An updated summary of long-term (2-year) data from FIREFISH, a clinical trial to establish the efficacy and safety of risdiplam for children with Type 1 SMA

Date of preparation: January 2022 | M-XX-00007889

About this summary

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

A document was made in 2020 that provided a summary of the 12-month results of Parts 1 and 2 of the FIREFISH study. The study started in December 2016 and met its main aims (endpoints) in November 2019, when the last child to take part had completed 12 months of treatment with risdiplam, the drug being investigated in this study. Please see **Figure 1** for an overview of the information that can be found in this summary. Please click **here** to view the 2020 summary.

This document provides a summary of the 24-month results of the FIREFISH study (from both Part 1 and Part 2) and the combined results from the whole FIREFISH study to date (12-month and 24-month results from both Parts 1 and 2).

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

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

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Key information about this study

The FIREFISH study included children with Type 1 SMA who were aged between 1 and 7 months when they entered the study.

This study is '**open label**', which means that the researchers and the families of the children taking part in the study all knew which treatment was being given. No one was given a '**placebo**' (a dummy drug with no active ingredient and which has no physical effect on the individual). All the children taking part in the study were given risdiplam.

This study was carried out in two parts:

- **Part 1** (the dose-finding part) had three aims: to define the optimal dose of risdiplam to give to children, to identify any side effects of risdiplam and to provide an initial assessment of the efficacy of risdiplam in treating children with SMA
- **Part 2** (the confirmatory part) was carried out to find out more detailed information about the efficacy of risdiplam in treating children with SMA, and to further assess side effects when using the dose identified in Part 1 of the study

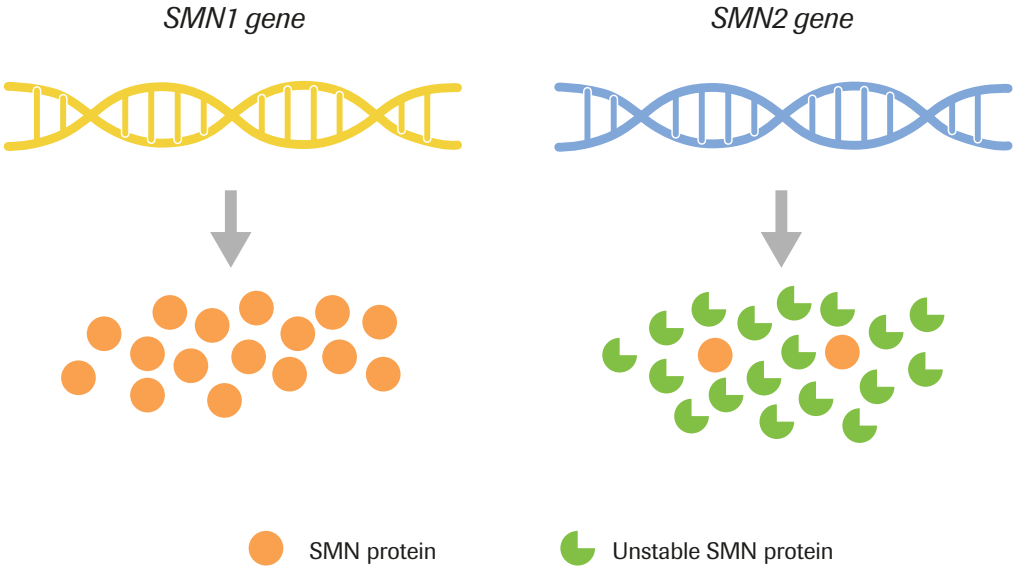
General information about this study

What is SMA?

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

SMA is caused by a change (mutation) in a specific gene called *SMN1* (survival of motor neuron 1). *SMN1* produces a protein called survival of motor neuron (SMN) that is critical to the function of the nerves that control the muscles. Without SMN protein, those nerve cells cannot properly function and eventually die, leading to debilitating and sometimes fatal muscle weakness. Individuals with SMA have low levels of SMN protein and are dependent on a related gene called *SMN2* as a 'back-up'. However, *SMN2* produces only approximately 10% of the working ('functional') SMN protein that the body needs (**Figure 2**). Without sufficient SMN protein, motor neurons degenerate and become non-functional. The more copies of the *SMN2* gene an individual has, the more SMN protein they can produce, which makes the symptoms of SMA less severe.

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



SMN, survival of motor neuron.

General information about this study

What is SMA?

Individuals with SMA have difficulty performing the basic functions of life, including breathing and swallowing. SMA does not affect emotional development or learning ability. The severity of SMA varies among individuals and depends on a range of factors, including age of onset. There are four primary types of SMA (**Table 1**), based on the age that symptoms begin and the highest physical milestone achieved. Some clinicians also refer to a Type 0 (also known as prenatal onset SMA). Type 0 is the most severe form of SMA and affects babies who are still in the womb.

Table 1: The four primary types of SMA

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

The symptoms of Type 1 SMA start showing in children between birth and 6 months of age and include inability to control the head, weak cry and cough and difficulty swallowing and feeding. Untreated children with Type 1 SMA are never able to sit independently.

General information about this study

What is the goal of treatments for SMA?

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

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

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

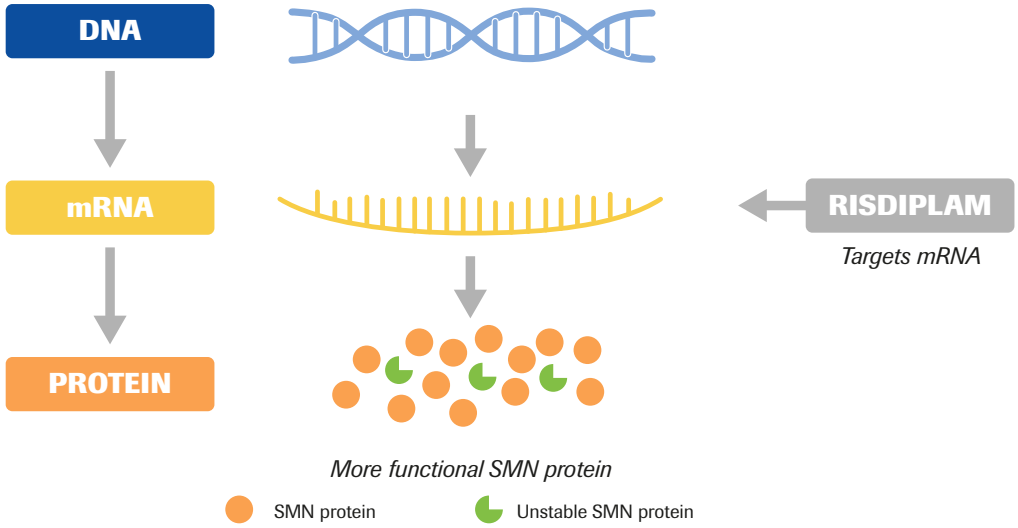
General information about this study

What is risdiplam and how does it work?

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

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

Figure 3: How risdiplam works



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

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

General information about this study

How was the study designed?

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

- An **exploratory, dose-finding part (Part 1)** to find the optimal dose of risdiplam to give to children and to make an initial assessment of the efficacy of risdiplam in treating children with SMA
- A **confirmatory part (Part 2)** to measure the efficacy and safety of risdiplam at the dose selected in Part 1

All children taking part in the FIREFISH study received risdiplam. Researchers and the families of the children taking part in the study were aware of the treatment that was being given; this is sometimes referred to as an '**open-label**' study design. No one was given a '**placebo**' (a dummy drug with no active ingredient and which has no physical effect on the individual).

In **Part 1** of the study, the children were divided into two groups, or 'cohorts', and received risdiplam for at least 12 months:

- Children in **group A** (a total of **four children**) were given a **low dose** of risdiplam
- Children in **group B** (a total of **17 children**) were given a **higher dose** of risdiplam

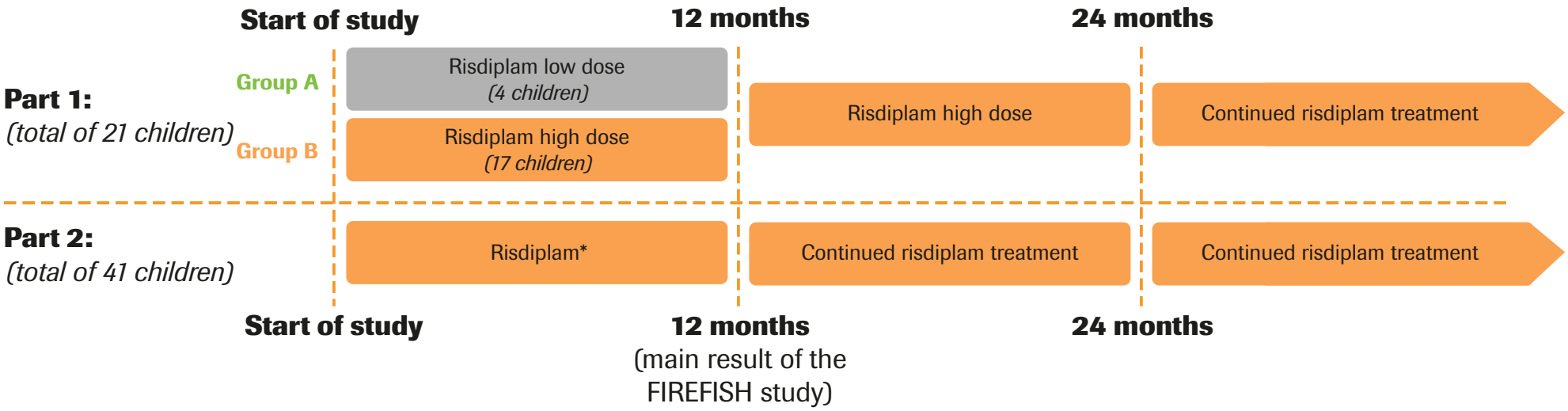
This allowed for the comparison of safety and efficacy between the two doses so that the best dose could be used in Part 2 of the study.

Part 2 of the study was designed to assess the safety and efficacy of risdiplam in 41 children receiving the dose selected from **Part 1**. Specifically, the main point the researchers wanted to assess (the primary endpoint) was the ability of children to sit unsupported for at least 5 seconds after 12 months of treatment with risdiplam.

General information about this study

How was the study designed?

Figure 4: The design of the FIREFISH study



*Same dose of risdiplam that was used for group B in Part 1 of the study.

Because 17 children from Part 1 (those in **group B**) were given the same dose of risdiplam as the children in Part 2 of the study, the results from all of these children can be combined. These combined results (called a 'pooled analysis') enable us to see how well risdiplam works in a larger group of children, rather than examining the results from Part 2 of the study only.

General information about this study

What were the aims of the study?

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

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

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

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

Because SMA affects the ability of muscles to work correctly, many of the endpoints in the FIREFISH study were related to measures of mobility. Mobility assessment scales were used to take these measurements. 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.

General information about this study

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

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

The main question researchers wanted to answer (primary endpoint)	Other important questions the researchers wanted to answer (secondary endpoints)
What is the recommended dose of risdiplam for the treatment of children aged 1–7 months with Type 1 SMA to be used in Part 2 of the study?	How does risdiplam affect the amount of SMN protein in the blood?
	Any additional questions the researchers wanted to answer (exploratory endpoints)
	What is the efficacy of risdiplam, as assessed by the following? • Percentage of children sitting without support for 5 seconds (as assessed by the BSID-III*) • Percentage of children achieving a score of at least 40 points in the CHOP-INTEND* • Percentage of children achieving motor milestones (as assessed by HINE-2*) • Percentage of children alive and without permanent breathing support (ventilation) • Percentage of children able to swallow and feed by mouth

*Please see the section '**How is mobility (motor function) measured in this study?**' for a full description of the assessment scales used.
BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2; SMN, survival of motor neuron.

General information about this study

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

Table 3: Primary, secondary and exploratory endpoints for Part 2

The main question researchers wanted to answer (primary endpoint)	Other important questions the researchers wanted to answer (secondary endpoints)
What is the efficacy of risdiplam, as measured by the percentage of children sitting without support for 5 seconds at Month 12 (as assessed by the BSID-III*)?	What is the efficacy of risdiplam, as assessed by the following? • Percentage of children sitting without support for 5 seconds at Month 24 (as assessed by the BSID-III*) • Percentage of children sitting without support for 30 seconds at Month 24 (as assessed by the BSID-III*) • Percentage of children standing without support at Month 24 (as assessed by the BSID-III*) • Percentage of children walking without support at Month 24 (as assessed by the BSID-III*) • Percentage of children who achieve an increase of at least 4 points in the CHOP-INTEND score* (assessed at Months 12 and 24) • Percentage of children who achieve a score of at least 40 in the CHOP-INTEND* (assessed at Months 12 and 24) • Percentage of children achieving motor milestones (assessed at Months 12 and 24 by the HINE-2*) • Percentage of children alive and without permanent breathing support (ventilation) (assessed at Months 12 and 24)
	Any additional questions the researchers wanted to answer (exploratory endpoints)
	What is the efficacy of risdiplam as assessed by the percentage of children able to swallow and feed by mouth (assessed at Months 12 and 24)?

*Please see the section '**How is mobility (motor function) measured in this study?**' for a full description of the assessment scales used.
BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

General information about this study

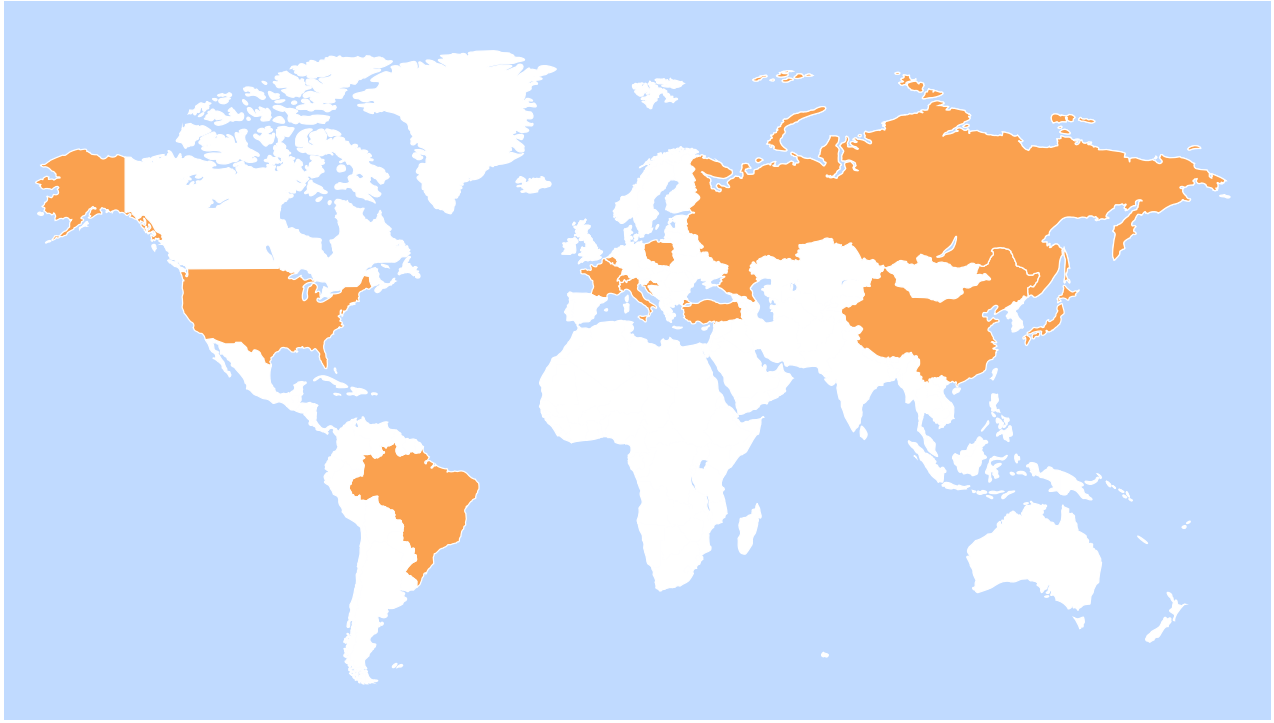
In which countries is the study taking place?

In both parts of the study, a key endpoint was to assess the safety of risdiplam.

The FIREFISH study is a global, multicentre trial taking place in 31 centres across 12 countries. The map below (**Figure 5**) shows the countries (in orange) where the FIREFISH study is taking place. Children enrolled in Part 2 were from a wider geographical area than children in Part 1.

The countries that have taken part in the FIREFISH study are Belgium, Brazil, China, Croatia, France, Italy, Japan, Poland, Russia, Switzerland, Turkey and the USA.

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



Who took part in this study?

In total, 21 children aged between 3 months and 7 months took part in Part 1 of the study, and 41 children aged between 2 months and 7 months took part in Part 2 of the study. All had Type 1 SMA. See **Table 4** for more information about the characteristics collected for each child (e.g. age, sex, SMA type, mobility) at the beginning of each part of the study.

If a child met the following requirements (inclusion criteria), they could take part in either Part 1 or Part 2 of the study:

- Had developed symptoms of Type 1 SMA between 1 month and 3 months of age, with a confirmed genetic diagnosis of the disease (5q SMA)
- Had two copies of the *SMN2* gene
- Had recovered from any short-term illness at the time of the study screening process and were considered well enough to take part

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

- Had taken part in another clinical trial within the past 3 months
- Had previously received gene or cell therapy
- Needed 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

Children who had taken part in Part 1 of the study could not take part in Part 2.

Full details of the inclusion/exclusion criteria can be found at: **https://clinicaltrials.gov/ct2/show/study/NCT02913482**

Who took part in this study?

The baseline characteristics of the children who took part

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

The baseline characteristics of the children who took part in Part 1 and Part 2 of the study are shown in the below table (**Table 4**).

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

Baseline characteristic	Part 1 (21 children)	Part 2 (41 children)
Number of girls (%)	15 (71)	22 (54)
Number of boys (%)	6 (29)	19 (46)
Average age in months at first appearance of symptoms (alongside range)	2.0 (0.9–3.0)	1.5 (1.0–3.0)
Average age in months at enrolment (alongside range)	6.7 (3.3–6.9)	5.3 (2.2–6.9)
Motor function ability		
Average CHOP-INTEND score (alongside range)	24.0 (10.0–34.0)	22.0 (8.0–37.0)
Average HINE-2 score (alongside range)	1.0 (0.0–3.0)	1.0 (0.0–4.0)
Number of children sitting without support for 5 seconds (measured by the BSID-III)	0	0

BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

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

Mobility can be measured by assessing how well a child can use different parts of their body to perform certain tasks, or whether a child has achieved motor milestones such as sitting or rolling.

Fine motor function measures how well a child can use their wrists, hands and fingers. This could be measured by assessing whether the child can grasp objects.

Gross motor function measures how well a child can use their larger muscles (arms, legs and torso). This could be measured by assessing whether a child can lift their arm or sit without support.

When measuring the effectiveness of a drug such as risdiplam on mobility, it is important to put the results into context with the mobility that can be expected from individuals with SMA who have not been treated with a disease-modifying therapy. This information can be provided by a '**natural history study**', which is a study that measures mobility and other results such as survival and use of ventilation machines to help with breathing.

Motor function assessment scales are used by clinicians in clinical trials and in the clinic. In FIREFISH, the following scales were used:

- The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), which is used to measure whether children can sit without support for at least 5 seconds, or at least 30 seconds, in this study
  - The BSID-III uses a series of play tasks to assess the development of infants aged 1–42 months; it was developed to test whether children with neuromuscular disorders could perform activities similarly to unaffected children their age
  - A modified version of the gross motor scale section is used in FIREFISH for children with Type 1 SMA. In this modified version, certain tasks have been selected to better reflect the motor abilities of these children, such as sitting without support for 5 seconds or more
  - Untreated children with Type 1 SMA are never able to sit without support

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

- The Hammersmith Infant Neurological Examination, Module 2 (HINE-2), which measures whether a child can achieve **motor milestones,** including head control, rolling, sitting and standing
  - These milestones are based on what is expected from the development of a child who does not have SMA
  - In a study of 24 untreated infants with Type 1 SMA aged 1–6 months at the onset of symptoms, most infants did not achieve the motor milestone 'head control' (2 infants achieved head control for a short period of time), and no infants achieved the following motor milestones: rolling over, independent sitting, crawling, standing or walking (as assessed by the HINE-2)

- The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), which measures **fine and gross motor function**, such as moving the head, arms and legs, grasping objects and rolling
  - The CHOP-INTEND was developed to assess motor function in infants with neuromuscular disorders. This scale is designed so that even children who have limited mobility will be able to complete some of the items
  - CHOP-INTEND scores have been observed to decrease over time in untreated infants with Type 1 SMA. A CHOP-INTEND score over 40 is rarely seen in untreated infants with Type 1 SMA

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

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FIREFISH Part 1: 24 months

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

This summary provides an overview of the safety and exploratory efficacy results from Part 1 of the FIREFISH study, after children had received treatment with risdiplam for 24 months.

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

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FIREFISH Part 1: 24 months

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

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

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

Serious side effects – those that are considered life-threatening or that need hospital care – were seen in 15 children (71%). All children who had serious side effects continued taking risdiplam without interruption.

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

Side effects, number of children (% of children)		Total (21 children)
Children with at least one side effect		21 (100)
Children with at least one serious side effect		15 (71)
Most common side effects	Fever	15 (71)
	Upper respiratory tract infection	11 (52)
	Cough	7 (33)
	Vomiting	7 (33)
	Diarrhoea	6 (29)
	Respiratory tract infection	6 (29)
Most common serious side effects	Pneumonia	5 (24)
	Acute respiratory failure	2 (10)
	Respiratory distress	2 (10)
	Respiratory tract infection	2 (10)
	Viral respiratory tract infection	2 (10)

FIREFISH Part 1: 24 months

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

Additional safety results

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

Three children died, all in the high-dose group. One of these children died after withdrawing from the study.

In the second year of treatment, compared with the first year of treatment:

- The total number of serious side effects was reduced by half (from 20 to 10 serious side effects reported)
- Three children died (one of these children died after withdrawing from the study). During the first year of treatment, one child died

FIREFISH Part 1: 24 months

Efficacy results of Part 1 of the study in the high-dose group after 24 months of treatment

The outcome for children with Type 1 SMA who do not receive any treatment is death or the need for permanent breathing support by the age of 2 years; they are never able to sit without support and are not expected to reach other motor milestones, such as rolling over, crawling, standing or walking. The efficacy results of the high-dose group (17 children) in Part 1 of the study show that 24 months of treatment with risdiplam improves efficacy outcomes and allows children with Type 1 SMA to reach major milestones.

Survival without the need for permanent breathing support (event-free survival) after 24 months of treatment with risdiplam

Event-free survival in FIREFISH is defined as being alive without needing permanent breathing support (ventilation; i.e. no tracheostomy or BiPAP [bilevel positive airway pressure] for ≥16 hours per day continuously for >3 weeks or continuous intubation for >3 weeks, in the absence of, or following the resolution of, an acute reversible event).

In total, **88% of children (15/17)** were alive and event-free after 24 months of treatment with risdiplam.

Untreated children survive without needing permanent breathing support until approximately 10.5 months of age (on average†).*

*Children with two copies of the *SMN2* gene.
†Median 10.5 months, interquartile range 8.1–13.6 months.

Number of hospitalisations after 24 months of treatment with risdiplam

29% of children (6/21) did not need to stay overnight in hospital over a 24-month period.

Untreated children with Type 1 SMA need to stay overnight in hospital between ~4.2 and 7.6 times every year.

Sitting without support for at least 5 seconds after 24 months of treatment with risdiplam (as assessed by the BSID-III scale)

59% of children (10/17) were able to sit without support for at least 5 seconds after 24 months of treatment with risdiplam.

Without treatment, children with Type 1 SMA are never able to sit without support.

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FIREFISH Part 1: 24 months

Efficacy results of Part 1 of the study in the high-dose group after 24 months of treatment

Motor function after 24 months of treatment with risdiplam

The CHOP-INTEND scale measures fine and gross motor function, such as moving the head, arms and legs, grasping objects and rolling.

In **82% of children (14/17)**, the CHOP-INTEND score increased by at least 4 points after 24 months of treatment with risdiplam.

CHOP-INTEND scores have been observed to decrease over time in untreated children with Type 1 SMA.

71% of children (12/17) achieved a CHOP-INTEND score of at least 40 after 24 months of treatment with risdiplam.

A CHOP-INTEND score over 40 is rarely seen in untreated children with Type 1 SMA.

Motor milestones after 24 months of treatment with risdiplam

The HINE-2 measures whether a child can achieve **motor milestones**, including moving the head, rolling, sitting and standing. These age-appropriate milestones are based on what is expected during the development of a child who does not have SMA.

The figure on the following page (**Figure 6**) shows the percentage of children who achieved certain milestones.

Head control: either being able to wobble their head or hold their head upright all the time

Rolling: being able to roll onto their side, roll from their front to their back or roll from their back to their front

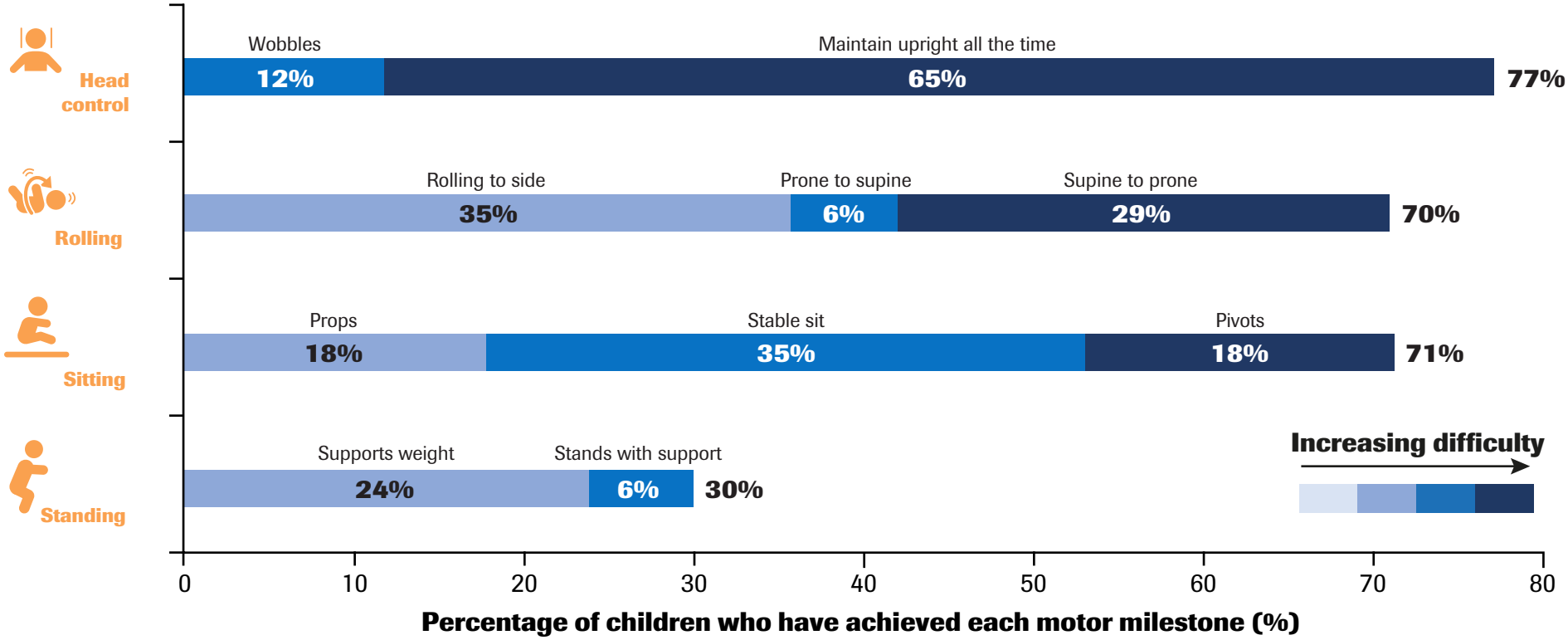
Sitting: being able to sit by propping themselves up with their arms, sit in a stable position (i.e. without supporting themselves with their arms) or reach for objects while sitting in a stable position

Standing: either being able to support most of their weight with their legs (while they are being supported for balance) or stand with support (e.g. by holding onto a chair)

FIREFISH Part 1: 24 months

Efficacy results of Part 1 of the study in the high-dose group after 24 months of treatment

Figure 6: Motor milestones achieved by children who took part in the FIREFISH study (total of 17 children)



Untreated children with Type 1 SMA are unlikely to achieve a major motor milestone (as assessed by the HINE-2), such as rolling over, sitting without support, crawling, standing or walking.

FIREFISH Part 1: 24 months

Efficacy results of Part 1 of the study in the high-dose group after 24 months of treatment

Swallowing and feeding ability after 24 months of treatment with risdiplam (assessed in children alive at Month 24)

0 children (0/14) lost the ability to swallow.

93% of children (13/14) were able to swallow and feed by mouth or feed by mouth in combination with a feeding tube.

86% of children (12/14) were able to feed exclusively by mouth.

Untreated children with Type 1 SMA who are older than 12 months are likely to need feeding support, such as feeding tubes.

In the second year of treatment, compared with the first year of treatment:

- Three more children gained the ability to sit without support for at least 5 seconds
- Children continued to improve their mobility
- In children alive at Month 24, most maintained the ability to swallow, feed by mouth or feed by mouth in combination with a feeding tube

FIREFISH Part 2: 24 months

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

This summary provides an overview of the efficacy and safety results after the children had received 24 months of treatment. The main question researchers wanted to answer for this part of the study was what percentage of children were able to sit without support for at least 5 seconds after 24 months of treatment with risdiplam (according to the BSID-III scale). This question was answered; after 24 months of treatment with risdiplam, children were able to sit without support for at least 5 seconds and showed improvement in mobility as assessed by other scales.

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

FIREFISH Part 2: 24 months

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

As outlined previously, the outcome for children with Type 1 SMA who do not receive any treatment is death or permanent breathing support by the age of 2 years; they are never able to sit without support and are not expected to reach other major milestones, such as rolling over, crawling, standing or walking.

Sitting without support for at least 5 seconds, or for at least 30 seconds, after 24 months of treatment with risdiplam

As assessed by the BSID-III scale

61% of children (25/41) were able to sit without support for at least 5 seconds after 24 months of treatment with risdiplam.

44% of children (18/41) were able to sit without support for at least 30 seconds after 24 months of treatment with risdiplam.

Without treatment, children with Type 1 SMA are never able to sit without support.

Survival without the need for permanent breathing support (event-free survival) after 24 months of treatment with risdiplam

Event-free survival in FIREFISH is defined as being alive without needing permanent breathing support (ventilation; i.e. no tracheostomy or BiPAP [bilevel positive airway pressure] for ≥16 hours per day continuously for >3 weeks or continuous intubation for >3 weeks, in the absence of, or following the resolution of, an acute reversible event).

83% of children (34/41) were alive and event-free after 24 months of treatment with risdiplam.

Untreated children survive without needing permanent breathing support until approximately 10.5 months of age (on average[†]).*

*Children with two copies of the *SMN2* gene.
[†]Median 10.5 months, interquartile range 8.1–13.6 months.

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FIREFISH Part 2: 24 months

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

Number of hospitalisations after 24 months of treatment with risdiplam

34% of children (14/41) did not need to stay overnight in hospital over a 24-month period.

There were **22 overnight stays in hospital** in the second 12 months of treatment (Months 12–24) compared with **50 overnight stays in hospital** in the first 12 months of treatment (from the start of the study to Month 12).

Untreated children with Type 1 SMA need to stay overnight in hospital between ~4.2 and 7.6 times every year.

Motor function after 24 months of treatment with risdiplam

The CHOP-INTEND scale measures fine and gross motor function, such as moving the head, arms and legs, grasping objects and rolling. An increase in score over time shows that a child has improved in fine and gross motor function.

A total of **76% of children (31/41)** achieved a CHOP-INTEND score of at least 40 after 24 months of treatment with risdiplam.

A CHOP-INTEND score over 40 is rarely seen in untreated children with Type 1 SMA.

The average (median) change from the start of the study in CHOP-INTEND score was **27 points**.

CHOP-INTEND scores have been observed to decrease over time in untreated children with Type 1 SMA.

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FIREFISH Part 2: 24 months

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

Motor milestones after 24 months of treatment with risdiplam

The HINE-2 measures whether a child can achieve **motor milestones**, including moving the head, rolling, sitting and standing. These age-appropriate milestones are based on what is expected during the development of a child who does not have SMA.

The figure on the following page (**Figure 7**) shows the percentage of children who achieved certain milestones:

Head control: either being able to wobble their head or to hold their head upright all the time

Sitting: being able to sit with support at their hips, sit by propping themselves up with their arms, sit in a stable position (i.e. without supporting themselves with their arms) or reach for objects while sitting in a stable position

Rolling: being able to roll onto their side, roll from their front to their back or roll from their back to their front

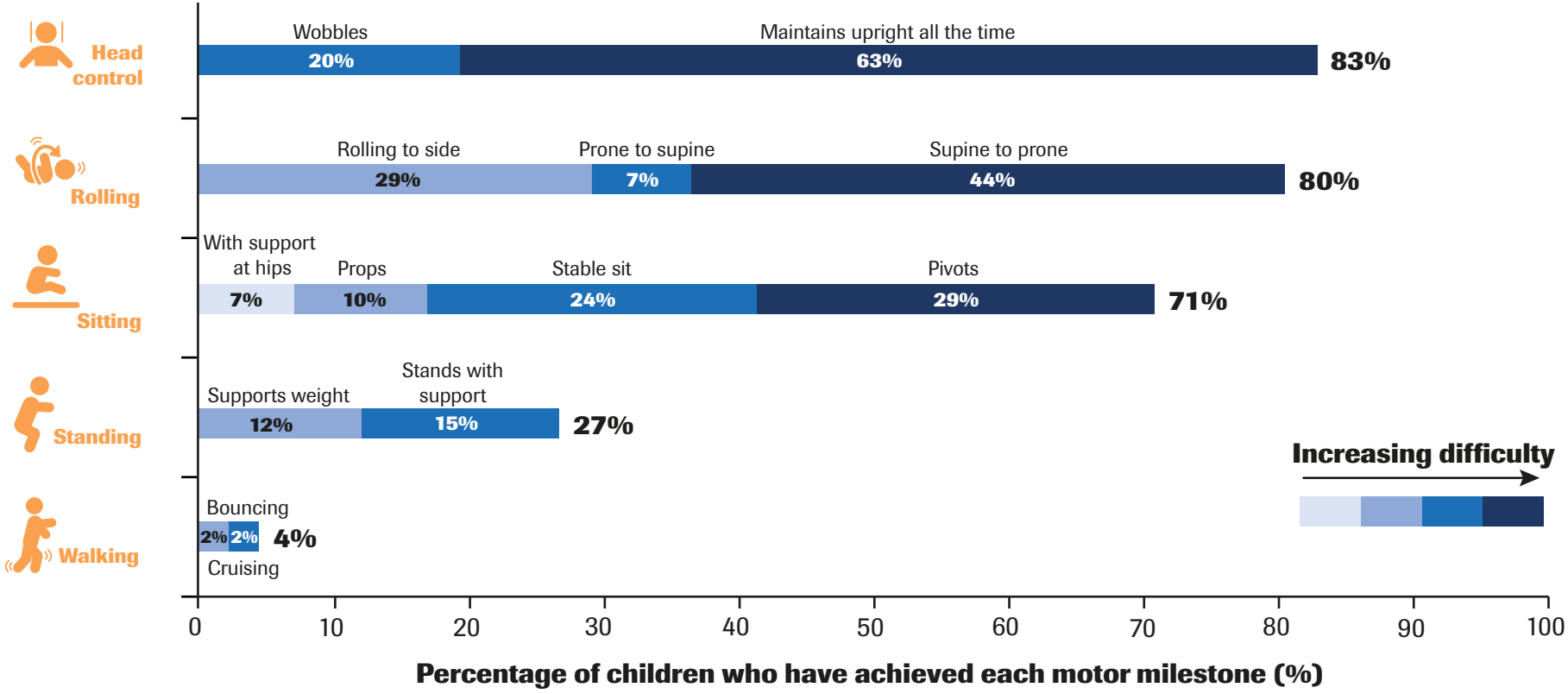
Standing: either being able to support most of their weight with their legs (while they are being supported for balance) or to stand with support (e.g. by holding onto a chair)

Walking: either being able to bounce up and down while standing or being able to take sliding steps while holding on to objects (such as furniture) for support (cruising)

FIREFISH Part 2: 24 months

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

Figure 7: Motor milestones achieved by children who took part in the FIREFISH study (total of 41 children)



Untreated children with Type 1 SMA are unlikely to achieve a major motor milestone (as assessed by the HINE-2), such as rolling over, sitting without support, crawling, standing or walking.

FIREFISH Part 2: 24 months

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

Swallowing and feeding ability after 24 months of treatment with risdiplam (assessed in children alive at Month 24)

95% of children (36/38) were able to swallow.

92% of children (35/38) were able to swallow and feed by mouth or feed by mouth in combination with a feeding tube.

76% of children (29/38) were able to feed exclusively by mouth.

Untreated children with Type 1 SMA older than 12 months are likely to need feeding support.

Most of the results for Part 2 of the FIREFISH study are shown for 41 children. However, the swallowing and feeding ability results were reported for the 38 children alive at Month 24 and do not include the three children who died due to causes related to the disease before the date of the assessment.

In the second year of treatment, compared with the first year of treatment:

- All children who were able to sit independently after 12 months of treatment were still able to do so
- Children continued to reach motor milestones and improve in mobility
- Of the children alive at Month 24, one more child was able to feed by mouth (making a total of 35 children), and one more child was able to feed exclusively by mouth (making a total of 29 children)

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FIREFISH Part 2: 24 months

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

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

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

Serious side effects – those that are considered life-threatening or that need hospital care – were seen in 28 children (68%). One child who had serious side effects had a change in dose or an interruption of treatment with risdiplam.

Table 6: Side effects of children who took part in Part 2 of the FIREFISH study, after 24 months of treatment with risdiplam

Side effects, number of children (% of children)		Total (41 children)
Children with at least one side effect		41 (100)
Children with at least one serious side effect		28 (68)
Most common side effects	Upper respiratory tract infection	22 (54)
	Pneumonia	19 (46)
	Fever	18 (44)
	Constipation	12 (29)
	Cold	7 (17)
	Lung infection	6 (15)
	Diarrhoea	6 (15)
	Inflammation of the nose	5 (12)
Most common serious side effects	Pneumonia	16 (39)
	Respiratory distress	3 (7)
	Other	2 (5)

FIREFISH Part 2: 24 months

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

Additional safety results

The reported side effects and serious side effects were in line with those expected in untreated individuals with SMA; seven children had side effects that were considered related to risdiplam and none of the serious side effects were considered related to risdiplam.

Three children died during the study, all due to causes related to the disease.

In the second year of treatment, compared with the first year of treatment:

- The number of pneumonia side effects reduced by two-thirds (from 39 to 13 pneumonia side effects per child per year)
- The number of overnight stays in hospital reduced by about half (from 50 to 22 overnight stays in hospital)
- No children died. During the first year of treatment, three children died

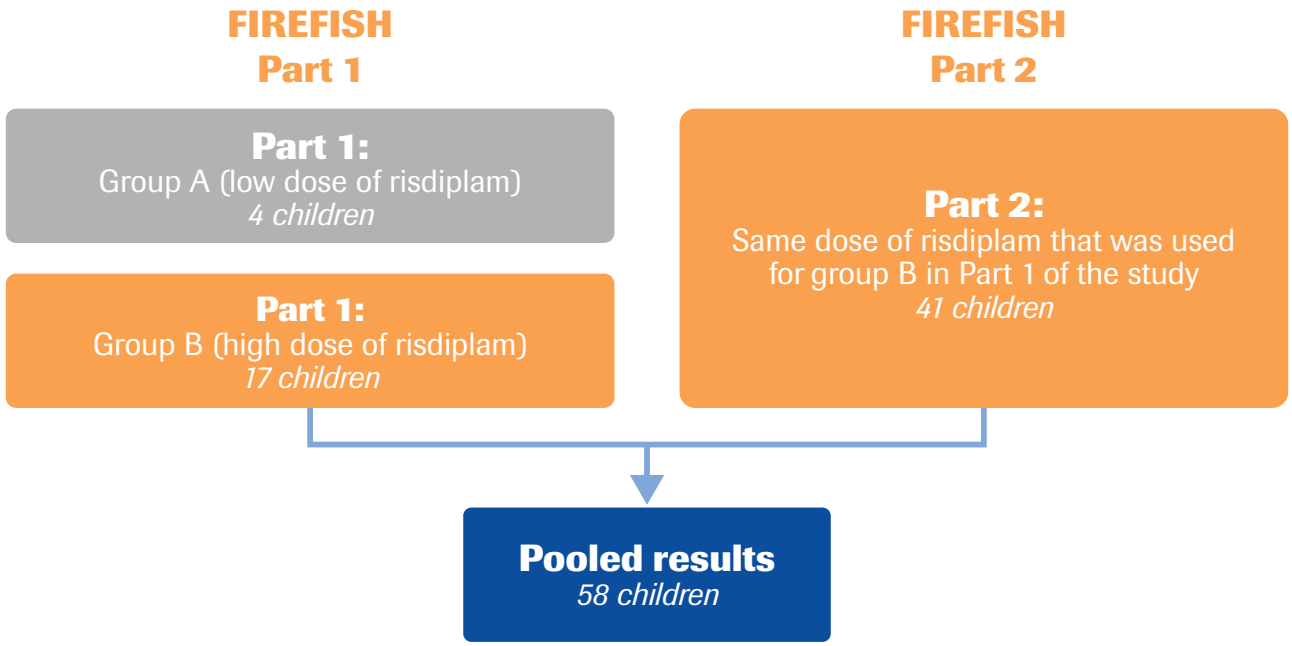
FIREFISH Parts 1 and 2: Pooled results (12 and 24 months)

What are pooled results and how will these be presented?

As 17 children (out of 21) from Part 1 were given the same dose of risdiplam as the children in Part 2 of the study (which included 41 children), the results from all of these children can be combined (**Figure 8**). These combined (pooled) results enable us to assess how well risdiplam works in a larger group of children (58 in total), compared with examining the results from Part 2 of the study only.

This section of the summary confirms the results presented separately for children in Part 1 (24 months) and Part 2 (24 months) of the FIREFISH study shown in earlier sections (**Table 7**).

Figure 8: How Part 1 and Part 2 of the FIREFISH study were combined for the pooled results



FIREFISH Parts 1 and 2: Pooled results (12 and 24 months)

What were the pooled efficacy results of the study (Parts 1 and 2)?

Table 7: Pooled efficacy results of the study

Which result was measured?		What was the result after 2 years of treatment with risdiplam?
Sitting without support	Percentage of children who could sit without support for at least 5 seconds (as assessed by the BSID-III)	**60%** (35/58 children)
	Percentage of children who could sit without support for at least 30 seconds (as assessed by the BSID-III)	**40%** (23/58 children)
Survival without the need for permanent breathing support	Percentage of children who were alive	**91%** (52/58 children)
	Percentage of children who were alive without the need for permanent breathing support (event-free survival)	**84%** (48/58 children)
Staying overnight in hospital	Percentage of children who did not need to stay overnight in hospital	**34%** (20/58 children)
	Number of overnight stays in hospital	**31**
Mobility	Percentage of children with a CHOP-INTEND score of at least 40	**74%** (43/58 children)
	Percentage of children who improved more than they worsened in the following motor milestones: controlling the head, rolling, sitting, standing and walking	**83%** (48/58 children)
Swallowing and feeding	Percentage of children who were able to swallow	**96%** (50/52* children)
	Percentage of children who were able to swallow and feed by mouth or feed by mouth in combination with a feeding tube	**92%** (48/52* children)
	Percentage of children who were able to feed exclusively by mouth, without needing to use feeding tubes	**79%** (41/52* children)

*Most of the pooled efficacy results are reported for the total of 58 children. However, the swallowing and feeding results were reported for the 52 children who were alive at Month 24 and do not include the six children who died due to causes related to the disease before the date of the assessment.

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FIREFISH Parts 1 and 2: Pooled results (12 and 24 months)

What were the pooled efficacy results of the study (Parts 1 and 2)?

In the second year of treatment, compared with the first year of treatment:

- Children continued to improve their ability to sit independently and continued to gain motor skills and reach motor milestones
- Of those children alive at Month 24, one more child was able to feed by mouth (making a total of 48 children), and one more child was able to feed exclusively by mouth (making a total of 41 children)

FIREFISH Parts 1 and 2: Pooled results (12 and 24 months)

What were the pooled safety results of the study (Parts 1 and 2)?

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

A table summarising the safety results is shown below (**Table 8**). The percentage of children who had each of the most common side effects, or serious side effects, during the 24 months of treatment with risdiplam is included in brackets.

Serious side effects – those that are considered life-threatening or that need hospital care – were seen in 40 children (69%). Two children who experienced serious side effects had a change in dose or an interruption of treatment with risdiplam.

Table 8: Side effects of children who took part in Part 1 or Part 2 of the FIREFISH study, after 24 months of treatment with risdiplam

Side effects, number of children (% of children)		Total (58 children)
Children with at least one side effect		58 (100)
Children with at least one serious side effect		40 (69)
Most common side effects	Upper respiratory tract infection Pneumonia Cold Inflammation of the nose Lung infection Gastroenteritis Flu Respiratory tract infection	32 (55) 23 (40) 12 (21) 10 (17) 6 (10) 4 (7) 4 (7) 4 (7)
Most common serious side effects	Pneumonia Other*	20 (35) 2 (3)

*Other common serious side effects include bronchiolitis [a type of lower respiratory tract infection], lower respiratory tract infection, pneumonia viral, respiratory tract infection, and viral upper respiratory tract infection.

FIREFISH Parts 1 and 2: Pooled results (12 and 24 months)

What were the pooled safety results of the study (Parts 1 and 2)?

Additional safety results

The reported side effects and serious side effects were in line with those expected in untreated individuals with SMA; eight children had side effects that were considered related to risdiplam and none of the serious side effects were considered related to risdiplam.

A total of six children died in the pooled analysis, one of whom died approximately 3.5 months after discontinuing treatment; all deaths were related to the disease.

In the second year of treatment, compared with the first year of treatment:

- The rate of serious side effects reduced by about half (from 105 to 57 serious side effects per 100 children per year, on average)
- The number of overnight stays in hospital reduced by about half (from 68 to 31 overnight stays in hospital)
- Three children died (one child died after withdrawing from the study) of treatment. During the first year of treatment, three children died

Additional information

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

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

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

Building on previous research, the study results from FIREFISH have given researchers and those living with SMA a better understanding of the effectiveness and safety of risdiplam in Type 1 SMA. The results have enabled the sponsoring company (Roche) to submit risdiplam for regulatory approval by health authorities around the world. Risdiplam received first approval for use in the USA for the treatment of SMA in infants/individuals 2 months of age and older in August 2020. Since then, it continues to be reviewed and approved by national and regional health authorities on a global scale.

This summary included results from over a longer period of time (up to 24 months of treatment) compared with the 2020 summary (which included results up to 12 months of treatment). These longer-term results are important to help us understand how children with SMA respond to the second year of treatment. They are also important to confirm the continued acceptable safety profile of risdiplam after 24 months.

The results from FIREFISH over 24 months show that, in the second year of treatment:

- A high percentage of children are alive without needing permanent breathing support
- Children continue to gain new motor milestones or keep the milestones they gained in the first year of treatment
- Children continue to improve their mobility
- A high percentage of children keep their ability to feed by mouth and swallow

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

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Additional information

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

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

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

The full title of this study is: A Two Part Seamless, Open-label, Multicenter 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'.

Address and telephone number for the sponsor of this trial:

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

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