# Summary of Clinical Trial Results

## A study to compare how well ralmitaront works versus a placebo in people experiencing worsening symptoms of schizophrenia or schizoaffective disorder - and how safe this medicine was

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 September 2020 and stopped in June 2022 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



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

The people who took part in this study have helped researchers to answer important questions about the medicine studied – 'ralmitaront'.

## Key information about this study

- This study was done to compare the study medicine ralmitaront with a 'placebo' which looked the same as the study medicine but did not contain any real medicine – in people with an acute exacerbation of schizophrenia or schizoaffective disorder.
- In this study, people were given either the medicine being studied (called 'ralmitaront'), the standard treatment (called 'risperidone') or a placebo - it was decided by chance which treatment each person was given.
- This study included 276 people in four countries.
- The main finding was that people who were given 45mg or 150mg of ralmitaront daily for 4 weeks did not experience improvement in the symptoms of schizophrenia or schizoaffective disorder compared to placebo.
- One person taking ralmitaront had a serious side effect – worsening of schizophrenia symptoms.
- This study stopped because ralmitaront did not work as well as expected.

## 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 acute exacerbations of schizophrenia, which are followed by periods of time with fewer symptoms. Symptoms can be classed as positive symptoms – any change in behaviour or thoughts e.g. few or no hallucinations, or negative symptoms – where people take no interest or pleasure in things. Neurotransmitters, such as dopamine and serotonin, are chemicals that carry messages between brain cells. An abnormal increase in dopamine activity has been linked to schizophrenia. Drugs that target dopamine are known to help manage symptoms of schizophrenia. During an acute schizophrenic episode, medicines called antipsychotics, such as risperidone, are the standard treatment, which work by blocking the effect of dopamine on the brain. Antipsychotics can cause side effects such as drowsiness, weight gain and blurred vision and new treatments are needed.

Ralmitaront is a new investigational medicine – 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. Lab 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 an acute exacerbation of schizophrenia or schizoaffective disorder.

## What were the study medicines?

This study looked at 2 medicines:

- **Risperidone** – existing medicine
- **Ralmitaront** – the medicine that was studied.

'Risperidone' is an existing medicine called an 'atypical antipsychotic' given to people to treat schizophrenia or schizoaffective disorder.

- You say this as 'ris-PER-i-doan'
- Risperidone works by blocking certain 'receptors' on brain cells and decreasing dopamine activity in the brain.

'Ralmitaront' is the medicine that was studied here – it works in a different way to risperidone.

- You say this as 'ral-MIT-a-ront'
- Ralmitaront affects the activity of a receptor in the brain called TAAR1 which is involved in the regulation of dopamine.
- This may mean that ralmitaront could be used to treat acute exacerbations of schizophrenia or schizoaffective disorder.
- Ralmitaront was tested at two different doses in this study: 45mg and 150mg

The effects of ralmitaront were compared to a 'placebo'.

- You say this as 'plah-SEE-bow'
- The placebo looked the same as ralmitaront and risperidone but did not contain any real medicine. This means it had no medicine-related effect on the body.

Researchers compared the medicine being studied to a placebo so they could show which benefits or side effects are actually caused by ralmitaront. Risperidone was given to people as an 'active control', this means researchers expected risperidone to have an effect on the acute symptoms of schizophrenia and schizoaffective disorder. This will help researchers to check that the study was designed and carried out well and see any benefits of ralmitaront.

## 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. Does ralmitaront modify the intensity of the acute exacerbation of schizophrenia or schizoaffective disorder compared with placebo?

**Another question that researchers wanted to answer was:**

2. How many participants have side effects when given ralmitaront?

## What kind of study was this?

This study was a 'Phase 2' study. This means that ralmitaront had been tested in a number of people without schizophrenia and schizoaffective symptoms before this study. In this study, people with schizophrenia and schizoaffective disorder took either ralmitaront, risperidone or a placebo, in order to find out if ralmitaront worked to improve the acute exacerbation of schizophrenia or schizoaffective disorder.

The study was 'randomised'. This means that it was decided by chance which of the medicines people in the study would have – like tossing a coin. 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.

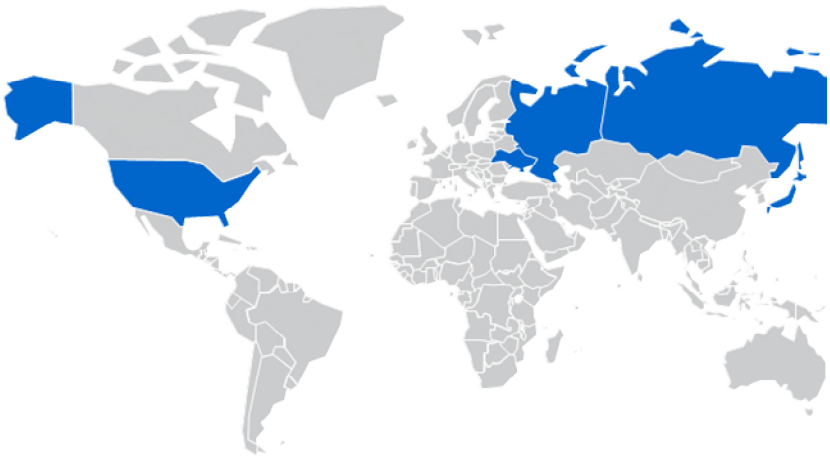
## When and where did the study take place?

The study started in September 2020 and stopped in June 2022 because ralmitaront did not work as well as expected. This summary presents the results of the study up until it was stopped.

The study took place at study centres across four countries in Asia, Europe, and North America.

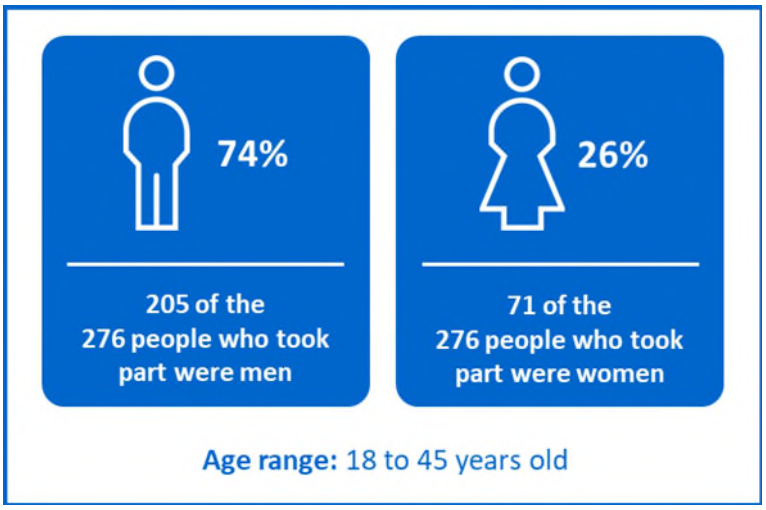
The following map shows the countries where this study took place.

- Japan
- Russia
- Ukraine
- USA



## 2. Who took part in this study?

In this study, 276 people with an acute exacerbation of schizophrenia or schizoaffective disorder took part.




People could take part in the study if they had:

- schizophrenia or schizoaffective disorder for up to 10 years
- a current acute exacerbation of schizophrenia or schizoaffective disorder for no more than eight weeks before the study, that required a stay in the hospital (as an 'inpatient') for treatment
- A body mass index (BMI) of between 18 and 35kg/$m^2$.

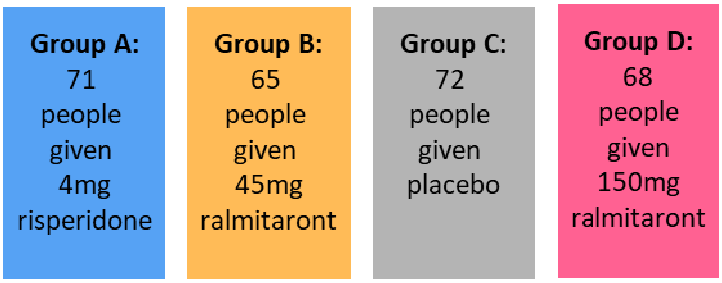
People could not take part in the study if they:

- Were a hospital inpatient for more than one week within the eight weeks prior to the study
- Had history of suicidal thoughts, homicidal behaviour, or substance abuse within a certain time
- Had other health conditions such as bipolar disorder or certain infections
- Were not able to be treated with risperidone, or if previous risperidone treatment did not work.

## 3. What happened during the study?

During the study, people were selected by chance to get one of four treatments. The treatments were selected at random – by a computer.

The treatment groups were:




All treatments were given as a pill to be taken by mouth once a day.

There were four parts to this study:

- **Part 1 – this lasted about one week in the hospital**
    - People were screened to see if they met the criteria to take part

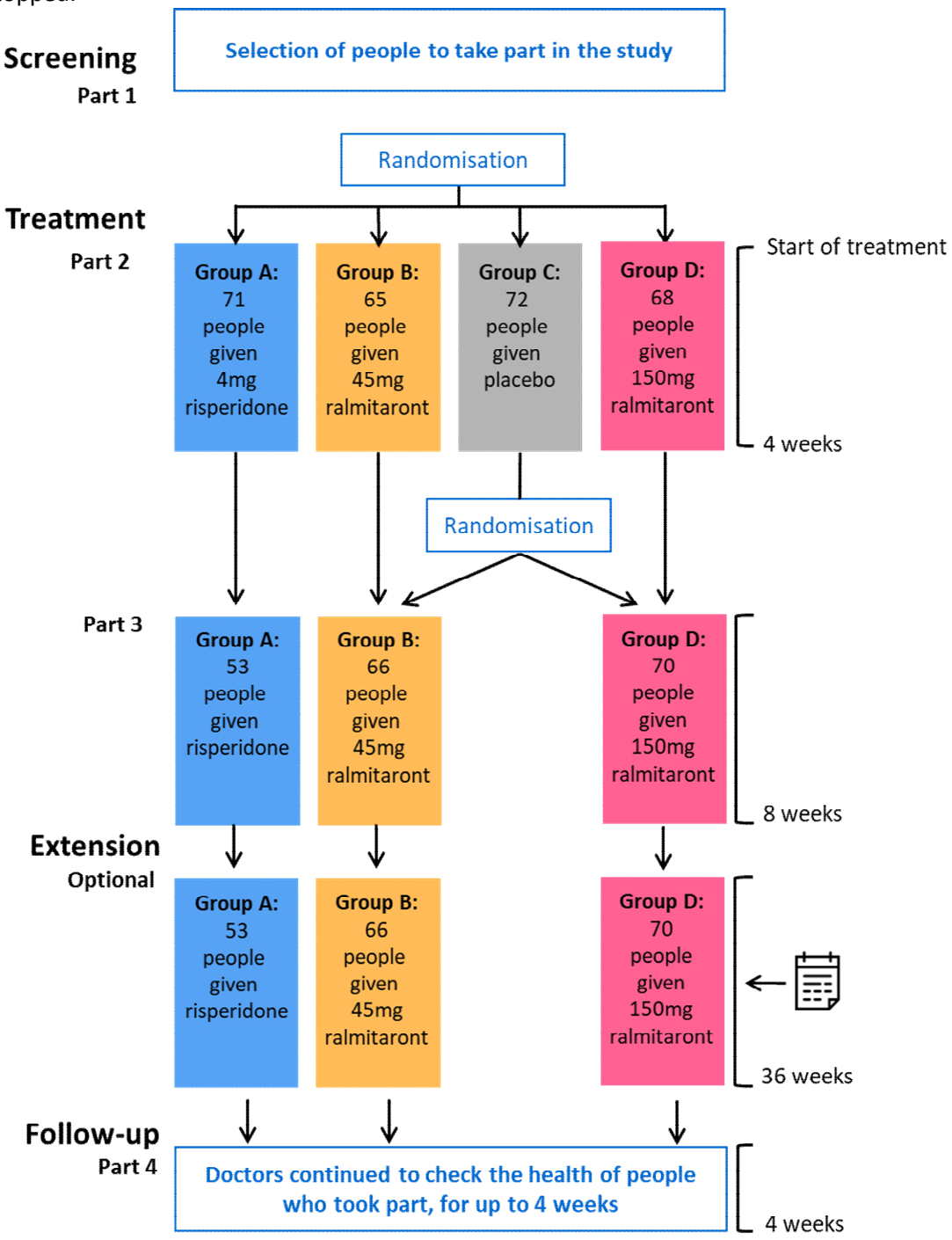
- **Part 2 – this lasted about four weeks in the hospital**
    - People received either ralmitaront, risperidone or placebo treatment

- **Part 3 – this lasted about eight weeks (two months) in the hospital or at home**
    - People continued to take ralmitaront or risperidone. Those who took a placebo in Part 2 joined Group B or Group D at random.

- **Part 3 Extension – this was planned to last about 36 weeks (nine months) at home**
    - People could take part in an optional safety extension and continue taking ralmitaront or risperidone. This part of the study did not continue for as long as planned.

- **Part 4 – this lasted about four weeks at home**
    - People had follow-up safety assessments and no treatment was given.

The study stopped because ralmitaront did not work as well as expected. After people finished taking their medicine for this study, they were asked to go back to their study centre for a follow-up visit – to check their overall health. The study flow chart shows all stages planned for the study and the symbol (📋) shows the point where the study was stopped.

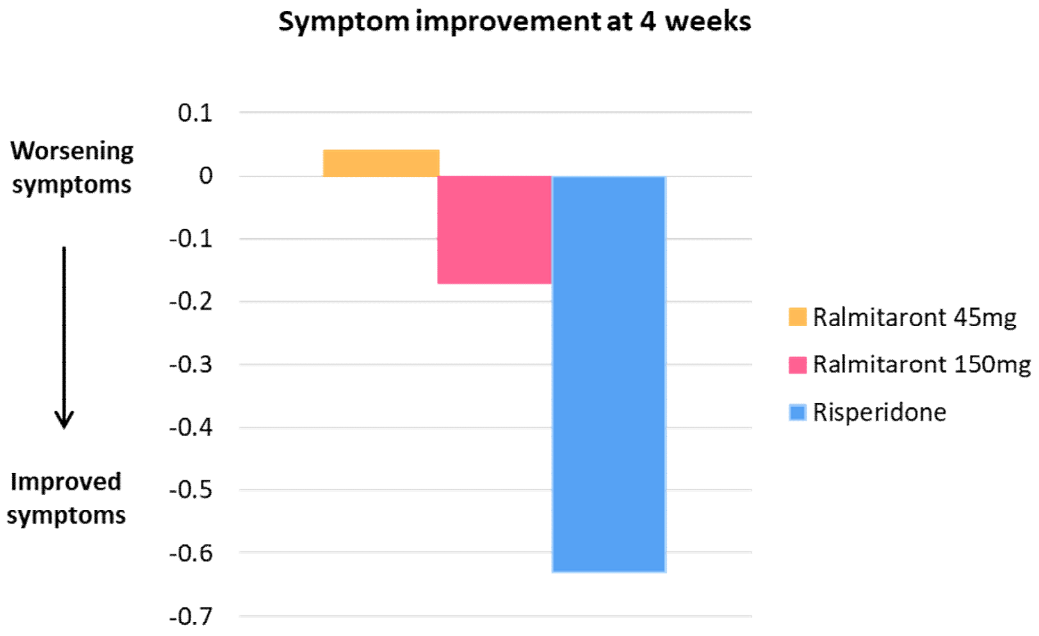


## 4. What were the results of the study?

### Question 1: Does ralmitaront modify the intensity of the acute exacerbation of schizophrenia or schizoaffective disorder compared with placebo?

Researchers looked at people's exacerbation of schizophrenia or schizoaffective disorder at the start of the study and after four weeks. Any effect of the treatment on the schizophrenia symptoms was measured using the Positive and Negative Syndrome Scale (PANSS). The PANSS is a medical interview used to measure the intensity and frequency of the various symptoms present in schizophrenia and schizoaffective disorder.

- People who were given ralmitaront for 4 weeks at either 45mg daily or 150mg daily did not have improved symptoms of compared to placebo.
- People who were given four weeks of risperidone did show an improvement in the acute exacerbation of schizophrenia compared to placebo, as expected.

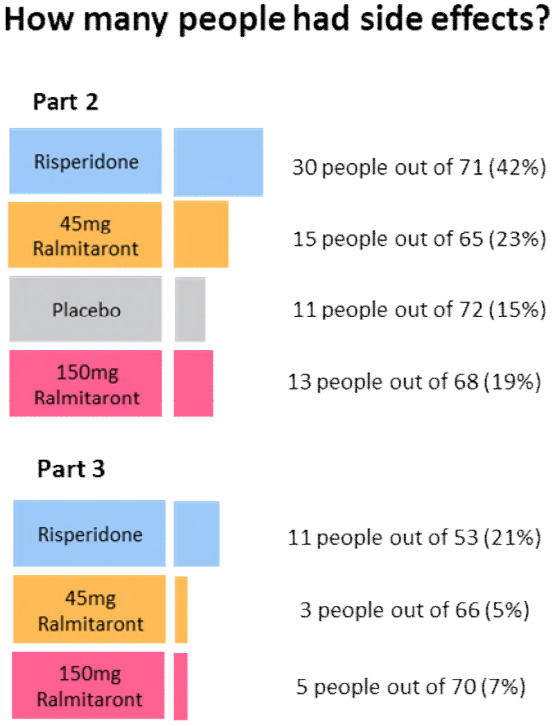



This graph shows the symptom change after four weeks of treatment with ralmitaront or risperidone. Higher scores indicate more symptoms. Negative values show an improvement in symptoms.

### Question 2: How many participants have side effects when given ralmitaront?

Researchers looked at the number and seriousness of side effects when people were given ralmitaront, risperidone and placebo.

In this study, ralmitaront was well-tolerated and did not cause serious side effects. The number of people in each group who had side effects that were related to ralmitaront, risperidone or placebo is shown in the picture below, and most of them experienced only mild side effects. Out of 276 people, 69 people in Part 2 and 19 people in Part 3 experienced side effects. The side effects are described in more detail in Section 5.




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 and 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, or those for risperidone that appear on the medicine leaflet
- 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, one person had a serious side effect that was considered to be related to the study medicine ralmitaront. This person was in the 150mg group (Group D) in Part 3, and the serious side effect was worsening of schizophrenia symptoms.

| **Serious side effects reported in Part 3 of this study** | **People taking risperidone**<br><br>(53 people total) | **People taking 45mg ralmitaront**<br><br>(66 people total) | **People taking 150mg ralmitaront**<br><br>(70 people total) |
|---|---|---|---|
| Worsening schizophrenia | 0%<br>(0 out of 53) | 0%<br>(0 out of 66) | 1%<br>(1 out of 70) |

No-one in the study died due to side effects that may have been related to the study medicine.

During the study, 30 out of 276 people (11%) decided to stop taking their medicine because of side effects.

## Most common side effects

During this study, around 1 in 4 people (25%) in Part 2, and 1 in 10 people (10%) in Part 3 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 across all treatment groups. 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 Part 2 of this study** | **People taking risperidone** (71 people total) | **People taking 45mg ralmitaront** (65 people total) | **People taking placebo** (72 people total) | **People taking 150mg ralmitaront** (68 people total) |
|---|---|---|---|---|
| Headache | 0% (0 out of 71) | 3% 2 out of 65 | 4% 3 out of 72 | 0% (0 out of 68) |
| Drowsiness | 0% (0 out of 71) | 0% (0 out of 65) | 0% (0 out of 72) | 4% 3 out of 68 |
| Shaking or trembling (tremor) | 0% (0 out of 71) | 5% 3 out of 65 | 0% (0 out of 72) | 0% (0 out of 68) |
| Feeling sick (nausea) | 7% 5 out of 71 | 0% (0 out of 65) | 0% (0 out of 72) | 0% (0 out of 68) |
| Being sick (vomiting) | 4% 3 out of 71 | 0% (0 out of 65) | 0% (0 out of 72) | 0% (0 out of 68) |
| Difficulty sleeping (insomnia) | 0% (0 out of 71) | 3% 2 out of 65 | 0% (0 out of 72) | 0% (0 out of 68) |
| Anxiety | 4% 3 out of 71 | 0% (0 out of 65) | 0% (0 out of 72) | 0% (0 out of 68) |
| Weight increase | 7% 5 out of 71 | 0% (0 out of 65) | 0% (0 out of 72) | 0% (0 out of 68) |

| **Most common side effects reported in Part 3 of this study** | **People taking risperidone** (53 people total) | **People taking 45mgralmitaront** (66 people total) | **People taking 150mg Ralmitaront** (70 people total) |
|---|---|---|---|
| Weight increase | 6% (3 out of 53) | 0% (0 out of 66) | 0% (0 out of 70) |
| Feeling an uncontrollable need to move (akathisia) | 4% (2 out of 53) | 0% (0 out of 66) | 4% (1 out of 70) |
| Feeling agitated | 0% (0 out of 53) | 0% (0 out of 66) | 4% (1 out of 70) |
| Acne | 0% (0 out of 53) | 4% (1 out of 66) | 0% (0 out of 70) |

## 6. How has this study helped research?

The information presented here is from a single study of 276 people with schizophrenia and schizoaffective disorder. These results helped researchers learn more about schizophrenia and schizoaffective disorder and 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 at the current time.

## 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/NCT04512066

### 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: “A Phase II, Multi-Center, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Trial of the Efficacy and the Safety of RO6889450 (Ralmitaront) vs Placebo in Patients with an Acute Exacerbation of Schizophrenia or Schizoaffective Disorder”.

The study is known as ‘TWAIN-II’.

- The protocol number for this study is: BP41743.
- The ClinicalTrials.gov identifier for this study is: NCT04512066.
- The EudraCT number for this study is: 2019-003788-23.