A summary of 1-year data from JEWELFISH, a clinical trial to establish the safety, tolerability and pharmacokinetics/ pharmacodynamics of risdiplam in individuals with SMA who were previously treated with other SMA therapies

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

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

The JEWELFISH study started in March 2017 and is still ongoing. This document provides a summary of the initial (interim) results from the first year of the study. Please see **Figure 1** for an overview of the information that can be found in this summary.

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

All individuals taking part in the JEWELFISH study are receiving risdiplam. Researchers and the individuals/families are aware of the treatment that is being given; this is sometimes referred to as an '**open-label**' study design.

In this study, researchers are aiming to see how risdiplam works in people who have previously received other treatments for SMA and what side effects it causes. The results from this study will help researchers to work out:

- What the side effects of taking risdiplam are in individuals who have previously received other treatments for SMA

- How risdiplam is handled and processed by the body (this is known as 'pharmacokinetics')

- How risdiplam works inside the body (this is known as 'pharmacodynamics')

All of the individuals taking part in this study have previously been treated with other therapies for SMA. These therapies are:

- Nusinersen (SPINRAZA®)

- Onasemnogene abeparvovec (ZOLGENSMA®)

- RG7800 (the drug that was given to individuals taking part in the MOONFISH study)
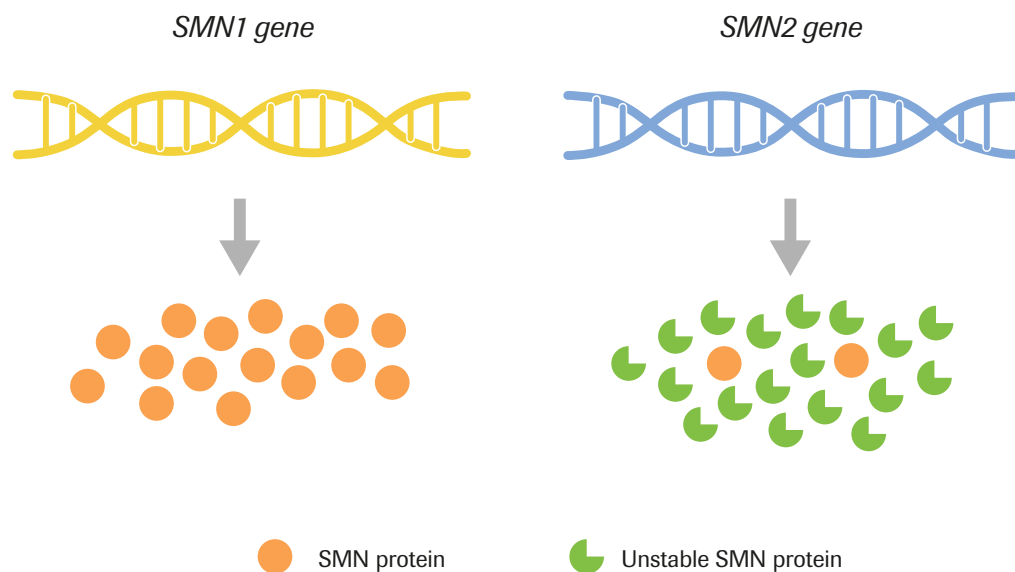
- Olesoxime

Nusinersen and onasemnogene abeparvovec are both therapies that have been approved in some countries for the treatment of individuals with specific types of SMA. Both RG7800 and olesoxime have been given to individuals with SMA who took part in other studies, but they are no longer being tested for their use as treatments for SMA.

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What is 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

SMN1 gene   *SMN2 gene*

● SMN protein   ◖ Unstable SMN protein

SMN, survival of motor neuron.

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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

General information about this study
What is risdiplam and how does it work?

Risdiplam is the treatment that is being studied in JEWELFISH. 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

Targets mRNA

More functional SMN protein

● SMN protein ◖ Unstable SMN protein
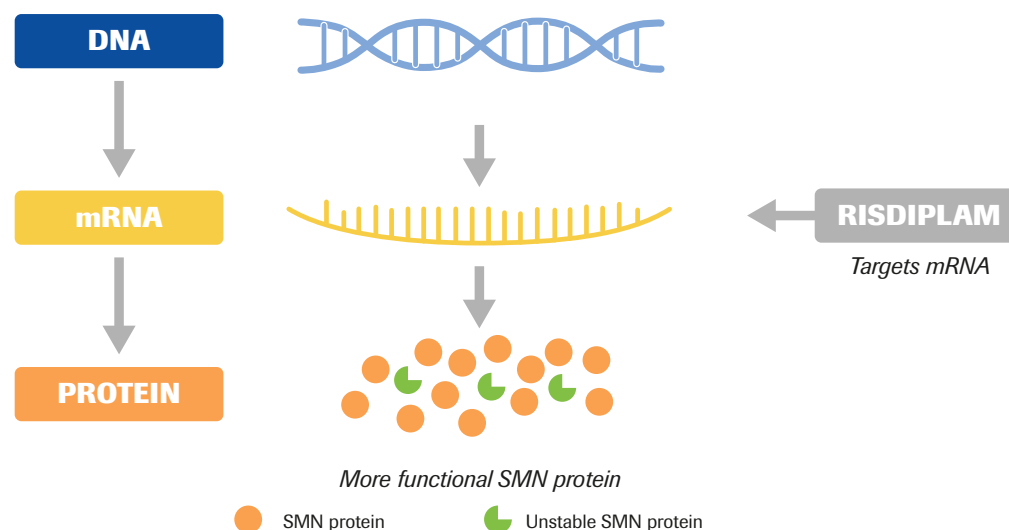
DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; SMN, survival of motor neuron.
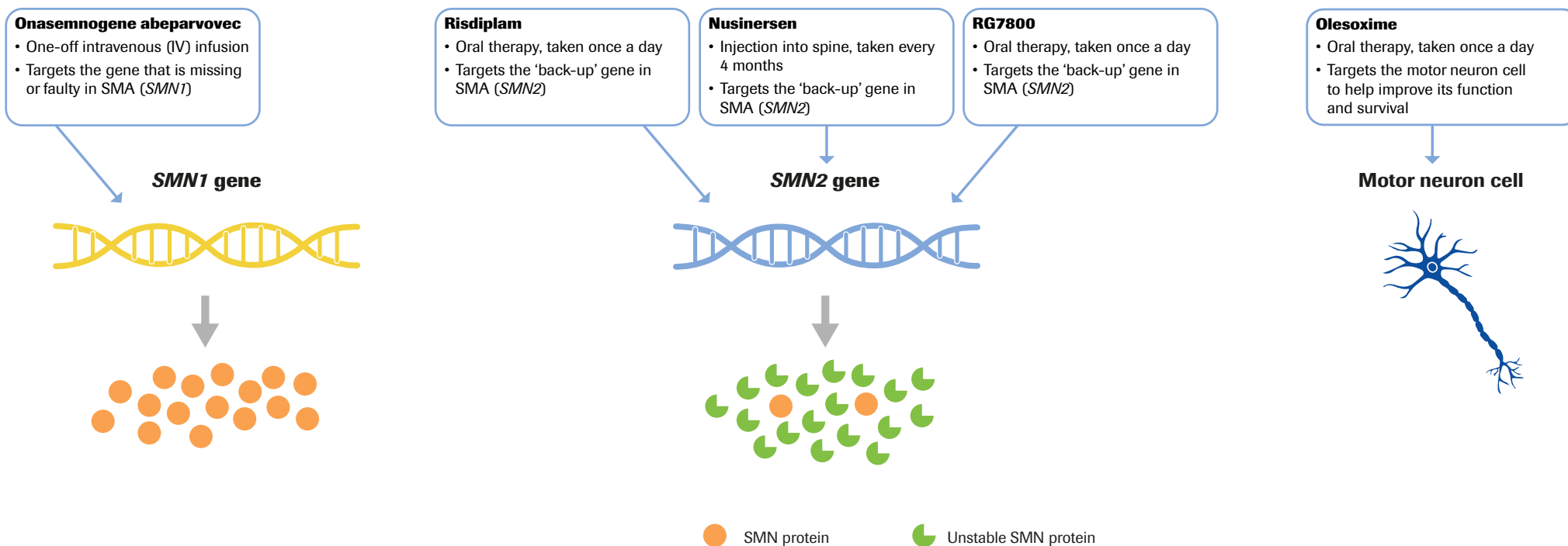
The aim is to prevent the loss of motor neurons and maintain muscle function. Risdiplam is distributed throughout the body, raising the levels of SMN protein in the brain, spinal cord (central nervous system) and other organs.

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Why is the JEWELFISH study being carried out?

Previous risdiplam studies included only individuals who did not receive any prior disease-modifying therapies to treat SMA; these individuals are usually called '**treatment-naïve**'. Unlike other risdiplam studies, all of the individuals taking part in the JEWELFISH study have previously been treated with other therapies for SMA (nusinersen, onasemnogene abeparvovec, RG7800 or olesoxime). SMA therapies may work in different ways and have different routes of administration. These are shown in **Figure 4**.

Figure 4: The route of administration of different SMA therapies, and how these therapies work

Onasemnogene abeparvovec
- One-off intravenous (IV) infusion
- Targets the gene that is missing or faulty in SMA (*SMN1*)

Risdiplam
- Oral therapy, taken once a day
- Targets the 'back-up' gene in SMA (*SMN2*)

Nusinersen
- Injection into spine, taken every 4 months
- Targets the 'back-up' gene in SMA (*SMN2*)

RG7800
- Oral therapy, taken once a day
- Targets the 'back-up' gene in SMA (*SMN2*)

Olesoxime
- Oral therapy, taken once a day
- Targets the motor neuron cell to help improve its function and survival

SMN1 gene

SMN2 gene

Motor neuron cell

● SMN protein   ◖ Unstable SMN protein

SMN, survival of motor neuron.

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Although other SMA therapies are effective for many individuals with SMA, they may not work in all individuals receiving them, and some individuals may experience unacceptable side effects or may decide to stop taking them for other reasons. In addition, some individuals with SMA may hope that a new treatment, such as risdiplam, may give them additional benefits to those they have experienced with a previous treatment. Therefore, it is important to assess the safety of risdiplam in individuals who have previously received other SMA treatments.

The JEWELFISH study will allow researchers to assess the side effects (safety) of risdiplam in individuals with SMA who have been previously treated with other SMA therapies. It will also show how risdiplam works in the body (pharmacokinetics/pharmacodynamics) of these individuals.

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How was the study designed?

All individuals taking part in the JEWELFISH study received risdiplam. Researchers and the individuals/families were aware of the treatment that was being given, this is sometimes referred to as an '**open-label**' study design. No one was being given '**placebo**' (a dummy drug with no active ingredient and which has no real physical effect on the individual).
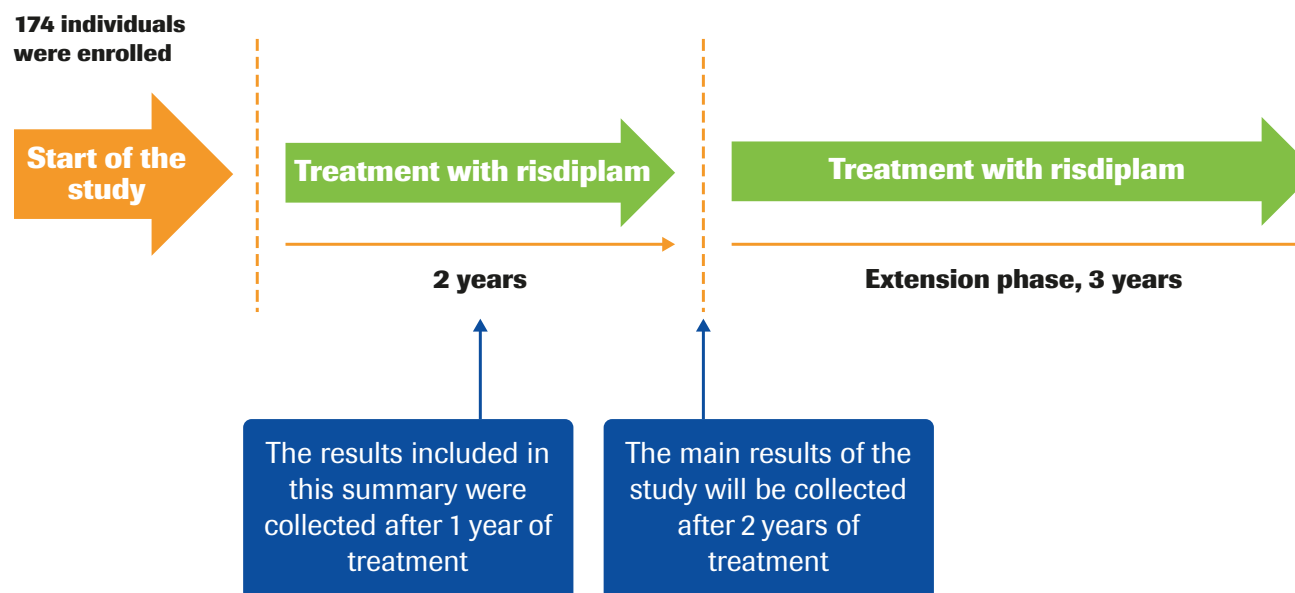
All of the individuals taking part in the study are given risdiplam once a day for 2 years. After 2 years, they will be asked whether they would like to carry on receiving risdiplam for another 3 years (the extension phase of the study). The main results of the study will be reported after the individuals taking part in the study have been treated for 2 years.

This summary includes results from 1 year of treatment with risdiplam. These results are called an '**interim**' analysis (**Figure 5**).

Figure 5: The design of the JEWELFISH study

Previous SMA treatment
- RG7800
- Nusinersen
- Olesoxime
- Onasemnogene abeparvovec

174 individuals were enrolled

Start of the study

Treatment with risdiplam

2 years

Treatment with risdiplam

Extension phase, 3 years

The results included in this summary were collected after 1 year of treatment

The main results of the study will be collected after 2 years of treatment

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General information about this study

What are the aims of the study?

The JEWELFISH study aims to answer a number of different questions about risdiplam, as shown in the table on the following page (**Table 2**).

In order to understand the effects of risdiplam and help answer the different questions set by researchers, the study is assessing 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

The JEWELFISH study includes several main measures (primary endpoints) as well as other measures (secondary and exploratory endpoints).

To take some of these measurements, assessment scales are used to evaluate mobility in the individuals taking part in the study. You can find a full description of the scales in the section '**How is mobility (motor function) measured in this study?**' later in this document.

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What are the study endpoints for JEWELFISH?

Table 2: Questions the researchers wanted to answer during the JEWELFISH study (primary, secondary and exploratory endpoints)

The main questions the researchers want to answer (primary endpoints)	Other important questions the researchers want to answer (secondary endpoints)
• What are the side effects of risdiplam in individuals who have previously received other treatments for SMA? • How is risdiplam handled and processed by the body (pharmacokinetics)?	How does risdiplam affect the amount of SMN protein in the blood?
	Any additional questions the researchers want to answer (exploratory endpoints)
	What is the effect of risdiplam on mobility (as measured by the change in MFM-32* total score from the start of the study)?

*Please see the section '**How is mobility (motor function) measured in this study?**' for a full description of the assessment scales used.

MFM, motor function measure; SMN, survival of motor neuron.

The effect of risdiplam on mobility was one of the main questions that researchers wanted to answer (primary endpoints) in other risdiplam studies (FIREFISH and SUNFISH). The FIREFISH and SUNFISH studies included individuals who had not received any prior disease-modifying therapies to treat SMA (treatment-naïve individuals).

The JEWELFISH study is the first study focussed on the safety of risdiplam in individuals who have previously received other disease-modifying therapies to treat SMA. Therefore, it is important for the main research questions in this study to be about the safety of risdiplam treatment (rather than the efficacy) as these questions have not been answered before.

General information about this study

Where is the JEWELFISH study taking place?

The JEWELFISH study is a global, multicentre trial, taking place in 24 centres located across nine countries. The countries that are taking part in the JEWELFISH study are shown in the below map (**Figure 6**).

The countries that are taking place in the JEWELFISH study are Belgium, France, Germany, Italy, the Netherlands, Poland, Switzerland, the UK and the USA.

Figure 6: The countries in which the JEWELFISH study is taking place
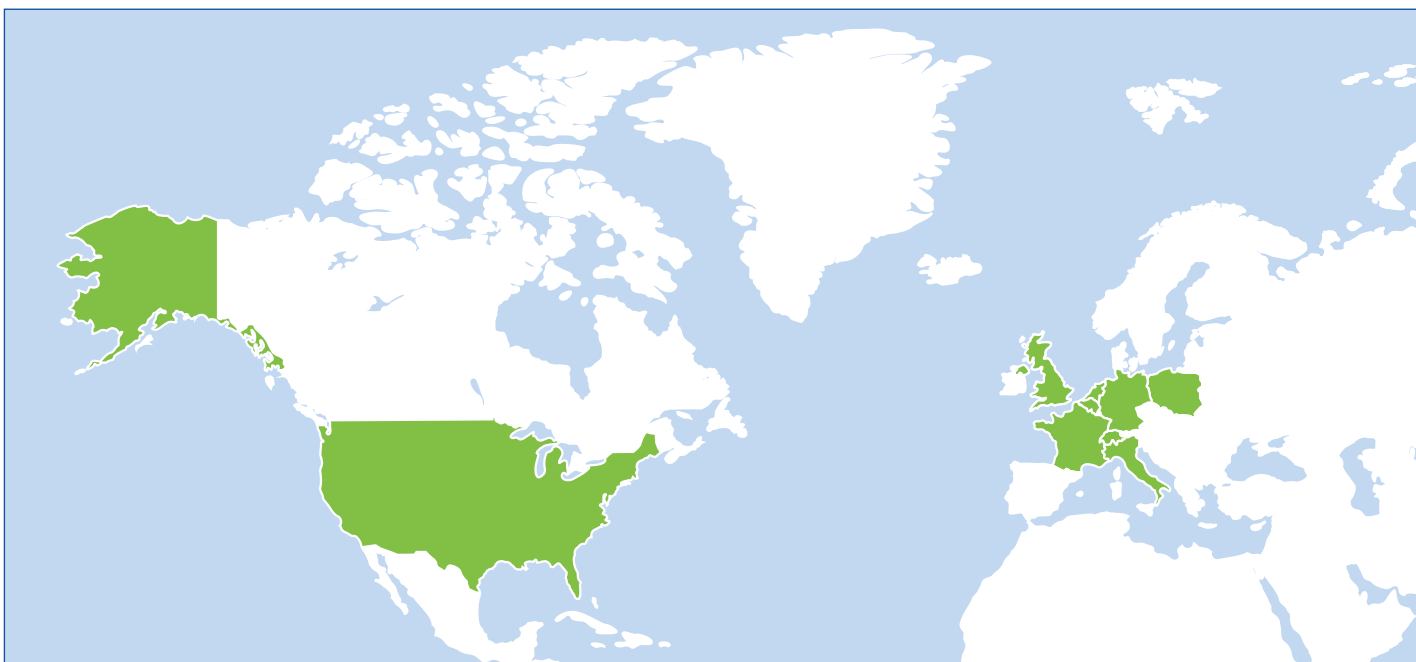
How is mobility (motor function) measured in this study?

It is important to remember that the primary aim of JEWELFISH is to understand the safety of risdiplam in individuals who have previously received other disease-modifying therapies to treat SMA. However, some additional exploratory assessments were included in the study to evaluate the mobility of individuals receiving risdiplam.

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.

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

In JEWELFISH, the MFM-32 was used to evaluate efficacy (as an exploratory endpoint). The HFMSE was used to assess the level of gross motor function at the start of the study, in order for the researchers to understand the severity of the motor function impairment of the individuals who took part in the study before they started risdiplam treatment.

Other assessment scales are also used in the JEWELFISH study to assess mobility, including the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), the Hammersmith Infant Neurological Examination, Module 2 (HINE-2), the Revised Upper Limb Module (RULM) and the 6-minute walk test (6MWT). These scales are not discussed in this summary, but detail on these scales can be found in the brochure '**Understanding the MFM and the SMAIS in the context of outcome measurements in SMA**'.

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Who is taking part in this study?

In total, 174 individuals with SMA aged between 6 months and 60 years are taking part (enrolled) in JEWELFISH. See **Table 3** for more information about these individuals (e.g. age, sex, SMA type, level of mobility) at the beginning of the study.

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

- Have Type 1, Type 2 or Type 3 SMA

- Aged between 6 months and 60 years

- Have been previously treated with RG7800 (enrolled in the MOONFISH trial), nusinersen, olesoxime or onasemnogene abeparvovec

If an individual met the following requirements (exclusion criteria), they could not take part in the study:

- Taken part in another study within the past 3 months (apart from a study with nusinersen, onasemnogene abeparvovec or olesoxime)

- Previously received gene or cell therapy, apart from onasemnogene abeparvovec

- Started treatment with oral salbutamol or another β_2-adrenergic agonist that is swallowed (oral) within the past 6 months

- Developed eye disease in the past year

Full details of the inclusion/exclusion criteria can be found at: **https://clinicaltrials.gov/ct2/show/NCT03032172**

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The baseline characteristics of the individuals who are taking 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 taking part in the study are shown in the table on the following page (**Table 3**).

The individuals enrolled in the JEWELFISH study are reflective of the diverse real-world population of individuals living with SMA. The population includes individuals with **severe disease and other SMA-related conditions**, such as scoliosis and hip dislocation.

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Table 3: Baseline characteristics of the individuals who took part in the study

Baseline characteristic		RG7800 (13 individuals)	Nusinersen (76 individuals)	Olesoxime (71 individuals)	Onasemnogene abeparvovec (14 individuals)	All patients (174 individuals)
		Previous treatment				
Average (median) age in years at enrolment (range)		30 (16-58)	12 (1–60)	16 (11–36)	2 (1–5)	14 (1–60)
Number of individuals who were over 18 years of age at enrolment (%)		11 (85)	21 (28)	31 (44)	0	63 (36)
Number of males (%)		9 (69)	40 (53)	35 (49)	11 (79)	95 (55)
Number of individuals with each SMA type (%)	1	0	9 (12)	2 (3)	4 (29)	15 (9)
	2	5 (39)	43 (57)	50 (70)	10 (71)	108 (62)
	3	8 (62)	24 (32)	19 (27)	0	51 (29)
Number of individuals with each number of *SMN2* gene copies (%)	1	0	0	0	1 (7)	1 (1)
	2	0	9 (12)	0	3 (21)	12 (7)
	3	6 (46)	56 (74)	64 (90)	10 (71)	136 (78)
	4	6 (46)	11 (15)	5 (7)	0	22 (13)
	Unknown	1 (8)	0	2 (3)	0	3 (2)
Number of individuals with each level of mobility (motor function) (%)	Non-sitters	7 (54)	21 (28)	29 (41)	2 (14)	59 (34)
	Sitters	3 (23)	42 (55)	42 (59)	12 (86)	99 (57)
	Walkers	3 (23)	13 (17)	0	0	16 (9)
Number of individuals with an HFMSE score of <10 (%)		8 (62)	35 (48)	59 (83)	3 (27)	105 (63)
Number of individuals with scoliosis (%)		9 (69)	61 (84)	66 (93)	3 (27)	139 (83)
Number of individuals with scoliosis with >40 degrees curvature (%)		3 (23)	27 (37)	36 (51)	0	66 (39)
Number of individuals with hip subluxation or dislocation (%)		2 (15)	25 (34)	20 (28)	4 (36)	51 (30)

Please note numbers may not add to 100 due to rounding. HFMSE, Hammersmith Functional Motor Scale Expanded; SMN, survival of motor neuron.

Who is taking part in this study?

Why did individuals with SMA begin treatment with risdiplam following treatment with other SMA therapies?

Although other SMA therapies are effective for many individuals with SMA, there may be reasons why individuals, their caregivers or their physicians decide to stop treatment and try a different SMA therapy.

The main reasons why individuals who had previously been treated with **nusinersen** or their caregivers decided to begin treatment with risdiplam in JEWELFISH were:

Individuals with a curved spine (scoliosis) or who had had surgery on their spine and were concerned about challenges with how the drug was given to them (nusinersen is injected into the spine), or their caregivers were concerned about this

Individuals or their caregivers did not feel that nusinersen was working (lack of efficacy) or had stopped working (loss of efficacy)

Personal preference

Other reasons, such as:

- Concerns about side effects related to treatment
- Challenges with getting funding for the treatment (treatment reimbursement or insurance policy challenges)
- Challenges with accessibility to hospitals that can give the treatment

The main reasons why the caregivers* of individuals who had previously been treated with **onasemnogene abeparvovec** decided to begin treatment with risdiplam in JEWELFISH were:

Caregivers hoped to receive additional benefit with risdiplam treatment

Personal preference

Caregivers did not feel that onasemnogene abeparvovec was working (lack of efficacy)

*All individuals treated with onasemnogene abeparvovec were infants and their caregivers provided these details.

Note: RG7800 and olesoxime (predecessors of risdiplam developed by Roche) are no longer in development as investigational treatments for individuals with SMA; therefore, the reasons for starting risdiplam treatment in individuals previously receiving these treatments were not collected.

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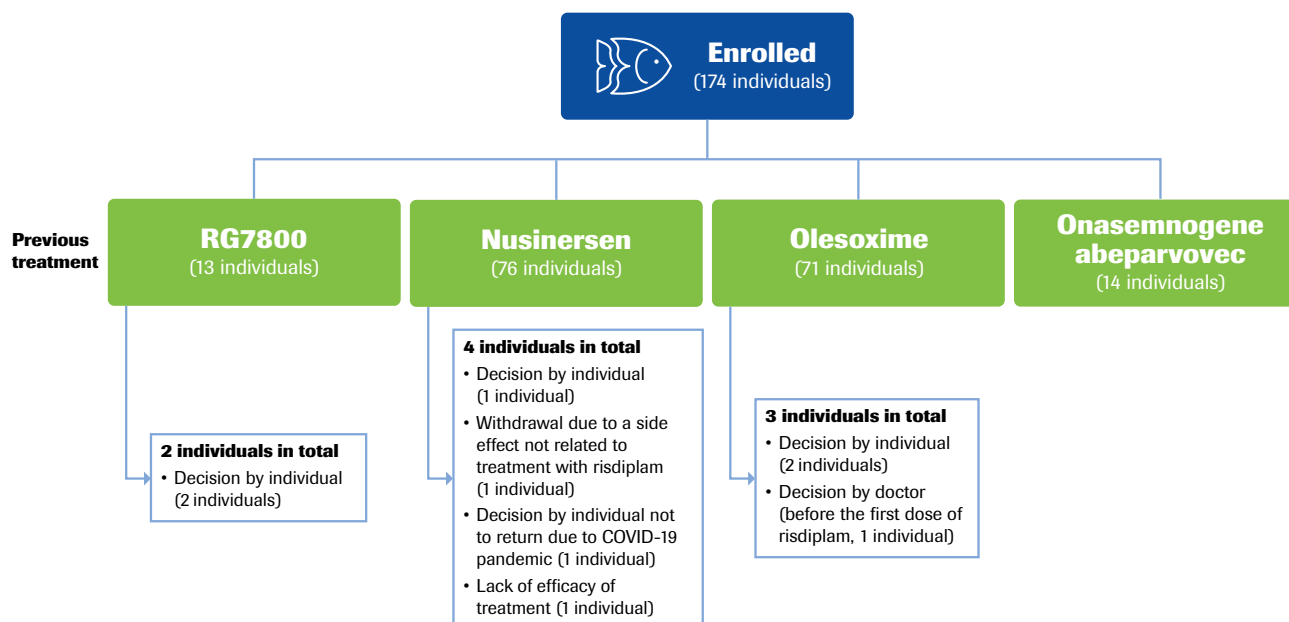
Who is taking part in this study?

How many individuals taking part in the JEWELFISH study have continued treatment since the start of the study?

Most individuals taking part in the JEWELFISH study have continued treatment since the start of the study. Overall, 5% of individuals (9/174) stopped treatment with risdiplam within the first year of treatment (**Figure 7**). The reasons for stopping treatment were:

- The individual or their caregiver decided to stop treatment with no reason given (five individuals)

- The individual or their caregiver decided not to return to the study due to the COVID-19 pandemic (one individual)

- The individual or their caregiver were concerned about a side effect that was not related to treatment (one individual)

- The individual or their caregiver did not feel that the treatment was working (lack of efficacy, one individual)

For one individual, the doctor decided not to start treatment due to difficulties in obtaining blood samples from the individual (poor venous access).

Figure 7: The reasons why individuals who were taking part in the JEWELFISH study stopped treatment with risdiplam within the first year of treatment

Enrolled
(174 individuals)

Previous treatment

RG7800
(13 individuals)

Nusinersen
(76 individuals)

Olesoxime
(71 individuals)

Onasemnogene abeparvovec
(14 individuals)

2 individuals in total
- Decision by individual (2 individuals)

4 individuals in total
- Decision by individual (1 individual)
- Withdrawal due to a side effect not related to treatment with risdiplam (1 individual)
- Decision by individual not to return due to COVID-19 pandemic (1 individual)
- Lack of efficacy of treatment (1 individual)

3 individuals in total
- Decision by individual (2 individuals)
- Decision by doctor (before the first dose of risdiplam, 1 individual)

All individuals who had previously received onasemnogene abeparvovec remained in the study.

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What are the results of this study after 1 year?
Safety results of the study (after 1 year of treatment)

No one left the study due to any side effects that were related to risdiplam. One individual (1%) who reported a side effect that was not related to risdiplam treatment withdrew from the study.

A table summarising the safety results is shown on the following page (**Table 4**). These safety results are split into four groups (for individuals previously treated with RG7800, nusinersen, olesoxime and onasemnogene abeparvovec) and are also shown combined for all individuals in the study. The percentage of individuals who had each of the most common side effects, or serious side effects, during the first year of treatment with risdiplam is included in brackets.

What are the results of this study after 1 year?

Safety results of the study (after 1 year of treatment)

Table 4: Side effects of individuals who took part in the JEWELFISH study, after 1 year of treatment with risdiplam

Side effects, number of individuals (% of individuals)		Previous SMA treatment				Total (173 individuals)
		RG7800 (13 individuals)	Nusinersen (76 individuals)	Olesoxime (70 individuals)	Onasemnogene abeparvovec (14 individuals)	
Individuals with at least one side effect		12 (92)	71 (93)	63 (90)	13 (93)	159 (92)
Individuals with at least one serious side effect		3 (23)	11 (15)	8 (11)	2 (14)	24 (14)
Most common side effects	Upper respiratory tract infection	0	14 (18)	14 (20)	2 (14)	30 (17)
	Fever	1 (8)	17 (22)	8 (11)	4 (29)	30 (17)
	Headache	1 (8)	15 (20)	12 (17)	0	28 (16)
	Feeling sick	0	14 (18)	5 (7)	1 (7)	20 (12)
	Diarrhoea	0	14 (18)	4 (6)	1 (7)	19 (11)
	Cold	2 (15)	7 (9)	6 (9)	2 (14)	17 (10)
	Vomiting	1 (8)	5 (7)	6 (9)	2 (14)	14 (8)
Most common serious side effects	Pneumonia	0	2 (3)	1 (1)	1 (7)	4 (2)
	Lower respiratory tract infection	0	1 (1)	2 (3)	0	3 (2)
	Upper respiratory tract infection	0	3 (4)	0	0	3 (2)
	Respiratory failure	0	3 (4)	0	0	3 (2)

What are the results of this study after 1 year?
Safety results of the study (after 1 year of treatment)

Additional safety results

The reported side effects and serious side effects were in line with those expected in untreated individuals with SMA of the same age.

Nevertheless, serious side effects (e.g. those that need hospital care) were seen in 24 individuals (14%).

- One individual (1%) had a serious side effect that was related to risdiplam treatment. This serious side effect was a sudden, faster heartbeat than normal (supraventricular tachycardia), and this side effect went away without change to risdiplam treatment

- Six individuals (4%) who had serious side effects had a change in dose or an interruption of treatment with risdiplam

There were no deaths.

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What are the results of this study after 1 year?

Results of the study that show how SMN protein levels changed over 1 year of risdiplam treatment

Risdiplam treatment led to rapid and sustained increases in SMN protein levels in individuals taking part in JEWELFISH

SMN protein is critical to the function of the nerves that control the muscles. Risdiplam is designed to help the *SMN2* gene to produce more functional SMN protein.

SMN protein levels were measured throughout the study to see how these levels change in individuals with SMA while they are being treated with risdiplam.
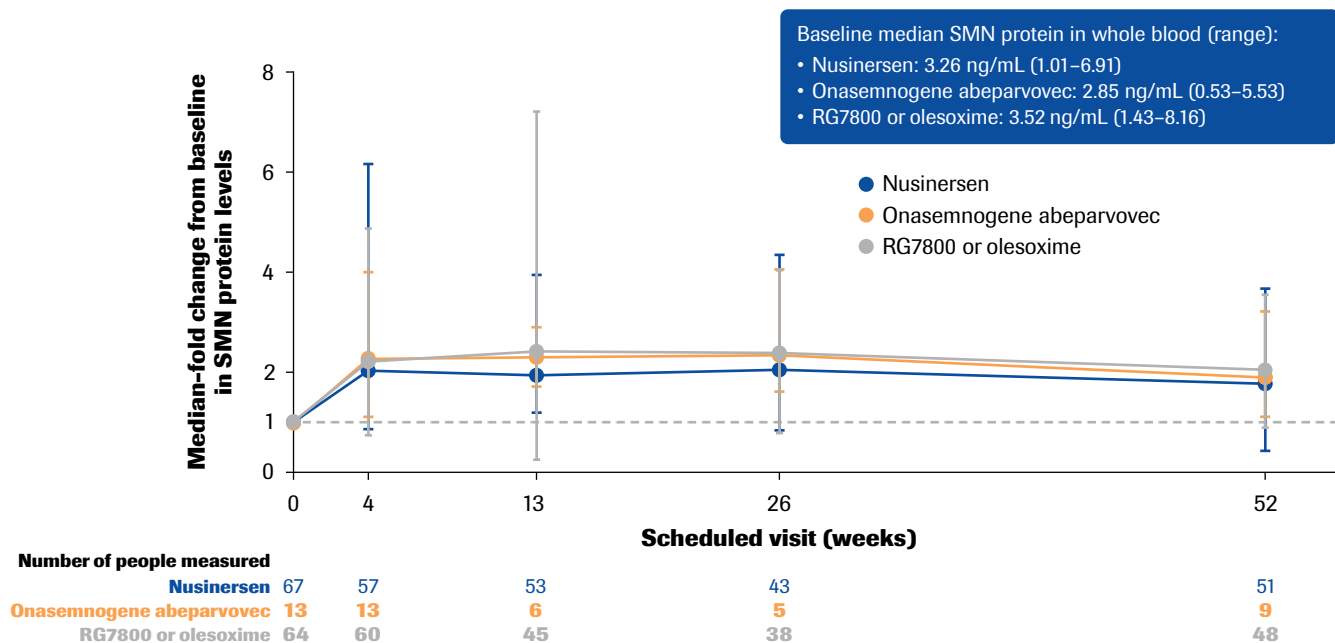
After starting risdiplam treatment, SMN protein levels increased quickly (within 4 weeks) and stayed at the increased level over the whole year of treatment (**Figure 8**). This change in SMN protein was similar for all individuals taking part in the study, no matter which SMA therapy they had previously received.

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What are the results of this study after 1 year?

Results of the study that show how SMN protein levels changed over 1 year of risdiplam treatment

Figure 8: Average (mean) SMN protein levels over 1 year of risdiplam treatment in individuals who are taking part in the JEWELFISH study

Baseline median SMN protein in whole blood (range):
- Nusinersen: 3.26 ng/mL (1.01–6.91)
- Onasemnogene abeparvovec: 2.85 ng/mL (0.53–5.53)
- RG7800 or olesoxime: 3.52 ng/mL (1.43–8.16)

● Nusinersen
● Onasemnogene abeparvovec
● RG7800 or olesoxime

Y-axis: Median-fold change from baseline in SMN protein levels
X-axis: Scheduled visit (weeks)

Number of people measured

	0	4	13	26	52
Nusinersen	67	57	53	43	51
Onasemnogene abeparvovec	13	13	6	5	9
RG7800 or olesoxime	64	60	45	38	48

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. The number of people at each hospital visit was lower in 2020 than in previous years.
Error bars represent range (minimum–maximum values).
SMN, survival of motor neuron.

These results are similar to the SMN protein level results from other risdiplam studies, called FIREFISH and SUNFISH. FIREFISH is a study that included children aged between 1 and 7 months with Type 1 SMA, and SUNFISH is a study that included individuals aged between 2 and 25 years with Type 2 or Type 3 SMA. For more information on these studies, please click **here** for FIREFISH and **here** for SUNFISH.

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What are the results of this study after 1 year?
Exploratory efficacy results of the study (after 1 year of treatment)

> **Over 1 year of treatment with risdiplam, exploratory results showed stabilisation in overall motor function in individuals with SMA**

The individuals enrolled in the JEWELFISH study are reflective of the diverse real-world population of individuals living with SMA. Most of the individuals who took part in JEWELFISH had **severe mobility impairment** at the beginning of the study (of 168 evaluable participants at baseline, 83% experienced scoliosis and 30% had hip subluxation or dislocation).

For the 1-year (interim) results, mobility was assessed by the MFM-32. Motor function was stabilised (further progression of the disease was prevented) over 1 year of risdiplam treatment in individuals aged between 2 and 60 years who had been previously treated with other SMA therapies (**Figure 9**). A complete set of mobility measurements, using more motor function assessments, will be performed at the end of the 2-year study treatment period.

What are the results of this study after 1 year?

Exploratory efficacy results of the study (after 1 year of treatment)

Figure 9: Average (mean) change in mobility (measured by the MFM-32) over 1 year of risdiplam treatment in individuals aged 2–60 years
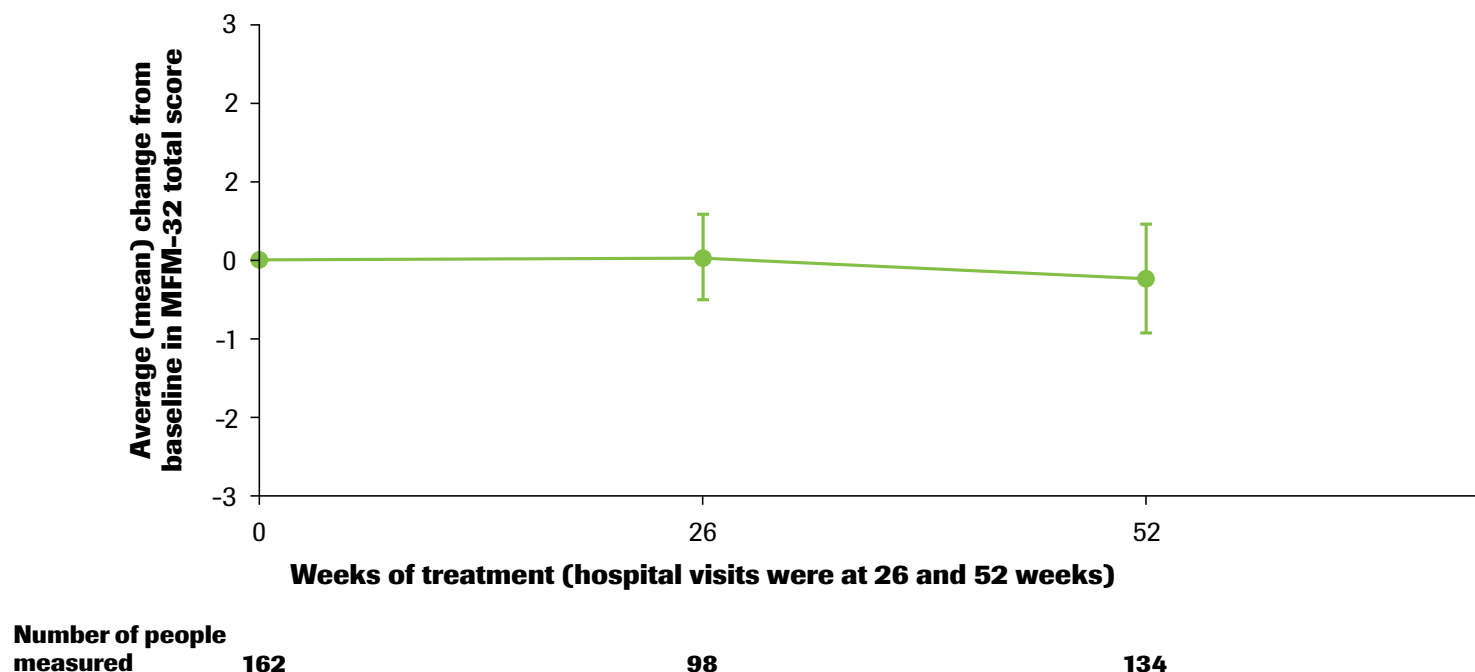
Number of people measured: 162 (week 0), 98 (week 26), 134 (week 52)

The number of people measured at each hospital visit may not add up to the total number of individuals taking part in the study. The number of people at each hospital visit was lower in 2020 than in previous years.
MFM-32, Motor Function Measure.

The current results support the benefit of risdiplam treatment in this diverse population of individuals, which is reflective of the real-world SMA population. For people living with SMA, disease stabilisation is considered to be progress. **In a recent survey of nearly 1500 individuals with SMA in Europe, over 96% considered disease stabilisation to be progress**.

KEY INFORMATION ABOUT THIS STUDY

GENERAL INFORMATION ABOUT THIS STUDY

HOW IS MOBILITY (MOTOR FUNCTION) MEASURED IN THIS STUDY?

WHO IS TAKING PART IN THIS STUDY?

WHAT ARE THE RESULTS OF THIS STUDY AFTER 1 YEAR?

ADDITIONAL INFORMATION

Additional information

How has this study helped individuals with SMA and researchers?

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

Although other SMA therapies are effective for many individuals with SMA, some individuals may not respond well to a particular treatment, may experience side effects or may not wish to continue treatment for personal reasons. The lack of results in previously treated individuals may mean that these individuals have no alternative treatment option.

The JEWELFISH trial is the first study of its kind and enrolled individuals reflecting the real-world SMA population, including:

- Individuals aged between 1 and 60 years, including >30% teenagers and >35% adults. The adult population has been under-represented in previous SMA studies

- Individuals with both high and low levels of mobility, including individuals who can walk, as well as individuals with more severe disease who need a great deal of help from their caregivers in their day-to-day life

Individuals who took part in JEWELFISH have experienced improvements in their symptoms and continue to take risdiplam.

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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KEY INFORMATION ABOUT THIS STUDY

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ADDITIONAL INFORMATION

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/NCT03032172
- A Study of RO7034067 in Adult and Pediatric Participants With Spinal Muscular Atrophy (JEWELFISH) (roche.com)

If you or your child are taking part in this study and you 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: An Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Risdiplam (RO7034067) in Adult and Pediatric Patients With Spinal Muscular Atrophy.

The study is known as 'JEWELFISH'.

Address and telephone number for the sponsor of this trial:

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