# Summary of Clinical Trial Results

## A summary of 2-year results from RAINBOWFISH, a study of risdiplam as a treatment for babies with SMA who were not yet showing symptoms

See the end of the summary for the full title of the study.

## About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- members of the public and
- people who took part in the study.

This summary is based on information known at the time of writing.

The study started in June 2019. This summary includes 2-year results that were collected in March 2024. At the time of writing this summary in January 2025, this study is still ongoing – meaning that study doctors are still collecting information.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same study medicine.

- **This means that gathering as much information as possible will help you to make an informed decision – always speak to your doctor before making any decisions about your treatment.**

### Contents of the summary



### Abbreviations

**BiPAP** = 'bilevel positive airway pressure'
**BSID-III** = 'Bayley Scales of Infant and Toddler Development, Third Edition'
**CMAP** = 'compound motor action potential'
**EC** = 'European Commission'
**FDA** = 'U.S. Food and Drug Administration'
**HINE-2** = 'Hammersmith Infant Neurological Examination, Module 2'
**mV** = 'millivolt'
**SMA** = 'spinal muscular atrophy'
**SMN** = 'survival of motor neuron'
**WHO** = 'World Health Organization'

### Thank you to the people who took part in this study.

The people who took part have helped researchers to answer important questions about spinal muscular atrophy (SMA) and the medicine being studied – 'risdiplam'.

## 1. General information about this study

### What is SMA?

- Spinal muscular atrophy (SMA) is a rare, genetic disease that causes the nerve cells (motor neurons) that control muscle movements to die.

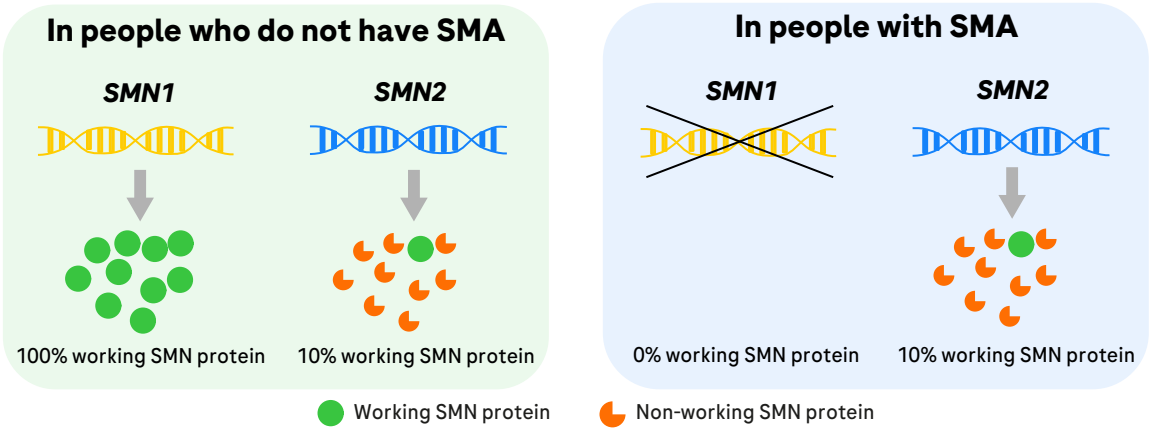
SMA destroys the nerve cells in the brain stem and spinal cord that control muscle.

The loss of these nerve cells causes muscle weakness and loss of movement due to muscle wasting (atrophy).

- People living with SMA have muscle weakness and wasting that impact on many bodily functions, including sitting, standing and walking, and also swallowing and breathing.
- 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 start, and the highest physical milestone achieved (such as being able to sit or walk). Type 0 SMA is the most severe form and Type 4 SMA has the mildest symptoms.

### What causes SMA?

- 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*).
- People have a similar gene called 'survival of motor neuron 2' (also known as *SMN2*) that makes a smaller amount of SMN protein.
- *SMN2* cannot make enough protein to make up for the loss of *SMN1*.
- The number of *SMN2* gene copies a person has varies. The more copies of the *SMN2* gene a person has, the more SMN protein they can make and the milder their SMA symptoms are.
- With more *SMN2* gene copies, SMA symptoms start later in life and causes less nerve cell damage. Ultimately a person could have a longer life expectancy with less disability.




## What was the medicine being studied?

- Risdiplam is the drug that was studied in the **RAINBOWFISH** study.
- You say this as 'ris-di-plam'.
- Risdiplam is a liquid taken once a day by mouth (orally) or by feeding tube for those with difficulty swallowing.
- Risdiplam works by helping the *SMN2* gene to produce more working SMN protein.
- This may mean that people treated with risdiplam may see an improvement in their symptoms.
  - Risdplam is approved by the U.S. Food and Drug Administration (FDA) for the treatment of SMA in adult and paediatric patients.
  - Risdiplam is approved by the European Commission (EC) 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.

## Why was this study done?

- In SMA, nerve cell damage starts before people show symptoms of the disease.
- Previous studies on SMA have shown that people who receive medication early or before symptoms start, have better outcomes than people who started treatment later in life.

## What did researchers want to find out?

- The goal of this study was to test:
  - the correct dose of risdiplam for treatment of babies under 2 months of age.
  - the effects and safety of risdiplam in young babies who were diagnosed with SMA but started treatment before showing any signs or symptoms of the disease.

## The main question that researchers wanted to answer was:

- How many of the babies could sit without support for at least 5 seconds, after 1 year of risdiplam treatment?
  - To make sure that this was measured fairly across all the hospitals, sitting was measured using the Bayley Scales of Infant and Toddler Development (known as

the BSID-III), which told the researchers what to look for.

- This was measured in a small group of five babies in **RAINBOWFISH** who had two copies of the *SMN2* gene.
- This group was chosen because people with SMA with two copies of the *SMN2* gene who do not receive treatment, are typically not able to sit without support. This allowed researchers to see if risdiplam was working.

**Other questions that researchers wanted to answer were:**

- What dose of risdiplam should be given to babies under 2 months of age?
  - The chosen dose of risdiplam was selected within the first year of the **RAINBOWFISH** study.
  - The approved dose for risdiplam is 0.15 milligrams per kilogram of body weight for babies under 2 months of age.
- How well does risdiplam work as a medicine for SMA in babies and how safe is it to use this study medicine in young babies?
  - This part of the study measured how well all 23 babies who completed 2 years of risdiplam treatment did.
  - Researchers wanted to see how many of the babies:
    - needed support to breathe?
    - achieved motor milestones?
    - were able to swallow and eat food safely?
    - had started to develop SMA?
    - experienced unwanted effects?

## What kind of study is this?

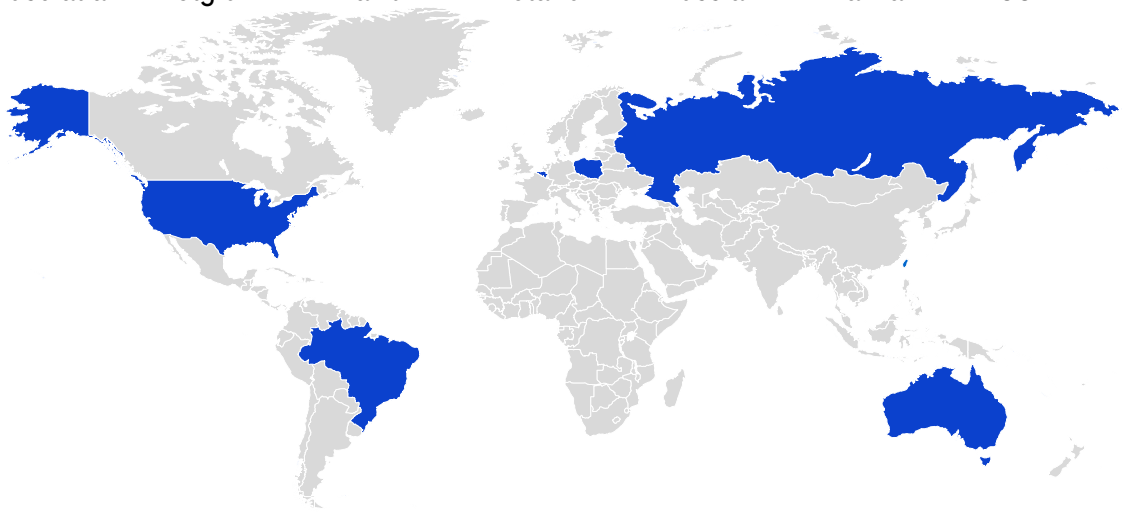
- This was a 'Phase 2' study. This means that risdiplam had been tested in a number of people with SMA before this study. In this study, all the babies took risdiplam – this was to find out about the safety of risdiplam and if risdiplam worked as a medicine for babies with SMA.

## When and where did this study take place?

- The **RAINBOWFISH** study started in June 2019 and was still ongoing at the time of writing this summary in December 2024. The study is expected to end in March 2027.
- This summary was written after the babies had completed at least 2 years of risdiplam treatment.
- **RAINBOWFISH** was a global study that took place in seven hospitals across seven locations. The map below shows where the study took place.

**The locations where RAINBOWFISH took place were:**

Australia Belgium Brazil Poland Russia Taiwan USA



## 2. Who took part in this study?

| Babies could take part in the study if: | Babies could not take part in the study if: |
|---|---|
| • they were between 1 day and 42 days (6 weeks) old.<br>• they did not have any signs or symptoms of SMA.<br>• they had a genetic diagnosis of SMA (a test confirmed that they did not have the *SMN1* gene). | • they had previously received or were currently being treated with another drug treatment or gene or cell therapy for SMA.<br>• they needed significant medical support to breathe. |

Full details of the inclusion/exclusion criteria can be found at: https://clinicaltrials.gov/study/NCT03779334#participation-criteria.

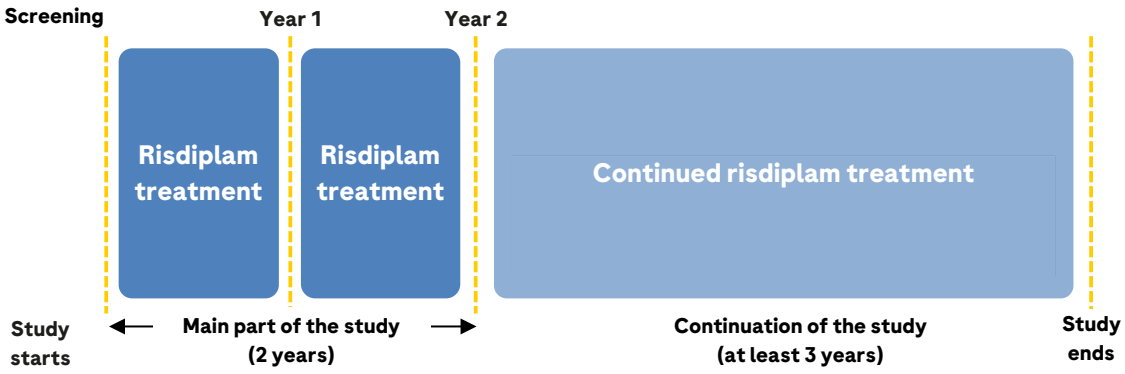
- In this study, 26 babies took part.
- The babies were between 16 and 41 days old at the start of the study.
- Sixteen babies (61.5%) were male and 10 babies (38.5%) were female.
- The study included babies with 1, 2, 3 and 4 or more copies of the *SMN2* gene.
  - The more copies of the *SMN2* gene a person with SMA has, the more SMN protein they can produce, which makes the symptoms of SMA less severe.

| | |
|---|---|
| **Two copies of the *SMN2* gene** | 8 out of 26 (31%) babies had two *SMN2* copies. |
| **Three copies of the *SMN2* gene** | 13 out of 26 (50%) babies had three *SMN2* copies. |
| **Four or more copies of the *SMN2* gene** | 5 out of 26 (19%) babies had four or more *SMN2* copies. |

## 3. What happened during the study?

- In **RAINBOWFISH**, every baby who took part received risdiplam.
- Risdiplam is a liquid. It is administered into the mouth using a syringe.
- All babies were given a single dose of risdiplam every day.
  - Babies under 2 months of age were given risdiplam at a dose of 0.15 milligrams per kilogram of body weight.
  - From 2 months onwards, up to 2 years of age, babies were given a risdiplam dose of 0.2 milligrams per kilogram of body weight.
- 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).
- This document provides a summary of the results after all of the babies had been treated with risdiplam for at least 2 years, or had withdrawn from the study.

The **RAINBOWFISH** study design:



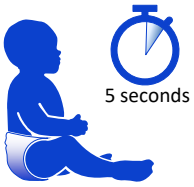
## 4. What were the results of the study?

### Question 1: What percentage of babies could sit without support for at least 5 seconds, after 1 year of treatment?

- This main question was assessed in five babies after 1 year of risdiplam treatment.
  - These five babies had two copies of the *SMN2* gene.
    - This group was chosen because babies with two copies of the *SMN2* gene who do not receive treatment, are typically not able to sit without support.
  - The babies also had compound motor action potential (CMAP) values of at least 1.5 mV.
    - CMAP is a measure of how well a muscle responds to signals from motor neurons.
    - 1.5 mV was chosen as the minimum CMAP value as it was likely that these babies did not have significant nerve cell (motor neuron) loss.

After 1 year of risdiplam treatment,

4 out of 5 babies (80%) could sit without support for at least 5 seconds.




### Question 2: The babies have now been in the study for 2 years. How many completed 2 years of risdiplam treatment?

23 out of 26 babies (88%) completed 2 years of risdiplam treatment.

- Three babies withdrew from the study before they received 2 years of risdiplam treatment.
- All three babies had two copies of the *SMN2* gene.

### Question 3: Out of the babies who completed 2 years of risdiplam treatment, how many were alive?

23 out of 23 babies (100%) were alive after 2 years of treatment.

### Question 4: How many babies were able to breathe without permanent support* after 2 years of risdiplam treatment?

All 23 babies (100%) who completed two years of treatment were able to breathe without permanent support*.

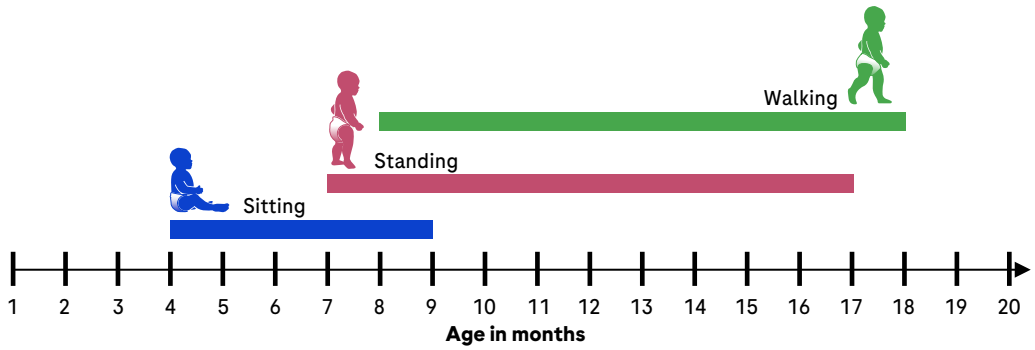
*Permanent breathing support is defined as tracheostomy or bilevel positive airway pressure (BiPAP) for at least 16 hours per day continuously for over 3 weeks, or continuous intubation for over 3 weeks, in the absence of, or following the resolution of, an acute reversible event (i.e. a short-term illness).

- 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.

## Question 5: How many babies are achieving milestones and are developing as expected for their age, after 2 years of risdiplam treatment?

- Babies usually develop and reach milestones (things most babies are able to do) by certain ages.
- The World Health Organization (WHO) gives advice on when you can expect babies to typically reach milestones, for example:
  - Babies typically sit when they are 6 months old (or anytime between 4 months and 9 months).
  - Babies typically stand when they are 11 months old (or anytime between 7 months and 17 months).
  - Babies typically start to walk when they are 12 months old (or anytime between 8 months and 18 months).
- Babies from the **RAINBOWFISH** study were assessed to see if they had reached these milestones and if they did it at the same ages as babies who do not have SMA.

**The expected window of time for babies to reach milestones of sitting, standing and walking**




More information on the WHO milestones and typical ages when babies reach these milestones can be found at: World Health Organization – Motor development milestones.

## Five babies with two copies of the *SMN2* gene completed 2 years of treatment.

5 out of 5 babies (100%) could sit without support.

3 out of 5 achieved sitting within the age range for babies who do not have SMA.

3 out of 5 babies (60%) could stand and walk without support.

1 out of 5 achieved standing and walking within the age range for babies who do not have SMA.

## Thirteen babies with three copies of the *SMN2* gene completed 2 years of treatment.

13 out of 13 babies (100%) could sit without support.

9 out of 13 achieved sitting within the age range for babies who do not have SMA.

13 out of 13 babies (100%) could stand without support.

13 out of 13 achieved standing within the age range for babies who do not have SMA.

13 out of 13 babies (100%) could walk without support.

12 out of 13 achieved walking within the age range for babies who do not have SMA.

## Five babies with four or more copies of the *SMN2* gene completed 2 years of treatment.

5 out of 5 babies (100%) could sit without support.

3 out of 5 achieved sitting within the age range for babies who do not have SMA.

5 out of 5 babies (100%) could stand and walk without support.

4 out of 5 achieved standing and walking within the age range for babies who do not have SMA.

## Question 6: How many babies are able to swallow and eat food by mouth after 2 years of risdiplam treatment?

23 out of 23 babies (100%) who completed two years of treatment could swallow and eat food by mouth.

### Question 7: How many babies showed development of SMA after 2 years of risdiplam treatment?

- All babies who participated in the **RAINBOWFISH** study started on risdiplam treatment before they had any symptoms of SMA.
- In the **RAINBOWFISH** study, babies were considered to have developed SMA (clinically manifested SMA) after 2 years of risdiplam treatment, if one of the following things happened:
  1. If they could not sit after 1 year of treatment.
  2. If they could not walk after 2 years of treatment.
  3. If they had a low weight for their age, together with one of the following:
     - Lasting twitches of the tongue muscle.
     - Feeding or swallowing problems.
     - A need for tube feeding.
  4. If they withdrew from the study to start a different treatment for SMA, even if they did not have any signs and symptoms of SMA.

**Six out of 26 babies (all with two copies of the *SMN2* gene) met the criteria for developing SMA.**

1 out of 26 babies (4%) could not sit after 1 year of treatment.
This baby also withdrew from the study to start another treatment for SMA.

3 out of 26 babies (12%) could not walk after 2 years of treatment.

A further 2 of the 26 babies (12%) withdrew from the study to start another treatment for SMA.

## 5. What were the unwanted effects in the study?

- Unwanted effects are medical problems (such as a rash) that happen during the study.
- In RAINBOWFISH, information about unwanted effects was collected from all 26 babies who received a dose of risdiplam.
- They are described in this summary because the study doctor believes the unwanted effects were related to the study medicine.
- Not all the babies in this study had all of the unwanted effects.
- It is important to be aware that the unwanted effects reported here are from this single study. Therefore, the unwanted effects shown here may be different from those seen in other studies, or those that appear on the study medicine leaflet.
- Unwanted effects may be mild to very serious and can be different from person to person.
- Serious and common unwanted effects are listed in the following sections.

### How many babies experienced serious unwanted effects?

- An unwanted effect is considered 'serious' if it is life-threatening, needs hospital care or causes lasting problems.
- In **RAINBOWFISH**, none of the 26 babies had serious unwanted effects that were related to risdiplam.

### How many babies experienced non-serious unwanted effects?

- Researchers reported non-serious unwanted effects that were related to risdiplam in 7 out of 26 babies (27%).

### What were the unwanted effects reported in RAINBOWFISH?

- There were nine non-serious unwanted effects reported overall in seven out of 26 babies. Some babies had more than one.
- All the unwanted effects related to risdiplam and reported over 2 years of treatment are listed in this section.

**Each of the following unwanted effects were reported in at least one baby:**

| Most common unwanted effects | Percentage of babies who experienced the unwanted effect |
|---|---|
| Dry skin, itching and redness (dermatitis atopic) | 1 out of 26 babies (4%) each |
| Dry, itchy and red skin (eczema) | |
| Skin discolouration | |
| Eye disease that causes loss of vision (retinal pigmentation) | |
| Disease of the blood vessels in the eye (retinal vascular disorder) | |
| Frequent watery stools (diarrhoea) | |
| Liver dysfunction (alanine aminotransferase increased) | |
| Liver dysfunction (aspartate aminotransferase increased) | |
| Received higher dose than advised (incorrect dose administered) | |

You can find information about other unwanted effects (not shown in the section above) on the websites listed at the end of this summary – see section 8.

## 6. How has this study helped research?

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

- The information presented here is from a single study of babies with SMA.
  - This summary includes results from the **RAINBOWFISH** study. Babies were treated with the study medicine (risdiplam) for at least 2 years.

- 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.

- 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 methods of administering treatment is important to advance patient outcomes and care.
- The **RAINBOWFISH** study provides results on how well risdiplam works and how safe it is in young babies diagnosed with SMA but not yet showing symptoms.
- The results helped to find the most effective risdiplam dose for babies diagnosed with SMA early in life and led to risdiplam being approved by health authorities for the treatment of SMA from birth.

## 7. Are there plans for other studies?

- Studies with the study medicine (risdiplam) are still happening.
- Other studies are looking at the use of risdiplam together with other treatments.

## 8. Where can I find more information?

- You can find more information about this study on the websites listed below:
  - https://clinicaltrials.gov/study/NCT03779334
  - https://forpatients.roche.com/en/trials/muscle-and-peripheral-nerve-disease/sma/a-study-of-risdiplam-in-infants-with-genetically-diagno-31840.html

### What is the full title of this study?

**If you would like to find out more about the results of this study, the full title of the scientific study is:**

- A Study of Risdiplam in Infants with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (RAINBOWFISH).
- The study is known as '**RAINBOWFISH**'.

- The protocol number for this study is: BN40703.
- The ClinicalTrials.gov identifier for this study is: NCT03779334.
- The EudraCT number for this study is: 2018-002087-12.

### Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

### Who can I contact if I have questions about this study?

- 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 and telephone number for the sponsor of this trial:

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