Summary of Clinical Trial Results

A study to compare different doses of ralmitaront with a 'placebo' – to see how well ralmitaront worked in people with schizophrenia or schizoaffective disorder symptoms that affect their mood, motivation and social interactions with people

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 December 2018 and stopped early – in March 2023 – because the medicine being studied did not work as well as expected.

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

Glossary

- PANSS – Positive and Negative Syndrome Scale
- NSFS – Negative Symptom Factor Score
- BNSS – Brief Negative Symptoms Scale

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 medicine studied – 'ralmitaront'.

Key information about this study

- Ralmitaront is a new investigational medicine – which means it has not been approved for any illness or disorder
- This study was done to see if ralmitaront could help to treat people with schizophrenia or schizoaffective disorder and negative symptoms
- In this study, people were given either the medicine being studied (called 'ralmitaront') or a non-active medicine (known as a 'placebo') – it was decided by chance which treatment each person was given
- This study included 131 people in 4 countries
- The main finding was that people who were given ralmitaront or placebo had a similar change in their negative symptoms (this includes a lack of motivation, interest, enthusiasm and concern) after 3 months compared with the start of the trial
- 1 person (1%) taking ralmitaront had a serious side effect, compared with no people (0%) taking a placebo
- This study stopped early because not enough people joined the study in Part A and the medicine being studied (ralmitaront) did not work as well as expected in Part B

1. General information about this study

Why was this study done?

The symptoms of schizophrenia can be experienced in episodes, during which they are particularly severe (known as an acute schizophrenic episode), which are followed by periods of time with fewer symptoms. Symptoms can be classed as either 'positive' or 'negative'. Positive symptoms include any change in behaviour or thoughts, such as experiencing things that do not exist (hallucinations) or believing things that are not true (delusions). Negative symptoms include changes in emotions, avoiding social interactions with people and a loss of interest or pleasure in things, such as a lack of motivation.

Neurotransmitters, such as dopamine and serotonin, are chemicals that carry messages between brain cells. It is thought that people with schizophrenia have an abnormal increase of dopamine activity in their brain. Medicines that help lower dopamine levels are known to help manage the symptoms of schizophrenia in some people. During an acute schizophrenic episode, medicines called antipsychotics such as risperidone are used, which work by blocking the effect of dopamine on the brain. Other antipsychotics include clozapine, which is used for schizophrenia that has not gotten better with treatment. Antipsychotics can cause side effects such as drowsiness, weight gain and blurred vision so new treatments are needed.

Ralmitaront is a new medicine that is being studied – this means that it is not approved for sale by any national health authority, including in the United States by the U.S. Food and Drug Administration. Tests show ralmitaront balances the level of dopamine in the brain and has the potential to be used to treat schizophrenia. Researchers wanted to learn more about whether ralmitaront could help to treat people with schizophrenia or schizoaffective disorder.

What was the medicine being studied?

This study looked at a medicine called '**ralmitaront**'.

- You say this as 'ral-MIT-a-ront'
- Ralmitaront works by partially blocking a protein (known as a TAAR1 receptor) found on the surface of brain cells. This changes how the brain responds to dopamine and serotonin
- This may mean that ralmitaront could reduce symptoms of schizophrenia
- Ralmitaront was tested at different amounts (doses)

Ralmitaront was compared with a 'placebo'.

- You say this as 'plah-see-bo'
- The placebo looked the same as ralmitaront but did not contain any real medicine. This means it had no medicine-related effect on the body
- Researchers compared ralmitaront with a placebo so they could show which benefits or side effects are actually caused by the medicine

What did researchers want to find out?

- Researchers did this study to compare ralmitaront with a placebo – to see how well ralmitaront worked (see Section 4 'What were the results of the study?')
- They also wanted to find out how safe the medicine was – by checking how many people had side effects and seeing how serious they were, when taking each of the medicines during this study (see Section 5 'What were the side effects?')

The main question that researchers wanted to answer was:

1. How do participants' negative symptoms change 3 months after the start of the trial with ralmitaront compared with placebo?

What kind of study was this?

This study was a 'phase II' study. This means that ralmitaront had already been tested in a number of people without schizophrenia or schizoaffective disorder **before** this study. In this study, people with schizophrenia or schizoaffective disorder and negative symptoms either took ralmitaront or a placebo – this was to find out if ralmitaront worked to improve schizophrenia negative symptoms.

The study was 'randomised'. This means that it was decided by chance which of the medicines people in the study would have. Randomly choosing which medicine people take, makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. Apart from the exact medicines being tested in each group, all other aspects of care were the same between the groups.

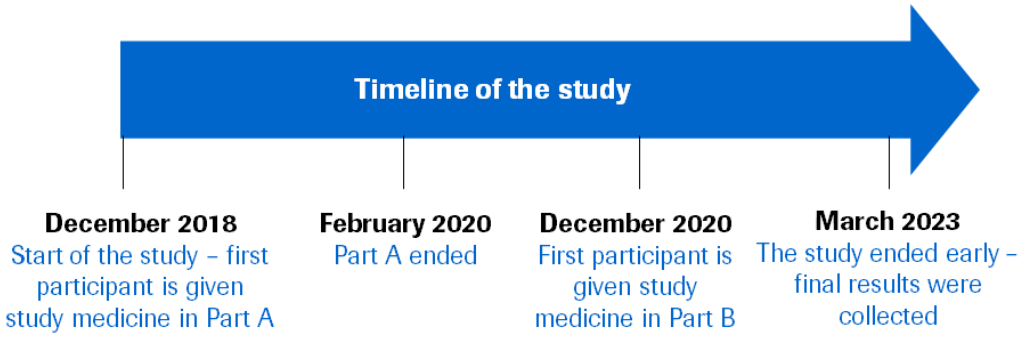
This was a 'double-blind' study. This means that neither the people taking part in the study, nor the study doctors knew which of the study medicines people were taking. 'Blinding' of a study is done so that any effect seen from the medicine is not due to something people expected to happen – if they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

When and where did the study take place?

This study was split into 2 parts – Part A and Part B.

Part A started in December 2018 and stopped early – in February 2020 – because not enough people joined this part of the study.

Part B started after Part A finished in December 2020. Part B stopped early because the medicine being studied (ralmitaront) did not work as well as expected. This summary presents the results of the study up until it was stopped in March 2023.

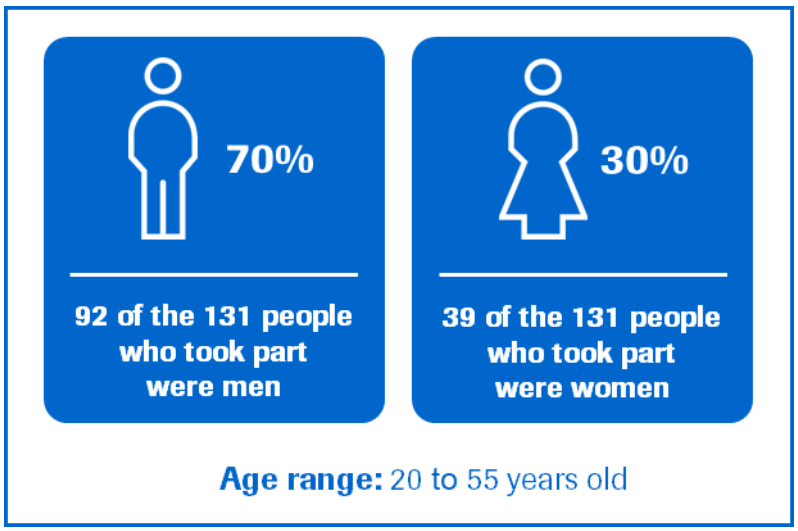


The study took place at 56 study centres – across 4 countries. The countries were: Japan, Spain, Ukraine and the United States of America.

2. Who took part in this study?

In this study, 131 people with schizophrenia or schizoaffective disorder took part. 27 people joined Part A and 104 people joined Part B.

People who took part in the study were between 20 and 55 years of age. 92 of the 131 people (70%) were male and 39 of the 131 people (30%) were female.



People could take part in the study if they:

- Were aged 18 to 55 years old
- Had a Positive and Negative Syndrome Scale for Schizophrenia (PANSS)-Negative Symptom Factor Score (NSFS) score of 18 or higher. The PANSS-NSFS is a scale used to measure the symptoms of schizophrenia. The score of the negative symptoms can be between 7 and 49, where a score of 7 means the symptoms are not severe and a score of 49 means the symptoms are very severe
- Had low PANSS scores for negative symptoms such as being unable to cooperate with others, delusions, hallucinations, over excitement, being over suspicious, being hostile and being impulsive
- Had someone who could help them take the study medicine correctly and attend visits with the study doctor

- **Part B only:** Were taking at least one antipsychotic, but no more than two, for at least 6 months before joining the study

People could not take part in the study if they:

- Had side effects from other medicines that affected their movement
- Had certain medical conditions such as bipolar disorder, depression or an active COVID-19 infection
- Were taking more than one antidepressant
- Had received clozapine (an antipsychotic) treatment up to 5 years before joining the study (however, a low dose that was stopped over 1 year before they joined the study was allowed)
- Were recently involved in another clinical study
- Were pregnant or breastfeeding or were planning to become pregnant during or within 1 month of their last dose of the study medicine
- **Part A only:** Had a history of behaviour related to hurting themselves or other people

3. What happened during the study?

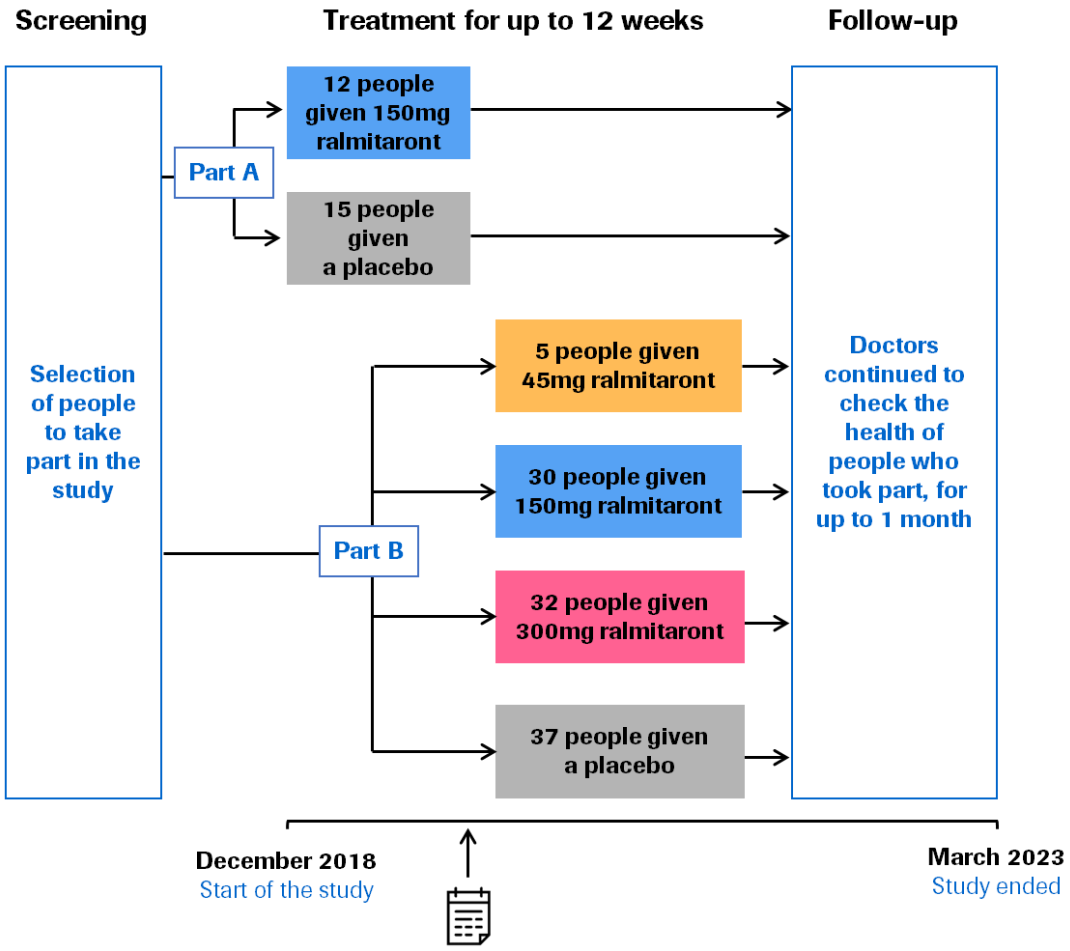
During Part A of the study, people were selected by chance to get 1 of 2 treatments. The treatments were selected at random – by a computer. The treatment groups were:

- **150mg ralmitaront** (the medicine being studied) – given as capsules to be swallowed once a day
- **Placebo** – given as capsules to be swallowed once a day

During Part B of the study, people were selected by chance to get 1 of 4 treatments. The treatments were selected at random – by a computer. The treatment groups were:

- **45mg ralmitaront** (the medicine being studied) – given as capsules to be swallowed once a day
- **150mg ralmitaront** – given as capsules to be swallowed once a day
- **300mg ralmitaront** – given as capsules to be swallowed once a day
- **Placebo** – given as capsules to be swallowed once a day

Part A of the study stopped early because not enough people joined it. Part B stopped early because the medicine being studied (ralmitaront) did not work as well as expected. People in the study took the treatments for 12 weeks. After people finished taking their medicine for this study, they were asked to go back to their study centre for more visits – to check their overall health. The study flowchart shows all stages planned for the study.



The symbol on the timeline (📋) shows when the information in this summary was collected for Part A – after 1 year (February 2020).

4. What were the results of the study?

Question 1: How much do participants' negative symptoms change 3 months after the start of the trial with ralmitaront compared with placebo?

Researchers looked at how much participants' negative symptoms (such as lack of motivation, interest, enthusiasm and concern) changed 3 months after the start of the trial. They did this using a Positive and Negative Syndrome Scale for Schizophrenia -Negative Symptom Factor Score (PANSS-NSFS) and a Brief Negative Symptoms Scale (BNSS) score. The PANSS-NSFS and BNSS measures how severe a person's schizophrenia symptoms are.

- People in Part B who were given ralmitaront or placebo had a similar change in their PANSS-NSFS after 3 months compared with the start of the trial
- People in Part A and Part B who were given ralmitaront or placebo had a similar change in their BNSS score after 3 months compared with the start of the study

Overall, there was no treatment benefit of ralmitaront compared to placebo.

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 side effects?

Side 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 side effects were related to the treatments in the study
- Not all of the people in this study had all of the side effects
- Side effects may be mild to very serious any can be different from person to person
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies
- 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.

During this study, 1 out of 131 people (1%) had at least one serious side effect. 1 person (1%) taking ralmitaront had a serious side effect of constipation, compared with no people (0%) taking a placebo.

During the study, some people decided to stop taking their medicine because of side effects:

- In the ralmitaront groups, 6 out of 79 people (8%) stopped taking their medicine
- In the placebo groups, 2 out of 52 people (4%) stopped taking their medicine

Most common side effects

During this study, around 17 out of every 100 people (17%) had a side effect that was not considered serious. Around 18 out of every 100 people (18%) taking ralmitaront had a side effect that was not considered serious, compared with around 15 out of every 100 people (15%) taking a placebo.

The most common side effects across all treatment groups in both Part A and B are shown in the following table – these are the 7 most common side effects across all treatment groups that affected more than 1 person. Some people had more than one side effect – this means that they are included in more than one row in the table.

Most common side effects reported in this study	People taking ralmitaront (79 people total)	People taking a placebo (52 people total)
Dizziness	4% (3 out of 79)	0% (0 out of 52)
Drowsiness	1% (1 out of 79)	4% (2 out of 52)
Headache	1% (1 out of 79)	2% (1 out of 52)
Constipation	3% (2 out of 79)	0% (0 out of 52)
Feeling sick (nausea)	3% (2 out of 79)	0% (0 out of 52)
Rash	3% (2 out of 79)	0% (0 out of 52)
Reduced appetite	1% (1 out of 79)	2% (1 out of 52)

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 131 people with schizophrenia or schizoaffective disorder. These results helped researchers learn more about ralmitaront.

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?

At the time of writing this summary, no more studies looking at ralmitaront 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/NCT03669640
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004752-16/results

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

If you have any further questions after reading this summary:
- 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: 'Phase II, multicenter, randomized, double-blind, two-part, placebo-controlled, parallel-group, study to assess the effects of ralmitaront in participants with schizophrenia or schizoaffective disorder and negative symptoms'.

The study is known as 'TWAIN I'.

- The protocol number for this study is: BP40283
- The ClinicalTrials.gov identifier for this study is: NCT03669640
- The EudraCT number for this study is: 2020-004752-16