



Once-nightly sodium oxybate (FT218) improved symptoms of disrupted nighttime sleep in people with narcolepsy: a plain language summary

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Summary

What is this summary about?

This is a plain language summary of a published article in the journal *CNS Drugs*. Narcolepsy is a rare sleep condition. Most people with narcolepsy experience disrupted nighttime sleep and have poor quality of sleep. Sometimes these symptoms are not easily diagnosed as a symptom of narcolepsy.

Sodium oxybate is an approved treatment for narcolepsy. The only version of sodium oxybate that was available until 2023 required people to take their sodium oxybate at bedtime and then again in the middle of the night. The US Food and Drug Administration (FDA for short) has approved a once-nightly bedtime dose of sodium oxybate (ON-SXB for short, also known as FT218 or LUMRYZ™) to treat symptoms of narcolepsy in adults. These symptoms are daytime sleepiness and cataplexy, which is an episode of sudden muscle weakness. The once-nightly bedtime dose of ON-SXB removes the need for a middle-of-the-night dose of sodium oxybate.

The REST-ON clinical study compared ON-SXB to a placebo (a substance that contains no medicine) to determine if it was better at treating symptoms of disrupted nighttime sleep associated with narcolepsy. This summary looks at whether ON-SXB was better than placebo at treating symptoms of disrupted nighttime sleep.

What were the results?

Compared to people who took placebo, people who took ON-SXB had fewer number of changes from deeper to lighter sleep stages and woke up less during the night. They also reported that they slept better at night and felt more refreshed when waking up in the morning. People with narcolepsy sometimes take alerting agents to help with sleepiness during the day, but alerting agents can cause difficulty sleeping at night. This study showed that people who took ON-SXB had better nighttime sleep even if they were taking alerting agents during the day. The most common side effects of ON-SXB included dizziness, nausea (feeling sick to your stomach), vomiting, headache, and bedwetting.

What do the results mean?

A once-nightly bedtime dose of ON-SXB is a narcolepsy treatment option for people without the need for a middle-of-the-night dose of sodium oxybate.

How to say (double click on the sound icon to play the sound)

Narcolepsy: NAAR-kuh-lep-see 

Cataplexy: KAT-uh-plek-see 

Sodium oxybate: SOH-dee-um AAK-see-bayt 

Who is this article for?

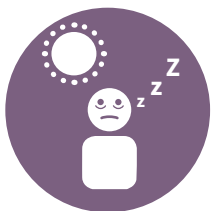
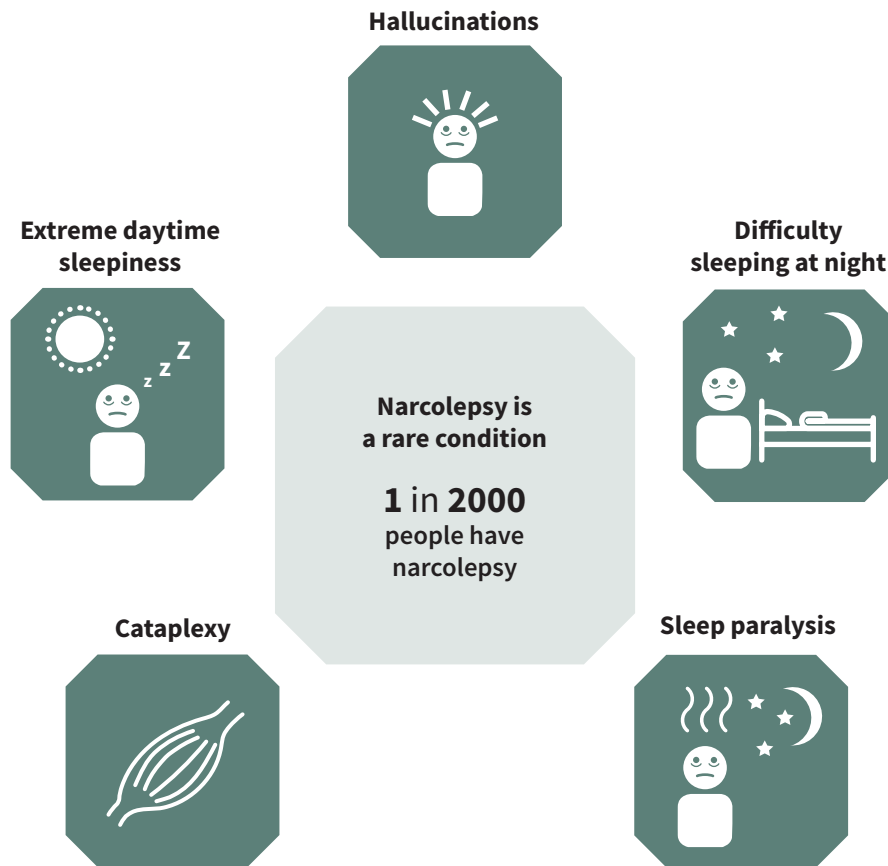
This article is for people with narcolepsy and their families, caregivers, and doctors.



Who sponsored this study?

Avadel Pharmaceuticals supported this work.

What is narcolepsy?



During the day, people with narcolepsy may feel extremely sleepy.

Some people may experience muscle weakness called cataplexy. Cataplexy may be partial, such as facial drooping, stumbling, or dropping things. It may also be a full-body collapse, where the person can't move but is conscious during the episode. It is often triggered by an emotional response such as laughter, surprise, or anger. Cataplexy is a symptom of narcolepsy type 1 (NT1 for short) but not narcolepsy type 2 (NT2 for short).



People with narcolepsy often have difficulty sleeping at night and wake up frequently during the night. People with narcolepsy may have other symptoms, such as being unable to move (called sleep paralysis) and hallucinations while falling asleep or waking up.

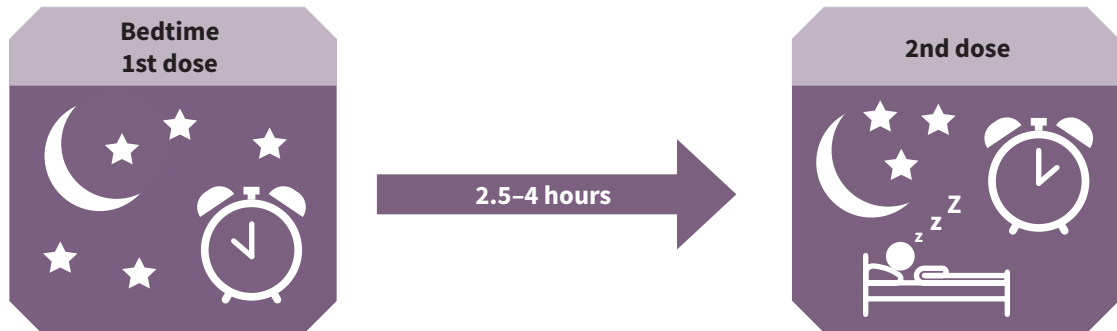
Some people with narcolepsy take a medicine called an alerting agent to help with their daytime sleepiness and allow them to stay awake during the day. They are sometimes called a "stimulant" or "wake-promoting agent."

Why was the study done?

For more than 20 years, doctors have used fast-acting sodium oxybate (called immediate-release, IR for short) to treat narcolepsy.

People with narcolepsy take two doses of IR sodium oxybate every night.

- People with narcolepsy take the first dose at bedtime, followed by a second dose 2.5 to 4 hours later



- People with narcolepsy often already sleep poorly at night. Waking up to take a second dose in the middle of the night may cause further sleep disturbance for people with narcolepsy and their families
- Being forced to wake up for the second dose may further disrupt the sleep cycles of people with narcolepsy. This can lead to people missing the second dose or taking it at the wrong time, making it challenging to take the medicine as prescribed

A new form of sodium oxybate called once-nightly sodium oxybate (ON-SXB for short; also known as FT218 or LUMRYZ™) was approved by the US Food and Drug Administration (FDA for short) in May 2023 for treating narcolepsy.

- ON-SXB allows people with narcolepsy to take only 1 dose of sodium oxybate medicine at bedtime each night. They do not need to take a second dose in the middle of the night



The REST-ON study was a double-blind study. This means neither the study participants nor the researchers performing the study knew if the participants were receiving ON-SXB or an alternative with no medicine in it (called a placebo).

- The primary outcomes (known as the main aim of the study) were 3 main measures to see whether ON-SXB improved narcolepsy symptoms compared to placebo. The researchers found that compared to people who took a placebo, people on ON-SXB had:
 - Improved daytime alertness and felt less sleepy
 - Fewer cataplexy episodes
 - Greater improvement in their narcolepsy symptoms as per their doctor's rating
- The researchers also looked at other measures (also known as secondary outcomes) to see whether ON-SXB improved disrupted nighttime sleep in people with narcolepsy

This summary looks at whether ON-SXB was better than placebo at treating symptoms of disrupted nighttime sleep. This was a secondary outcome in the study.

How was the study done?

Half the people took:

ON-SXB



Placebo



212 people took part in this study

Average age: 31 years old
Age range: 16–72 years



212
participants

Participants had at least 1 dose of the drug

68%
Female

76%
had NT1

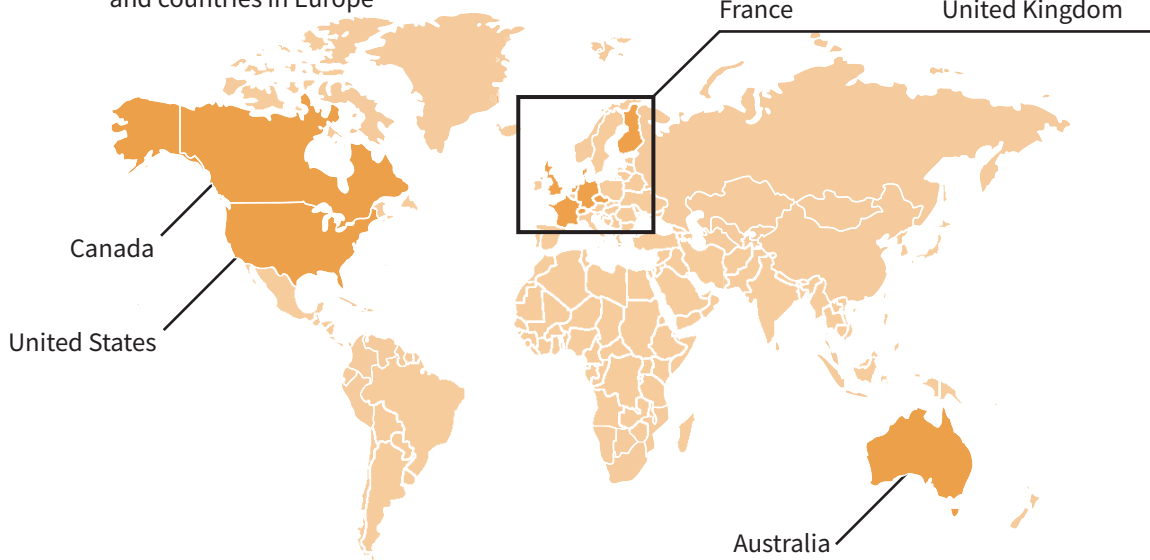
75%
White

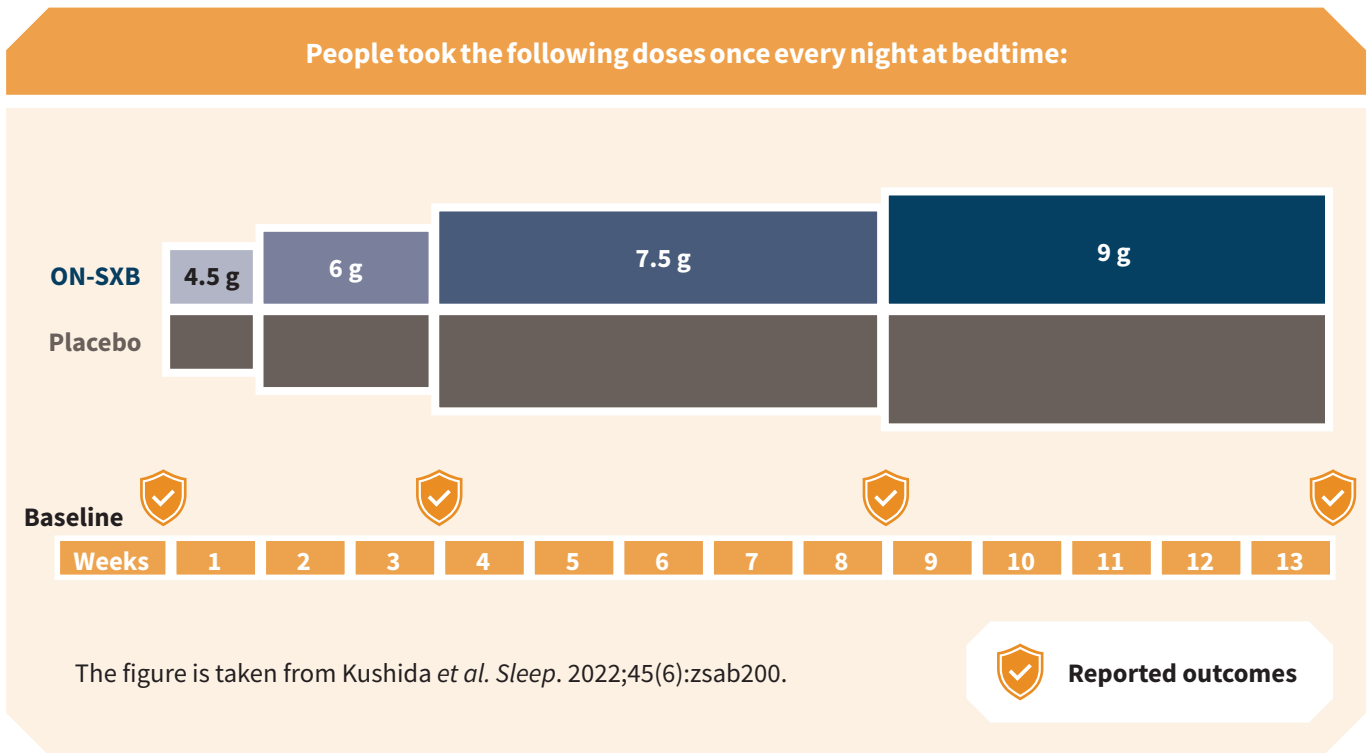
55% of participants lived in the US

45% of participants lived in Australia, Canada,
and countries in Europe

Czech Republic
Denmark
Finland
France

Germany
Netherlands
Switzerland
United Kingdom





Researchers looked at people’s nighttime narcolepsy symptoms at different timepoints during the study. They used four measures to determine if ON-SXB improved narcolepsy symptoms related to disrupted nighttime sleep.

Two of these measures were tested objectively in the sleep laboratory

The other 2 measures were based on diaries kept by the people in the study

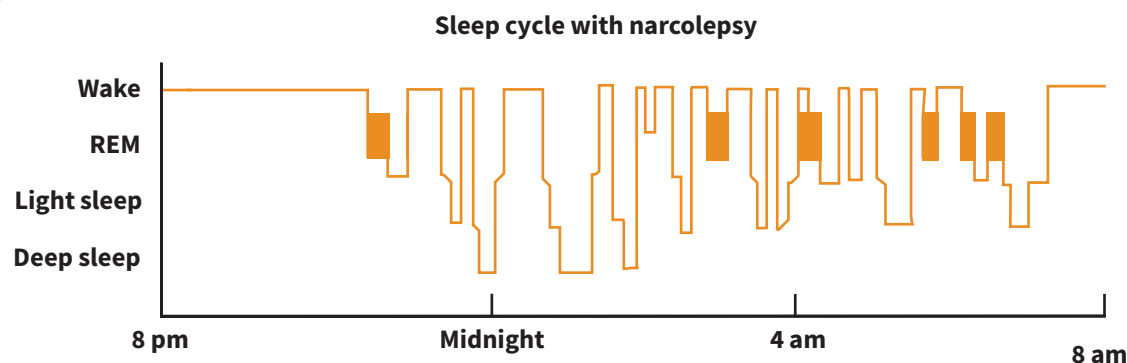
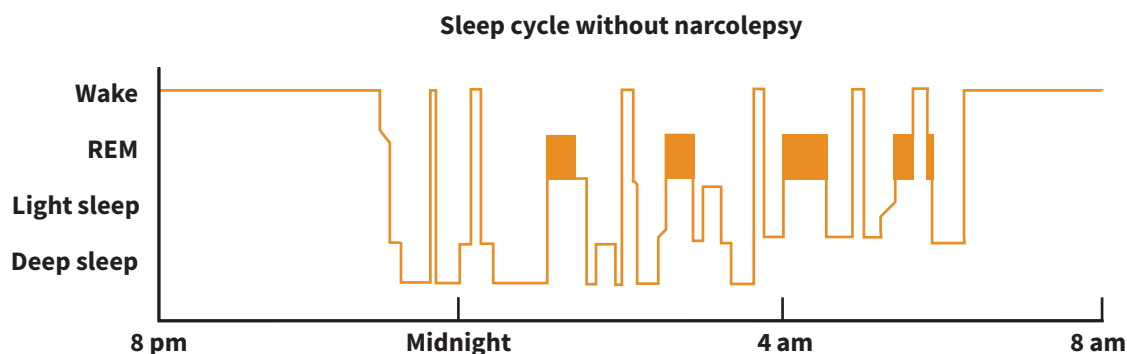


- All 4 measures were tested at the beginning of the study, which is known as baseline, prior to taking ON-SXB or placebo
- People’s brain and body activity during sleep was measured in a sleep laboratory. This is an overnight sleep study (also called a polysomnography or PSG for short). The PSG test was done at baseline and weeks 3, 8, and 13

- The researchers used the overnight PSG test to count the number of transitions in sleep stages. These are shifts from:
 - Light sleep, deeper stages of sleep, and dream state sleep (called rapid eye movement sleep, REM sleep for short) to wake
 - Deeper stages of sleep and dreaming to light sleep
- Light sleep is the first stage of sleep, and a person can be easily awakened. Restful deep sleep is the last stage of sleep, and a person’s heart rate and breathing decrease, and brain activity slows down

- A graph called a hypnogram shows all the sleep stages a person goes through during a PSG test. During nighttime sleep, there are usually 4–5 sleep cycles. Each sleep cycle is about 90–110 minutes long and includes all the sleep stages. Deep sleep typically occurs early in the night and REM sleep happens late within each sleep cycle

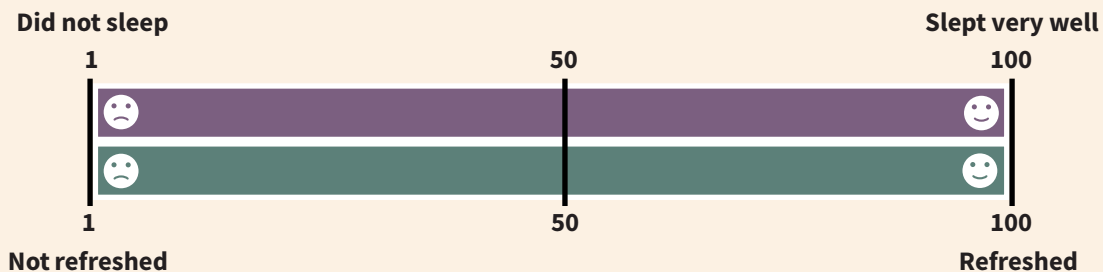
Example hypnograms of a person without narcolepsy and a person with narcolepsy:



The images are for illustrative purposes and do not represent a particular person.

- People in the study wrote in their sleep and symptom diaries every day. They scored how well they slept and how refreshed they felt in the morning on a scale from 1 to 100 called the visual analog scale

Visual analog scale



The researchers took average scores for weeks 3, 8, and 13 using the scores from the preceding 2 weeks. Then they compared these scores with the scores taken at baseline.

The researchers used statistical methods to compare the results from all 4 tests at baseline to the results at weeks 3, 8, and 13. They wanted to find out whether any improvement in people taking ON-SXB rather than placebo was more likely due to ON-SXB rather than due to chance. This is called statistical significance.

What were the overall results of the study?

1 The researchers looked for a decrease in the number of changes between sleep stages (called sleep stage transitions). This can indicate an improvement in narcolepsy symptoms.

At baseline, people who received ON-SXB and people who received a placebo had 60 sleep stage transitions to a lighter stage of sleep or wake.



During the study, people who received ON-SXB had fewer sleep stage transitions than those who received a placebo.

With 6 grams of ON-SXB at week 3:

People who received ON-SXB had about 10 fewer sleep stage transitions compared to baseline



People who received a placebo had about 1 more sleep stage transition compared to baseline



With 7.5 grams of ON-SXB at week 8:

People who received ON-SXB had about 15 fewer sleep stage transitions compared to baseline



People who received a placebo had about 3 more sleep stage transitions compared to baseline



With 9 grams of ON-SXB at week 13 (the end of the study):

People who received ON-SXB had about 21 fewer sleep stage transitions compared to baseline



People who received a placebo had about 2 more sleep stage transitions compared to baseline



These findings are statistically significant, which means they are not due to chance and ON-SXB likely reduced sleep stage transitions.

2

A decrease in the number of nocturnal arousals. This is the number of times a person experiences a change from deeper to lighter stages of sleep or from sleep to waking up during nighttime sleep. These were counted during the overnight sleep study.

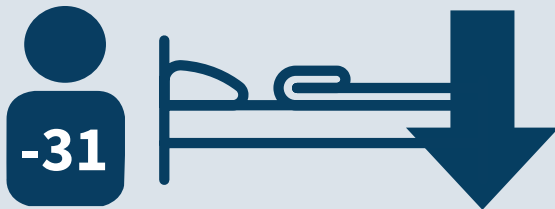
At baseline, people who received ON-SXB had 82 nocturnal arousals and people who received a placebo had 77 nocturnal arousals.



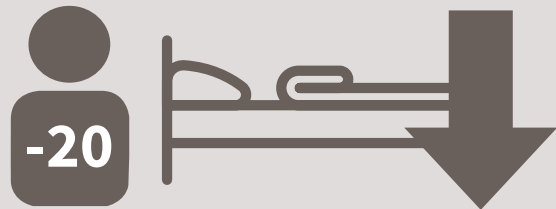
During the study, participants who received ON-SXB had fewer nocturnal arousals than those who received a placebo.

With 6 grams of ON-SXB at week 3:

People who received ON-SXB had about 31 fewer nocturnal arousals compared to baseline

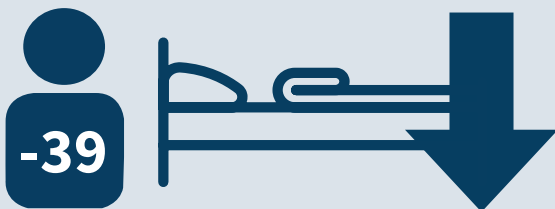


People who received a placebo had about 20 fewer nocturnal arousals compared to baseline

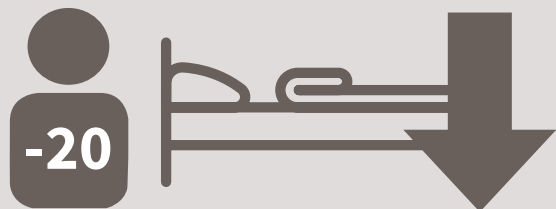


With 7.5 grams of ON-SXB at week 8:

People who received ON-SXB had about 39 fewer nocturnal arousals compared to baseline

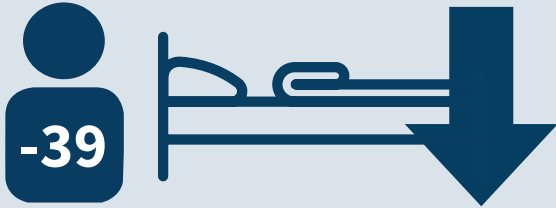


People who received a placebo had about 20 fewer nocturnal arousals compared to baseline

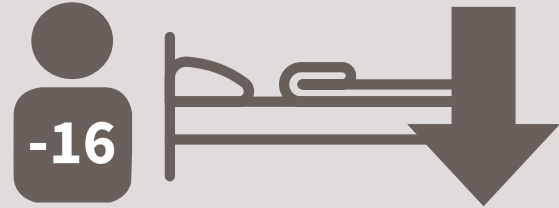


With 9 grams of ON-SXB at week 13 (the end of the study):

People who received ON-SXB had about 39 fewer nocturnal arousals compared to baseline



People who received a placebo had about 16 fewer nocturnal arousals compared to baseline



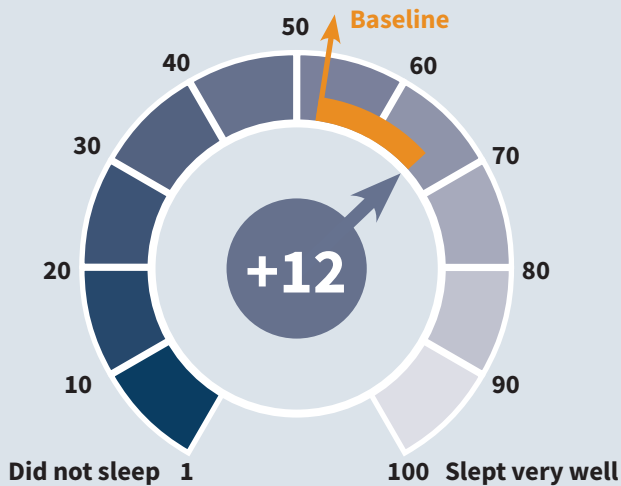
These findings are statistically significant, which means they are not due to chance and ON-SXB likely reduced nocturnal arousals.

3 Improvement in quality of sleep

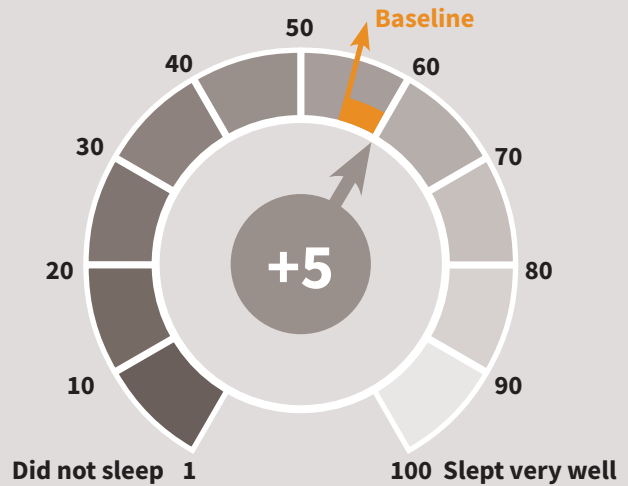
People who received ON-SXB rated themselves as having improved sleep quality than those who received a placebo.

With 6 grams of ON-SXB at week 3:

People who took ON-SXB had scores that were higher by 12 points compared to baseline

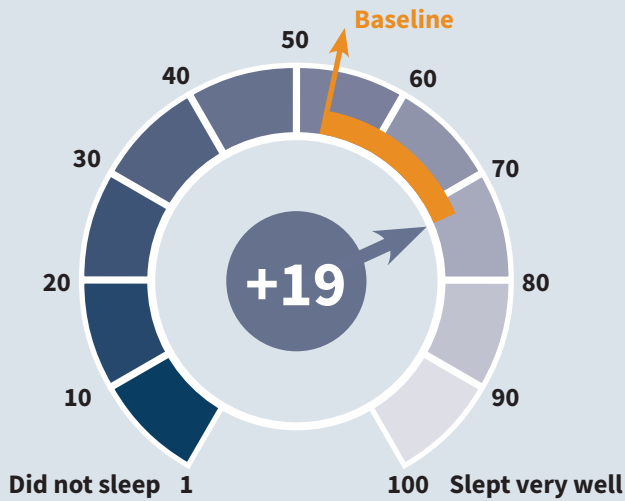


People who took a placebo had scores that were higher by 5 points compared to baseline

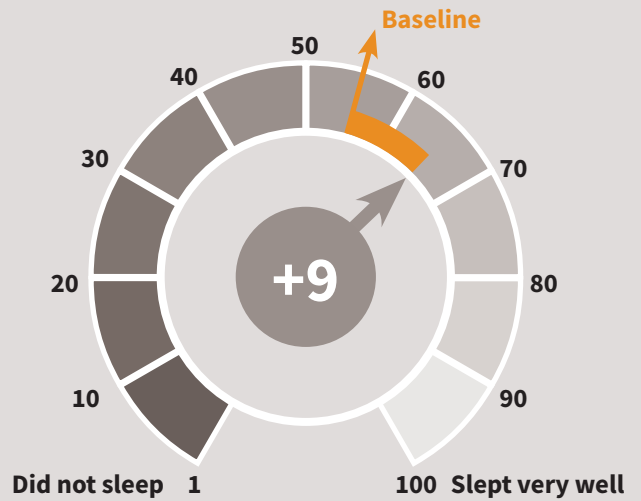


With 7.5 grams of ON-SXB at week 8:

People who took ON-SXB had scores that were higher by 19 points compared to baseline

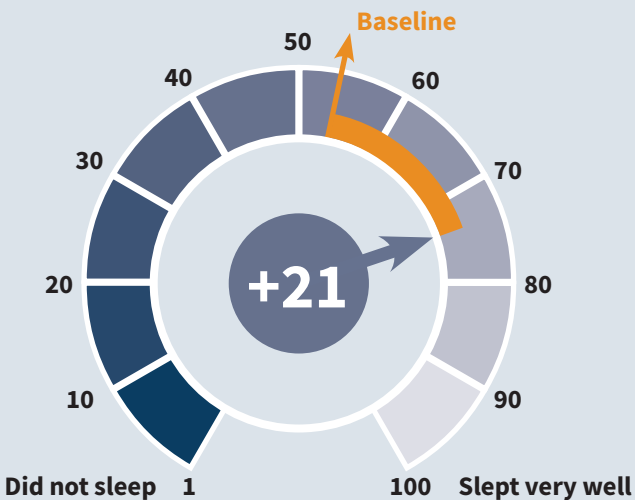


People who took a placebo had scores that were higher by 9 points compared to baseline

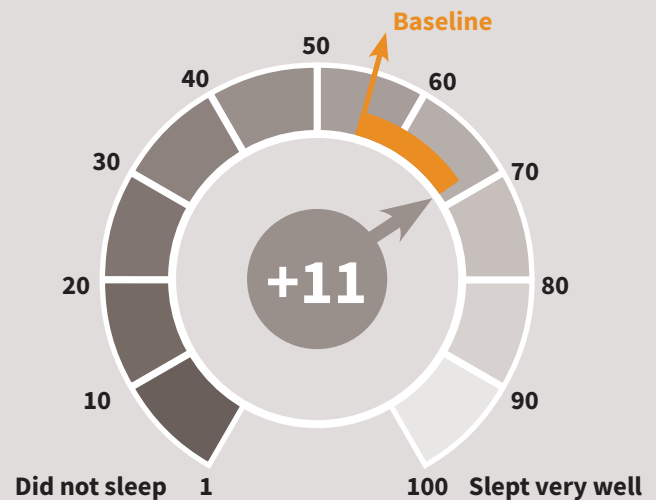


With 9 grams of ON-SXB at week 13 (the end of the study):

People who took ON-SXB had scores that were higher by 21 points compared to baseline



People who took a placebo had scores that were higher by 11 points compared to baseline



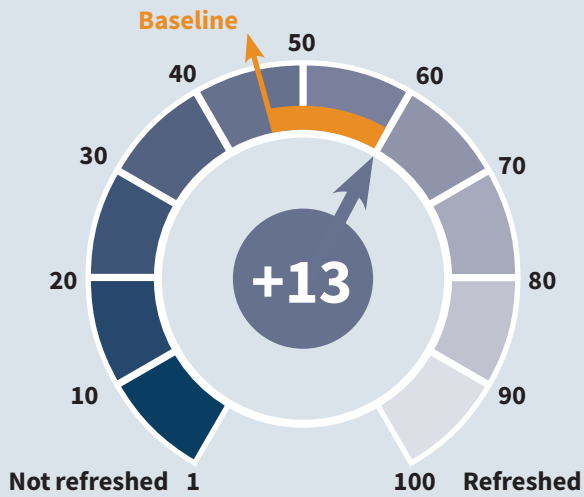
These findings are statistically significant, which means they are not due to chance and ON-SXB likely improved sleep.

4 Improvement in the refreshing nature of sleep

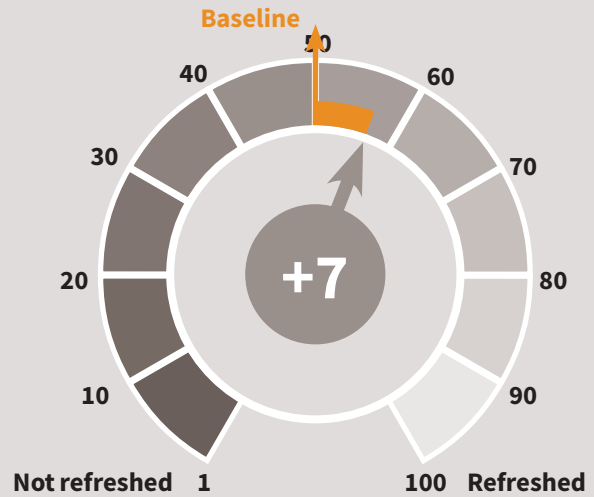
People who received ON-SXB rated themselves as more refreshed in the morning than those who received a placebo.

With 6 grams of ON-SXB at week 3:

People who took ON-SXB had scores that were higher by 13 points compared to baseline

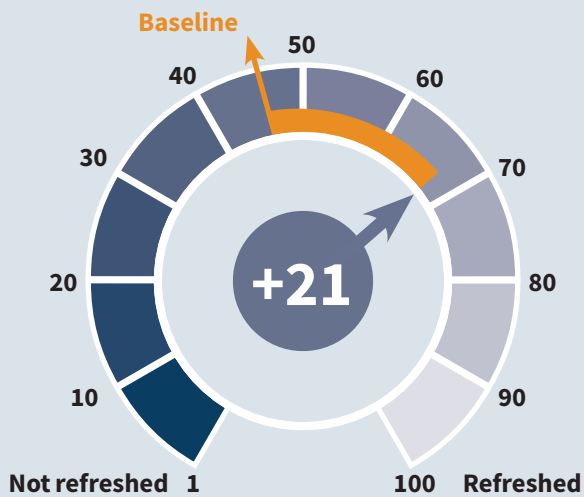


People who took a placebo had scores that were higher by 7 points compared to baseline

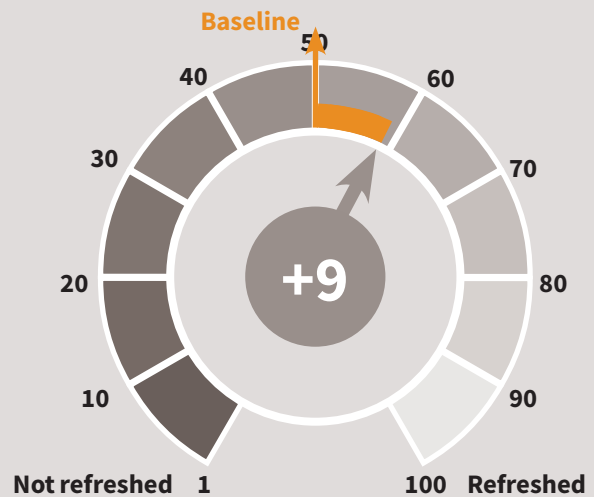


With 7.5 grams of ON-SXB at week 8:

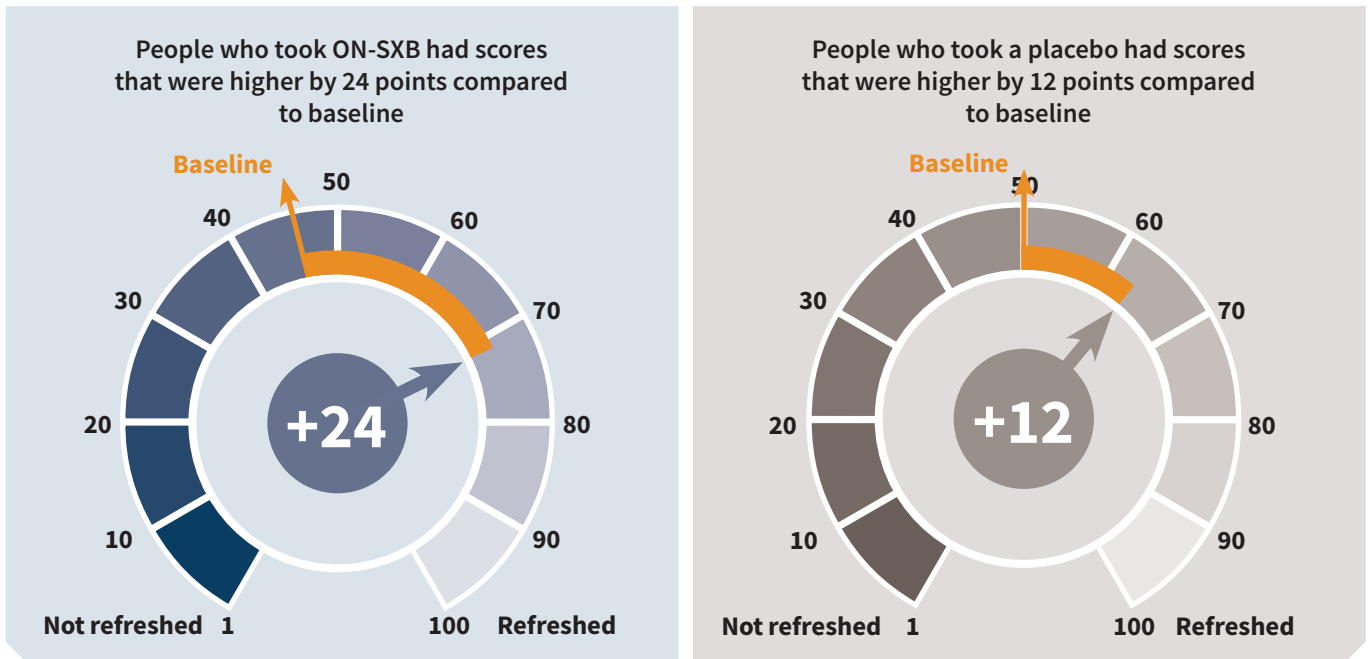
People who took ON-SXB had scores that were higher by 21 points compared to baseline



People who took a placebo had scores that were higher by 9 points compared to baseline



With 9 grams of ON-SXB at week 13 (the end of the study):



These findings are statistically significant, which means they are not due to chance and ON-SXB likely improved how refreshed people felt after waking up in the morning.

5

After all the data were collected in REST-ON, researchers looked at some additional results that were not included in the original plan for analyzing the study data. This is called post hoc analysis.



Researchers looked at other measures of sleep stages from the PSG test. For example, whether how much time people spent in each sleep stage was different with ON-SXB compared with placebo.

Some people in the REST-ON study were taking alerting agents.

- Alerting agents for narcolepsy include modafinil, armodafinil, methylphenidate, and amphetamines
- No people were taking the alerting agent medicine called pitolisant because it was not approved by FDA when this study was conducted



Researchers looked to see if ON-SXB was better than a placebo for the 4 measures of nighttime narcolepsy symptoms in 2 groups of people:

- People taking alerting agents
- People not taking alerting agents



Overall, at the end of the study, people who took ON-SXB spent more time in deep, restful sleep and less time in light sleep than people who took a placebo.

Whether or not people were taking alerting agents, those who took ON-SXB had improvement in their nighttime symptoms compared to those who took a placebo.

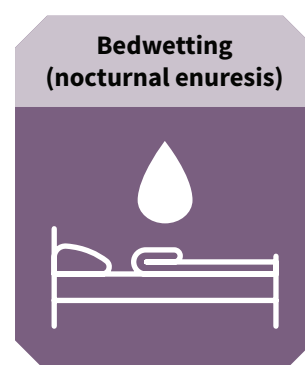
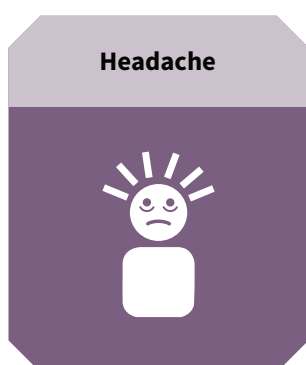
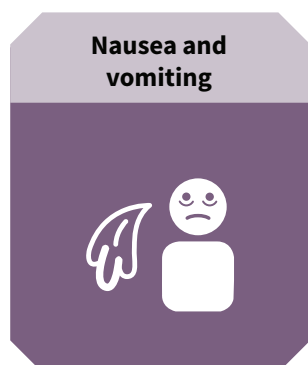


	ON-SXB dose (grams)	Fewer sleep stage transitions	Fewer nocturnal arousals	Improved sleep quality	More refreshed in the morning
People taking alerting agents	6	✓		✓	✓
	7.5	✓	✓	✓	✓
	9	✓	✓	✓	✓
People not taking alerting agents	6	✓	✓	✓	✓
	7.5	✓	✓	✓	✓
	9	✓	✓	✓	✓

The statistically significant findings mean it is likely that ON-SXB is responsible for improving narcolepsy symptoms in people who are taking or are not taking alerting agents and the improvement is not due to chance.

What were the most common side effects?

The most common side effects people taking ON-SXB reported in the REST-ON study were:



Percent of people		Nausea	Vomiting	Dizziness	Headache	Bedwetting
Placebo		3	2	0	6	0
ON-SXB dose	4.5 grams (week 1)	6	3	6	7	2
	6 grams (weeks 2-3)	8	3	4	5	4
	7.5 grams (weeks 4-8)	7	6	6	6	9
	9 grams (weeks 9-13)	1	5	5	0	9

Of people who experienced side effects while taking ON-SXB, most were mild or moderate.

- Mild means the side effects cause very little discomfort, allowing people to do their daily activities
- Moderate means they interfere with normal everyday activities and may need other treatment for them to be managed

What do the results of this study mean?



People who took ON-SXB had less disrupted nighttime sleep, woke up less during the night, felt that they slept well, and felt more refreshed after waking up in the morning than those who took a placebo.

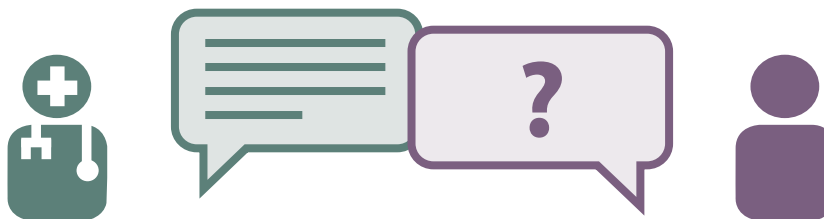
- These improvements were consistent for people who were or were not taking alerting agents with ON-SXB

Also, people who took ON-SXB spent more time in deep sleep and less time in light sleep than people who took a placebo. Findings from the REST-ON study show that ON-SXB helps treat narcolepsy symptoms and most people can tolerate the medicine.

Now that ON-SXB has received final approval from the FDA, it is a sodium oxybate treatment option for people with narcolepsy.

- ON-SXB treatment allows people to take only 1 dose at night, removing the need to take a second dose in the middle of the night

These results can help people and their healthcare providers when discussing the best treatment plan for their narcolepsy.



Where can readers find more information about this study?

The original article is called “Effect of FT218, a Once-Nightly Sodium Oxybate Formulation, on Disrupted Nighttime Sleep in Patients With Narcolepsy: Results From the Randomized Phase III REST-ON Trial.” It was published in *CNS Drugs* in 2022. The article is free to access. You can find it at the links below:

- <https://pubmed.ncbi.nlm.nih.gov/35380374/>
- <https://link.springer.com/article/10.1007/s40263-022-00904-6>

You can read more about the REST-ON study in the original primary article called “Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy” published in *Sleep* in 2022 and the plain language summary of that article published in *Future Neurology* in 2022. The articles are free to access. You can find them at the links below

- <https://pubmed.ncbi.nlm.nih.gov/34358324/>
- <https://academic.oup.com/sleep/article/45/6/zsab200/6343406>
- <https://www.futuremedicine.com/doi/10.2217/fnl-2022-0005>

You can find more information about narcolepsy at these websites:

- <https://www.ninds.nih.gov/>
- <https://project-sleep.com/>
- <https://narcolepsynetwork.org/>
- <https://www.narcolepsydisrupts.com/>

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