Clinical Trial Results Summary

NOVARTIS

The effects and safety of MIJ821 for people with treatment-resistant depression

Thank you!

Thank you to the participants who took part in the clinical trial for the trial drug **MIJ821**. All of the participants helped the researchers learn more about how well MIJ821 works and how safe it is to take.

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public.

We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CMIJ821X2201
Drug studied: MIJ821
Sponsor: Novartis

This clinical trial at a glance

What was the main purpose of this trial? Read more on **page 3**

The main purpose of this trial was to learn:

- If the trial drug MIJ821 could reduce the participants' depression symptoms more than the placebo after 24 hours
- About the safety of MIJ821

Who was in this trial? Read more on **page 3**

- 70 men and women received trial treatment
- The participants were 19 to 65 years old and had treatment-resistant depression, also called TRD

What trial treatments did participants receive? Read more on **page 4**

Each participant was assigned one of these trial treatments:

- High dose of MIJ821
- Low dose of MIJ821
- Placebo – looks like the trial drug but has no trial drug in it. Using a placebo helps researchers better understand the actual effects of a trial drug.
- Ketamine – a drug that research shows may work to treat TRD. Only the trial sites in Spain could assign ketamine to participants.

The participants received trial treatment directly into the blood through an intravenous infusion or IV infusion.

What were the main results of this trial? Read more on **pages 5-7**

- The participants who received any dose of MIJ821 had less severe depression symptoms after 24 hours than those who received the placebo.
- Most participants had medical problems, some of which were considered serious. More participants who received MIJ821 or ketamine had medical problems than those who received the placebo. The most common medical problems were feeling dizzy and brief memory loss lasting 1-9 hours.

Read about other results of this trial on **pages 8-9**

You can find **more information** about this trial by going to the websites listed on **page 10**.

What was the main purpose of this trial?

The purpose of this trial was to learn if MIJ821 could reduce depression symptoms in participants with treatment-resistant depression, also called TRD.

What is TRD?
TRD is depression that has not been well-treated by prescribed antidepressants.

Past research has shown that the drug **ketamine** can sometimes be used to treat TRD and may reduce depression symptoms in 24 hours. However, research has also shown that ketamine can cause **dissociation**. A person with dissociation may feel detached from their body, emotions, memories, and reality.

MIJ821 is a trial drug designed to work like ketamine, but with a lower chance of dissociation. This trial compared the dissociation symptoms for participants who received ketamine to those who received MIJ821. Before a drug can be approved for doctors to prescribe, researchers do many trials to find out how safe it is and how well it works.

The main questions this trial was designed to answer:

- Did MIJ821 reduce the participants' depression symptoms more than the placebo after 24 hours?
- What medical problems did the participants have during this trial?
  Keeping track of the medical problems helped to learn about the safety of MIJ821.

How long was this trial?

The trial began in February 2019 and ended in March 2020. The trial was planned to last up to 14 weeks for each participant. This included 6 weeks of treatment.

Who was in this trial?

70 participants received trial treatment – 35 men and 35 women. The participants were 19 to 65 years old. Their average age was 48.

Every participant in this trial had TRD. A participant couldn't be in this trial if they had:

- Other mental illnesses, such as schizophrenia or bipolar disorder
- Suicidal thoughts during the 2 weeks before starting treatment
- Suicidal thoughts after taking ketamine

17 participants did not complete their trial treatment.

This trial took place in Spain and the United States.

Visit novctrd.com for more information about:

- Who could and could not be in this trial
- The participants in this trial, such as their age, gender, and race
- The reasons why participants left the trial

Use trial number **CMIJ821X2201** to find the scientific summary.

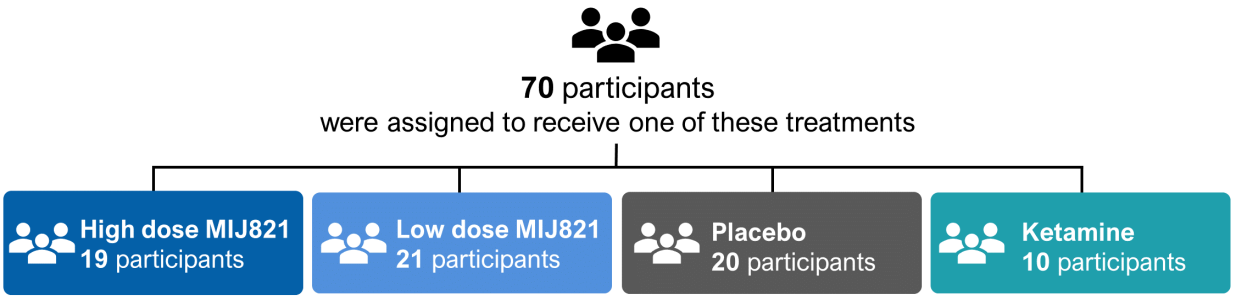
What trial treatments did the participants receive?

A computer program was used to randomly assign each participant **one** of these trial treatments:

- **High dose of MIJ821:** 0.32 milligrams (mg) for every kilogram (kg) of their weight (mg/kg)
- **Low dose of MIJ821:** 0.16 mg/kg
- **Placebo:** A placebo looks like the trial drug but has no trial drug in it. Using a placebo helps researchers better understand the actual effects of a trial drug.
- **Ketamine:** Up to 40 mg. Only the trial sites in Spain could assign ketamine to participants. The trial included ketamine to compare the medical problems – especially dissociation – of participants who received MIJ821 to those who received ketamine.

Using a computer program to assign the treatments helped make sure the team compared the results as fairly as possible.

The participants received trial treatment directly into the blood through an intravenous infusion or IV infusion.



For a total of 6 weeks, the participants received a dose either every week or every 2 weeks. They could continue their regular treatments during this trial.

The participants, sponsor staff, and trial staff did not know what treatment each participant received during the trial. Some trials are done this way because knowing what treatment participants receive can influence the results. Not knowing what treatment participants receive helps make sure the results are looked at fairly.

What were the main results of this trial?

This is a summary of the overall results of this trial. Individual results from each participant may be different and are not included in this summary.

Researchers need many trials to learn if a drug or other treatment is safe and works well. Other trials may provide new information or different results.

Always talk to a doctor before making any changes to your health care.

Did MIJ821 reduce the participants' depression symptoms more than the placebo after 24 hours?

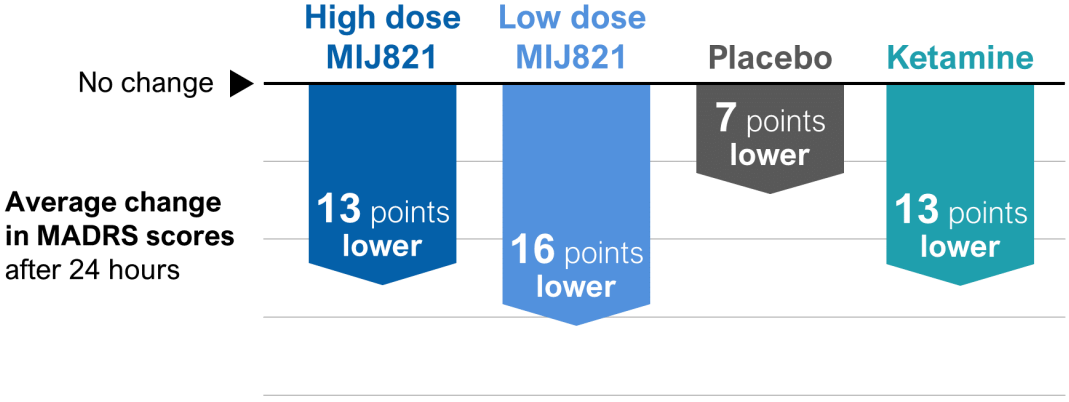
The participants who received any dose of MIJ821 had less severe depression symptoms after 24 hours than those who received the placebo.

The trial doctors measured the severity of the participants' depression symptoms before and 24 hours after their first dose. To do this, they used the **MADRS**, also called the **Montgomery Asberg Depression Rating Scale**. The MADRS is a set of questions that a doctor asks a person to rate the severity of their depression symptoms. A person's MADRS score can range from 0 to 60.
A lower score means a person's depression symptoms are less severe.

On average, the MADRS scores of participants who received any dose of MIJ821 went down more than those who received the placebo. The participants who received ketamine also had their MADRS scores go down. However, the trial was not designed to learn if ketamine could reduce depression symptoms. Therefore, the clinical trial team could not conclude if this change was meaningful.

Change in severity of depression symptoms after 24 hours

Below shows the average change in the participants' MADRS scores from before their first dose to after 24 hours. A **lower** score means their depression symptoms are **less severe**.



What medical problems did the participants have during the trial?

Medical problems that happen during trials are called “adverse events”. Trial doctors looked for any adverse events during the visits to the trial site. The participants also reported adverse events. This section includes the adverse events that happened during and after trial treatment.

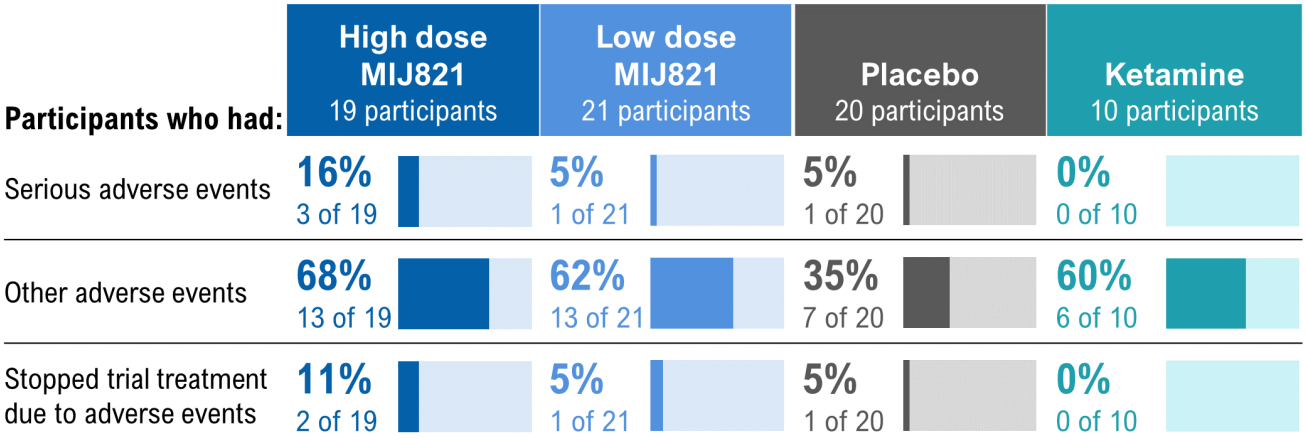
Many trials are needed to know if a drug or treatment causes an adverse event. Trial doctors keep track of all adverse events that happen in trials, even if they do not think the adverse events are related to the trial treatments.

What is an adverse event?

- Adverse events **may or may not be caused** by treatments in the trial.
- An **adverse event** is any unwanted sign or symptom that the participants have during a trial.
- It is considered “**serious**” when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death.

Most participants had adverse events, some of which were considered serious. More of the participants who received MIJ821 or ketamine had adverse events than those who received the placebo. The most common adverse events were feeling dizzy and brief memory loss (amnesia) from dissociation.

Participants who had adverse events



What serious adverse events did participants have?

A total of 5 participants had a serious adverse event during this trial. These were:

- **High dose of MIJ821:**
  - **Irregular heartbeat** (atrial fibrillation)
  - **Depression that got worse** (major depression)
  - **Suicide threat**
- **Low dose of MIJ821: Asthma attack**
- **Placebo: Suicide attempt**
- **Ketamine: None reported serious adverse events**

No other serious adverse events were reported, including no deaths.

What other adverse events did participants have?

Most participants in this trial had adverse events that were not serious. The table below shows the adverse events that happened to **5 or more** participants. Other adverse events were reported by fewer participants.

Other adverse events

	High dose MIJ821 19 participants	Low dose MIJ821 21 participants	Placebo 20 participants	Ketamine 10 participants
Memory loss (lasting about 1-9 hours) Amnesia	42% 8 of 19	10% 2 of 21	0% 0 of 20	0% 0 of 10
Dizziness	11% 2 of 19	24% 5 of 21	5% 1 of 20	20% 2 of 10
Feeling sleepy Somnolence	21% 4 of 19	14% 3 of 21	0% 0 of 20	10% 1 of 10
Headache	16% 3 of 19	5% 1 of 21	5% 1 of 20	10% 1 of 10
Not feeling like themself Feeling abnormal	11% 2 of 19	19% 4 of 21	0% 0 of 20	0% 0 of 10
Feeling detached from themselves or reality Depersonalization-derealization disorder	0% 0 of 19	0% 0 of 21	0% 0 of 20	50% 5 of 10
Feeling tired Fatigue	16% 3 of 19	0% 0 of 21	5% 1 of 20	10% 1 of 10

For more information about the adverse events the participants in this trial had, visit novctrd.com. Use trial number **CMIJ821X2201** to find the scientific summary.

What other results were learned?

The trial staff measured different aspects of the participants' mental health by asking several sets of questions during the trial. They compared a participant's answers before, during, and after treatment to look for any changes to their mental health.

Did MIJ821 reduce depression symptoms over 6 weeks?

On average, the participants who received the low dose of MIJ821 every 2 weeks reported less severe depression symptoms than the participants who received other doses of MIJ821 or the placebo.

The clinical trial team also found:

- The participants who received MIJ821 were more likely to have their MADRS scores down by at least 50% compared to those who received the placebo.
- A few participants in all treatment groups had their MADRS score go down enough for their depression symptoms to be considered gone.

Was MIJ821 more likely to reduce depression symptoms in certain participants?

Participants who did not have certain symptoms at the start of the trial were more likely to report a meaningful change in their depression symptoms. These symptoms were:

- Extreme loss of pleasure
- Feeling physically and mentally slowed down
- High anxiety when they started the trial

The participants who did not have these symptoms were more likely to report a meaningful change in their depression symptoms after receiving any of the trial treatments, including the placebo.

Did MIJ821 affect other aspects of depression?

On average, these symptoms went down by about the same amount in all treatment groups:

- Anxiety symptoms
- Extreme loss of pleasure and feeling physically and mentally slowed down
- Mixed-mood periods, which are periods of excitement and overactivity mixed with periods of depression

Did MIJ821 have any unwanted effects on the participants' thinking?

The participants who received MIJ821 or ketamine showed more symptoms of dissociation than those who received the placebo. The clinical trial team concluded that more research is needed to find out how different doses of MIJ821 affect symptoms of dissociation.

Before trial treatment, the participants had low or no suicidal thoughts and mania symptoms, such as feelings of excitement and overactivity. These thoughts and symptoms stayed about the same in all treatment groups throughout treatment.

What was learned from this trial?

This was the first trial to learn about how well MIJ821 works for people with TRD. The participants who received any dose of MIJ821 had less severe depression symptoms after 24 hours than those who received the placebo. More participants who received MIJ821 had adverse events than those who received the placebo. However, most of the adverse events were short-term and didn't need medical treatment.

This was one of many trials a drug must go through before it can be approved for doctors to prescribe for people with TRD. This type of trial learns about the safety of a trial drug and how well it works in a small number of participants.

The results presented here are for one trial. One trial cannot give a complete picture of the benefits and risks of a trial drug. The results of many trials are needed to find out which treatments can be used for people with TRD. This summary shows only the main results from this trial. Other trials may provide new information or different results.

Where can I learn more about this and future clinical trials?

You can find detailed results and more information about this clinical trial on the Novartis Clinical Trial Results website:

1. Visit novctrd.com
2. Click on “Clinical Trial Results” at the top right of the page
3. Read and scroll down, then click “I accept” to agree to use the information and the website
4. Select “Study number” from the drop-down menu
5. Type **“CMIJ821X2201”** in the search box and click search

If you would like to view the website in a language other than English, you can click the “Google Translate” button on the top right of the page.

If you participated in the trial and have **questions** about the results, please speak with the trial doctors or staff at your trial site.

This trial was registered on the following websites:

- ClinicalTrials.gov – https://clinicaltrials.gov/
  To find this trial, type **CMIJ821X2201** in the **Other terms** search box
- European Union Clinical Trials Register – https://www.clinicaltrialsregister.eu/ctr-search
  To find this trial, type **CMIJ821X2201** in the search box

Full trial title:

A multi-center, randomized, subject and investigator-blinded, placebo-controlled, active comparator, parallel-group proof of concept study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of MIJ821 in patients with treatment-resistant depression

If more trials are planned, they will appear on the public websites listed above. When there, search for **MIJ821.**

Thank you!

Novartis would like to thank all of the people who participated in this clinical trial. The participants made this clinical trial possible and helped researchers answer important health questions and learn about a possible medical treatment. Many participants and many clinical trials are needed to advance medical science.

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