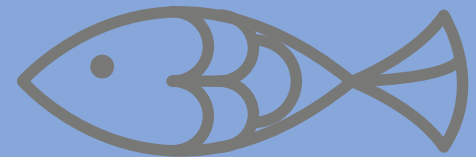
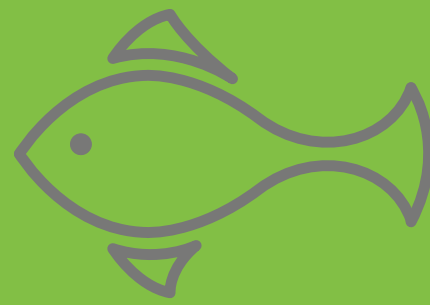
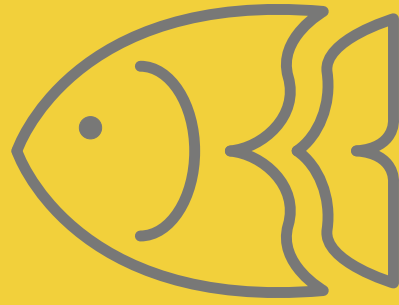


**Roche and Genentech Spinal Muscular Atrophy (SMA)
Clinical Development Programme:**

Risdiplam and the FISH trials



in collaboration with



SMA
FOUNDATION

and



Date of preparation: November 2019 M-XX-00000117

Spinal muscular atrophy: An overview of disease understanding



Spinal muscular atrophy, normally called 'SMA', describes a genetic disorder with different degrees of severity associated with **the loss of motor neurons and disease-related complications** affecting the entire body.^{1,2} Depending on the type of SMA, this could lead to the loss of physical strength and the ability to walk, eat or breathe.² As a disease of the entire body, SMA affects not only muscles but also many other organs.²

The **SMN1 gene** provides instructions for **making the survival of motor neuron (SMN) protein**, which is necessary for the survival of motor neurons and other cell types in the body.²



People with SMA **lack a functioning SMN1 gene**; as a result they have low levels of SMN protein throughout the body.² This suggests that SMA could affect more than just motor neurons outside of the central nervous system (CNS). People with SMA **are dependent on the related SMN2 gene**.² However, this gene **cannot produce enough functional SMN protein**.²

Loss of motor neurons leads to a **loss of muscle mass**, which is **translated to muscle atrophy** – this means that **people with SMA have reduced movement**, thus experiencing a **significant impact** on their **quality of life**.^{2,3}



What is a gene?⁴ A gene is the basic unit of DNA instructions. Each gene has a very specific job to do; some carry the instructions for making proteins (the building blocks for cells) or for turning DNA off or on, whereas others carry the instructions for how to modify other proteins or DNA within a cell.⁴

Spinal muscular atrophy: An overview of disease understanding



The **severity of SMA varies** among individuals and depends on the **age of onset** and the **number of SMN2 copies** they have.² **Type 0**, also called **prenatal onset SMA**, is the **most severe form of this disorder**; it affects babies that are still in the womb.²

These babies experience **severe hypotonia** and are **unable to sit or roll**.² **Type 1**, found in **infants under the age of 2 years**, is a **very severe form of SMA**.² Just like Type 0, infants have **severe hypotonia** and are also **unable to sit or roll**.² The age of onset for **Type 2 SMA** is **6–18 months**; infants with this form of SMA



are **able to sit** but **unable to walk independently**.² **Type 3** is usually diagnosed **after 18 months of age**, but the actual **age of onset is very variable** and may not happen **until late childhood or early adulthood**.²

Individuals with this type of SMA have a **normal life span** but **may lose the ability to walk**.² Finally, **Type 4**, also known as **adult-onset SMA** is the **least severe form of this disorder**.² It is **most often diagnosed in early adulthood**, with individuals experiencing **mild motor impairment**.²



What are motor neurons? Motor neurons are nerve cells that control muscle movement.⁵ Upper motor neurons send messages from the brain to the spinal cord, and lower motor neurons send messages from the spinal cord to the muscles.⁵ They form part of the neuromuscular system and are essential for day-to-day activities like breathing, holding your head up, walking and even holding a book.⁵

Risdiplam is an investigational oral small molecule for people with SMA

Roche/Genentech are committed to investigating potential SMA treatments to address the unmet needs for adults and children with SMA. One of these treatments is risdiplam.

Risdiplam is an investigational (unapproved) medicine developed by Roche/Genentech in partnership with the SMA Foundation and PTC Therapeutics.



Risdiplam is an orally given small molecule, designed to **target the SMN2 gene** and **increase the expression of SMN protein**.⁶ Increasing the amount of available SMN protein should prevent motor neuron degeneration and preserve muscle function.² **Risdiplam is given orally** (it is a liquid taken once daily by mouth or feeding tube if required).



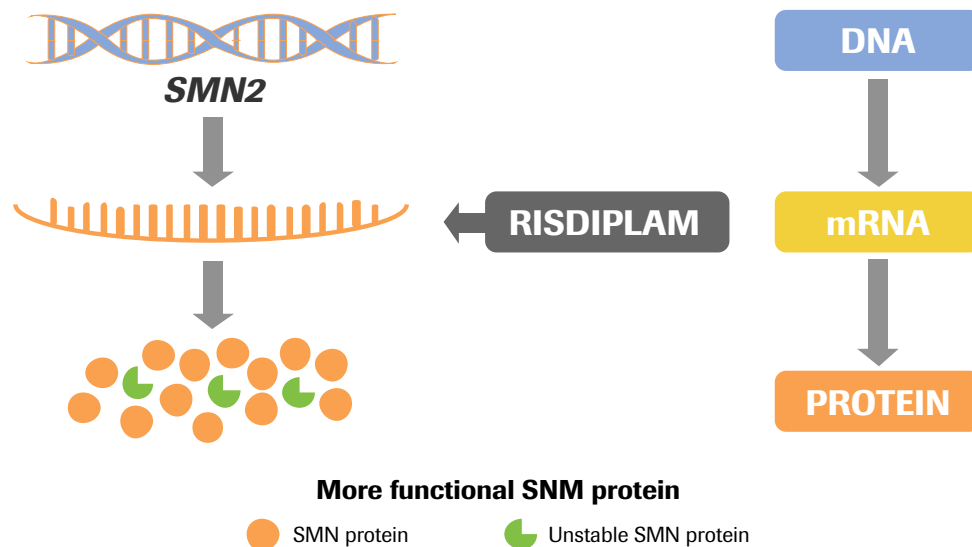
Risdiplam is distributed throughout the body, **raising the levels of SMN protein in various organs, not just the central nervous system** (brain and spinal cord).^{6,7}

The **risdiplam clinical development programme**, sponsored by Roche/Genentech, is designed to help **advance our understanding of the safety and clinical efficacy of risdiplam** in a wide variety of individuals, including multiple age groups, **from birth to 60 years old**.⁸⁻¹¹ This programme includes four ongoing clinical trials, **FIREFISH, SUNFISH, JEWELFISH** and **RAINBOWFISH** taking place in various countries all over the world.⁸⁻¹¹

How risdiplam works

Risdiplam is an investigational “splicing modifier”

Designed to act on the *SMN2* gene



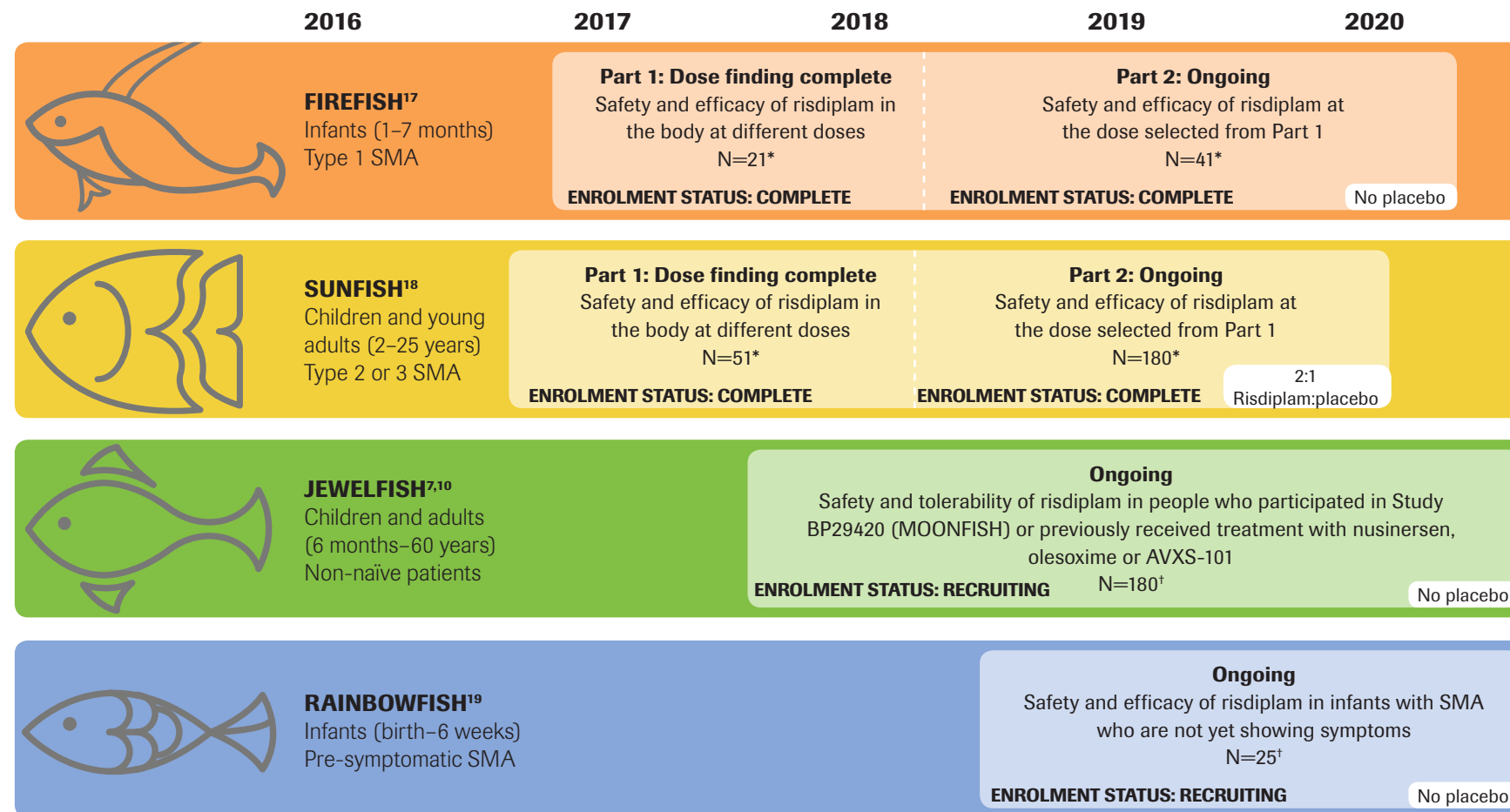
In individuals with SMA, the ***SMN2* gene cannot produce** enough **functional SMN protein** because of the **abnormal splicing of the gene and exclusion of exon 7** from ~90% of the SMN protein produced.¹²

Risdiplam is a selective *SMN2* gene splicing modifier.² It is believed to work by controlling the *SMN2* gene splicing by **promoting the inclusion of exon 7**, leading to the **production of a functional SMN protein** from the *SMN2* gene.^{13,14}



What is splicing? In biology, splicing is a process where **gene introns are removed** and **gene exons are joined together**.^{15,16} This process ends with the formation of messenger RNA (mRNA) that is then used to produce a protein via a process called translation. **Introns** are non-coding parts of a gene that are usually discarded during protein production. On the other hand, **exons are included** and code for specific sequences within proteins.¹⁶

An overview of the risdiplam clinical development programme



*Final participant study numbers; †Number of participants based on planned enrolment.

Figure 1 | The risdiplam clinical trial programme: an overarching programme covering infants to adults with SMA Types 1, 2 and 3^{8–11}

An overview of the risdiplam clinical development programme

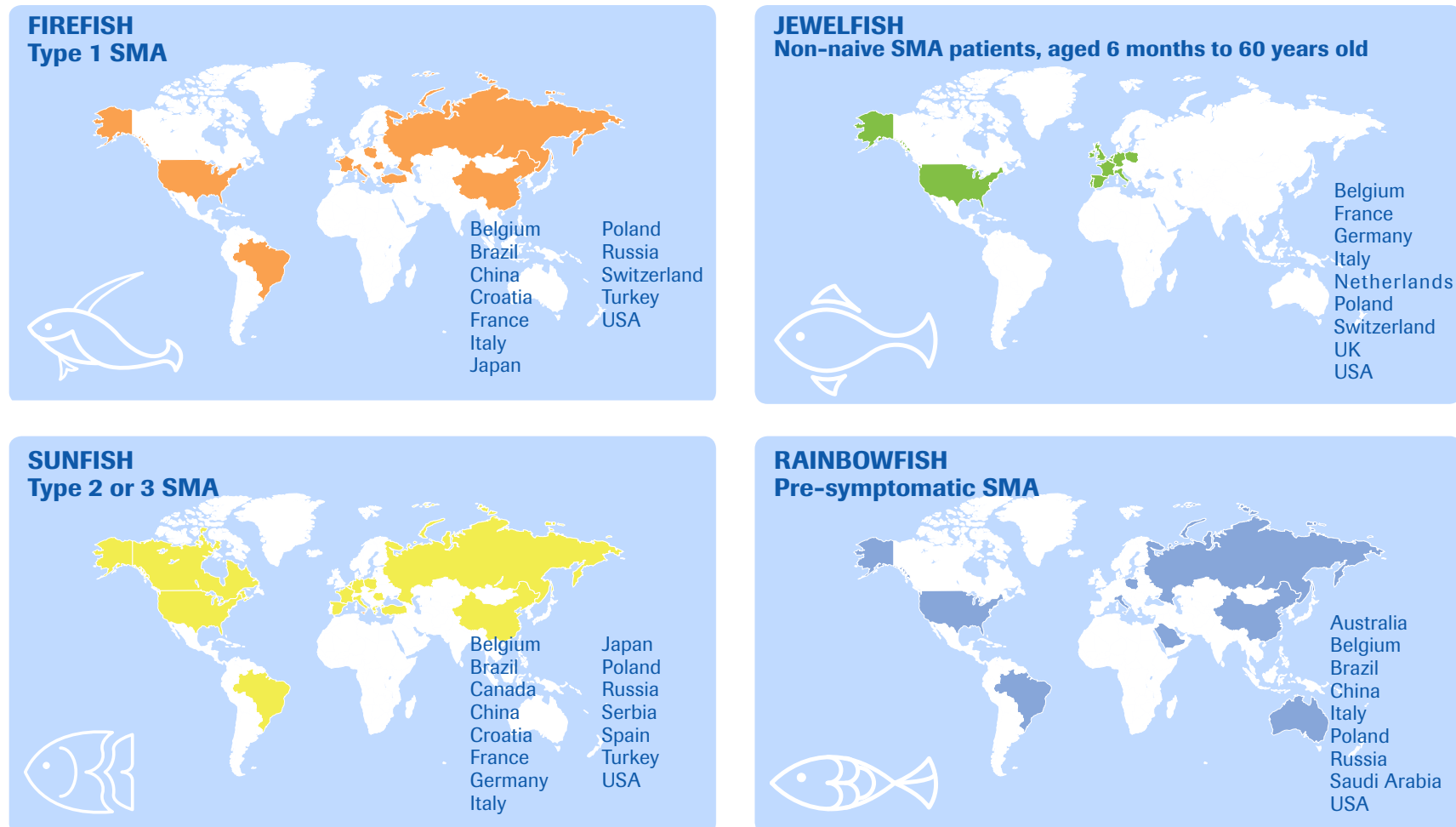


Figure 2 | The risdiplam clinical trial programme: a global overarching programme ⁸⁻¹¹

The FIREFISH trial: Overview and key objectives

The aim of the **FIREFISH trial** is to evaluate the **safety and efficacy of risdiplam** in infants with **Type 1 SMA aged 1–7 months with two SMN2 copies**.⁸ FIREFISH is an open-label study—this is a type of clinical study in which all individuals receive the drug; no placebo is given.⁸

This trial was divided into two parts. Part 1 was a dose-finding study that assessed the safety of risdiplam at two different doses—a high dose tested in 17 infants and a low dose tested in four infants. Its aim was to **select the safest and most effective dose to use for FIREFISH Part 2**.⁸ This part of the study was not designed to fully test the effects of risdiplam on motor function. All patients have now been treated for a minimum duration of 16 months.

Part 2 of the trial began in March 2018 and is **assessing the safety and efficacy of risdiplam** in 41 infants at the dose selected from Part 1.¹⁷ In more detail, the study is assessing the **ability of infants to sit unsupported for at least 5 seconds** using the BSID-III scale after 12 months of treatment with risdiplam.¹⁷

It is worth mentioning that patients with Type 1 SMA will never be expected to sit unsupported.² **Part 2 of FIREFISH is also evaluating additional motor measurements/milestones**, including head control, rolling, voluntary grasp, as well as **SMN protein levels in the blood, survival and permanent ventilation**, and the **proportion of infants that were able to be fed orally**.⁸

Recruitment into FIREFISH Part 2 is complete. Part 2 is ongoing; the main analysis will be carried out after 12 months of treatment.⁸ Results are estimated to be available in the first half of 2020.



Type 1 SMA: Clinical presentation and treatment goals

The age of onset for Type 1 SMA is **0–6 months** and this type is characterised by **severe muscle weakness** and **poor muscle tone**, weak cry and cough, tongue twitches, and difficulties with swallowing, feeding, clearing mucus, breathing and holding the head up.^{20–22} The defining difference between Type 1 and Type 2

SMA is that infants with the former are **unable to sit unsupported**.^{20–23} Type 1 SMA **treatment goals** include **lessening symptoms, improving quality of life**, and gains in function and strength, however small.^{2,24}



A placebo is a dummy drug with no active ingredient and has no real physical effect on an individual. A placebo-controlled trial is a way of testing a novel therapeutic approach in which, in addition to a group of patients receiving the active treatment to be evaluated, a separate control group receives a placebo treatment.



The FIREFISH trial: Part 1 results

Part 1 of FIREFISH was the dose-finding part of the study, which mainly assessed the safety and tolerability of two different doses of risdiplam.^{8, 17}

So far, **no infants have left the trial due to risdiplam-related adverse events.**²⁵ The most common adverse events observed included upper respiratory tract infections, pneumonia, inflammation, cough, diarrhoea, vomiting, constipation, fever and ear infections.²⁵ Serious adverse events were observed in 10 infants. The most common one was pneumonia (reported in three infants).²⁵ **The reported adverse events were not risdiplam-related**, that is, they are events commonly associated with SMA. There have been **no risdiplam-related eye complications*** reported during Part 1 of the FIREFISH study.²⁵

There were three deaths and one infant withdrew from the study; none of these events were related to risdiplam treatment.²⁵

During **Part 1** of the trial, the efficacy of risdiplam was also evaluated in exploratory analyses, in a similar way to those being carried out in Part 2.¹⁷ The results of these exploratory analyses after 12 months of treatment, will give us a good indication of what the efficacy of risdiplam will look like in infants with Type 1 SMA.¹⁷

Most of the infants started to receive risdiplam when they were nearly 7 months of age.¹² **Four patients** were included in **Cohort A** and treated with a **low dose of risdiplam; 17** were included in **Cohort B** and treated with a **high dose of risdiplam.**¹⁷

By at least Month 12 of treatment, **33% (7/21)** of all infants treated with risdiplam and 41% (7/17) treated with the high dose **were able to sit without support for at least 5 seconds**, as assessed by the BSID-III scale.¹⁷ It is worth mentioning that patients with Type 1 SMA are not able to sit unsupported.²



While a **primary endpoint** in a clinical trial is a specific measure that if met or verified throughout the duration of the study that will define its success, an **exploratory endpoint** assesses an outcome or a hypothesis that was not set upfront as a key point to evaluate during the study. An exploratory endpoint might provide valuable information about what is being tested, e.g. in the case of FIREFISH Part 1, the effects of risdiplam on motor function.⁸



An **adverse event** is a negative consequence of care, reported by a doctor during a clinical trial. It could be related to a particular treatment or to the disease itself. These are graded 1–4, according to how severe they are. Anything classed as grade 3 or above is a serious adverse event.

*Retinal toxicity was observed in a preclinical study evaluating the efficacy of an investigational splice-modifying compound for the treatment of SMA. Although these adverse events were seen with higher doses than those used in the MOONFISH study (more information on MOONFISH can be found on page 12), the study was stopped as a precautionary measure. Nevertheless, these animal toxicity results have never been reported in humans. All FISH trials use optical coherence tomography to assess any retinal changes as a result of the use of risdiplam. So far, no ophthalmological findings have been reported across all FISH trials. (More information on assessment scales can be found from page 14 onwards.)

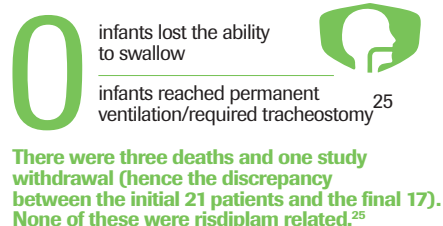
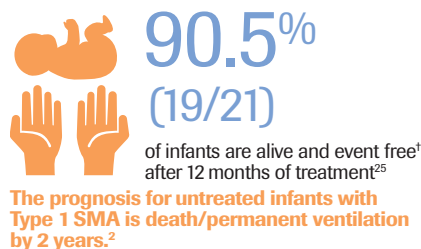


In addition, **86% (18/21) of all infants**, 75% (3/4) of those receiving the low dose, and 88% (15/17) of those receiving the high dose **showed a ≥ 4 -point improvement in CHOP-INTEND score** compared with the score at the start of treatment.¹⁷ This is an important milestone, as an **improvement of ≥ 4 points is viewed by SMA experts as a clinically meaningful improvement** that would **not typically happen with SMA Type 1** infants (according to studies that evaluated the natural course of disease in infants not receiving any treatment).^{17,26}

A total of **59% (10/17) of infants** receiving the **high dose of risdiplam** had a **CHOP-INTEND score of ≥ 40** , which is **rarely seen in infants with Type 1 SMA who have two SMN2 gene copies**.^{17,27} Treatment with risdiplam also improved motor function and milestones, as assessed by the HINE-2 scale.¹⁷

At 12 months, the majority of all infants (90.5%; 19/21)

What do these preliminary results potentially mean to you?*



receiving risdiplam were event free, which was **defined as being alive with no permanent ventilation**.²⁵ In fact, no infant treated with risdiplam required tracheostomy, bilevel positive airway pressure (BiPAP) support for 16 or more hours during a day, or received awake-assisted ventilation.²⁵

Risdiplam treatment over a period of 12 months also had a positive effect on infants' ability to swallow and feed.²⁰ **The majority of infants who were still alive** after 12 months of treatment (95%; 18/19) **were able to feed orally or in combination with a feeding tube**, with 79% (15/19) able to feed exclusively by mouth.²⁵ A total of 84% (16/19) did not experience coughing or choking during or after eating/drinking, and **no infant lost the ability to swallow**.

Treatment with risdiplam was associated with an increase in **SMN protein** that **was maintained over the 12 months of treatment**.¹⁷

41%
(7/17)

were able to sit without support for at least 5 seconds (as assessed by BSID-III)¹⁷



1/17
infants

59%
(10/17)

were able to stand supporting their weight (as assessed by HINE-2)¹⁷



had a CHOP-INTEND score ≥ 40 ¹⁷



Tracheostomy is an artificial opening created in the front of the neck that is held open by a tube; this helps an individual to breathe more easily. In some instances, non-invasive breathing support using ventilator machines can help with breathing, mainly during the night. A BiPAP is a type of ventilator machine that uses a mask placed over the face to increase air flow into the lungs.

*When a treatment completes its clinical trial programme and becomes available for use in clinical practice, individual eligibility must be considered in consultation with a treating physician, i.e. the doctor will discuss whether they are suited to the treatment or not. ¹A response to a treatment is individual.

The SUNFISH trial: Overview and key objectives

The aim of the **SUNFISH trial** is to evaluate the **safety and efficacy of risdiplam in children and young adults with Type 2 or Type 3 SMA aged 2–25 years compared to treatment with placebo.**⁹

This trial was divided into two parts. Part 1 tested the safety of risdiplam at different doses (high dose and low dose) in 51 children and young adults **with the aim to select the safest and most effective dose for SUNFISH Part 2.**¹⁸ Part 1 of the SUNFISH trial is now complete.

Based on the results of Part 1 of the study, the risdiplam dose with the best safety and efficacy profile was then

used in Part 2 of the trial, which is a double-blind, placebo controlled trial.¹⁸ **Part 2** includes 180 children and young adults and further **evaluates the safety and efficacy of the chosen dose.** Specifically, it assesses the ability of risdiplam to **improve the overall score on the Motor Function Measure scale (MFM-32*)** from Day 1 to Month 12.^{5,9}

Part 2 is also evaluating additional motor milestones, SMN protein levels in the blood, how easy it is to breathe and overall safety of risdiplam.⁹

*More information on assessment scales can be found from page 16 onwards.

Recruitment into SUNFISH Part 2 is complete.⁹ Part 2 is ongoing to assess the effects and safety of risdiplam; the main analysis will be carried out after 12 months of treatment.¹⁸ Results are estimated to be available in the first half of 2020.

TYPE 2/3 SMA

Type 2 and Type 3 SMA: Clinical presentation and treatment goals

The age of onset for **Type 2 SMA** is **≤18 months** and this type is characterised by **progressive muscle weakness and worsening muscle tone**, weakness in the tongue muscles with swallowing difficulties, breathing difficulties, curvature of the spine and joint stiffness, difficulty coughing and clearing the lungs, and fine hand tremors.^{3, 20–22} People with Type 2 SMA are **able to sit**, but are **unable to stand or walk.**²

The age of onset for **Type 3 SMA** is **>18 months** and this type is characterised by **muscle aching** and joint overuse symptoms, fine hand tremors, potential difficulty in getting enough oxygen during sleep, and weaker leg muscles compared with the arm muscles.^{3, 20, 28} Generally, people with Type 3 SMA are able to stand and walk until late childhood and sometimes into adulthood—this depends on the age that symptoms begin.^{20–22, 29} There is much more variation in the symptoms of individuals with Type 2 and Type 3 SMA compared with Type 1.³ People with Type 3 SMA have more gradual muscle weakness than Types 1 and 2.^{3, 29, 30}

The SUNFISH trial: Part 1 results

Part 1 of this study included a wide range of individuals, from **2-year-old infants to 25-year-old adults** with **Type 2 and 3 SMA**.⁹ Both people that are able and unable to sit were included in the study, as well as those with scoliosis.^{9,18} Finally, ambulatory and non-ambulatory individuals were also assessed in SUNFISH.¹⁸

So far, **no individuals have left the trial due to risdiplam-related adverse events**.¹⁸ The most common adverse events observed included vomiting, cough, fever and upper respiratory tract infections.¹⁸ At least one serious adverse event was observed in nine individuals, the most common one being pneumonia, which was reported in two individuals.¹⁸ **The reported adverse events are not risdiplam related**, that is, they are commonly associated with SMA. There have been no **risdiplam-related eye complications reported** during Part 1 of the SUNFISH study.¹⁸

Treatment with risdiplam was associated with an **increase in SMN protein** that was maintained over 12 months of treatment.³¹ **Individuals receiving risdiplam** in Part 1 showed **improvements in motor function measure** (exploratory endpoint) **compared with results from studies that evaluated the natural course of disease** (also known as natural history studies).¹⁸

A total of **58% of all individuals, 71% of those aged 2–11 years** and **42% of those aged 12–25**, achieved a **≥3-point change in MFM-32 score at Month 12**, which is an outcome rarely observed in individuals with SMA Type 2 and 3 according to natural history studies.¹⁸ This improvement seems to be independent of disease severity at the start of the trial.¹⁸

What do these preliminary results potentially mean to you?*

SUNFISH Part 1: Conclusions

All patients in SUNFISH have been treated for at least 12 months¹⁸



No drug-related safety findings leading to withdrawal to date¹⁸



Exploratory MFM showed risdiplam treatment led to improvement compared with natural history^{18†}



A natural history study follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease. It collates health information over time in order to understand how the medical condition or disease develops and to give insight into how it might be treated.

Part 2 of SUNFISH is now ongoing globally⁹

Part 1 of SUNFISH has helped determine the dose for Part 2 of the study



*A response to a treatment is individual. When a treatment completes its clinical programme and becomes available for use in clinical practice, individual eligibility must be considered in consultation with a treating physician, i.e. the doctor will discuss whether they are suited to the treatment or not. †A clinically meaningful increase in total MFM as seen in patients, including a broad range of ages and functional status at baseline.⁵

The JEWELFISH trial: Overview, key objectives and preliminary results

The aim of the **JEWELFISH trial** is to evaluate **the safety of risdiplam in individuals with SMA aged 6 months to 60 years who participated in the BP29420 (MOONFISH) study or have already been treated with other therapies**, including nusinersen (Spinraza®), olesoxime and onasemnogene abeparvovec (Zolgensma®).^{7,10}

The **JEWELFISH trial** is aiming to recruit 180 individuals worldwide and will **determine the safety of risdiplam, its levels in the blood and its metabolism** (how it is broken down and eliminated from the body).^{7,10}

Additionally, investigators in this trial will use the **BSID-III, HINE-2, MFM and HFMSE** scales* to assess **motor function and milestones** expected of normal individuals at the same age (exploratory assessments).^{7,10}

Preliminary results of JEWELFISH: So far, 84/180 individuals have been enrolled.* **No individuals have left the trial due to risdiplam-related adverse events.**⁷

The most common adverse events observed include headache, cold and fever. **No serious adverse events or risdiplam-related eye complications have been reported so far.**⁷

To date, **treatment with risdiplam** is showing **sustained increases in SMN protein levels** over 12 months of treatment.⁷ **The levels of SMN protein are similar** to those reported in the **SUNFISH and FIREFISH trials.**⁷

Results of this study will be important to evaluate **if people who did not respond as expected to prior SMA treatments show a response when treated with risdiplam.**

Global recruitment into JEWELFISH is ongoing.⁷ Results are estimated to be available by the end of 2020.



MOONFISH was a clinical study assessing the safety of RG7800 in adults and children with SMA.³²

The study was stopped in July 2015.³²

RG7800 was an investigational medicine that was studied as a potential treatment for adults and children with SMA.³³ RG7800 was an oral treatment thought to help the *SMN2* gene make more SMN protein.³³ When investigational medicines are developed, they are studied at increasingly higher doses and durations in animals before trials in humans. This is important as it identifies any potential safety issues. Unexpected eye findings (changes to specialised cells located in the retina—the thin layer of tissue that lines the back of the eye) were observed in monkeys receiving the investigational medicine RG7800.^{33,34} Although these adverse effects were seen with higher doses than those used in MOONFISH, the study was stopped as a precautionary measure.³³

*More information on assessment scales can be found from page 16 onwards. †As of 23 September 2019.

The RAINBOWFISH trial : Overview and key objectives

The aim of the **RAINBOWFISH trial** is to **evaluate the safety and efficacy of risdiplam in neonates aged up to 6 weeks old who were genetically tested and diagnosed with SMA, but do not yet show disease symptoms** (pre-symptomatic).¹⁹

The **RAINBOWFISH trial** is aiming to recruit pre-symptomatic infants worldwide regardless of the number of *SMN2* copies.¹¹ Nevertheless, **only those with two *SMN2* copies and a compound muscle action potential (CMAP) ≥ 1.5 mV at baseline will be included in the main analysis**, which **will determine the proportion that are able to sit without support**

for 5 seconds after being treated with risdiplam for 12 months.¹¹ Investigators in this trial will use the **BSID-III** and **HINE-2 scales*** to **evaluate motor milestones**, and the **CHOP-INTEND scale*** to **assess motor function**.¹⁹

The development of clinical symptoms of SMA, survival and permanent ventilation, growth measurements as well as nutritional status and respiratory effects, will also be studied.¹¹

In addition, investigators will also determine **the safety profile of risdiplam**, the **impact of this molecule on overall health status and health-related quality of life**, and the **impact on other developmental milestones, such as cognition and speech**.¹⁶

The RAINBOWFISH trial is currently enrolling globally and the study is estimated to be completed by the end of 2025.¹⁶



Genetic testing is a type of medical test that identifies changes in chromosomes, genes or proteins. The results of a genetic test can confirm or rule out a suspected genetic disease or help determine a person's chance of developing or passing on a genetic disorder to their children.³⁵ Routine parental screening is not currently recommended in the US or UK^{36,37}; it is only offered to adult patients/parents with a confirmed or suspected family history of SMA.³⁸

When SMA is suspected, an individual can undergo a genetic test, which involves taking a small blood sample that is sent to a laboratory for testing.³⁹ **It can detect 95% of all SMA cases** – those that are caused by a mutation to both copies of the *SMN1* gene. However, rare types of SMA can also be caused by other types of mutations.³⁹ These are not assessed as part of standard SMA genetic tests, but may be requested if a diagnosis is strongly suspected and initial tests are negative.³⁹ Genetic testing may also include checking how many copies a person has of the related gene, *SMN2*. This gene produces a very low amount of a functional SMN protein, and the more copies an individual has, the less severe disease symptoms may be.³⁹

*More information on assessment scales can be found from page 16 onwards.



Updated data on the FIREFISH, JEWELFISH and RAINBOWFISH trials

Outcomes from the various FISH trials are continuously being updated as more data become available and are analysed.

Below you can find the latest updates on the **FIREFISH**, **JEWELFISH** and **RAINBOWFISH** trials presented at the 2019 World Muscle Society Congress on 1–5 October 2019 in Copenhagen, Denmark.



1 **86% (18/21) of all infants** were **event free*** after receiving risdiplam for **16 months**⁴⁰

1 There is a **sustained, 2-fold increase in median SMN protein** versus baseline levels over **12 months of treatment**⁴¹

1 There is a **sustained, >2-fold increase in median SMN protein** compared with baseline levels over **12 months** of treatment⁴²

1 The **first two** participants were enrolled in **August 2019**⁴³

2 **82% (14/17) of infants** treated with the **high dose** had a **CHOP-INTEND score ≥40** after receiving risdiplam for **16 months**⁴⁰

2 To date,[†] there have been **no drug-related adverse events leading to withdrawal** in any individuals with SMA exposed to risdiplam⁴¹

2 To date,[†] there have been **no drug-related adverse events leading to withdrawal** in any individuals with SMA exposed to risdiplam⁴²

2 Countries participating in RAINBOWFISH so far are Australia, Belgium, Brazil, China, Italy, Poland, Russia, Saudi Arabia and USA⁴³

3 **12% (2/17) of infants** treated with the **high dose achieved bouncing** after **16 months** of treatment⁴⁰

3 Risdiplam treatment led to **improvement in MFM-32 scores versus natural history** (exploratory analysis)⁴¹

4 **No infant** has **required tracheostomy** or **permanent ventilation**⁴⁰

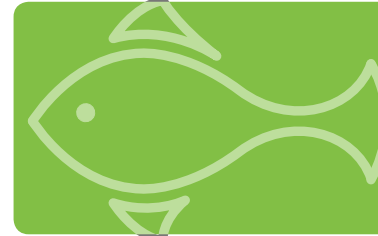
4 **All patients** in SUNFISH have been treated for **at least 19 months**[‡]

*Comments related to the same infant. Caregiver comments on infants in FIREFISH Part 1 within the 16-month treatment period. Data cut-off: 2 July 2019; [†]Data cut-off: 28 June 2019; [‡]As of the most recent safety analysis (data cut-off: 28 June 2019).

Overall summary

1.

So far, results from the various **FISH trials** have shown that **risdiplam has a tolerable safety profile**, with most reported adverse events being associated with the disease itself, and not related to treatment with risdiplam.



2.



Exploratory endpoints used in **Part 1 of the FIREFISH and SUNFISH** trials showed **improvements in motor function and milestones** that are not normally seen in studies that evaluated the natural course of the disease in people not receiving any treatment.

3.

Risdiplam has a broad clinical trial programme that spans the range of SMA types and ages, from birth to 60 years. **The risdiplam clinical trial programme is currently testing the safety and efficacy of risdiplam**—JEWELFISH and RAINBOWFISH are still recruiting.

4.

Risdiplam is an oral investigational (unapproved) small molecule developed by Roche/Genentech in partnership with the SMA Foundation and PTC Therapeutics as **a new treatment option for patients with SMA.**



5.



Roche/Genentech is committed to continue investing in the SMA community and in the care and support of patients and caregivers.

Motor function scales used in the risdiplam clinical trial programme

In the various risdiplam trials, we have tested whether risdiplam was able to improve motor function using several types of clinical measures. These clinical measures **can test an individual's ability to move using a number of physical exercises or tasks**.^{8,9,11,17-19} Individuals are given a score by their healthcare provider (or their investigator during the FISH studies) based on how many exercises and tasks they can complete, which is associated with their level of movement.

Endpoint	FIREFISH ¹⁷	SUNFISH ¹⁸	JEWELFISH ^{7,10}	RAINBOWFISH ¹⁹
Primary	BSID-III (sitting)	MFM-32	N/A (safety and tolerability)	BSID-III*
Secondary	(BSID-III*) (other motor assessments) HINE-2 CHOP-INTEND	HFMSE RULM	N/A	(BSID-III) HINE-2 CHOP-INTEND

Table 1 | Scales used to assess the primary outcomes of the risdiplam trials

*Assessed in individuals with two *SMN2* copies and (CMAP) of ≥ 1.5 mV at the start of the study.

BSID-III, Bayley Scales of Infant and Toddler Development-Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale-Extended; HINE-2, Hammersmith Infant Neurological Examination, Section 2; MFM, Motor Function Measure; N/A, not applicable; RULM, Revised Upper Limb Module.

The Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III)

The BSID-III scale uses a series of play tasks to **assess the development** of **babies/infants aged 1–42 months**.^{44, 45}

It is made up of five sections: **thinking** (cognitive), **language** (communication), **movement** (motor), **social skills** (emotion) and **responding** (adaption).⁴⁴ A modified version of the movement section is used for babies with Type 1 SMA.⁴⁵ In this modified version, tasks have been re-ordered to reduce

tiredness and the scale has been adapted to better study the development of infants with Type 1 SMA.⁴⁵ In a study of untreated babies with Type 1 SMA aged 1–8 months at the onset of symptoms, none of the more severely affected infants achieved a major milestone, such as rolling over, independent sitting, crawling, standing or walking.⁴⁶

The Hammersmith Infant Neurological Examination, Section 2 (HINE-2) scale

The **HINE-2 scale** assesses an **infant's ability to move their head, kick, roll on their side, walk, crawl, sit up and grasp objects** – known as motor milestones.^{46,47} For each motor milestone, babies are scored from 0–4 based on their ability to perform the movements, with higher scores reflecting better

motor function.⁴⁶ In a study of untreated babies with Type 1 SMA who were between 1 and 8 months of age at the onset of symptoms, none of the more severely affected infants achieved a major milestone such as rolling over, independent sitting, crawling, standing or walking.⁴⁶

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale

The **CHOP-INTEND** scale **assesses how an infant moves**. The scale contains **16 items assessing: head, arm and leg movement; the ability to grasp an object; and the ability to roll around**.⁴⁸ CHOP-INTEND scores can range from 0 to 64 (higher scores reflect more movement).⁴⁸

CHOP-INTEND scores have been observed to decrease over time in babies with Type 1 SMA who did not receive treatment.⁴⁷ A CHOP-INTEND score over 40 is rarely seen for babies with Type 1 SMA who have two *SMN2* gene copies.²⁶

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

The **MFM-32** is a scale that **examines the motor function of individuals affected by a neuromuscular disease**.⁴⁹ Individuals are scored from 0–3 on their **ability to complete 32 tasks**; higher scores reflect better function.⁴⁹ A shorter 20-item version (MFM-20) can be used in infants up to 7 years of age.⁵⁰ However, we have recently finished a study showing that the long version, MFM-32, can reliably measure motor function

in individuals with Type 2 SMA and non-ambulant Type 3 SMA aged 2–25 years.⁵¹

MFM-32 scores have been observed to decrease over time in individuals with Type 2 and Type 3 SMA who are not receiving any treatment.⁵²

The Hammersmith Functional Motor Scale–Extended (HFMSE)

The **HFMSE examines 33 exercises** from the Gross Motor Function Measure **related to lying/rolling, crawling, kneeling, standing** and **walking/running/jumping**.⁵³⁻⁵⁵

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 tasks.⁵⁶

Individuals with Type 2 and Type 3 SMA may demonstrate progressive decline in HFMSE scores. In a study of untreated individuals with SMA, HFMSE scores declined by mean of 0.56 over 12 months.²⁹

The Revised Upper Limb Module (RULM) scale

The **RULM** has been developed to **test arm movement and coordination in individuals with SMA**.⁵⁷ Individuals are scored on their ability to complete a series of exercises and tasks

(e.g. lift a 20 g weight, open ziplocked containers, trace a path using a pencil on a map).⁵⁷ Higher scores reflect greater strength and ability to complete tasks.

Additional information about the FISH trials

FIREFISH and SUNFISH are no longer recruiting. JEWELFISH and RAINBOWFISH are currently enrolling worldwide. Further information about the studies, including detailed inclusion and exclusion criteria, will be posted on www.clinicaltrials.gov and shared with SMA healthcare professionals.

- FIREFISH (NCT02913482): more information available here <https://clinicaltrials.gov/ct2/show/NCT02913482>
- SUNFISH (NCT02908685): more information available here <https://clinicaltrials.gov/ct2/show/NCT02908685>
- JEWELFISH (NCT03032172): more information available here <https://clinicaltrials.gov/ct2/show/NCT03032172>
- RAINBOWFISH (NCT03779334): more information available here <https://clinicaltrials.gov/ct2/show/NCT03779334>

For more information on clinical trials in general, please visit: <https://www.clinicaltrials.gov/ct2/about-studies/learn>.

All these links and information were correct as of July 2019.

We would also kindly suggest you consult a doctor with expertise in SMA to ask about ongoing and upcoming clinical trials. In addition, patient organisations may be able to provide further helpful information.

For those living outside of the USA only, we have a website on which information about our studies can be obtained: <https://forpatients.roche.com/en/search.htmlquery=spinal+muscular+atrophy.html#e30=>

Who sponsored the FISH trials?

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