplam.

SUNFISH Part 1: 24 months

Exploratory efficacy results of Part 1 of the study (after 24 months of treatment)

Research showing how SMA naturally progresses over time in individuals with Type 2 or Type 3 SMA who do not receive any treatment (natural history) demonstrates that improvements in mobility are not usually possible without treatment. Instead, the mobility and independence of individuals with Type 2 or Type 3 SMA, as measured by a number of different scales such as the MFM-32, declines over time without treatment (see section '**How are mobility and independence measured in this study?**' for more information).

SUNFISH Part 1: 24 months

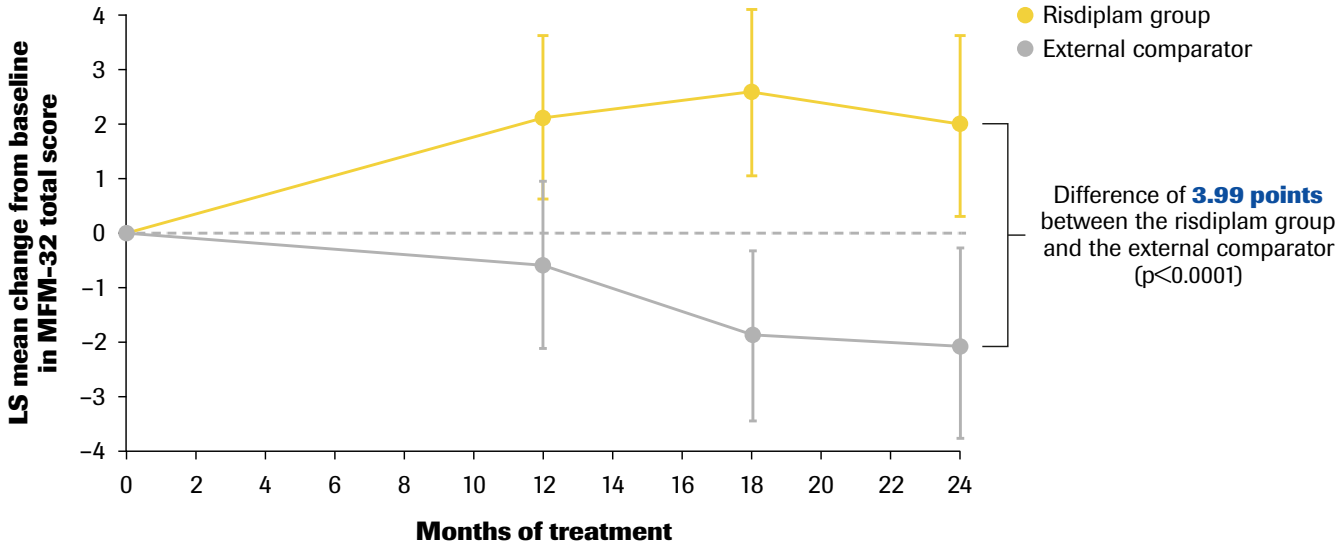
Exploratory efficacy results of Part 1 of the study (after 24 months of treatment)

Mobility after 24 months of treatment with risdiplam

The MFM-32 total score increased in individuals who had been treated with risdiplam over 24 months, compared with:

- Their scores at the beginning of the study
- The scores of the external comparator group (untreated individuals with Type 2 or Type 3 SMA) (**Figure 7**)

Figure 7: Average (LS mean) change in mobility (as measured by the MFM-32) over 24 months in individuals with Type 2 or Type 3 SMA in SUNFISH Part 1



Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
LS, least squares (a standard method for fitting a curve to a set of points); MFM, Motor Function Measure.

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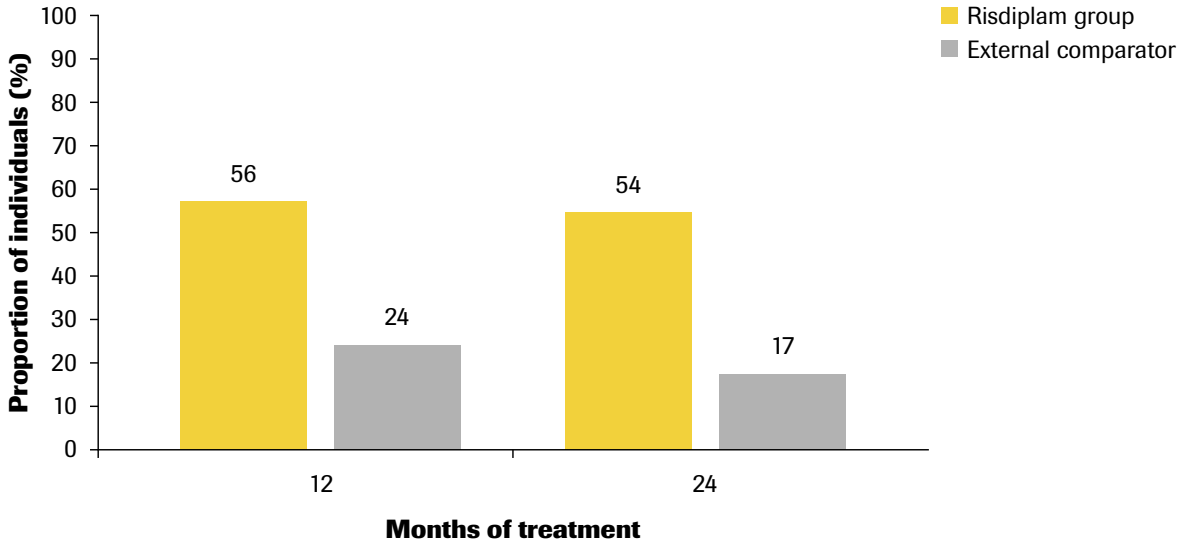
SUNFISH Part 1: 24 months

Exploratory efficacy results of Part 1 of the study (after 24 months of treatment)

After 24 months of treatment in SUNFISH Part 1, **54% (26/48)** of individuals achieved an increase in MFM-32 total score of at least 3 points compared with their score at the start of the study (**Figure 8**).

Figure 8: Percentage of individuals whose MFM-32 score increased by at least 3 points compared with their score at the start of the study, over 12 months (left) or over 24 months (right)



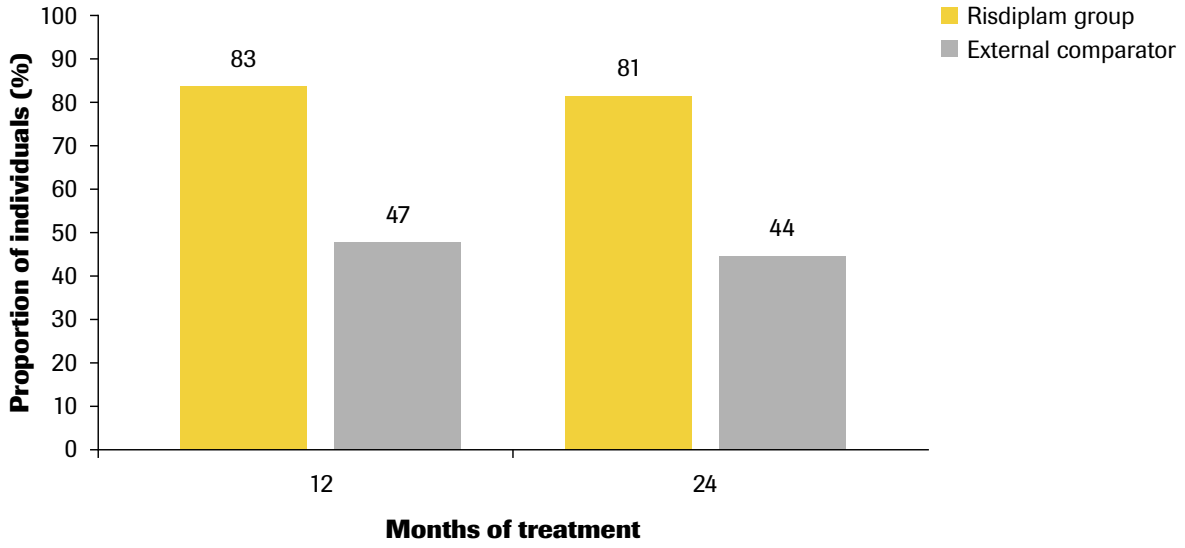
MFM, Motor Function Measure.

SUNFISH Part 1: 24 months

Exploratory efficacy results of Part 1 of the study (after 24 months of treatment)

After 24 months of treatment in SUNFISH Part 1, **81% (39/48)** of individuals from the SUNFISH study either maintained their MFM-32 total score or achieved an increase in their MFM-32 total score compared with their score at the start of the study (**Figure 9**).

Figure 9: Percentage of individuals with either a maintained or increased MFM-32 total score compared with the start of the study, over 12 months (left) or over 24 months (right)



MFM, Motor Function Measure.

SUNFISH Part 2: 24 months

What were the results of Part 2 of the study after 24 months?

This summary provides an overview of the efficacy and safety results after the individuals taking part in SUNFISH Part 2 had received 24 months of treatment with risdiplam. Risdiplam was shown to preserve or improve mobility successfully in individuals with Type 2 or Type 3 SMA.

A 2020 summary of the SUNFISH study included an overview of the 12-month results of Part 2 of the SUNFISH study. The 2020 summary can be found **here**.

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SUNFISH Part 2: 24 months

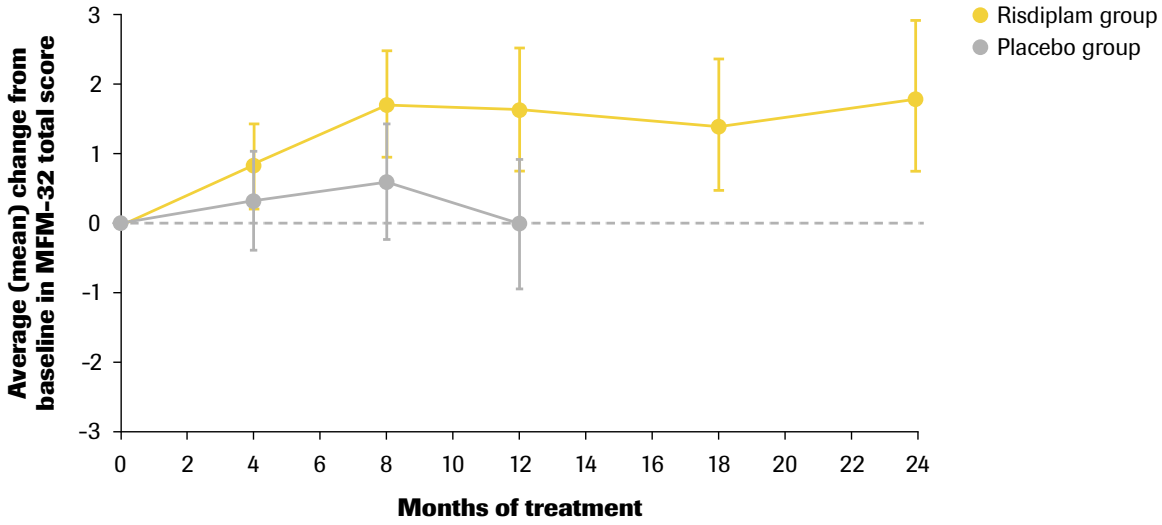
Part 2 efficacy results after 24 months of treatment

As explained previously, the likely outcome for individuals with Type 2 or Type 3 SMA who do not receive any treatment is a decline in mobility and independence.

Overall mobility: results measured by the MFM-32

The increase in mobility that was shown in the first year of Part 2 was maintained from 12 months to 24 months (**Figure 10**).

Figure 10: Average (mean) change in mobility (as measured by the MFM-32, from the start of the study) in individuals who took part in SUNFISH Part 2



Number of individuals measured from the risdiplam group	115	113	113	112	107	103
Number of individuals measured from the placebo group	59	57	58	58		

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
MFM, Motor Function Measure.

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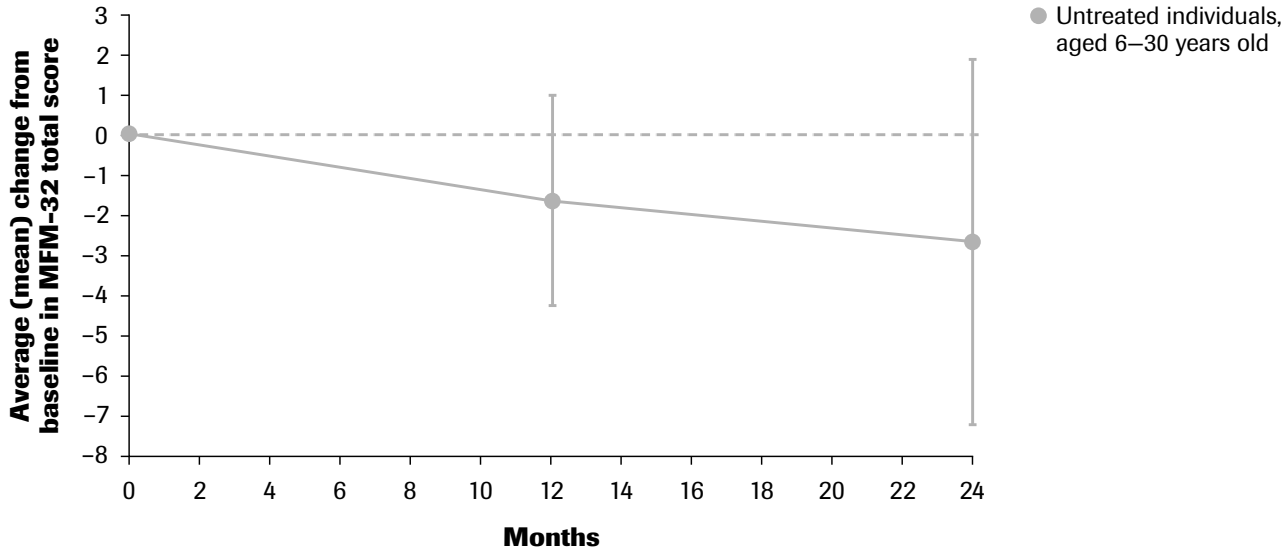
SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

As a point of comparison, individuals with Type 2 or Type 3 SMA who took part in a natural history study (NatHis-SMA) and did not receive any treatment experienced a decline in mobility (**Figure 11**).

Figure 11: Average (mean) change in mobility (as measured by the MFM-32, from the start of the study) in untreated individuals who took part in a natural history study (NatHis-SMA) over 24 months



Number of individuals measured	20	15	9

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
MFM, Motor Function Measure.

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SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

The significance of the MFM-32 results from the SUNFISH study are highlighted by two recent studies looking at how the items on the MFM-32 and changes in the MFM-32 total score relate to the daily life of an individual living with SMA.

In one study, all items on the MFM-32 were considered to be related to at least one important activity of daily living from the perspective of both individuals with Type 2 or Type 3 SMA and their caregivers. These included getting dressed, eating without help and using a touchscreen device.

The other study examined the level of change in the MFM-32 total score that would be considered meaningful to an individual living with Type 2 or Type 3 SMA aged between 2 and 25 years. Overall, the study showed:

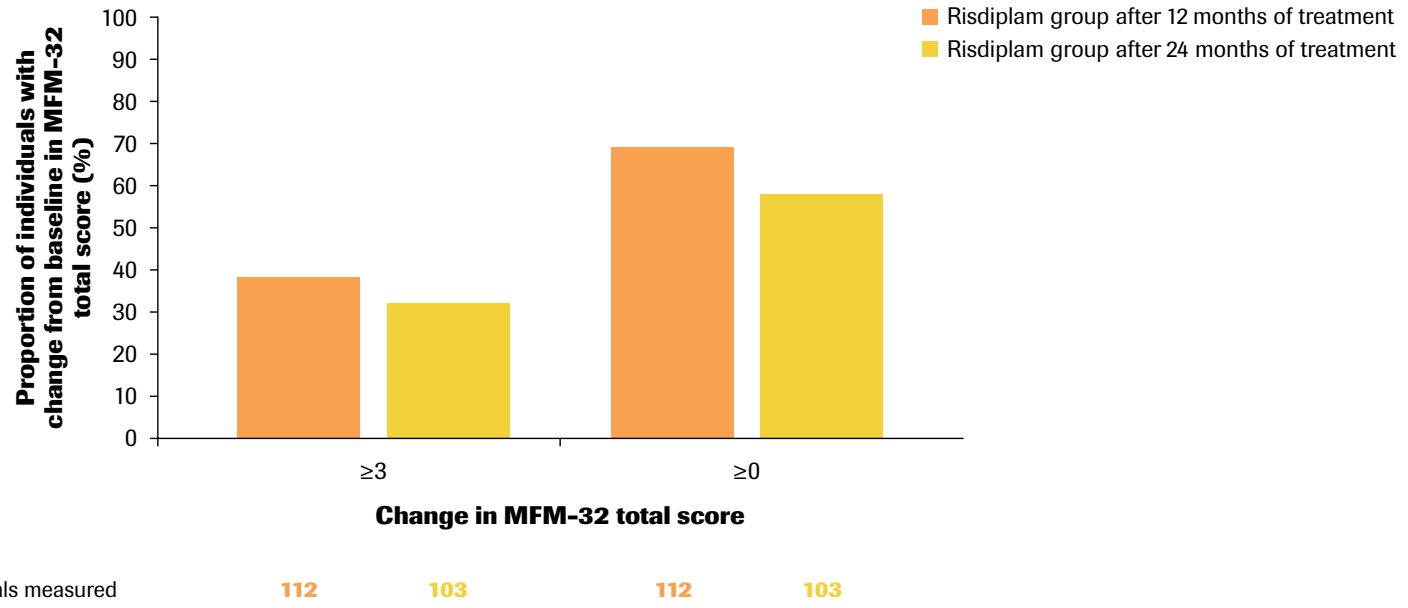
- Disease stabilisation is considered a meaningful outcome
- Even small improvements (2- or 3-point improvement in the MFM-32 total score) may represent a substantial level of change for these individuals
  - Smaller changes are meaningful in late childhood and for adolescents and adults with more progressed disease

Together, these data highlight the importance of the MFM-32 results from the SUNFISH study as they were validated by individuals living with Type 2 or Type 3 SMA.

SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

Figure 12: Percentage of individuals receiving risdiplam who experienced improvement or stabilisation in mobility, as measured by the MFM-32 total score, at Month 12 and Month 24



The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study.
MFM, Motor Function Measure.

The percentage of individuals who improved in overall mobility by 3 or more points (as measured by the MFM-32) was similar for the first year of treatment and the second year of treatment with risdiplam (**Figure 12, left**).

The percentage of individuals who did not experience a decline in overall mobility (as measured by the MFM-32) was similar for the first year of treatment and the second year of treatment with risdiplam (**Figure 12, right)**.

SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

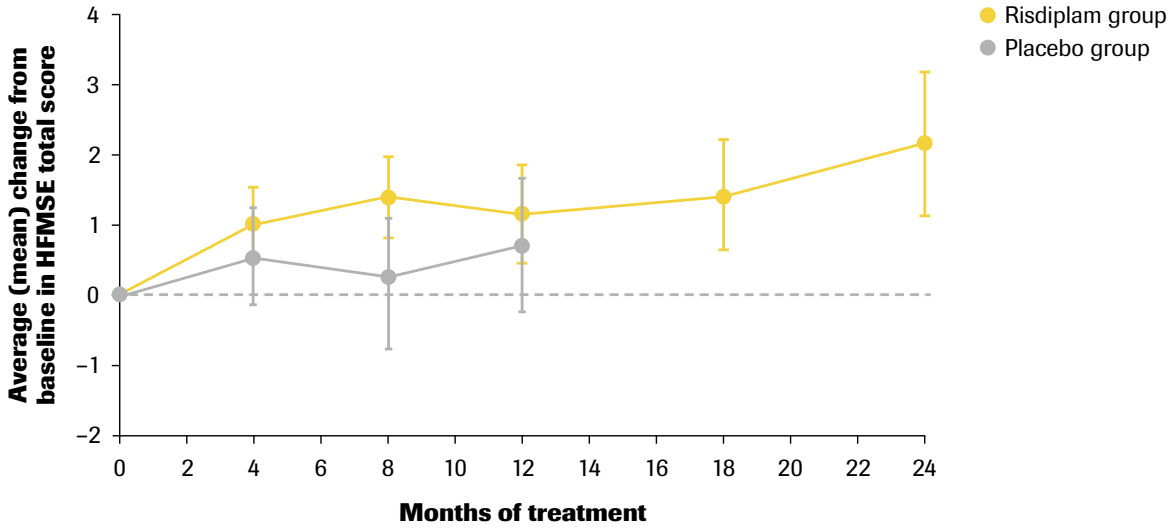
Mobility of the arms, legs and torso (gross motor function): results measured by the HFMSE

Individuals taking part in SUNFISH Part 2 who were treated with risdiplam over 24 months showed improvements in motor function in the arms, legs and torso (compared with the start of the study; **Figure 13**). The increase in HFMSE score (which measures gross motor function) that was shown in the first year of Part 2 continued to improve in the second year.

SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

Figure 13: Average (mean) change in gross motor function (as measured by the HFMSE, from the start of the study) in individuals who took part in SUNFISH Part 2



Number of individuals measured from the risdiplam group	120	120	119	117	109	106
Number of individuals measured from the placebo group	60	60	58	58		

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
HFMSE, Hammersmith Functional Motor Scale Expanded.

To understand what changes in the HFMSE score mean to individuals living with SMA, a different study used focus groups and surveys to explore the views of individuals with SMA and their caregivers about the clinical relevance of the HFMSE. The results from this study suggested that small improvements in the HFMSE total score (even improving by just one or two points) could result in a meaningful change for individuals with SMA.

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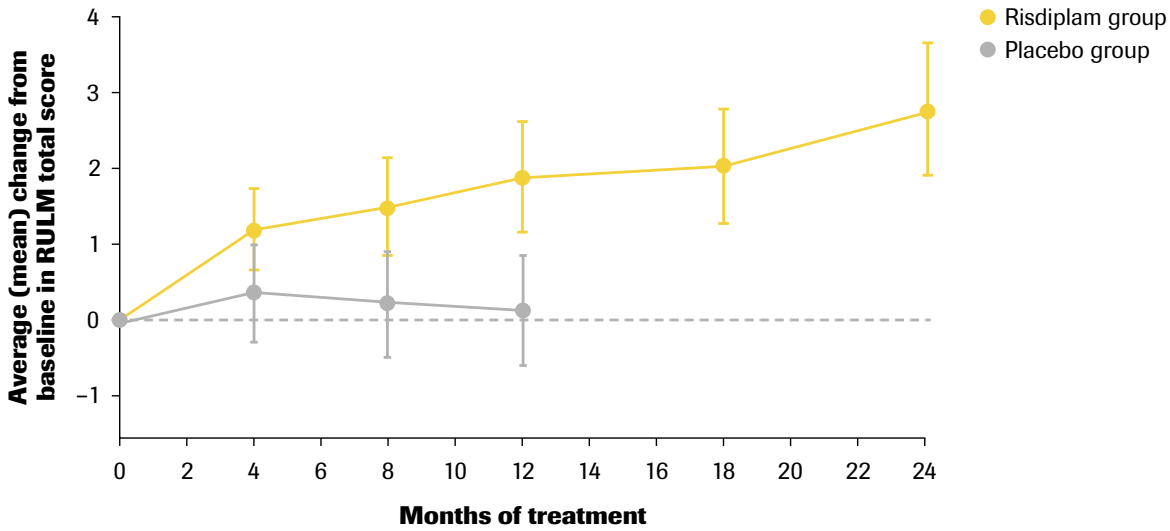
SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

Mobility of the arms and hands (upper limb function): results measured by the RULM

The increase in RULM score (which measures upper limb function) that was shown in individuals treated with risdiplam in the first year of Part 2 continued to improve in the second year (**Figure 14**).

Figure 14: Average (mean) change in upper limb function (as measured by the RULM, from the start of the study) in individuals who took part in SUNFISH Part 2



Number of individuals measured from the risdiplam group	119	119	117	116	108	105
Number of individuals measured from the placebo group	58	57	56	56		

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
RULM, Revised Upper Limb Module.

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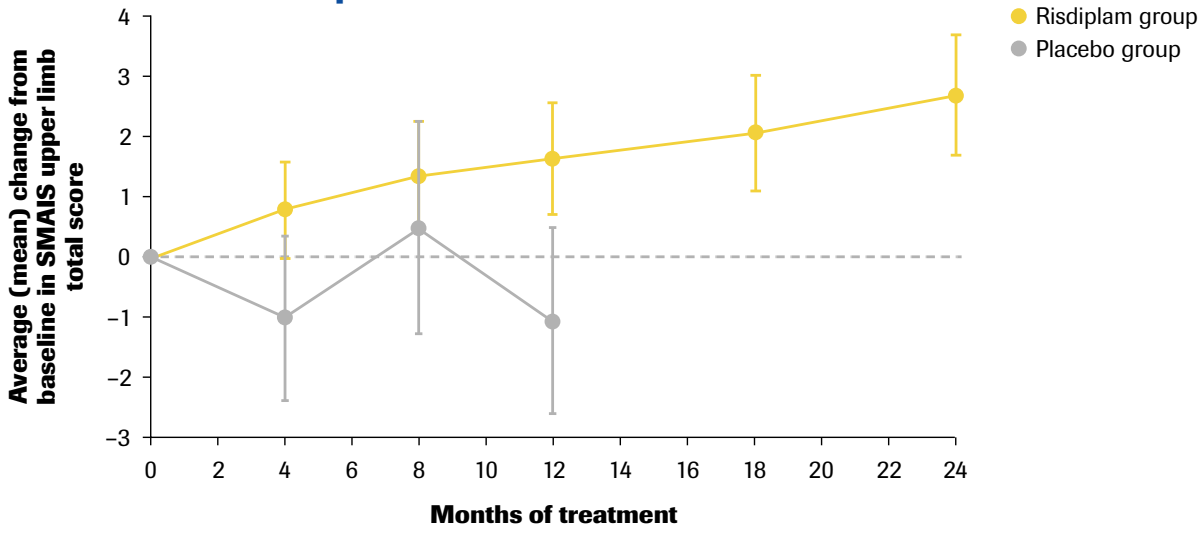
SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

Independence: results measured by the SMAIS upper limb module

Caregivers of the individuals treated with risdiplam over 24 months in SUNFISH Part 2 reported continued improvements in independence compared with the start of the study (**Figure 15**).

Figure 15: Average (mean) change in independence (as measured by the SMAIS upper limb total score, from the start of the study), reported by the caregivers of individuals who took part in SUNFISH Part 2



Number of individuals measured from the risdiplam group	116	114	114	112	108	103
Number of individuals measured from the placebo group	60	60	59	58		

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
SMAIS, Spinal Muscular Atrophy Independence Scale.

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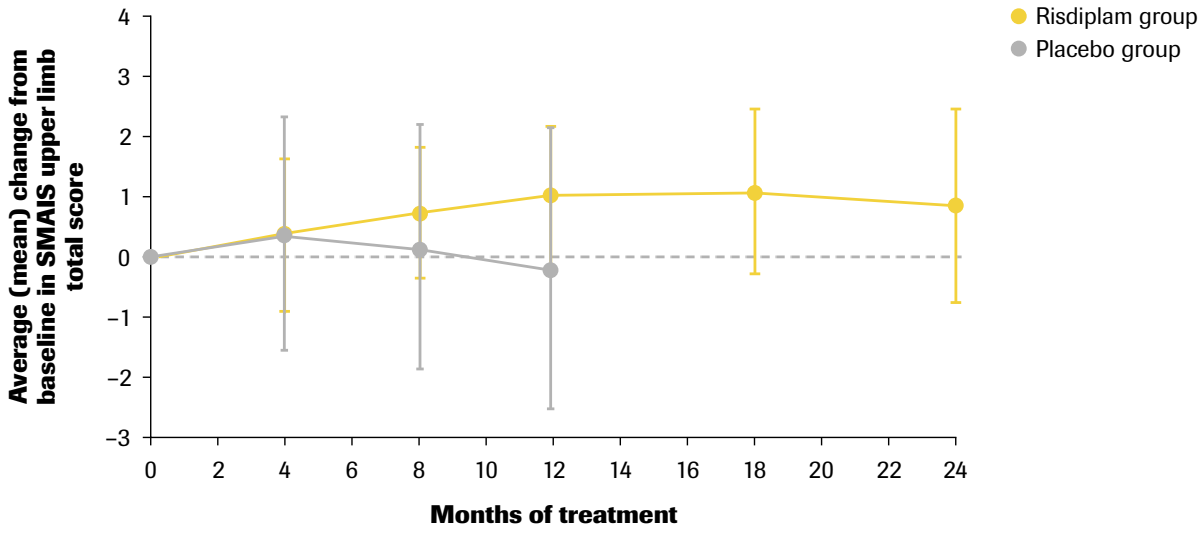
SUNFISH Part 2: 24 months

Part 2 efficacy results after 24 months of treatment

Individuals aged at least 12 years treated with risdiplam over 24 months in SUNFISH Part 2 reported maintained independence compared with the start of the study (**Figure 16**).

Figure 16: Average (mean) change in independence (as measured by the SMAIS upper limb total score, from the start of the study), reported by individuals aged 12 years and older who took part in SUNFISH Part 2



Number of individuals measured from the risdiplam group	43	42	41	43	39	39
Number of individuals measured from the placebo group	23	23	23	23		

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
SMAIS, Spinal Muscular Atrophy Independence Scale.

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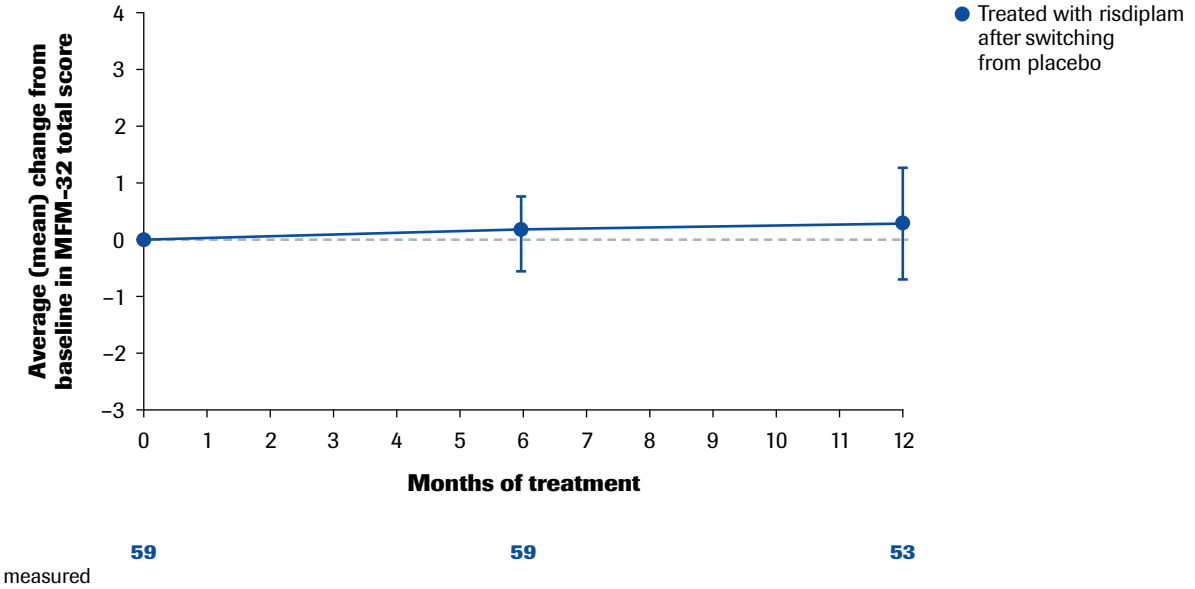
SUNFISH Part 2: 24 months

Part 2 efficacy results for individuals who switched to risdiplam from placebo (12 months of risdiplam treatment)

Mobility (motor function): results measured by the MFM-32 (overall motor function), the HFMSE (gross motor function) and the RULM (upper limb function)

Individuals treated with risdiplam for 12 months after switching from placebo showed stable overall motor function, gross motor function and upper limb function (**Figures 17–19**). For these results, baseline was defined as the last measurement before treatment with risdiplam was started.

Figure 17: Average (mean) change in mobility (as measured by the change in MFM-32 total score, from the last measurement before treatment with risdiplam was started)



The placebo period is not shown in this figure.
The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
MFM, Motor Function Measure.

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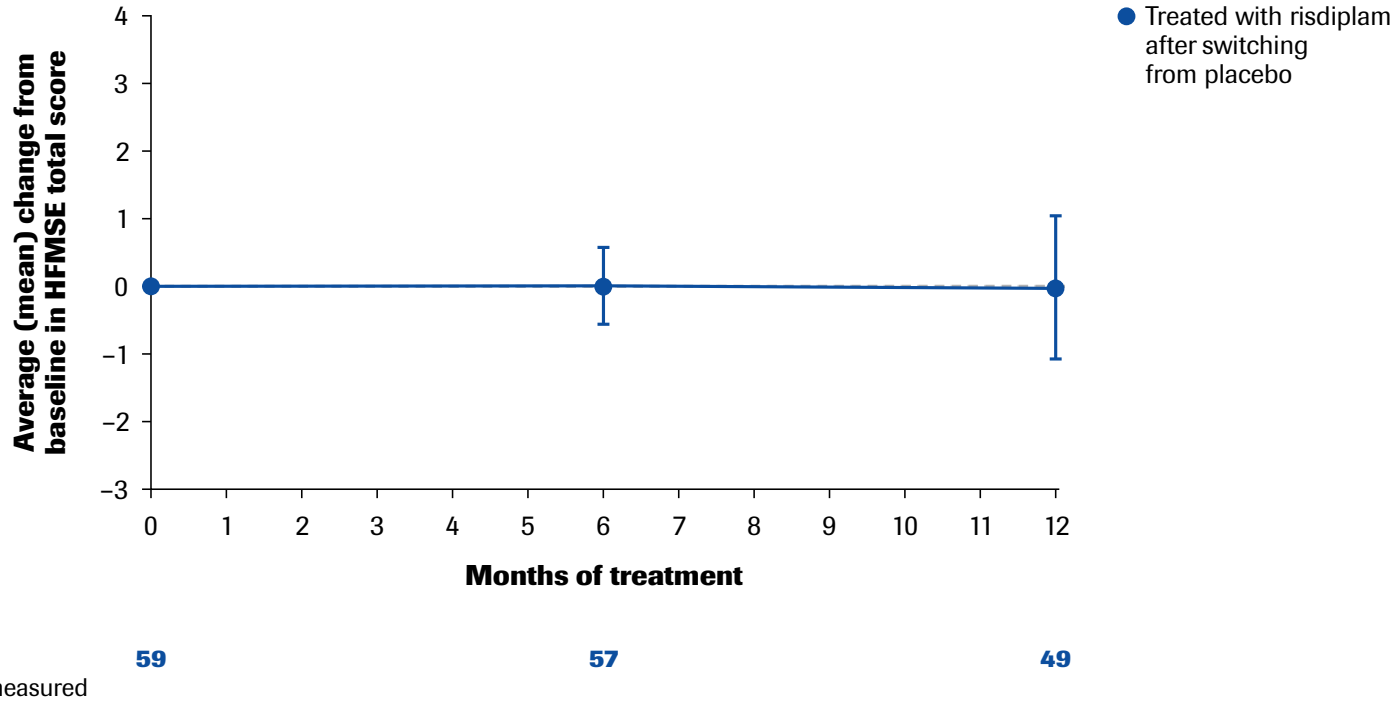
SUNFISH Part 2: 24 months

Part 2 efficacy results for individuals who switched to risdiplam from placebo (12 months of risdiplam treatment)

Figure 18: Average (mean) change in gross motor function (as measured by the change in HFMSE total score, from the last measurement before treatment with risdiplam was started)



The placebo period is not shown in this figure.
The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
HFMSE, Hammersmith Functional Motor Scale Expanded.

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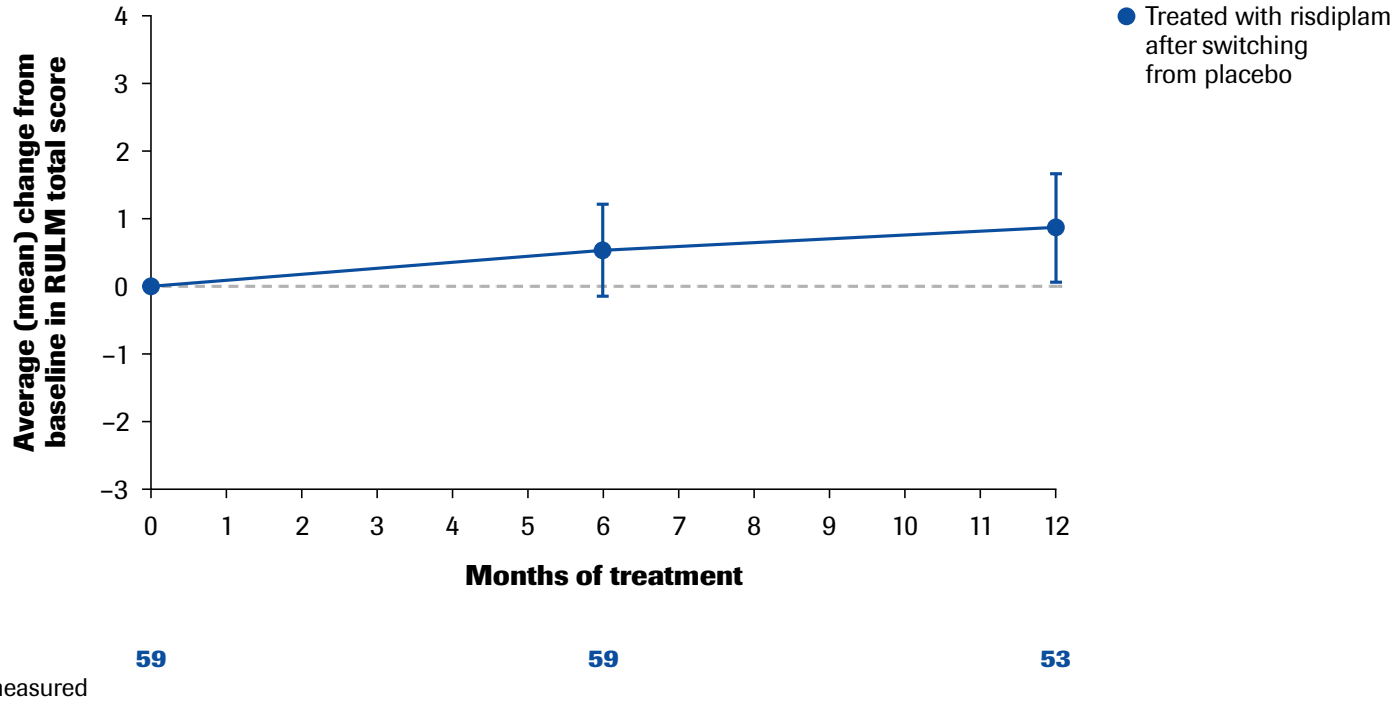
SUNFISH Part 2: 24 months

Part 2 efficacy results for individuals who switched to risdiplam from placebo (12 months of risdiplam treatment)

Figure 19: Average (mean) change in upper limb function (as measured by the RULM total score, from the last measurement before treatment with risdiplam was started)



The placebo period is not shown in this figure.
The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
RULM, Revised Upper Limb Module.

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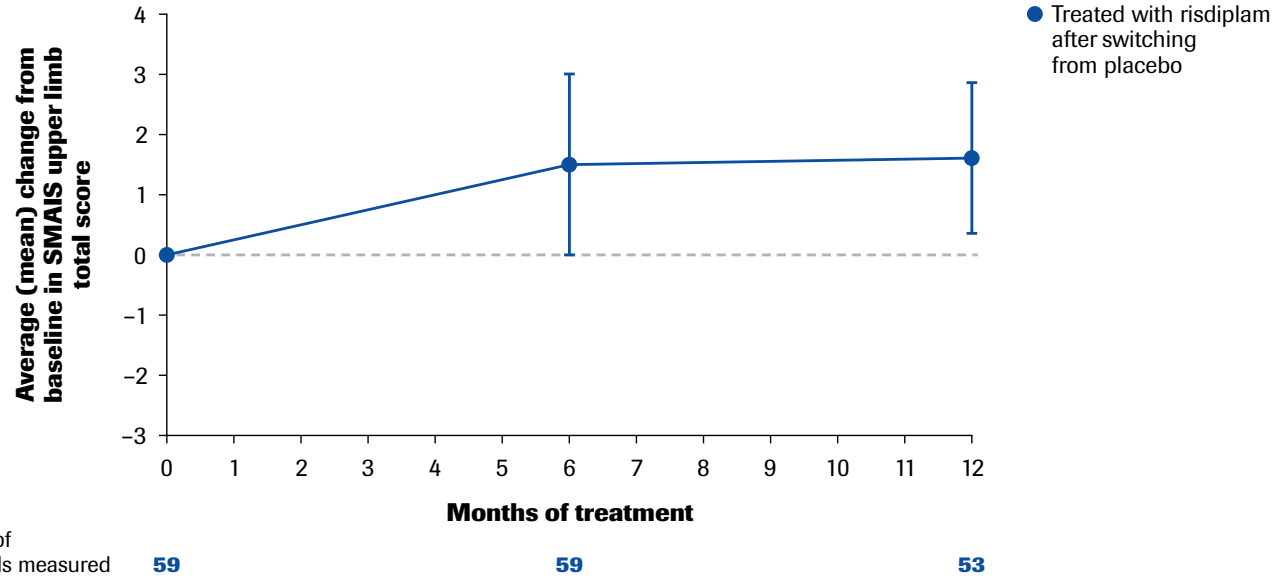
SUNFISH Part 2: 24 months

Part 2 efficacy results for individuals who switched to risdiplam from placebo (12 months of risdiplam treatment)

Independence: results measured by the SMAIS upper limb module

Caregivers of the individuals treated with risdiplam for 12 months (after switching from placebo) reported increased independence compared with baseline (**Figure 20**). Individuals treated with risdiplam over 12 months (after switching from placebo) reported maintained independence, compared with baseline (**Figure 21**). For these results, baseline was defined as the last measurement before treatment with risdiplam was started.

Figure 20: Average (mean) change in independence reported by the caregivers of individuals who took part in SUNFISH Part 2 (as measured by the SMAIS upper limb total score, from the last measurement before treatment with risdiplam was started)



The placebo period is not shown in this figure.
The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
SMAIS, Spinal Muscular Atrophy Independence Scale.

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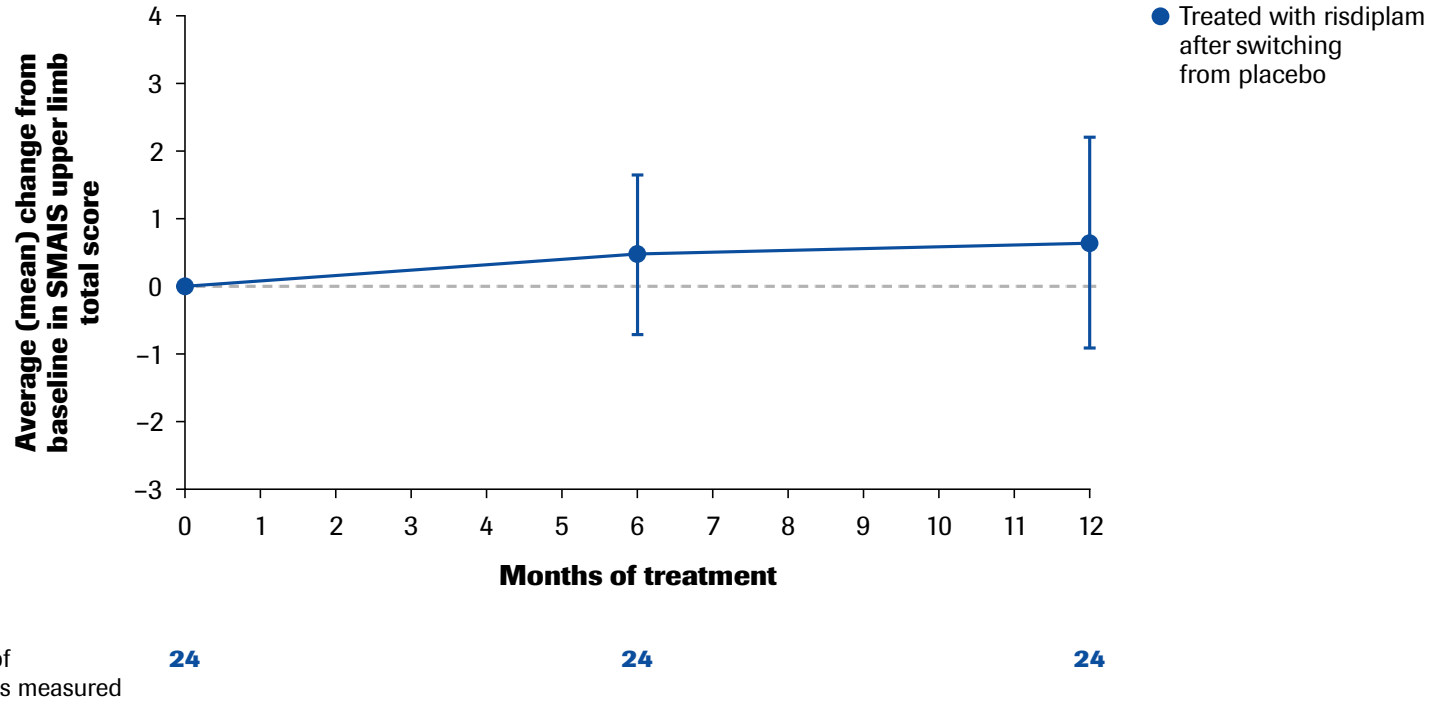
SUNFISH Part 2: 24 months

Part 2 efficacy results for individuals who switched to risdiplam from placebo (12 months of risdiplam treatment)

Figure 21: Average (mean) change in independence reported by individuals aged 12 years and older who took part in SUNFISH Part 2 (as measured by the SMAIS upper limb total score, from the last measurement before treatment with risdiplam was started)



The placebo period is not shown in this figure.
The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. Error bars represent the 95% confidence interval (this shows the degree of uncertainty or certainty in the result).
SMAIS, Spinal Muscular Atrophy Independence Scale.

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SUNFISH Part 2: 24 months

Safety results of Part 2 of the study (after 24 months of treatment)

No individuals left the study due to any side effects from risdiplam.

A table summarising the safety results is shown on the following page (**Table 6**). The percentage of individuals who had each of the most common side effects, or serious side effects, during the 24 months of treatment with risdiplam is included in brackets.

Serious side effects are those that are considered life-threatening or that need hospital care.

SUNFISH Part 2: 24 months

Safety results of Part 2 of the study (after 24 months of treatment)

Table 6: Side effects of individuals who took part in SUNFISH Part 2, after 12 months with risdiplam or placebo, and after 24 months of treatment with risdiplam

Side effects, number of individuals (% of individuals)		Risdiplam group 0–12 months (120 individuals)	Risdiplam group >12–24 months (120 individuals)	Placebo group: placebo from 0–12 months (60 individuals)	Placebo group: risdiplam from >12–24 months (60 individuals)
Most common side effects	Upper respiratory tract infection	38 (31.7)	19 (15.8)	18 (30.0)	6 (10.0)
	Cold	31 (25.8)	26 (21.7)	15 (25.0)	10 (16.7)
	Fever	25 (20.8)	16 (13.3)	10 (16.7)	6 (10.0)
	Headache	24 (20.0)	12 (10.0)	10 (16.7)	10 (16.7)
	Diarrhoea	20 (16.7)	9 (7.5)	5 (8.3)	6 (10.0)
	Vomiting	17 (14.2)	14 (11.7)	14 (23.3)	8 (13.3)
	Cough	17 (14.2)	12 (10.0)	12 (20.0)	5 (8.3)
Most common serious side effects	Pneumonia	9 (7.5)	8 (6.7)	1 (1.7)	0 (0)
	Flu	2 (1.7)	1 (0.8)	0 (0)	0 (0)

The reported side effects and serious side effects were in line with those seen in untreated individuals with SMA.

The number of side effects, severe side effects, serious side effects and side effects related to treatment reduced from the first year of treatment to the second year of treatment.

Additional information

How has this study helped individuals living with SMA and researchers?

For a disease like SMA in which 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.

Individuals 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 those living with SMA a better understanding of the effects of risdiplam on individuals with Type 2 and Type 3 SMA. The results have also enabled Roche to study risdiplam in a broader and older population than ever studied before.

SUNFISH is the first SMA study to involve individuals beyond the age of 9 years old, including teenagers and young adults up to the age of 25 years. The results have enabled the sponsoring company (Roche) to submit risdiplam for regulatory approval by health authorities to make this treatment available to individuals with Type 2 or Type 3 SMA around the world. Risdiplam received first approval for use in the USA for the treatment of SMA in individuals 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.

This summary included results from over a longer period of time (up to 24 months of treatment) compared with the 2020 summary (which included results up to 12 months of treatment). These longer-term results are important to help us understand whether motor function and independence will continue to be maintained or improved in individuals with Type 2 or Type 3 SMA in the second year of treatment. They are also important to confirm the continued acceptable safety profile of risdiplam after 24 months.

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.

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Additional information

How is the SUNFISH study different from the FIREFISH study?

The FIREFISH study was carried out to understand the safety and efficacy of risdiplam in treating children with Type 1 SMA, aged between 1 and 7 months at the time they entered the study.

The SUNFISH study was carried out to understand the safety and efficacy of risdiplam in treating children, adolescents and adults with Type 2 or Type 3 SMA, aged between 2 and 25 years at the time they entered the study.

The FIREFISH study was designed differently to the SUNFISH study.

- The whole of the FIREFISH study was '**open label**', meaning that all the individuals taking part in the study were given risdiplam, and all participants and researchers knew what treatment they were receiving
- The first year of the SUNFISH study was '**placebo controlled**', which means that individuals were randomly selected to receive either risdiplam or placebo. The second year of the SUNFISH study was '**open label**'

The reason placebo was not given to any child taking part in the FIREFISH study was that children with Type 1 SMA have a very short life expectancy without treatment: most untreated children would not live longer than 2 years or would need permanent breathing support. Therefore, it would have been unethical to give a placebo to these children.

In the FIREFISH study, because most of the infants from Part 1 and Part 2 received risdiplam at the same dose and for the same length of time, the results from these individuals can be combined (pooled results). However, in the SUNFISH study, the results from Part 1 and Part 2 cannot be combined as some of the individuals were given placebo for the first 12 months before switching to risdiplam, while the other participants were given risdiplam for the duration of the study (24 months); the two groups cannot be combined as they received different treatment.

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Additional information

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 taken 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

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