Summary of Clinical Trial Results

A summary of the final results from a study establishing the bioavailability and bioequivalence of two different risdiplam tablets in healthy volunteers

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 (NCT04718181) started in January 2021 and finished in January 2023. This summary was written after the study had ended.

No single study can tell us everything about the benefits and risks 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 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

Glossary

- SMA = spinal muscular atrophy
- Bioavailability = how much of a drug enters the blood and is able to have an effect
- Bioequivalence = the similarity of two or more medicines that share the same active ingredient

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about a new tablet formulation of risdiplam. Risdiplam in a liquid formulation is an approved treatment for spinal muscular atrophy (SMA).

1. General information about this study

What is SMA?

- Spinal muscular atrophy (SMA) is a rare, genetic condition that causes the nerve cells (motor neurons) controlling 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).

What is risdiplam?

- Risdiplam is the drug that was studied.
- You say this as 'ris-di-plam'.
- Risdiplam is a medicine designed to help people with SMA maintain and improve muscle function.
- The approved formulation of risdiplam is a liquid taken once a day by mouth (orally) or by feeding tube for those with difficulty swallowing.
- Risdiplam oral solution 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.

Why was this study done?

- The approved form of risdiplam is a liquid oral solution (to be taken by mouth), which provides flexibility for tailoring the dose for patients with lower body weights, such as young children.
- The oral solution is made up from a powder by a pharmacist or healthcare provider.

  - Patients who weigh 20 kg or more take a 5 mg dose each day.
  - Patients or caregivers prepare this dose by drawing up 6.6 mL of the oral solution in a syringe every day.

  - A tablet form of risdiplam that contains a 5 mg dose would provide an alternative option for patients over 20 kg.
  - The tablet could be swallowed whole or dissolved in water to drink.

- This study looked at if a new tablet formulation of risdiplam would be suitable as an alternative treatment option for patients with SMA.

- Two different tablet formulations were created and compared against the existing liquid oral solution.

What did researchers want to find out?

- Researchers did this study to compare two risdiplam tablet formulations to the oral solution (see section 4 'What were the results of the study?').
- They also wanted to find out more about the safety of the medicine. Researchers looked at how many people had unwanted effects and how serious they were when taking the tablets or oral solution during this study (see section 5 'What were the unwanted effects?').

- To see if the tablets had the same effects as the liquid oral solution, the study looked at two things:

    1. **Bioavailability** – how much of the drug enters the blood (is absorbed) and is able to have an effect.
    2. **Bioequivalence** – the similarity of the two formulations of the medicine that share the same active ingredient.

- **Bioavailability** and **bioequivalence** are measures that can be used to compare different forms of a drug.
- Both **bioavailability** and **bioequivalence** look at how the amount of drug in the blood changes over time.
- Both **bioavailability** and **bioequivalence** can also be affected by:
    - Whether the drug is taken with or without food.
    - How much digestive juices (stomach acid) are in the stomach when the drug is taken.

This study was divided into two parts.

Part 1:

- In **Part 1**, researchers compared the bioavailability of two different risdiplam tablet formulations with the liquid oral solution.
- The best tablet formulation was selected for **Part 2**.

The main question that researchers wanted to answer was:

- How does the bioavailability of two risdiplam tablet formulations compare with the liquid oral solution?
- For both the tablet formulations and the liquid oral solution, this was measured by looking at how much risdiplam entered the blood. Researchers measured the risdiplam levels when the tablets were taken compared with the liquid oral solution under three conditions:
    - When the tablet was swallowed whole or dissolved in water.
    - When taken with and without food.
    - When stomach acid levels were reduced.

After both tablets were tested, the best tablet was chosen for more investigations.

Other questions that researchers wanted to answer included:

- How is the bioavailability of risdiplam oral solution affected by food?

Part 2:

- **Part 2** looked in more detail at the risdiplam tablet formulation selected in **Part 1**.

The main question that researchers wanted to answer was:

- Is the selected risdiplam tablet formulation bioequivalent to the liquid oral solution?
- This was measured by looking at how similar the blood levels of risdiplam were for the selected tablet in comparison with the liquid oral solution:
  - When the tablet was taken with and without food.
  - When the tablet was swallowed whole or dissolved in water.

What kind of study was this?

This study was a 'Phase 1' study, which means that this was the first study for risdiplam in tablet form (studies have been completed for risdiplam as a liquid oral solution). A small number of healthy adult volunteers took part in the study, and the researchers did medical tests to find out how similar the tablet formulations were to the liquid oral solution.

The study was '**randomised**' and had a '**multi-period crossover**' design.

'Randomised' means that it was decided by chance what order each participant would take the study treatments (i.e. the risdiplam tablet or liquid oral solution) and under what treatment conditions (e.g. with or without food). Apart from the order of treatments, all other aspects of care were the same between the groups.

'Multi-period crossover' means that the treatment was given to people under one set of conditions (i.e. with food), and after a break, the same people took the treatment under different conditions (i.e. without food).

When and where did the study take place?

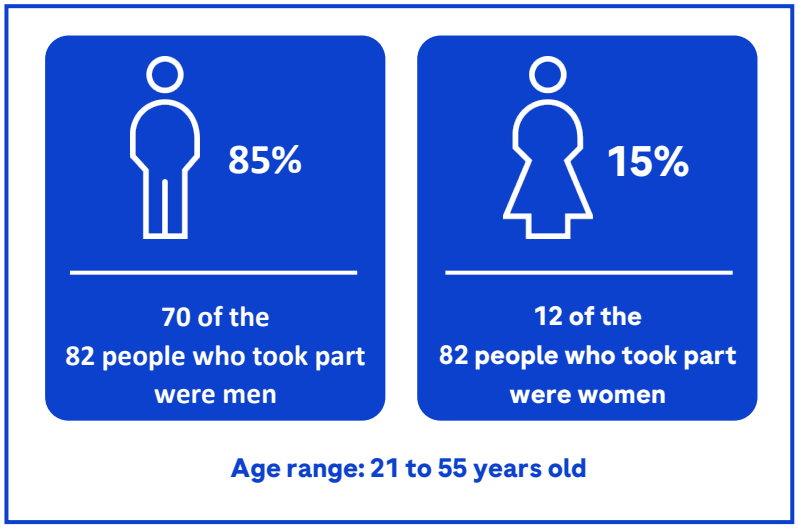
The study started in January 2021 and finished in January 2023. This summary was written after the study had ended.

The study took place at four study centres in the USA.

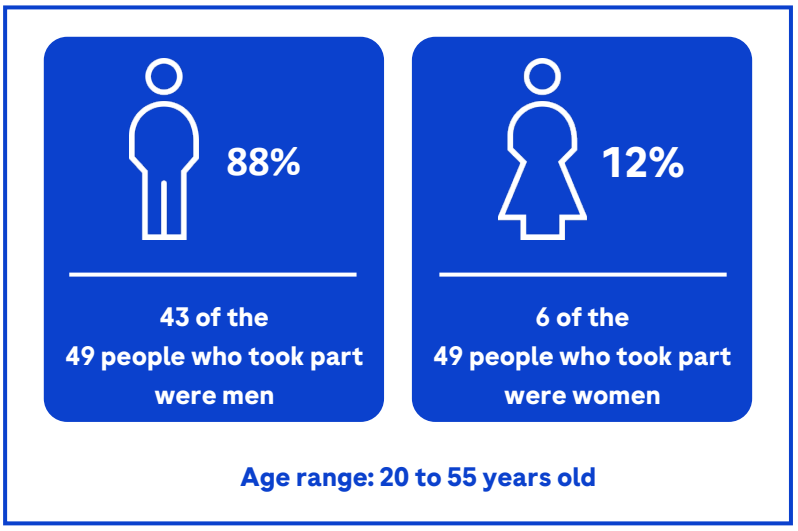
2. Who took part in this study?

Parts 1 and 2 of the study included different volunteers.

In Part 1, 82 healthy adult volunteers took part.



In Part 2, 49 healthy adult volunteers took part.



Healthy volunteers were chosen to minimise any potential effects on the bioavailability, bioequivalence and safety of the tablet formulation due to ill health or the use of other medicines.

People could take part in the study if they:

- were aged 18–55 years
- had a body mass index (BMI) of 18–32 kg/m^2
- were female of non-childbearing potential (to minimise risk to unborn children)
- were male using adequate contraception during the study and until 4 months after the final dose (to minimise risk to unborn children).

People could not take part in the study if they:

- had a history of or a current disease or condition that could pose an unacceptable risk for participation
- were using any prescription or over-the-counter medication from 1 month before the start and until the end of the study.

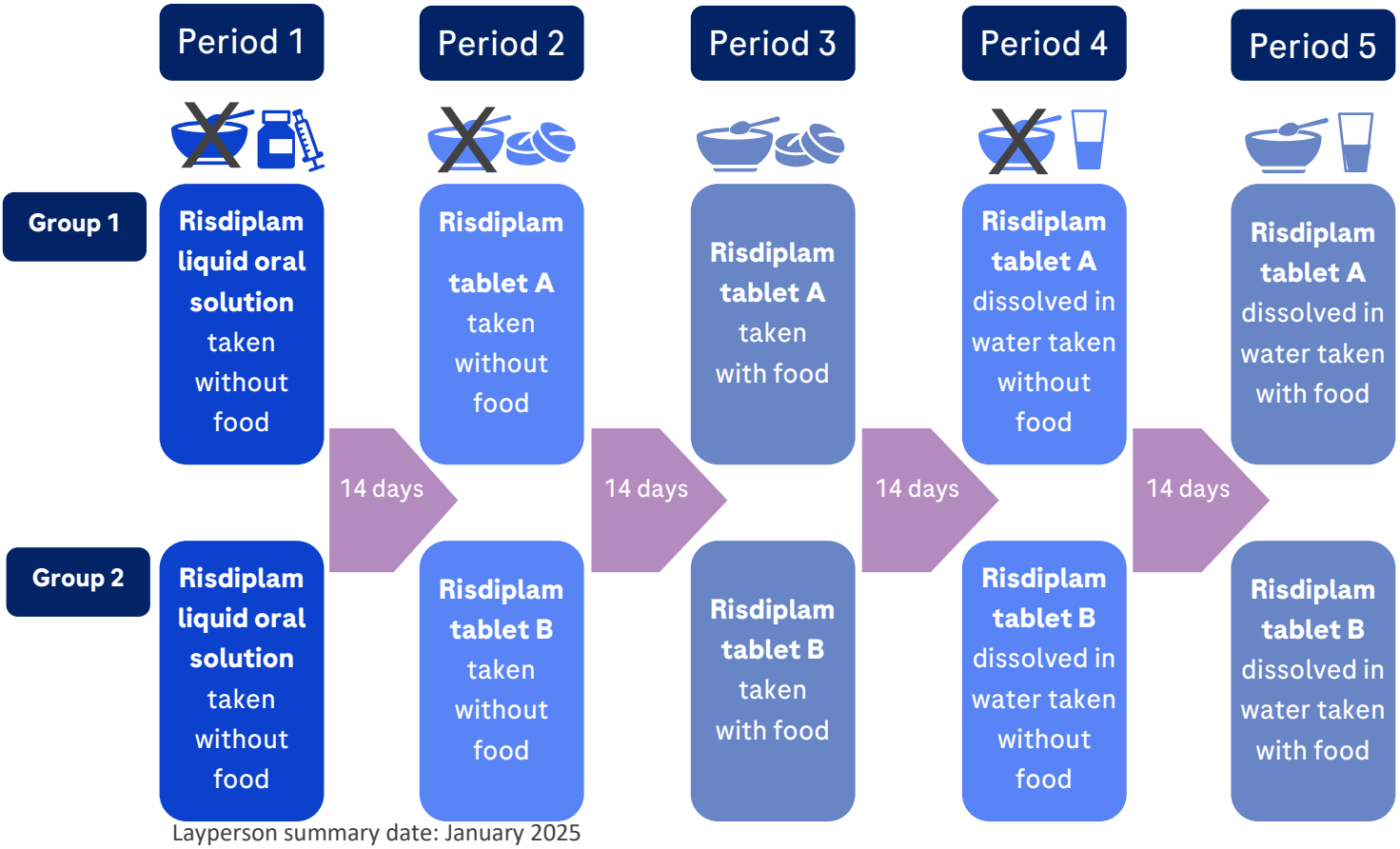
3. What happened during the study?

Part 1

Part 1 of this study explored the relative bioavailability of two new 5 mg tablet formulations and the 5 mg liquid oral solution of risdiplam.

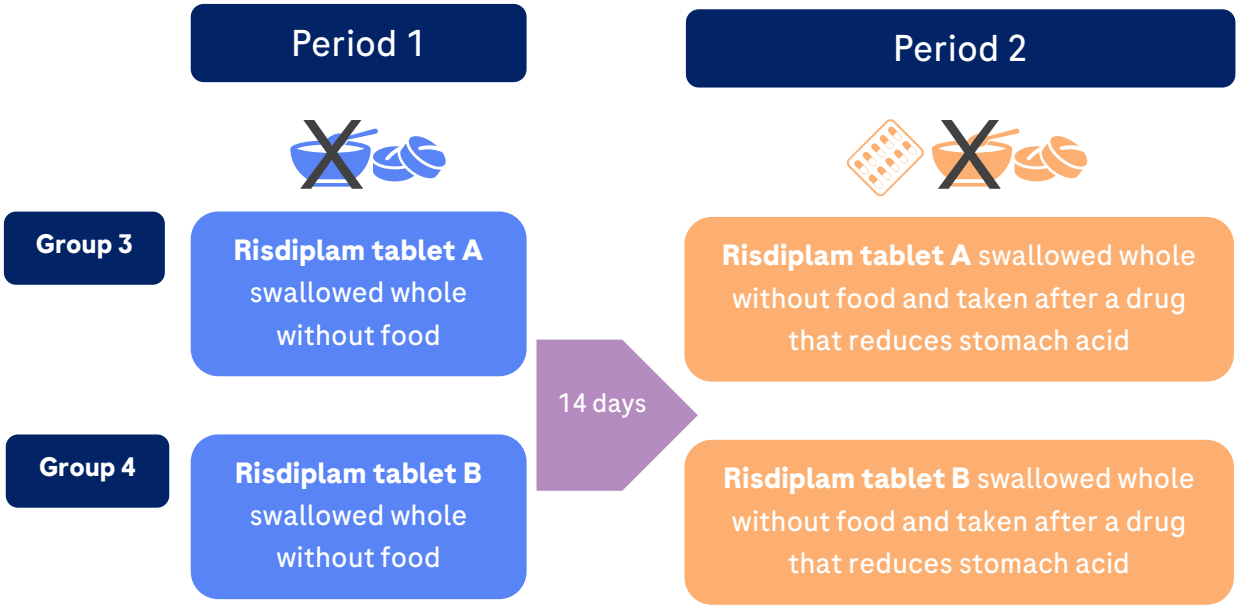
Groups 1 and 2:

- In Groups 1 and 2, researchers studied the effect of food and the effect of swallowing or dissolving tablets in water.
- Group 1 included 12 volunteers. They were given tablet formulation A.
- Group 2 included 13 volunteers. They were given tablet formulation B.
  - 1 volunteer discontinued the study after one dose of formulation B.
  - 12 volunteers from Group 2 completed the study.
- Both groups took the tablet by swallowing it whole and by dissolving it in water. The swallowed or dissolved tablets were also taken with and without food.
- The risdiplam tablet was taken as a single dose.
- There was a 14-day, treatment-free break between each risdiplam treatment, to ensure that there were no effects from the previous treatment.



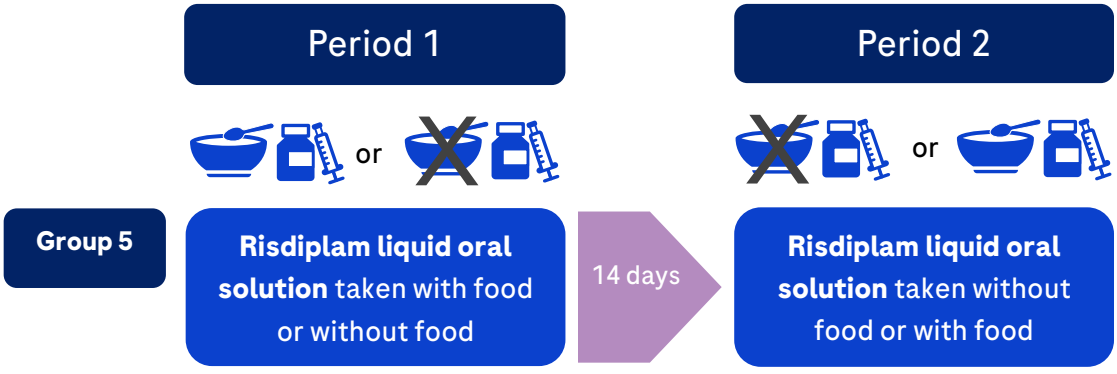
Groups 3 and 4:

- In Groups 3 and 4, researchers studied the effect of digestive juices (stomach acid).
- Both groups swallowed the risdiplam tablets whole, without food, as a single dose. They first took the tablet under normal conditions and then after a drug that reduces stomach acid.
- Group 3 included 15 volunteers. They were given tablet formulation A.
  - 3 volunteers discontinued the study after one dose of formulation A.
  - 12 volunteers from Group 3 completed the study.
- Group 4 included 14 volunteers. They were given tablet formulation B.
  - 2 volunteers discontinued the study after one dose of formulation B.
  - 12 volunteers from Group 4 completed the study.
- There was a 14-day treatment-free break between each treatment condition to ensure that there were no effects from the previous treatment.



Group 5:

- In Group 5, investigators studied the effect of food on the risdiplam liquid oral solution.
- Group 5 included 28 volunteers who took the liquid oral solution either with or without food in a randomised order.
  - 2 volunteers discontinued the study after one dose.
  - 26 volunteers from Group 5 completed the study.



- The liquid, oral solution was taken as a single dose for each treatment.
- There was a 14-day treatment-free break between each treatment to ensure that there were no effects from the previous treatment.

Part 2

Part 2 assessed the bioequivalence of the selected tablet formulation (tablet formulation A, see section 4) versus the oral solution without food and after eating.

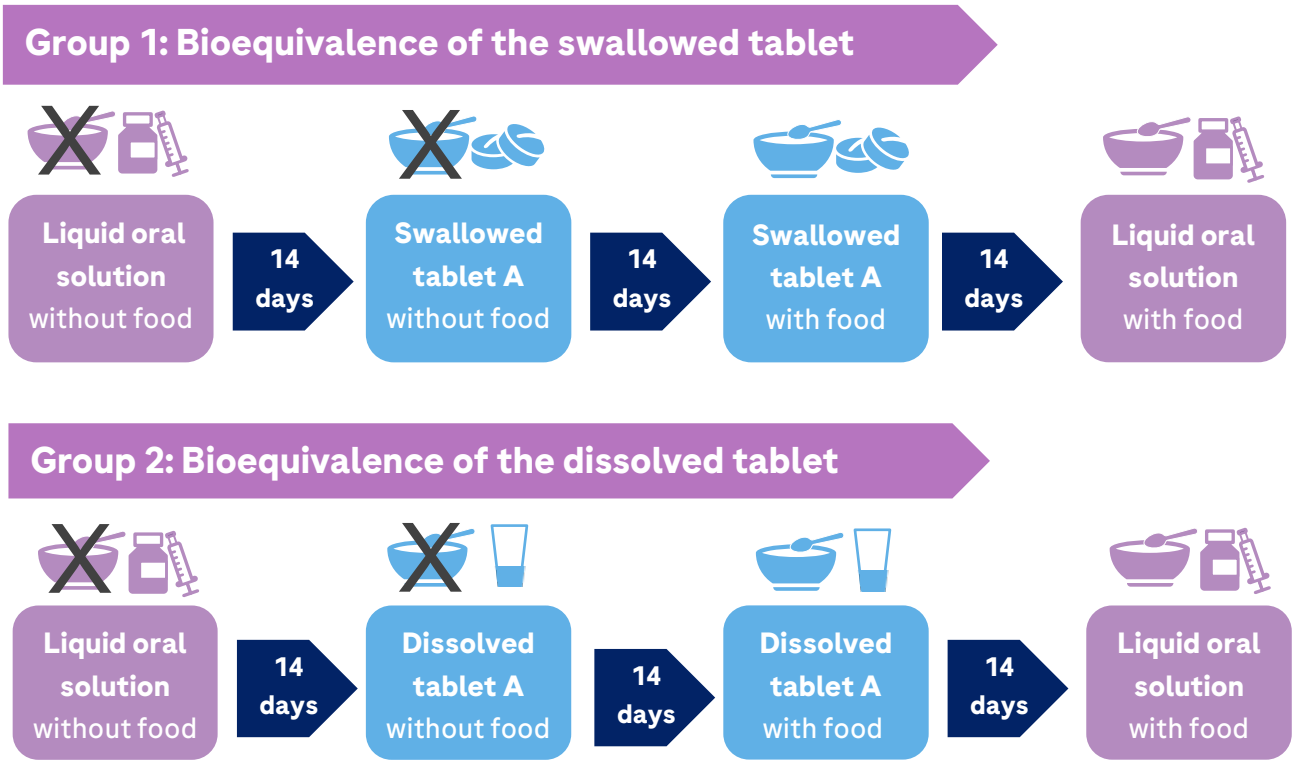
Group 1:

- Investigators studied whether the swallowed tablet is bioequivalent to the liquid oral solution, with and without food.
- Group 1 included 25 volunteers.
  - 1 volunteer discontinued the study after one dose.
  - 24 volunteers from Group 1 completed the study.

Group 2:

- Investigators studied whether the dissolved tablet is bioequivalent to the liquid oral solution, with and without food.
- Group 2 included 23 volunteers.
  - 2 volunteers discontinued the study after one or two doses.
  - 21 volunteers from Group 2 completed the study.

There was a 14-day treatment-free break between each treatment condition to ensure that there were no effects from the previous treatment.



4. What were the results of the study?

Part 1

Question 1: How does the bioavailability of two risdiplam tablet formulations compare with the oral solution?

Researchers looked at how much risdiplam entered the blood (absorbed) and able to have an effect.

The blood levels of risdiplam were similar for both tablet formulations A and B compared with the oral solution.

- No difference was seen when the tablets were taken with or without food.
- There was no difference seen whether the tablets were swallowed whole or dissolved in water.

Risdiplam tablet formulation A was less affected by changes in stomach acid levels.

Tablet formulation A was therefore selected for the bioequivalence assessment in Part 2

Question 2: How is the bioavailability of the risdiplam liquid oral solution affected by food?

The blood levels of risdiplam were affected by whether the liquid oral solution was taken with or without food.

Based on these results, the effect of food was further investigated in Part 2.

Part 2

Question: Is the risdiplam tablet (formulation A) bioequivalent to the oral solution?

The blood levels of risdiplam were bioequivalent for tablet formulation A compared with the oral solution:

- Whether it was taken with or without food
- Whether the tablet was swallowed or dissolved in water.

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

5. What were the unwanted effects?

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

- They are described in this summary because the study doctor believes the unwanted effects were related to the treatments in the study.
- Not all the people in this study had all the unwanted effects.
- Unwanted effects may be mild to very serious and can be different from person to person.
- 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 medicine leaflet.
  - The medicine leaflet for the liquid oral solution of risdiplam can be found online here: Risdiplam prescribing information

Serious unwanted effects

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

There were no serious unwanted effects reported in Part 1 or Part 2 of the study.

Most common unwanted effects

During **Part 1** of the study, 3 out of 82 people (4%) had an unwanted effect that were not considered serious.

One unwanted effect led to a participant leaving the study: a flat, red area on the skin that is covered with small bumps (maculo-papular rash)

All treatment-related, unwanted effects are shown in the following table.

Unwanted effects reported in Part 1	**People taking risdiplam** (82 people total)
Headache	2% (2 out of 82)
A flat, red area on the skin that is covered with small bumps *(maculopapular rash)*	1% (1 out of 82)

During **Part 2** of the study, 2 out of 49 people (4%) had an unwanted effect that was not considered serious.

Two participants reported three unwanted effects. Some participants experienced more than one unwanted effect or more than one instance of an unwanted effect.

Unwanted effects reported in Part 2	People taking risdiplam (49 people total)
Headache	2% (1 out of 49)
Increased blood pressure	2% (1 out of 49)
High blood pressure *(hypertension)*	2% (1 out of 49)

Other unwanted effects

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

6. How has this study helped research?

The information presented here is from a single study of 131 healthy people. These results helped researchers learn more about different tablet formulations of risdiplam.

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 tablets) is important to advance patient outcomes and care.

These study results have shown that the tablet form of risdiplam is bioequivalent to the approved risdiplam liquid oral solution.

These results will help to support the approval of the tablet form of risdiplam as an alternative to the oral solution.

Risdiplam as an oral solution is currently approved by the FDA for the treatment of SMA in adult and paediatric patients.

Risdiplam as an oral solution is currently 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.

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7. Are there plans for other studies?

Further studies with risdiplam are planned.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/results/NCT04718181
- https://forpatients.roche.com/en/trials/muscle-and-peripheral-nerve-disease/sma/bioavailability-and-bioequivalence-of-two-risdiplam-tab-67663.html

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "A Phase I, Open-label, Multi-Period Crossover Study to Investigate the Safety, Food Effect, Bioavailability and Bioequivalence of Oral Doses of Two Different Formulations in Healthy Subjects".

Full title of the study and other identifying information

The full title of this study is: "A Phase I, Open-label, Multi-Period Crossover Study to Investigate the Safety, Food Effect, Bioavailability and Bioequivalence of Oral Doses of Two Different Formulations in Healthy Subjects".

The study is known as 'Bioavailability and Bioequivalence of Two Risdiplam Tablets in Healthy Participants'.

- The protocol number for this study is: **BP42066**
- The ClinicalTrials.gov identifier for this study is: **NCT04718181**.

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

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/muscle-and-peripheral-nerve-disease/sma/bioavailability-and-bioequivalence-of-two-risdiplam-tab-67663.html
- Contact a representative at your local Roche office.
- Address and telephone number for the sponsor of this trial:
  F. Hoffmann-La Roche Ltd.,
  Grenzacherstrasse 124 CH-4070,
  Basel, Switzerland
  +41-61-688-1111

If you took part in this study and have any questions about the results, speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment, speak to the doctor in charge of your treatment.

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.