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A Study of TAK-994 in Adults With Narcolepsy

THANK YOU!

Thank you to all of the participants who took part in this study.

Takeda sponsored this study and thinks it is important to share the results with the study participants and the public.

This summary reports the main results of this study.

Key points of the study:

TAK-994 was being studied as a potential treatment for people with narcolepsy type 1. This study is an extension study that included participants who completed Part B of the earlier study TAK-994-1501. Researchers wanted to check if it was safe for participants to receive TAK-994 over a longer period of time.

The study was planned to be conducted in 2 parts. Participants were initially given one of 3 different TAK-994 doses for 8 weeks during the first part of the study. Participants could receive either TAK-994 or a placebo during the second part of the study. A placebo looks the same as TAK-994 but has no medicine in it. Researchers compared the continued effect of TAK-994 between participants who continued receiving it and those who switched to a placebo.

This study was stopped early due to safety concerns, and not as many participants took part in the study as the researchers had planned. Therefore, accurate conclusions could not be made in the study.

Why was this study done?

Narcolepsy is a sleep disorder that disturbs a person's normal sleep-wake cycle. This condition makes it very difficult for people to stay awake for long periods of time. It causes extreme sleepiness during the day, which is also called excessive daytime sleepiness (EDS). Sometimes people with narcolepsy also have sudden muscle weakness while staying conscious (cataplexy). This can be caused by strong emotions.

Other symptoms of narcolepsy include disturbed sleep at night, feeling paralyzed while falling asleep, or sensing things that are not there while waking up or falling asleep.

Narcolepsy can be divided into 2 types based on the presence or absence of cataplexy and the amount of orexin in the brain fluid. Orexin, a chemical in the brain fluid, helps to control many body functions including the sleep-wake cycle. Most people with narcolepsy type 1 (NT1) have cataplexy and very low levels of orexin in their body. However, people with narcolepsy type 2 (NT2) do not have cataplexy and their levels of orexin are not as low as in people with NT1 or can be normal.

Currently, there is no cure for narcolepsy, but certain medicines and lifestyle changes may help with narcolepsy symptoms. TAK-994 or firazorexton is a medicine that works like orexin and therefore may help control cataplexy, EDS, and other symptoms of narcolepsy. This study was an extension study. This study included participants who had already completed a part of the previous study TAK-994-1501. The main purpose of this study was to learn more about the long-term safety of TAK-994 in people with NT1. Researchers wanted to check participants for safety after they received TAK-994 for a longer period of time.

What were the main questions?

Researchers wanted to check how safe TAK-994 was in people with NT1. They wanted to answer the following questions:

- **How many participants had at least 1 medical problem during the 8 weeks of treatment?**

Medical problems are any new or worsening problems that the participants had after they took the study medications. They may or may not be related to the study drug or placebo.

- **How many participants had at least 1 abnormal laboratory value during the 8 weeks of treatment?**

Laboratory values help assess the overall health and functioning of the body. Some laboratory tests included measuring blood components, urine tests, and checking certain chemical levels in the body. Researchers checked for abnormal laboratory values after participants received the study treatment.

- **How many participants had at least 1 abnormal vital sign during the 8 weeks of treatment?**

Vital signs are measurements of the essential functions of the body. Important vital signs are blood pressure, heart rate, breathing rate, and body temperature. Researchers also recorded changes in participants' systolic and diastolic blood pressure compared to the study start.

Systolic blood pressure (SBP)*:* SBP is the pressure inside blood vessels when the heart pumps blood. It corresponds to the first, higher number in the blood pressure reading. The normal SBP is 120 millimeters of mercury (mmHg).

Diastolic blood pressure (DBP)*:* DBP is the pressure inside blood vessels when the heart rests in between pumping blood. It corresponds to the second, lower number in a blood pressure reading. The normal DBP is 80 mmHg.

- **How many participants had at least 1 abnormal electrocardiogram (ECG) test results during the 8 weeks of treatment?**

An ECG is a test that records electrical signals when the heart is beating. An abnormal ECG means that the heart may not be working properly.

How was the study done?

What type of study was this?

Clinical studies are done as part of the development of a new treatment. The type of clinical study depends on the stage, or phase, of development. These studies are called Phase 1 to Phase 4 studies.

- This was a Phase 2 study, where a small number of people with NT1 received TAK-994. This was to learn if the medicine was safe and could help people with this condition.

- This was a double-blinded study. This meant that none of the participants, doctors, or other study clinic staff knew which treatment each participant received. This is done because knowing what treatment the participants are receiving could affect the results of the study.

What treatments were studied?

Participants were assigned to their treatment group by chance (randomly). This helped to make the treatment groups as similar as possible.

The participants received 1 of the following treatments:

TAK-994, 30 milligrams (mg), 90 mg, or 180 mg, 2 times a day, taken by mouth, for 8 weeks.

After completing 8 weeks, participants were assigned to the same TAK-994 treatment dose or placebo for 4 weeks.

Placebo, taken by mouth, 2 times a day.

A placebo looks the same as TAK-994 but has no medicine in it. Using a placebo helps researchers learn about the real effects of the treatment.

What happened during the study?

In this study, researchers wanted to check the long-term safety of TAK-994 in participants who had already received TAK-994 in the previous study TAK-994-1501. The study doctors checked that each participant met the study rules before they joined the study.

The study was designed to have 2 parts. However, it ended early so researchers could not reach the number of participants as planned for Part 2.

The table below shows which treatments were planned to be given in Parts A and B.

Parts	Treatment twice a day
Part A	• TAK-994 30 mg • TAK-994 90 mg • TAK-994 180 mg
Part B	• TAK-994 30 mg • TAK-994 90 mg • TAK-994 180 mg • Placebo

The initial study TAK-994-1501 was conducted in 3 parts (Parts A, B, and C). During Part B, participants received either TAK-994 30 mg, 90 mg, or 180 mg or placebo. For this study, which is the extension of TAK-994-1501, researchers had planned to enroll participants with NT1 who had completed Part B of TAK-994-1501 and continued to meet the study rules as expected. There was no separate screening period for this study.

There were 2 parts planned for the study, which are as given below:

Part A:

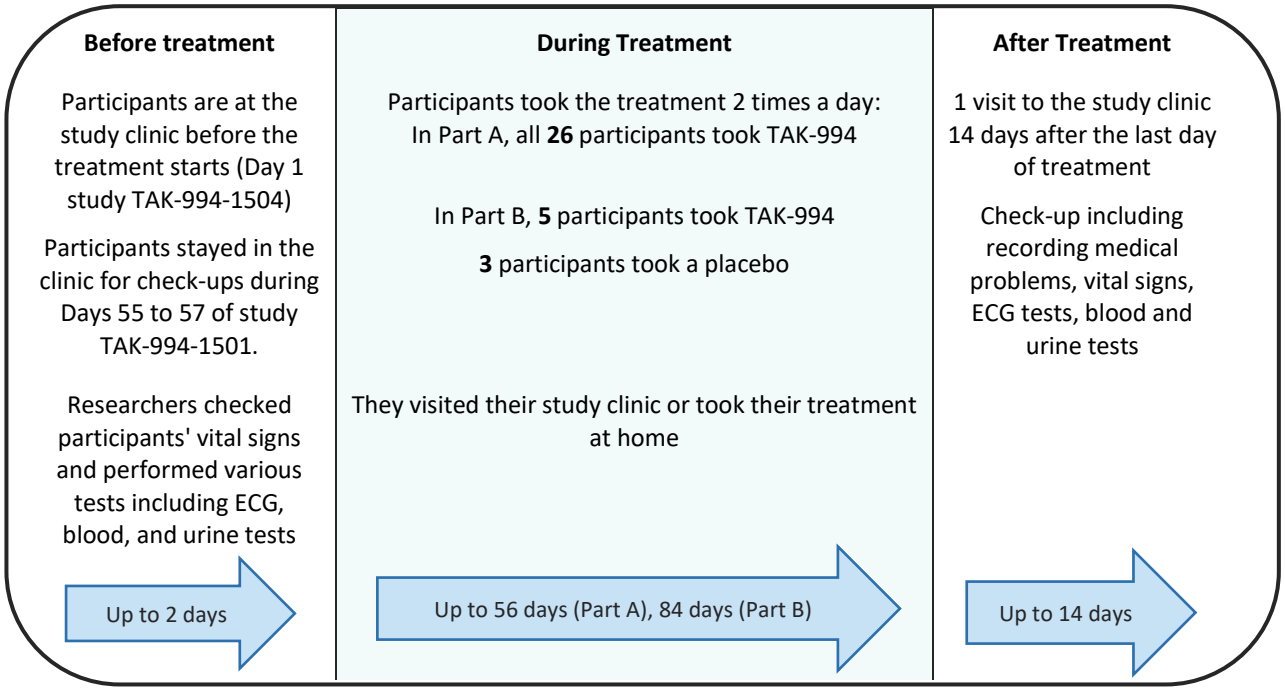
- Participants who had completed Part B of the study TAK-994-1501 were screened to make sure they were a good fit for the study. Participants could enter this study based on the tests performed towards the end of Part B of TAK-994-1501. This included physical exams, blood and urine tests, vital signs**,** ECG (to check heart function), and imaging scans.
- Participants stayed in the clinic for 2 days before starting the study treatment.
- Participants were treated with one of the 3 TAK-994-1501 treatment doses (30 mg, 90 mg, or 180 mg) for 8 weeks starting from Day 57 of the TAK-994-1501 study. Which is Day 1 of TAK-994-1504.
- For each participant in Part A of this study, the treatment period lasted for 8 weeks.
- Some participants were asked to stay at the clinic at certain times for tests and to receive the medicine. On other days, participants could take TAK-994 or placebo at home.
- Throughout the study, researchers checked for medical problems and performed various tests. These tests included laboratory tests, vital signs, physical exams, ECG, and blood and urine tests. Researchers also did tests to see if participants had trouble sleeping and to check if they were having any thoughts about harming themselves.

Part B:

- During this part of the study, participants received either TAK-994 or placebo for 4 weeks.
- As the study ended early, researchers could not reach the number of participants as planned.

Follow-up Period:

- Follow-up Period: Participants had a follow-up visit 14 days after completing treatment in Part B.
- Researchers performed multiple tests at the follow-up visit, which included vital signs, ECG, and blood and urine tests.



Who took part in the study?

Potential participants could take part if:

- They were 18 to 65 years of age.
- They had NT1 as recorded by sleeping tests
- They had completed Part B of the study TAK-994-1501

Potential participants could not take part if:

- They had a severe medical problem related to TAK-994 from the previous study TAK-994-1501

All the participants who joined Parts A and B were treated.

How many participants took part?
26 participants joined Part A and were treated 8 participants from Part A joined Part B and were treated
Which treatment group were the participants in?
For Part A: 8 participants were treated with TAK-994, 30 mg 9 participants were treated with TAK-994, 90 mg 9 participants were treated with TAK-994, 180 mg For Part B: 3 participants were treated with placebo 1 participant was treated with TAK-994, 30 mg 1 participant was treated with TAK-994, 90 mg 3 participants were treated with TAK-994, 180 mg
12 men 14 women
18 to 49 years old

Where was the study done?

This study took place in 13 study clinics in 5 countries: Spain, Italy, Japan, Korea, and the United States

When was the study done?

The study started in April 2021 and was stopped early in October 2021 due to safety concerns observed in the phase 2 studies of TAK-994.

What were the study results?

This summary gives the main results of this single study. Other studies may give different results. Researchers look at the results of many studies to decide which medicines work best and are safest for patients. Always speak with your doctor before changing your treatment.

This study was stopped early due to safety concerns observed in phase 2 studies of TAK-994. Therefore, researchers could not reach the number of participants as planned for Parts A and B.

Researchers wanted to answer the questions below during Part A of the study.

How many participants had at least 1 medical problem during the 8 weeks of treatment?

Researchers checked for medical problems during the study. The table below shows the number of participants with medical problems in each group in Part A during the 8 weeks of treatment.

Number of Participants With Medical Problems			
	TAK-994 30 mg 8 participants	**TAK-994 90 mg 9 participants**	**TAK-994 180 mg 9 participants**
Number of participants with medical problems	5 participants (63%)	4 participants (44%)	3 participants (33%)

How many participants had at least 1 marked abnormal laboratory value (MAV) during the 8 weeks of treatment?

Researchers checked the number of participants with laboratory values outside the normal limits after receiving the treatment.

A total of 10 participants reported MAV. The results were as follows:

- 3 participants (12%) had alanine aminotransferase (ALT), a liver protein, (3 times more than the normal limits of ALT)
- 3 participants (12%) had aspartate aminotransferase (AST), a liver protein, (3 times more than the normal limits of ALT)
- 2 participants (8%) had MAVs for bilirubin (1.5 times more than the normal units of bilirubin)
- 1 participant (4%) had MAVs for gamma-glutamyl transferase (GGT) (3 times more than the normal limits of GGT)
- 1 participant (4%) had MAVs for potassium (more than 5.3 micromoles per liter).

How many participants had at least 1 abnormal vital sign during the 8 weeks of treatment?

Researchers checked the number of participants with at least 1 abnormal vital sign during the study. 14 participants (54%) had at least 1 abnormal value in their SBP and DBP, and breathing rate after receiving the study treatment.

How many participants had at least 1 abnormal ECG test result during the 8 weeks of treatment?

Researchers checked for various measures of the heart's electric activity. The results showed that significant changes were not observed in any of these ECG measures. Although 2 participants (8%) had abnormal ECG results, these changes were not considered clinically important.

Were there any side effects?

In a clinical study, the study doctors record all medical problems the participants have during the study. They do this whether or not they think these problems were caused by the study treatment. These medical problems are called **adverse events**. If the study doctors think some of these medical problems might be caused by the study treatment, they are called **side effects**.

The side effects shown here are from a total of 26 participants who received study treatment.

How many participants had side effects?

During this study, 8 out of 26 participants (31%) in Part A had side effects.

Information on Side Effects during Part A			
	TAK-994 30 mg 8 participants	**TAK-994 90 mg 9 participants**	**TAK-994 180 mg 9 participants**
How many participants had side effects?	3 participants (38%)	2 participants (22%)	3 participants (33%)
How many participants stopped the study treatment due to side effects?	0	2 participants (22%)	3 participants (33%)

The side effects that happened in Part A are shown here.

Side Effects Reported during Part A			
	TAK-994 30 mg 8 participants	**TAK-994 90 mg 9 participants**	**TAK-994 180 mg 9 participants**
Dry mouth	1 participant (13%)	0	0
Nausea	1 participant (13%)	0	0
Inability to tolerate temperature changes (Intolerance to temperature)	0	0	1 participant (11%)
Sudden inflammation of the liver (hepatitis acute).	0	0	1 participant (11%)
Inflammation of the liver (hepatitis).	0	1 participant (11%)	0
Increased levels of liver proteins in the blood (AST increased)	0	0	2 participants (22%)
Increased blood pressure	0	1 participant (11%)	0
Headache	0	0	1 participant (11%)
Difficulty sleeping (Insomnia)	0	0	1 participant (11%)
Abnormally frequent urination (Pollakiuria)	1 participant (13%)	1 participant (11%)	1 participant (11%)
Sudden urge to pass urine (Micturition urgency)	0	0	1 participant (11%)

None of the participants in Part B had any side effects in this study.

How many participants had serious side effects?

Some side effects are called serious if they cause death, threaten life, cause ongoing health problems, or need a hospital stay or a longer stay in the hospital.

2 participants (8%) out of 26 participants in Part A had serious side effects in this study. The side effects were sudden inflammation of the liver (hepatitis acute) and inflammation of the liver (hepatitis).

None of the participants in Part B had any serious side effects.

How has this study helped?

This study has helped researchers learn about the long-term safety of TAK-994 in people with NT1. This study was stopped early due to safety concerns observed in phase 2 studies of TAK-994.

The results from several studies are needed to decide which treatments work best and are safest. This summary only shows the main results from this 1 study. Other studies may provide new information or give different results.

There are no plans for further studies with TAK-994.

More information about this study

The number of participants who took part in each country and region is shown here. This is out of a total of 26 participants who were treated in the study.

Country	Number of participants
Korea, South	1
Japan	2
Spain	5
Italy	9
United States	9

Where can I learn more about this study?

Title of this study:	A Dose-Blind Extension Study With Double-blind, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK-994 in Adults With Narcolepsy With Cataplexy (Narcolepsy Type 1)
Study number:	TAK-994-1504
Europe study number:	2021-000251-39
United States study number:	NCT04820842

More information about the study results is available here:

United States	www.clinicaltrials.gov Search this website using the study number NCT04820842
Europe	https://www.clinicaltrialsregister.eu/ctr-search/search Search this website using the study number 2021-000251-39
Takeda website	https://www.clinicaltrials.takeda.com/ Use the detailed search using the Study Identifier TAK-994-1504

Takeda sponsored this study.

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