Clinical Trial Results – Layperson Summary

A study to look at how safe different doses of RO6953958 were for healthy people to take, how this medicine was processed through the body when taken on a full or empty stomach, and if this medicine affects how other drugs are processed

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 (January 2023). More information may now be known.

The study started in July 2020 and finished in February 2022. This summary was written after the study had ended.

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 medicine.

- This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

Contents of the summary

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about the safety of different doses of RO6953958 and how the body processes them. This may help people in the future with sleep disorders due to psychiatric conditions such as bipolar disorder or those that affect brain development (known as neurodevelopmental disorders).

Key information about this study

- This study was done to look at the safety of different doses of RO6953958 and how the body processes them.
- This study was in 3 parts. In the first 2 parts of this study, people were given either the study medicine (called RO6953958) or a placebo – it was decided by chance which treatment each person was given. In the third part, everyone was given RO6953958 with another drug to see if RO6953958 affected how the body processed the other drug.
- This study included 88 people in the United Kingdom.
- The main finding was that RO6953958 was well-tolerated; side effects were mostly mild, even at the highest dose tested.
- No one taking RO6953958 or placebo had serious side effects.
- RO6953958 was detectable in blood shortly after being taken.
- RO6953958 was found at higher levels in the blood of people given higher doses and was removed quickly over time from the blood.
- RO6953958 and parts of RO6953958 that remained after the body had processed it (known as 'metabolites') were detectable in the blood.
- RO6953958 and its metabolites were able to reach the brain as expected.
- Overall, food had no major effect on the drug; when taken with food, RO6953958 and its metabolites reached slightly higher levels in the blood and took longer to reach the highest level.
- RO6953958 did not affect how the body processed another drug.

1. General information about this study

Why was this study done?

People with psychiatric conditions and/or conditions that affect brain development (known as neurodevelopmental disorders, or NDDs) can also have sleep issues. Sleep issues can worsen symptoms for people with bipolar disorder, autism spectrum disorder and attention-deficit/hyperactivity disorder (ADHD). This makes daily life more difficult for people with these conditions and their caregivers.

Nerves in the brain control the body's internal clock so that you wake and do not feel too sleepy during the day, and you feel tired and sleep when it is dark. When you sleep, your body slows down its activity, and your temperature drops slightly. When it is time to wake up, the body produces more of a molecule called vasopressin (you say this as 'vay–zo–press–in') that activates the nerves in the brain and tells the body to get ready for the day. This is known as the sleep-wake cycle, or circadian (you say this as 'ser–cay–dee–an') rhythm.

Sleep issues in people with psychiatric disorders and/or NDDs may be due to the circadian and vasopressin system not working correctly. RO6953958 is an experimental drug that blocks the activation of nerves by vasopressin in the brain and may help correct sleep/wake cycles in people with psychiatric disorders and/or NDDs.

What was the study medicine?

A medicine called 'RO6953958' was the focus of this study.

- RO6953958 works by blocking the activity of nerves in the brain that are involved in the body's sleep/wake cycle.
- This medicine may help to improve the quality of sleep for people with disturbed sleep/wake patterns.
- RO6953958 was tested at different doses and when taken on a full or empty stomach.

RO6953958 was compared to a 'placebo'.

- You say this as 'plah–see–bo'.
- The placebo looked the same as RO6953958 but did not contain any real medicine. This means it had no medicine-related effect on the body.

What did researchers want to find out?

- Researchers did this study to compare RO6953958 with a placebo – to see how the body processes RO6953958 when given with and without food and at different doses (see section 4, "What were the results of the study?").
- They also wanted to find out if RO6953958 affected the way the body processed another medicine because people with psychiatric conditions and/or NDDs may need to take other medicines at the same time (see section 4, "What were the results of the study?").
- Researchers also wanted to find out how safe the study medicine was – by checking how many people had side effects when taking the study medicine compared with the placebo (see section 5, "What were the side effects?").

The main question that researchers wanted to answer was:

1. How many people had side effects or serious side effects during the study?

Other questions that researchers wanted to answer included:

2. How is RO6953958 moved around the body and broken down?
3. How is RO6953958 moved around the body and broken down when taken on a full stomach compared with an empty stomach?
4. Does RO6953958 affect the way the body processes another medicine?

What kind of study was this?

This study was a 'Phase 1' study, which means that this was one of the first studies in people for RO6953958. A small number of healthy people (without conditions that affect brain development) took RO6953958, and the researchers did medical tests on the people who took part to find out more about RO6953958.

The study was in 3 parts. Parts 1 and 2 were done to decide the highest possible dose of RO6953958 that can be given without unmanageable side effects and whether it should be given on a full or empty stomach.

Parts 1 and 2 of the study were 'double-blinded'. This means that neither the people taking part, nor the study doctors knew which of the study medicines people were taking. 'Blinding' of a study is done so that any effect seen from the medicine is not due to something people expected to happen – if they had known which medicine they were taking.

Parts 1 and 2 of the study were also 'randomised'. This means that it was decided by chance which of the medicines (RO6953958 or placebo) people in the study would have – like tossing a coin.

Part 3 of the study was done to see how RO6953958 affects how the body processes other drugs (known as drug-drug interaction, or DDI) because people with NDDs may be already taking medications.

Part 3 of the study was 'open-label'. This means that both the people taking part and the study doctors knew the study medicines that people were taking.

When and where did the study take place?

The study started in July 2020 and finished in February 2022. This summary was written after the study had ended.

The study took place at one study centre in one country (the United Kingdom) located in Europe.

2. Who took part in this study?

In this study, 88 healthy, male adults took part.

People who took part in the study were between 19 and 54 years of age.

People could take part in the study if they:

- Had a body weight that was healthy to slightly obese based on their body mass index or BMI.
- Were a 'good sleeper', as tested using the Pittsburgh Sleep Quality Index – for people in Part 2 only.
- Had normal or mild daytime sleepiness, as tested using the Epworth sleepiness scale – for people in Part 2 only.
- Were prepared to keep a sleep diary and wear an activity monitor before starting the study – for people in Part 2 only.

People could not take part in the study if they:

- Have had certain medical conditions, such as cancer, heart, or back problems.
- Were unable to eat a standard-sized breakfast – for people in Part 1 'with food' group only.
- Were an extreme 'morning' or 'evening' type of person, as tested using the morningness–eveningness questionnaire – for people in Part 2 only.

3. What happened during the study?

During the study, people in Parts 1 and 2 were selected by chance to get one of two treatments. The treatments were selected at random – e.g. by a computer.

In Part 1, everyone was given either:

- A single dose of **RO6953958** (the study medicine) or **placebo** – taken by mouth (swallowed).
    - Groups of people were given different, single doses of RO6953958 or placebo on an empty stomach
    - One of the dose groups was given RO6953958 on an empty stomach, then they returned 4 weeks later and were given RO6953958 on a full stomach
    - One of the groups was given placebo on a full stomach.

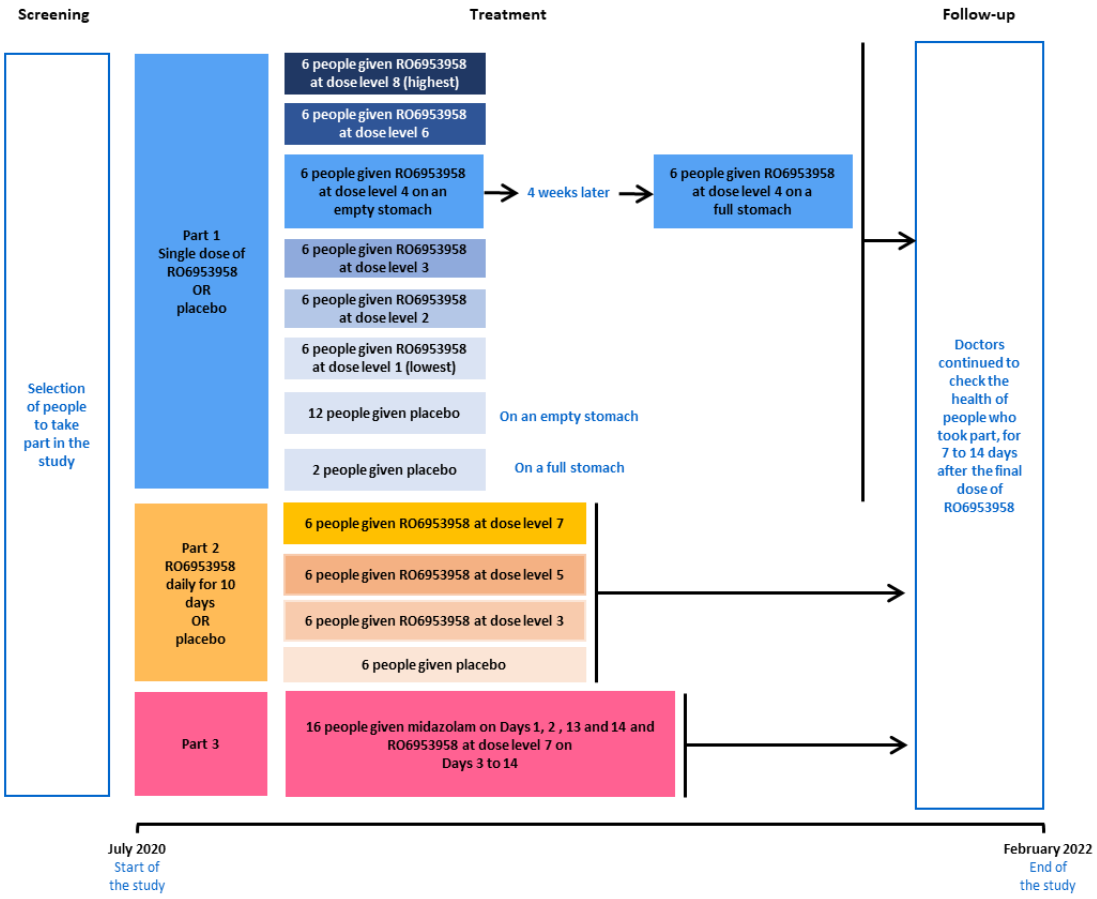
In Part 2, everyone was given either:

- Several different doses of **RO6953958** (the study medicine) or **placebo** – taken by mouth (swallowed) with food daily for 10 days.

Everyone in Part 3 was given **RO6953958** (the study medicine) taken by mouth (swallowed) and a second medicine called **midazolam** (you say this as 'mi–DA–zo–lam'). Midazolam was given as a drip (infusion) into a vein or was taken by mouth (swallowed) to see if RO6953958 affected how the body processed midazolam when given each way, as follows:

- Day 1 - **midazolam** given alone as drip (infusion) into a vein
- Day 2 - **midazolam** taken alone by mouth (swallowed)
- Days 3–12 - **RO6953958** taken alone by mouth (swallowed)
- Day 13 - **RO6953958** taken by mouth (swallowed) and **midazolam** given as drip (infusion) into a vein
- Day 14 - **RO6953958** and **midazolam** taken by mouth (swallowed)

When the study finished, the people who took part were asked to go back to their study centre for more visits – to check their overall health. This image shows more information about what happened in the study:



4. What were the results of the study?

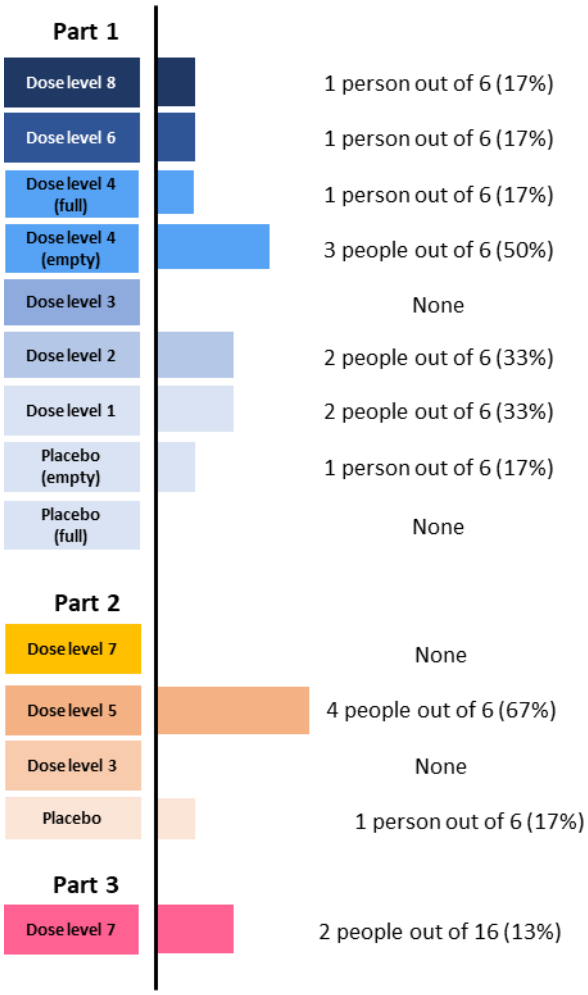
Question 1: How many people had side effects or serious side effects throughout the study?

Researchers looked at the number and seriousness of side effects when people were given different doses of RO6953958, either on its own (in Parts 1 and 2) or with midazolam (in Part 3).

In all parts of the study, RO6953958 was well-tolerated and did not cause serious side effects, even at the highest dose tested and when given with midazolam.

In Part 1, the group who were given a single dose of RO6953958 on a full stomach had fewer side effects than those given a single dose of RO6953958 at the same dose level on an empty stomach. The way that RO6953958 was broken down in the body was overall similar between people when it was taken with food than on an empty stomach. This meant that researchers decided to give RO6953958 to people on a full stomach in Parts 2 and 3.

The number of people who had side effects in each group is shown in the picture below. The side effects are described in more detail in Section 5.



Doses are of RO6953958 – dose level 1 was the lowest dose and dose level 8 was the highest. 'Empty' = taken on an empty stomach. 'Full' = taken on a full stomach.

Question 2: How is RO6953958 moved around the body and broken down?

Researchers also looked at the levels of RO6953958 and of parts of RO6953958 that remained after the body has processed it (known as 'metabolites' – you say this as 'meh–tab–oh–lytes') in each person's blood, urine and for Part 2 only, in the fluid surrounding the brain and spinal cord (known as cerebrospinal fluid, or CSF).

In Part 1 (RO6953958 given once only), RO6953958 and its metabolites were:

- Detectable in the blood very quickly (within 30 minutes) and reached their highest levels in the blood within 1 (at the lowest dose) to 7 hours (at the highest dose).
- Found in the blood at a higher level in people who were given higher doses.
- Removed from the blood by the body more quickly in people who were given lower doses:
    - Within 1 to 15 hours for RO6953958 and one of its metabolites
    - Within 21 to 28 hours for a second metabolite of RO6953958.
- Found in tiny amounts of the total dose given (less than 7%) in urine samples after 2 days (48 hours).

In Part 2 (RO6953958 given daily for 10 days), RO6953958 and its metabolites were:

- Detectable in the blood and urine with timings and at levels similar to Part 1 the first time it was given.
- Removed from the blood by the body more quickly at the end of the 10-day period in people who were given lower doses and at similar rates as in Part 1 (after a single dose).
- Not 'built-up' in the blood over the 10 days – the highest levels reached in the blood stayed similar at Day 10 compared with Day 1, except for one of the metabolites, which had slightly higher levels at Day 10 in all dose groups.
- Detectable in CSF which was measured 6 hours after taking RO6953958 on Day 6, and at high enough levels to reach the brain to potentially affect the sleep/wake cycle.

Question 3: How is RO6953958 moved around the body and broken down when taken on a full stomach compared with an empty stomach?

Researchers looked at the effect of having food in the stomach when taking RO6953958 in Part 1 of the study.

When taken on a full compared with an empty stomach, RO6953958 and its metabolites reached slightly higher levels in the blood.

Question 4: Does RO6953958 affect the way the body processes another medicine?

Researchers also looked at whether RO6953958 affected how the body processed a second medicine called midazolam. When midazolam was given on its own (via infusion into the vein or when taken by mouth) compared with when it was given with RO6953958, they saw:

- No difference in the time it took midazolam to be detected in the blood.
- No difference in the highest level of midazolam that was detected in the blood.

This section only shows the key results from the 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 side effects?

Side effects (also known as 'adverse reactions') are unwanted medical problems (such as a headache) that happen during the study.

- They are described in this summary because the study doctor believes the side effects were related to the treatments in the study.
- Not all of the people in this study had all of the side effects.

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

Serious side effects

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

None of the people taking part in this study had a serious side effect or died during the study due to side effects that may have been related to the study medicine.

During the study, none of the people taking part decided to stop taking the study medicine because of side effects.

Most common side effects

During this study, all side effects were mild or moderate, and most got better within 2 days for people in Parts 1 and 2, and within 5 days for people in Part 3.

- In Part 1, around 1 out of every 3 people (30%) had a side effect that was not considered serious. Around 24% of people taking RO6953958 had a side effect that was not considered serious, compared with around 7% of people taking placebo.
- In Part 2, around 1 out of every 5 people (20%) had a side effect that was not considered serious. Around 22% of people taking RO6953958 had a side effect that was not considered serious, compared with around 17% of people taking placebo.
- In Part 3, around 1 out of every 8 people (13%) had a side effect that was not considered serious.

The most common side effects are shown in the following table – these are the most common side effects that affected 2 or more people in at least one Part of the study.

Most common side effects reported in this study	**People taking RO6953958 in Part 1** (42 people total, including one dose level on an empty and full stomach)	**People taking RO6953958 in Part 2** (18 people total)	**People taking RO6953958 in Part 3** (16 people total)
Headache	12% (5 out of 42)	9% (2 out of 18)	8% (2 out of 16)
Drowsiness	5% (2 out of 42)	6% (1 out of 18)	None

Other side effects

You can find information about other side 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 88 healthy people. These results helped researchers learn more about how safe RO6953958 is at different doses and how the body processes it.

- In all parts of the study, RO6953958 was well-tolerated; side effects were mostly mild, even at the highest dose tested and when given with midazolam.
- The most common side effect was headache.
- There were no serious side effects, no one stopped treatment due to side effects, and no one died due to study treatment.
- RO6953958 was detectable in blood shortly after being taken, was found in the blood at a higher level in people who were given higher doses and was removed quickly over time from the blood.
- One part of RO6953958 that the body had broken down (metabolite) – was detectable in the blood for longer than RO6953958.
- RO6953958 and its metabolites were able to reach the brain.
- RO6953958 and its metabolites reached slightly higher levels in the blood when given with food.
- RO6953958 did not affect how the body processed another drug (midazolam).
- Researchers were unable to make strong conclusions about the effect of RO6953958 on sleep and circadian rhythm because of the small number of people in Part 2 of the study – as this study was primarily designed to look at the safety of RO6953958 at different doses.

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 medicine.

- This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

7. Are there plans for other studies?

More studies are planned to look at the effects of RO6953958 on psychiatric conditions.

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/NCT04475848
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-004486-41/results
- https://forpatients.roche.com/en/trials/neurodevelopmental-disorder/autism-spectrum-disorder/a-study-to-investigate-the-safety--tolerability--pharma-64337.html

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/neurodevelopmental-disorder/autism-spectrum-disorder/a-study-to-investigate-the-safety--tolerability--pharma-64337.html
- Contact a representative at your local Roche office.

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.

Full title of the study and other identifying information

The full title of this study is: “A Randomized, Investigator- /Subject-blind, Single- and Multiple-ascending Dose, Placebo-controlled Study to Investigate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Food Effect of RO6953958 (Including RO6953958 Effect on Midazolam) Following Oral Administration in Healthy Male Participants”.

- The protocol number for this study is: BP41695
- The ClinicalTrials.gov identifier for this study is: NCT04475848
- The EudraCT number for this study is: 2019-004486-41