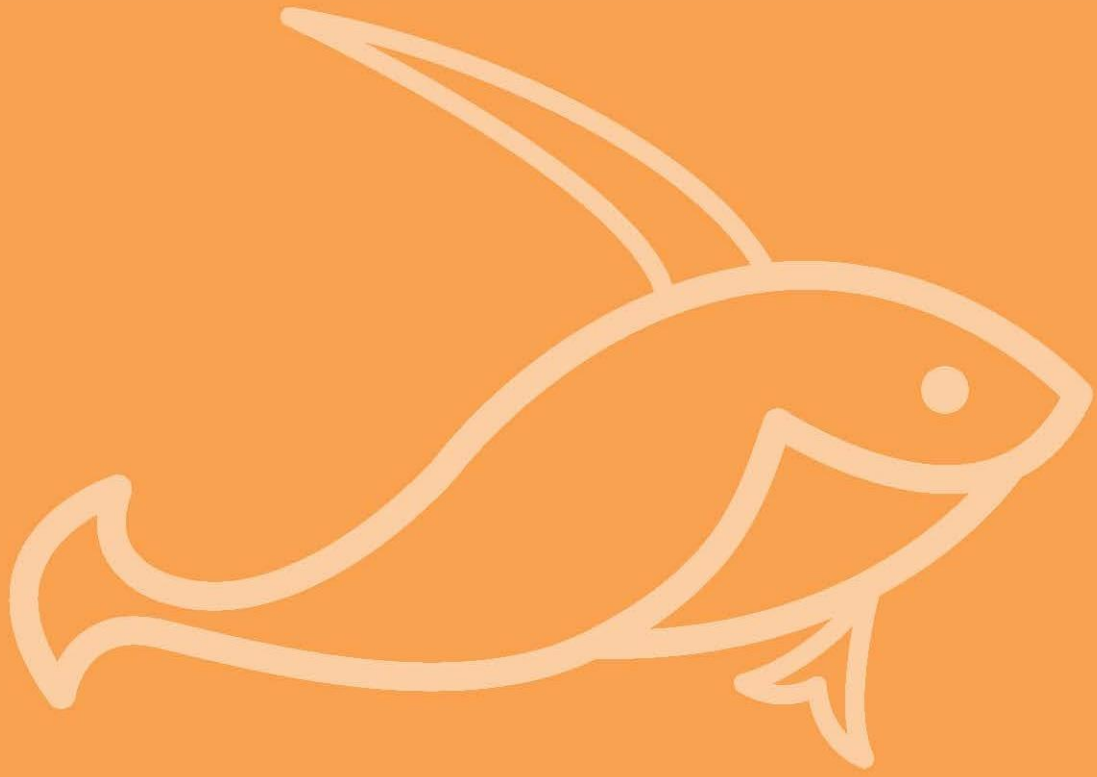
A summary of the final results from FIREFISH, a clinical trial to establish the efficacy and safety of risdiplam in children with Type 1 SMA



See the end of the document for the full title of the study

Date of preparation: September 2024 | M-XX-00017654

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document). It has been written for members of the public and for the people who took part in the study.

The FIREFISH study (NCT02913482) started in December 2016 and finished in December 2023. This summary was written after the study had ended. The drug being investigated in this study was risdiplam.

The FIREFISH study met its aims (endpoints) in November 2019 when the last participant to join the study completed 1 year of risdiplam treatment. This document provides a summary of the final results from FIREFISH after the study had ended.

This summary includes the following information:

Previous documents provided a summary of the results of the FIREFISH study after children had completed 1 year and 2 years of risdiplam treatment.

Please click here to view the 1-year summary.

Please click here to view the 2-year summary

What is SMA?

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disorder, which destroys muscle-controlling nerve cells, called motor neurons.

SMA destroys muscle-controlling nerve cells in the spinal cord called motor neurons.

The loss of motor neurons causes muscle weakness and loss of movement due to muscle wasting (atrophy).

People living with SMA have difficulty performing the basic functions of life, including breathing and swallowing.

The severity of SMA varies between people and depends on a range of factors, including the age at which symptoms begin. There are five types of SMA, based on the age that symptoms begin and the highest physical milestone achieved (such as being able to sit or walk).

Types of SMA

Type	Age that symptoms start	Effects on muscle and motor ability
0	Before birth	Babies do not move actively in the womb and are born with severe muscle weakness
1	Birth to 6 months	Children will never be able to sit independently
2	6 to 18 months	Children are typically able to sit, and some may stand with assistance, but they are not able to walk
3	18 months onwards	Children can walk, but they may lose this ability over time
4	18 years onwards	This form of SMA develops in adulthood. This is the least severe SMA type.

SMA, spinal muscular atrophy.

Why was this study done?

When this study began, there were no treatments available for people with SMA.

The goals of new treatments are to treat the underlying cause of SMA, help people with SMA live longer, reduce overall symptoms, maintain a person's ability to move (motor function), and improve quality of life.

The **FIREFISH** study was carried out to understand the safety and efficacy (how well a treatment works) of risdiplam in babies with Type 1 SMA, aged between 1 and 7 months old when they entered the study.

SMA, spinal muscular atrophy.

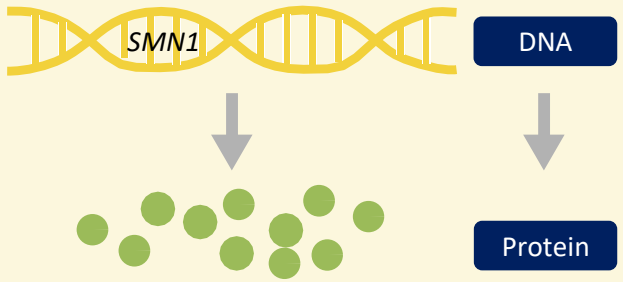
What causes SMA? (1/2)

SMA is caused by low levels of a protein called ‘survival of motor neuron’ (also known as SMN protein).

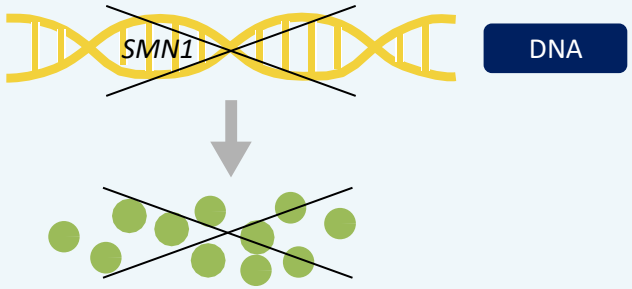
SMN protein is critical to the function of the nerves that control muscles. Without high enough levels of SMN protein, these nerves stop working properly (degenerate) and eventually die, causing muscles to become weak and waste away.

SMN protein is mostly made by a gene called ‘survival of motor neuron 1’ (also known as *SMN1*).

In healthy people, *SMN1* produces SMN protein



People with SMA have a change (mutation) in the *SMN1* gene that stops it from making SMN protein



Working SMN protein

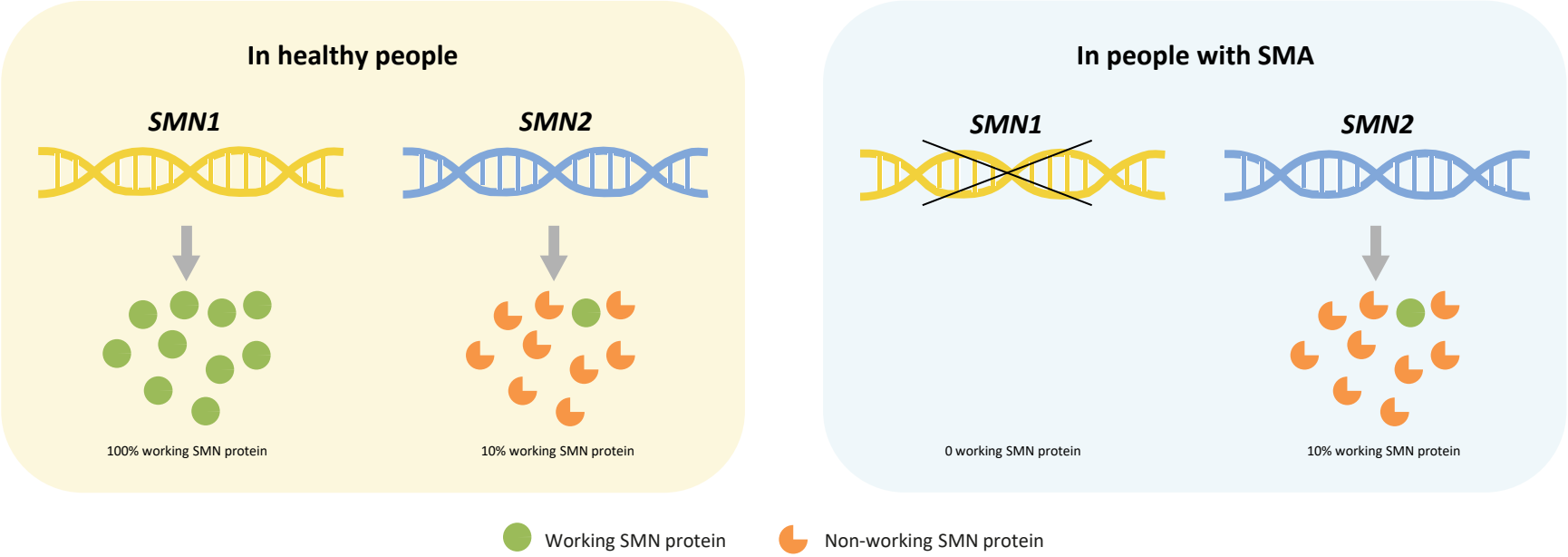
SMA, spinal muscular atrophy; SMN, survival of motor neuron.

What causes SMA? (2/2)

People have a similar gene called survival of motor neuron 2 (also known as *SMN2*) which can act as a 'back-up' gene to make SMN protein. People with SMA need to use *SMN2* to make SMN protein as they do not have *SMN1*.

However, only about 1 in 10 (10%) of the SMN protein produced by *SMN2* works properly. This is not enough protein to make up for the loss of the *SMN1* gene.

The more copies of the *SMN2* gene a person has, the more SMN protein they can produce, which makes the symptoms of SMA less severe.



SMA, spinal muscular atrophy; SMN, survival of motor neuron.

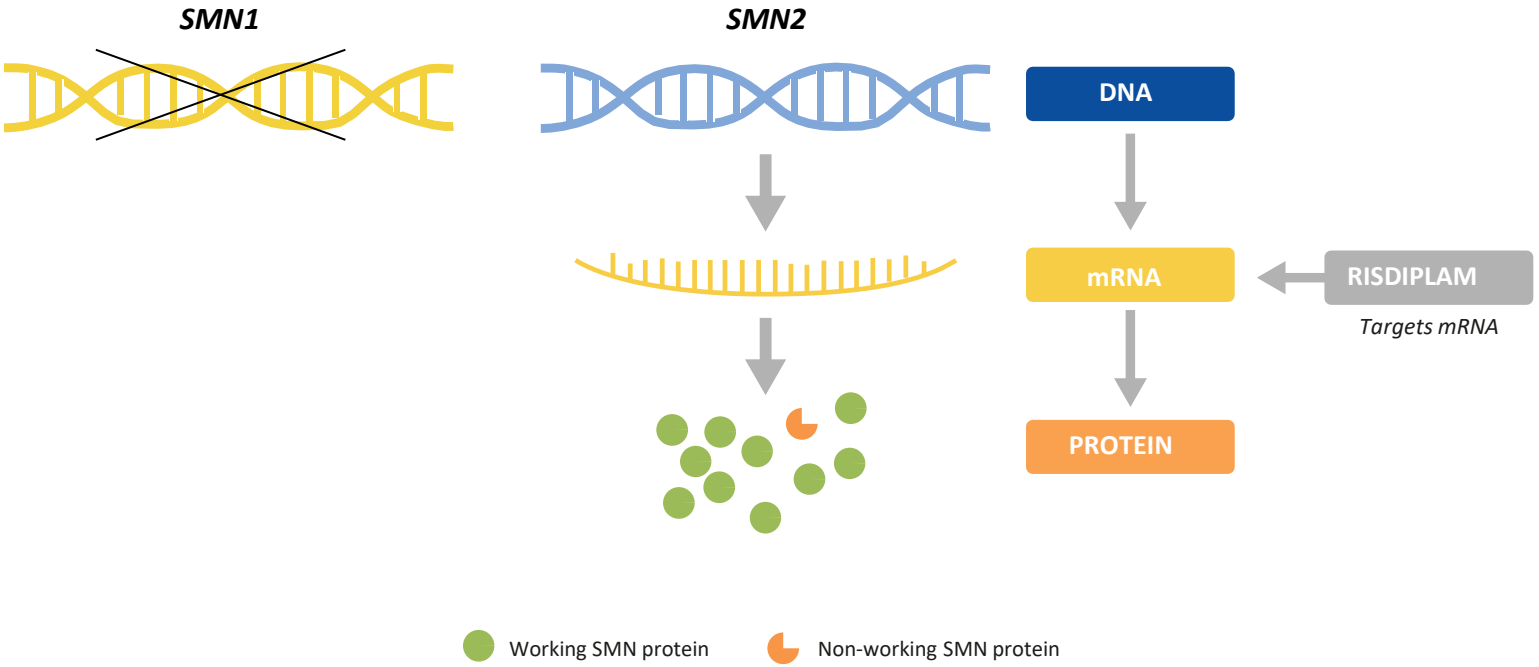
What is risdiplam and how does it work?

Risdiplam is the drug that was studied in **FIREFISH**.

Risdiplam is a liquid taken once a day by mouth (orally) or by feeding tube for those with difficulty swallowing.

Risdiplam is designed to help the *SMN2* gene to produce more working SMN protein to maintain and improve muscle function.

The instructions from the *SMN2* gene are faulty, and most of the SMN protein produced doesn't work. Risdiplam targets the instructions (mRNA) from the *SMN2* gene to make more working SMN protein.



SMN, survival of motor neuron.

What did researchers want to find out?

The **FIREFISH** study aimed to answer research questions about risdiplam.

To understand the effects of risdiplam, the study included several outcome measures (endpoints).

Endpoints are specific measures that researchers use to assess the effects of a study treatment.

- **Primary endpoints** are used to answer the main research question of the study. The study is considered successful if these outcomes or events happen at a certain point in the study (the primary endpoint is met).
- **Secondary and exploratory endpoints** provide additional information to help researchers understand the effects of the treatment studied.

The **FIREFISH** study was divided into two parts.

What did the researchers want to find out in FIREFISH Part 1?

What was the main question (the **primary endpoint**) that researchers wanted to find out in **FIREFISH Part 1**?

The recommended dose of risdiplam for the treatment of babies between the ages of 1 and 7 months with Type 1 SMA for use in **FIREFISH Part 2**.

- To measure this, researchers looked at the blood levels of risdiplam from babies in the study and measured how much SMN protein they had.
- The selected dose had to be safe and lead to a meaningful increase in SMN protein levels.

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

What did the researchers want to find out in FIREFISH Part 2?

- The risdiplam dose selected in **FIREFISH Part 1** was given to all babies in **Part 2**.
- What was the main question (the **primary endpoint**) that researchers wanted to find out in **FIREFISH Part 2**?

The **primary endpoint** of **FIREFISH Part 2** was to investigate the efficacy of risdiplam (i.e. how well risdiplam works).

- This was assessed as the percentage of children who could sit without support for at least 5 seconds, after 1 year of risdiplam treatment.
  - —This endpoint was chosen as children with Type 1 SMA who do not receive treatment are typically unable to sit without support

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

What did researchers want to find out during the whole 5-year FIREFISH study?

- After the **primary endpoints** were reached in **FIREFISH Parts 1** and **Part 2**, all children could continue in the study for up to 5 years.

- What were other important questions (the **secondary and exploratory endpoints**) that researchers wanted to find out in **FIREFISH** over the whole 5-year period?

Secondary and exploratory endpoints investigated how many children were:

- alive
- able to feed by mouth
- achieving movement (motor) milestones
- experiencing side effects

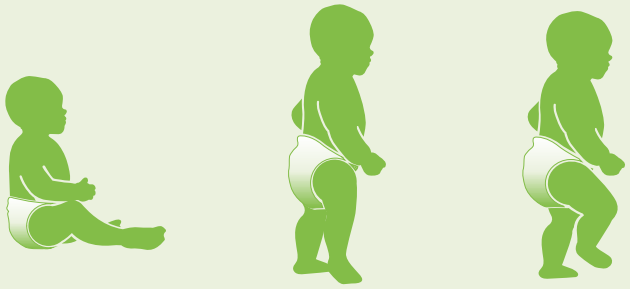
SMA, spinal muscular atrophy; SMN, survival of motor neuron.

How did researchers measure the physical ability of the children in FIREFISH?

Physical ability refers to how well a child can use different parts of their body to perform milestones such as sitting, standing and walking.

In **FIREFISH** different tests (outcomes) were used to assess the children receiving risdiplam.

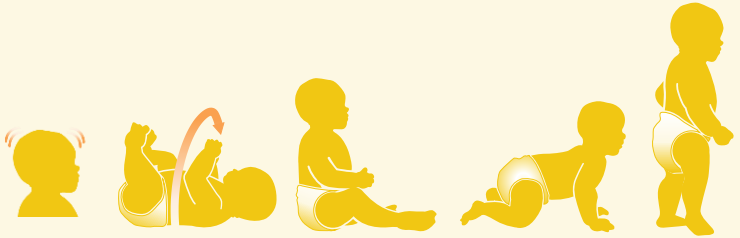
The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)



The **BSID-III** measures how well children perform a variety of activities (such as sitting, standing and walking) compared with other children of the same age.

Why this test? It is a tool to diagnose developmental delays in children aged between 1 and 42 months old.

Hammersmith Infant Neurological Examination, Module 2 (HINE-2)



The **HINE-2** measures whether children can achieve milestones such as holding their heads up, sitting, rolling, standing and walking.

Why this test? This test assesses whether a child can achieve movement (motor) milestones appropriate for their age.

For more information on these mobility measures, please see the brochure '[Understanding the MFM and the SMAIS in the context of outcome measurements in SMA]'.

BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; HINE-2, Hammersmith Infant Neurological Examination, Module 2; SMA, spinal muscular atrophy.

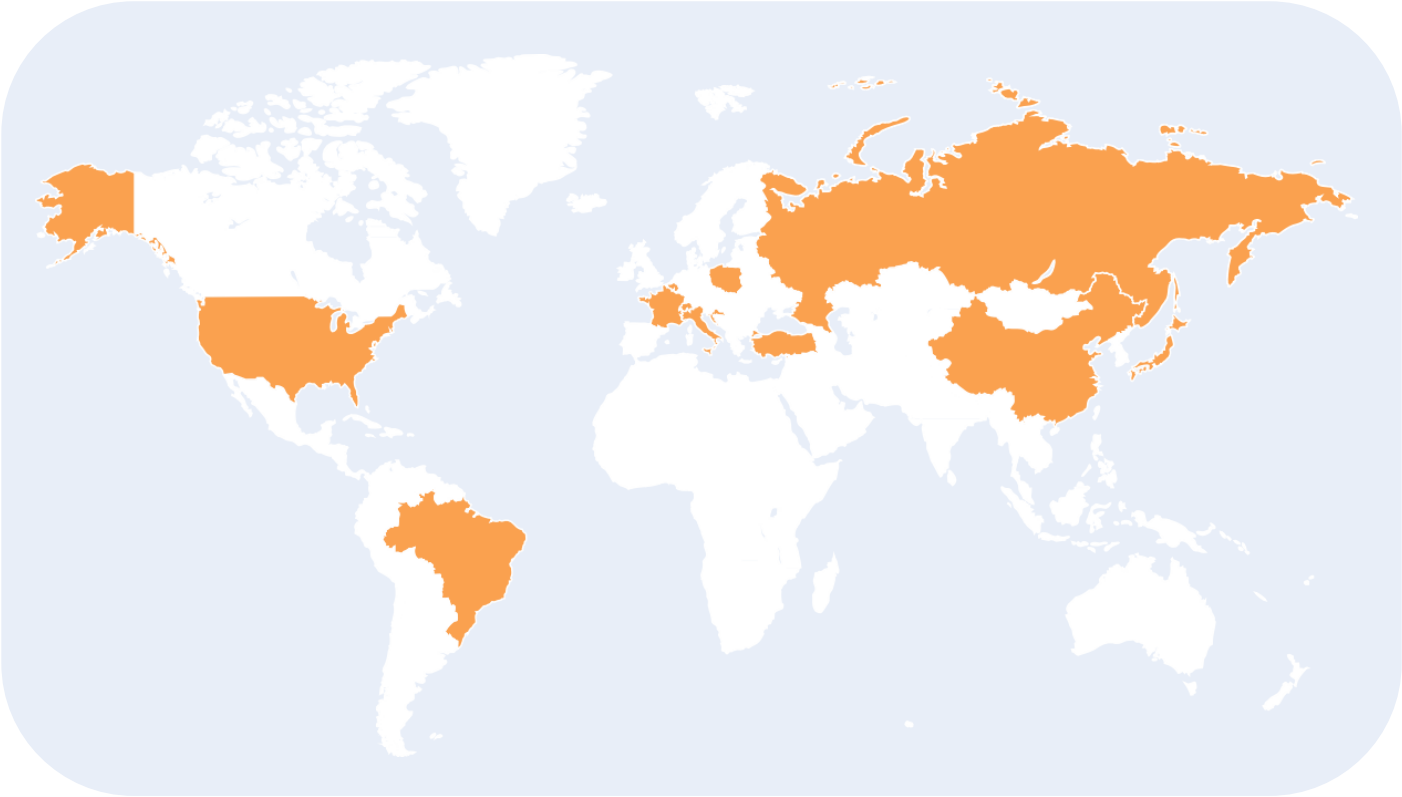
When and where did this study take place?

The **FIREFISH** study started in December 2016 and ended in December 2023, when all participating children had completed up to 5 years of risdiplam treatment. This summary was written after the study had ended.

FIREFISH was a global study that took place in 17 hospitals across 12 countries. The map below shows where the study took place.

The countries where FIREFISH took place were:

- Belgium
- Brazil
- China
- Croatia
- France
- Italy
- Japan
- Poland
- Russia
- Switzerland
- Turkey
- USA



Who could take part in the study?

The **FIREFISH** study included babies aged between 1 and 7 months at the time they enrolled in (entered) the study.
All of them had been diagnosed with SMA.

The following were the main requirements for babies to take part in the study:

Main inclusion criteria	Main exclusion criteria
Babies could take part in the study if they: • Developed symptoms of SMA between the ages of 1 and 3 months • Had a test that confirmed it was SMA (a genetic diagnosis) • Had two copies of the *SMN2* gene • Had recovered from any short-term illness at the time of study screening and were considered well enough to take part	**Babies could not take part in the study if they:** • Had taken part in another clinical trial within the past 3 months • Had previously received an SMA drug treatment or gene or cell therapy • Needed significant medical support to breathe for more than 16 hours per day • Had experienced any recent emergencies requiring an overnight stay in hospital or major illnesses from which they had not fully recovered

Full details of the inclusion/exclusion criteria can be found at: https://clinicaltrials.gov/ct2/show/NCT02908685.

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

How was the FIREFISH study designed?

FIREFISH was an **'open-label'** study:

- **'Open label'** means that everyone involved in the study, including the children taking part, their families and the study doctors, knew which treatment the participant was given.
- Everyone who took part in the study received risdiplam.
- Participants received risdiplam for 2 years in the main part of the study.
- After the main part of the study finished, participants could choose to continue to receive risdiplam for an additional 3 years (called the open-label extension period).

FIREFISH was designed in two parts:

- **Part 1** tested different doses of risdiplam to find the best dose to give to babies with Type 1 SMA.
- **Part 2** measured the efficacy (how well the treatment worked) and safety of risdiplam in babies with Type 1 SMA. Babies who received risdiplam in Part 2 were given the dose selected in Part 1.

Parts 1 and 2 included different children - those who took part in Part 1 did not participate in Part 2.

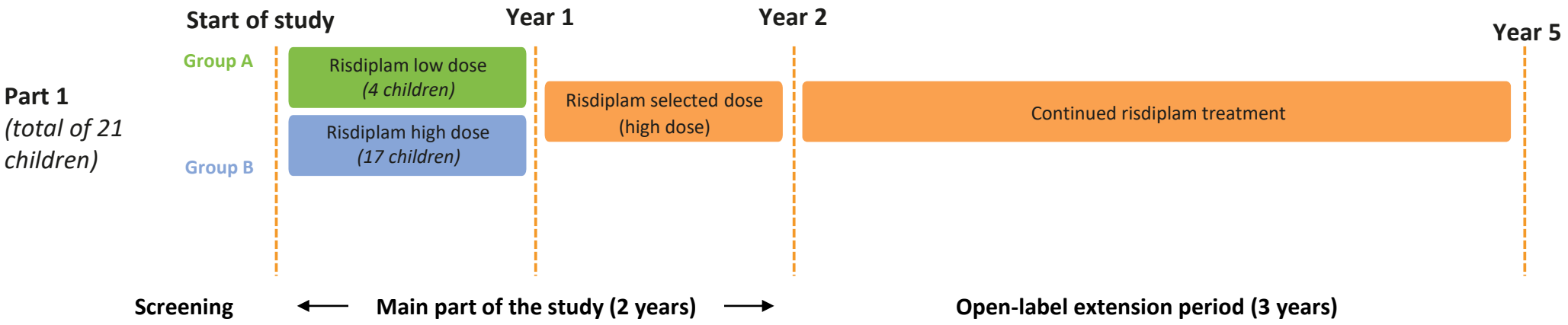
SMA, spinal muscular atrophy.

What happened during FIREFISH Part 1?

FIREFISH Part 1 aimed to find the best dose of risdiplam for babies with Type 1 SMA. This dose was to be used for the rest of the study.

Participants were divided into two groups and given different doses of risdiplam.

- **Group A** (a total of **4 babies**) was given a **low dose** of risdiplam
- **Group B** (a total of **17 babies**) was given a **higher dose** of risdiplam



The dose selected in **FIREFISH Part 1** was used in **Part 2** and the open-label extension period.

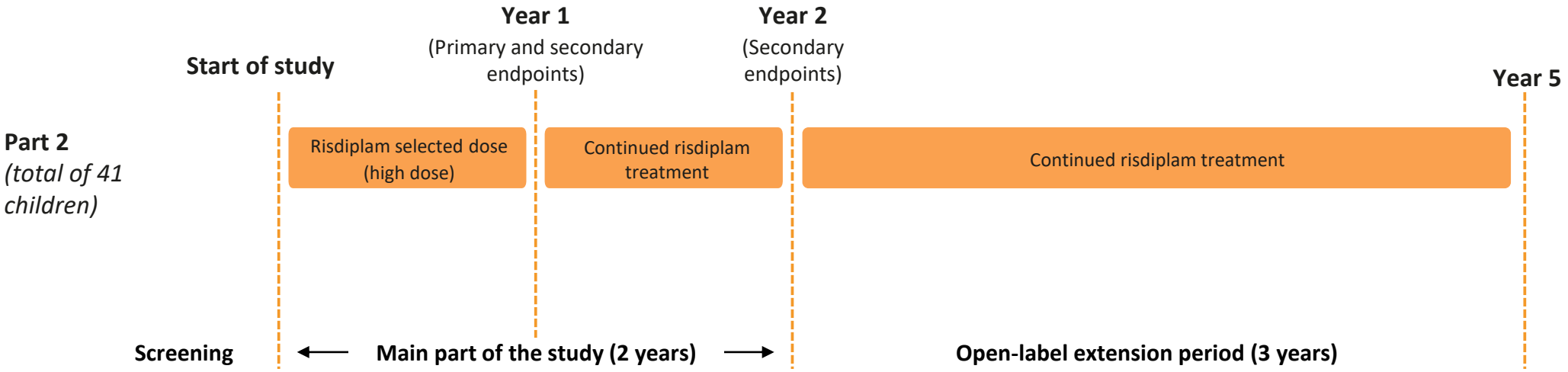
The four children who received the low risdiplam dose switched to the high dose after 1 year and could continue in the trial for up to 5 years.

SMA, spinal muscular atrophy.

What happened during FIREFISH Part 2?

FIREFISH Part 2 aimed to find out how effective risdiplam was for treating babies with Type 1 SMA.

- The risdiplam dose selected in Part 1 (the higher dose) was given to all babies in Part 2.



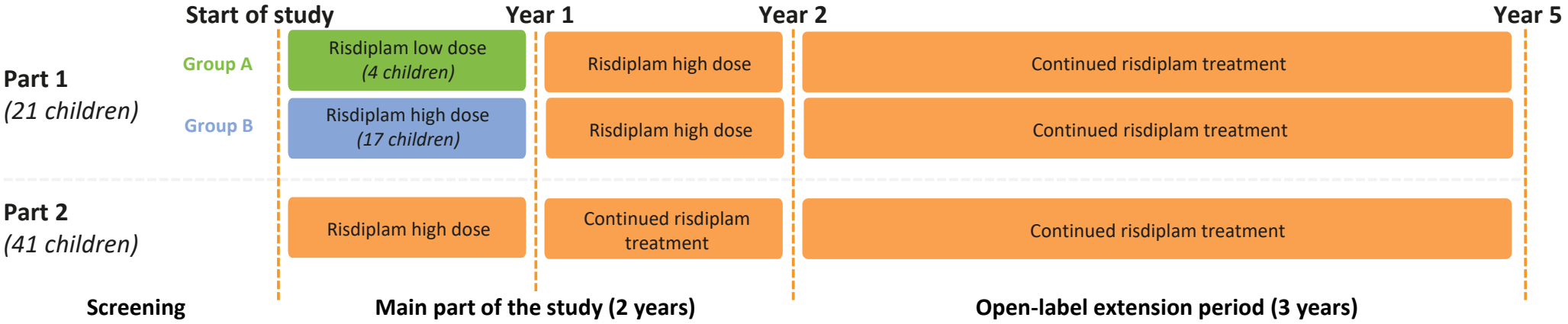
Parts 1 and 2 included different children - those who took part in Part 1 did not participate in Part 2.

SMA, spinal muscular atrophy.

What happened over the whole 5 years of the FIREFISH study?

After children in **FIREFISH Part 1** and **Part 2** had completed 2 years of risdiplam treatment, they entered the open-label extension period.

During this part of the study all children received risdiplam treatment at the higher dose for a further 3 years.



- Children who received the higher dose from the start of the study (**FIREFISH Part 1**, Group B and all the children in **FIREFISH Part 2**) can be pooled into a larger group known as the '**grouped population**'.
- Looking at the results from the larger, grouped population provides stronger evidence than if each group was assessed on its own. This means that researchers can have more confidence in the conclusions they make about risdiplam treatment.

All of the 5-year results for FIREFISH will be reported for the grouped population.

What were the characteristics of the babies in FIREFISH Part 1 and Part 2 before they started treatment?

Part 1 enrolled 21 babies

29%
(6 out of 21 babies) were male

71%
(15 out of 21 babies) were female

The average age at which symptoms started was 1.9 months

6

The average age at enrolment was 5.8 months

Part 2 enrolled 41 babies

46%
(19 out of 41 babies) were male

54%
(22 out of 41 babies) were female

The average age at which symptoms started was 1.6 months

5

The average age at enrolment was 5.2 months

What were the main results from FIREFISH Part 1?

The main research question (**primary endpoint**) in **FIREFISH Part 1** was to decide on the recommended dose of risdiplam for the treatment of babies with Type 1 SMA.

- The high dose of risdiplam was chosen for use in Part 2, because it increased the level of SMN protein without causing serious side effects.
- After the dose was chosen for Part 2, everyone in **FIREFISH Part 1** switched to receive that same dose of risdiplam until the study finished.

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

What were the main results from FIREFISH Part 2?

The main aim (the primary endpoint) of FIREFISH Part 2 was to investigate the efficacy of risdiplam (how well risdiplam works).

The ability to sit was selected as the best way to measure this, as untreated children with Type 1 SMA would not usually achieve this sitting milestone.

Researchers looked at the results once all the babies taking part in **FIREFISH Part 2** had completed 1 year of treatment.

After 1 year, researchers used the BSID-III scale to assess whether the babies could sit without support for at least 5 seconds

29%

(12 out of 41 babies)

could sit without support for at least 5 seconds.

A previous document provides a summary the **FIREFISH** study results after babies had completed 1 year of risdiplam treatment. Please click here to view the 1-year summary.

For more information on the the BSID-III, please see the brochure '[Understanding the MFM and the SMAIS in the context of outcome measurements in SMA]'.

BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; SMA, spinal muscular atrophy.

Children in FIREFISH Part 1 and Part 2 were treated with the chosen risdiplam dose for up to 5 years.

The **FIREFISH** study is now finished.

The following results report data on efficacy (how well risdiplam works) and safety (side effects) from the **FIREFISH** grouped population after 5 years of treatment.

These children all received the chosen, final dose (i.e. the high dose) from the start of the trial.

What were the characteristics of the children before they started treatment in FIREFISH?

Assessments were performed at the beginning of the study (baseline) before risdiplam was given.

The grouped population included the 17 children from Part 1 and the 41 children from Part 2 given the high dose of risdiplam.

Grouped population (58 children)

43%
(25 out of 58 children)
were male

57%
(33 out of 58 children)
were female

<2
Most children were less than 2 months old when they started showing symptoms of SMA

38
children (66%) had symptoms of SMA for longer than 3 months before they started treatment with risdiplam

SMA, spinal muscular atrophy.

What were the grouped population results after 5 years of treatment?

91% of children were alive

81% of children were alive and did not need permanent breathing support*

*Permanent breathing support is defined as **tracheostomy** or **BiPAP** (bilevel positive airway pressure) for at least 16 hours per day continuously for over 3 weeks or continuous **intubation** for over 3 weeks, in the absence of, or following the resolution of, an acute reversible event.

Tracheostomy is a procedure where a tube is inserted through the neck into the windpipe. This helps air enter the lungs.

BiPaP is a machine that helps with breathing using a facemask.

Intubation is when a tube is inserted through the mouth and down into the windpipe. This helps air enter the lungs.

How many children could sit without support after 5 years of risdiplam treatment?

62%
(36 out of 58 children)

could sit without support for at least 5 seconds, as measured by BSID-III.

59%
(34 out of 58 children)

could sit without support for at least 30 seconds, as measured by BSID-III.

59%
(34 out of 58 children)

could sit without support, as measured by HINE-2.

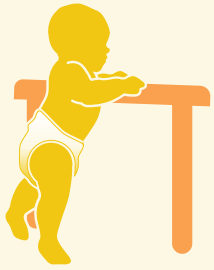
For more information on the physical ability measures, please see the brochure 'Understanding the MFM and the SMAIS in the context of outcome measurements in SMA'.

BSID-III, The Bayley Scales of Infant and Toddler Development, Third Edition; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

How many children could stand and walk after 5 years of risdiplam treatment?

7%
(4 out of 58 children)
were able to stand without support, as measured by BSID-III.

12%
(7 out of 58 children)
were able to stand with or without support, as measured by HINE-2.



0%
(0 out of 58 children)
were able to walk without support, as measured by BSID-III.

10%
(6 out of 58 children)
were able to walk with support, as measured by HINE-2.

For more information on the mobility measures, please see the brochure '[Understanding the MFM and the SMAIS in the context of outcome measurements in SMA]'.

BSID-III, The Bayley Scales of Infant and Toddler Development, Third Edition; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

How many children could swallow and feed by mouth after 5 years of risdiplam treatment?

96%
(46 out of 48 children)
were able to swallow.

91%
(42 out of 46 children)
were able to feed by mouth.

80%
(37 out of 46 children)
were able to feed by mouth, without any feeding support.

- Swallowing and feeding assessments looked at the children's ability to eat by mouth and how well they were able to swallow food or drinks.
- Feeding support was provided by a feeding tube.

Information about side effects is available from children in FIREFISH after 5 years of risdiplam treatment

The **FIREFISH** study is now finished. Children have completed up to 5 years of treatment.

The side effects are reported for the **FIREFISH** grouped population, which includes all children from Part 1 given the high dose of risdiplam and all the children from Part 2.

Side effects are medical problems (such as feeling dizzy or feeling sick) that happen during the study.

Not all side effects are related to the study medication, some occur by chance. Doctors report all medical problems that participants have during the study to Roche, so that they can look for patterns across every person taking part.

It is important to know that:

- Not all the people in this study had all the side effects listed.
- Side effects may be mild to serious and can be different from person to person.
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflet.

Serious and common side effects reported in **FIREFISH** are listed in the following sections.

What were the serious side effects in FIREFISH?

A side effect is considered 'serious' if it is life-threatening, needs hospital care or causes lasting problems.

Not all serious side effects reported are related to the study medicine.

In FIREFISH two children had serious side effects that were thought to be related to taking risdiplam by the study doctors. They were infection of the air sacs in the lungs (pneumonia) and a lack of oxygen in the body (asphyxia).

Serious side effects were reported in 47 out of 58 children (81%) in FIREFISH.

The most common serious side effects are reported here.

Each of these side effects was reported in at least four children.

Most common serious side effects	What percentage of children reported this side effect?
Infection of the air sacs in the lungs *(pneumonia)*	**45%** (26 out of 58 children)
Difficulty breathing *(respiratory distress)*	**10%** (6 out of 58 children)
Lung infection caused by a virus *(viral pneumonia)*	**9%** (5 out of 58 children)
Lack of oxygen in the body *(respiratory failure)*	**7%** (4 out of 58 children)

What were the side effects in FIREFISH?

Side effects are any medical problems (such as feeling dizzy or feeling sick) that happen during the study.
Not all side effects that are reported are related to the study medicine.

The most common side effects reported in **FIREFISH** are listed here.

Each of these side effects was reported in at least 11 children.

Most common side effects	What percentage of children reported this side effect?
Infection in the nose, throat and sinuses *(upper respiratory tract infection)* Fever *(pyrexia)*	**64%** (37 out of 58 children)
Infection of the air sacs in the lungs *(pneumonia)*	**50%** (29 out of 58 children)
Inflammation of the nose and throat *(nasopharyngitis)* Diarrhoea	**28%** (16 out of 58 children)
Constipation	**26%** (15 out of 58 children)
Being sick (vomiting) Cough COVID-19 Runny or stuffy nose, sneezing *(rhinitis)*	**21%** (12 out of 58 children)
Inflammation of the airways in the lung *(bronchitis)* Infection in the nose, throat and airways *(respiratory tract infection)*	**19%** (11 out of 58 children)

What were the side effects related to risdiplam treatment?

In FIREFISH doctors reported side effects that were thought to be related to risdiplam in 11 out of 58 children (19%).

The most common side effects related to taking risdiplam are listed here.

Each of these side effects was reported in at least two children.

Most common side effects related to risdiplam treatment	What percentage of children reported this side effect?
Blood in urine *(haematuria)*	**5%** (3 out of 58 children)
Infection of the air sacs in the lungs *(pneumonia)*	**3%** (2 out of 58 children)
Constipation	**3%** (2 out of 58 children)
Urinary tract infection	**3%** (2 out of 58 children)
Skin discolouration	**3%** (2 out of 58 children)
A flat, red area on the skin that is covered with small bumps *(maculo-papular rash)*	**3%** (2 out of 58 children)

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

For a health condition like SMA for which there are remaining medical gaps and unmet patient needs, the study of possible new drugs and different modes of administration (such as risdiplam as the only approved oral treatment for SMA) is important to advance patient outcomes and care.

The study results from **FIREFISH** have given researchers and those living with SMA a better understanding of the effects of risdiplam in children with Type 1 SMA.

Studies with risdiplam are ongoing and further studies are planned.

The results helped to find the most effective risdiplam dose for children with Type 1 SMA and led to risdiplam being approved by health authorities for the treatment of SMA.

Risdplam is approved by the US Food & Drug Administration (FDA) for the treatment of SMA in adult and paediatric patients.

Risdiplam is approved by the European Commission for the treatment of SMA in patients with SMA Type 1, Type 2 or Type 3 or with one to four copies of the *SMN2* gene.

This summary includes results from the whole **FIREFISH** study. Children were treated with risdiplam for up to 5 years.

These results are important to understand the safety profile of risdiplam for the treatment of children with Type 1 SMA with risdiplam.

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

FDA, U.S. Food and Drug Administration; EC, European Commission; SMA, spinal muscular atrophy.

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/NCT02913482
- https://forpatients.roche.com/en/trials/muscle-and-peripheral-nerve-disease/sma/investigate-safety--tolerability--pk--pd-and-efficacy-of-ro70340.html

The full title of this study is: A Two Part Seamless, Open-label, Multicentre Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Infants With Type 1 Spinal Muscular Atrophy.

The study is known as '**FIREFISH**'.

The protocol number for this study is: BP39056.

The ClinicalTrials.gov identifier for this study is: NCT02913482.

The EudraCT number for this study is: 2016-000778-40.

If you or your child have taken part in this study and have any questions about the results, please speak with your doctor.

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

Address for the sponsor of this trial:

F. Hoffmann-La Roche, Grenzacherstrasse 124 CH-4070,
Basel, Switzerland

Previous documents provided a summary of the results of the **FIREFISH** study after children had completed 1 year and 2 years of risdiplam treatment.

Please click here to view the 1-year summary.

Please click here to view the 2-year summary

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