Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

How once-nightly sodium oxybate is processed in the body in healthy volunteers: a plain language summary

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Summary

What is this summary about?
This is a plain language summary of an article originally published in the journal *Sleep Medicine*. Narcolepsy is a sleep condition in which people have periods of extreme sleepiness during the day. People with narcolepsy may also have symptoms of muscle weakness (cataplexy); seeing, hearing, smelling, tasting, or feeling something that seems real but isn't actually there before falling asleep or while waking up (hallucinations); an inability to move before falling asleep or while waking up (sleep paralysis); and poor sleep at night.

Sodium oxybate (SXB for short) has been used to treat narcolepsy for over 20 years. For more than 20 years, the only available form of SXB needed to be taken twice each night. Twice-nightly SXB (TN-SXB) requires people to take the first dose at bedtime. Most people fall asleep within 5 to 15 minutes after the first dose. Patients then need to wake up and take the second dose of TN-SXB 2.5 to 4 hours later, which is when most of the medicine has left the body.

The United States Food and Drug Administration (also called FDA) **approved** a once-nightly form of SXB called LUMRYZ™ (sodium oxybate for extended-release **oral suspension**; ON-SXB for short) in May 2023. ON-SXB treats excessive daytime sleepiness and muscle weakness, also known as cataplexy. People with narcolepsy who take ON-SXB only need to take 1 dose at bedtime.

This summary describes a study that looked at how ON-SXB enters, travels through, and exits the body of healthy volunteers (people without narcolepsy). The study measured the amount of SXB in the blood after taking SXB in 2 different ways: as a once-nightly version and as a twice-nightly version. Looking at the amount of ON-SXB and TN-SXB in the blood at different time points helps researchers see if people who take the 2 medicines, with different dosing, have the same amount of drug in the body overnight.

What were the results?
Overall, the study found that healthy volunteers had the same amount of SXB in their bodies after taking ON-SXB as they did after taking TN-SXB. When they took the same amounts of ON-SXB and TN-SXB, the SXB stayed in their bodies for similar amounts of time. The highest amount and the total amount of SXB in the participants' blood were similar with ON-SXB and TN-SXB. The amount of SXB in the participants' blood 8 hours after taking the medicine was significantly lower with ON-SXB than with TN-SXB. This means that people taking ON-SXB will have less medication in their blood when they wake up the next morning and may be less groggy.

Approved: A product that has been reviewed by the US Food and Drug Administration and deemed safe and effective.

Oral suspension: Medicine that is made up of particles and mixed with a liquid before it is taken.

What do the results mean?
The results mean that if people with narcolepsy take the same dose amount of ON-SXB or TN-SXB, their bodies will receive the same amount of SXB in their blood. ON-SXB provides an option for people with narcolepsy to take their medicine once at bedtime without the need for a middle-of-the-night dose, which can improve quality of life.

Becaris PUBLISHING

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

Apnea : AP-nee-uhs
Bioequivalence: BYE-oh-i-KWIV-uh-lents
Cataplexy: KAT-uh-plek-see
Dysarthria: diss-AR-three-uh
LUMRYZ: LOOM-rize
Narcolepsy: NAAR-kuh-lep-see
Nausea: NAW-zee-uh
Pharmacokinetics: FAR-muh-kow-kih-NEH-tiks
Sodium oxybate: SOH-dee-um AAK-see-bayt
Somnolence: SAHM-nuh-lents

Who is this article for?

This article may be useful for people with narcolepsy, their families, their caregivers, and healthcare professionals.

Who sponsored this study?

Avadel Pharmaceuticals funded the study and provided the medication.

Where can readers find more information?

The original article is titled "Randomized, crossover, open-label study of the relative bioavailability and safety of FT218, a once-nightly sodium oxybate formulation: Phase 1 study in healthy volunteers." You may access and read the article for free at this link: https://pubmed.ncbi.nlm.nih.gov/36252412/

What is narcolepsy?

Narcolepsy is a sleep condition with symptoms that include:

Excessive daytime sleepiness

Cataplexy

(muscle weakness)

Hallucinations

(seeing, hearing, smelling, tasting, or feeling something that seems real but isn't actually there before falling asleep or while waking up)

Sleep paralysis

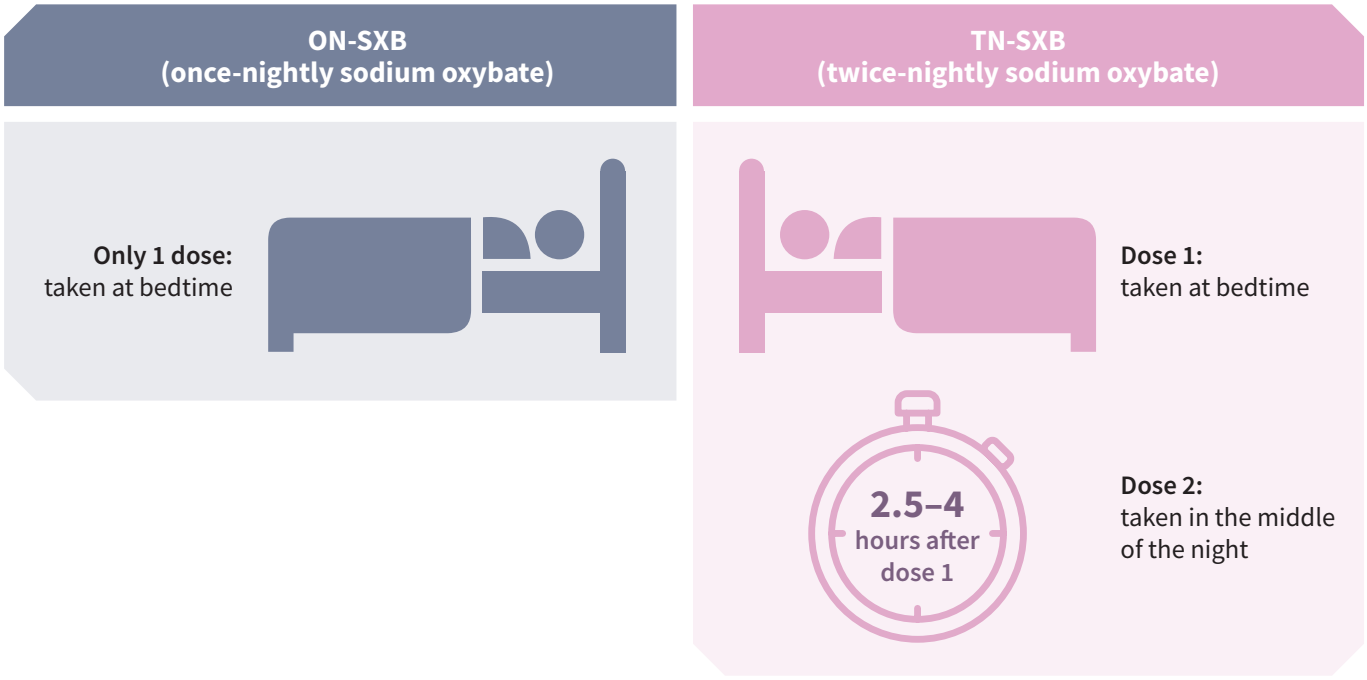
(inability to move before falling asleep or while waking up)

Poor sleep at night

1 in 2000
people living in the United States have narcolepsy

How do people with narcolepsy take sodium oxybate?

- Sodium oxybate (SXB for short) has been used to treat narcolepsy for over 20 years.
- It was first approved in the United States in 2002 to treat cataplexy and in 2005 to treat excessive daytime sleepiness in people with narcolepsy.
- Until 2023, the only available formulation was twice-nightly SXB (TN-SXB for short), which requires a dose at bedtime and a second dose 2.5 to 4 hours later.
  - TN-SXB is a liquid that is diluted further in water before taking the medicine.
- SXB is absorbed into the body, but the amount of medicine in the body decreases quickly. It is broken down in the liver and removed from the body when breathing. Around 2 to 5 hours after taking SXB, the medicine is out of the body.
- People with narcolepsy may find it difficult to wake up or may not want to wake up in the middle of the night for the second dose of TN-SXB.
- Having to wake up in the middle of the night may lead to reduced quality of life and might cause patients to miss or incorrectly time the second dose of the medicine. Some people may be anxious about being able to wake up to take their dose or have difficulty falling back asleep. Some people need to set an alarm to wake up to take their medicine. This middle-of-the-night alarm may also wake up their partners or family members.
- The United States Food and Drug Administration (also called FDA) approved a once-nightly form of SXB called LUMRYZ™ (sodium oxybate for extended-release oral suspension; ON-SXB for short) in May 2023.
- ON-SXB is different from TN-SXB because it has particles that release the drug at different times from only 1 dose.
  - Some particles release the drug right away. These are called immediate-release particles. Other particles release the drug later, when they are in a part of the digestive tract that has a different pH. These are called extended-release particles. This means that some ON-SXB stays in the body longer than TN-SXB does. People with narcolepsy who take ON-SXB only need to take 1 dose at bedtime.
- ON-SXB only requires 1 dose before bedtime.
  - ON-SXB is made up of immediate-release and controlled-release particles. These particles are added to water and mixed by shaking. This mixture, which will show some clumps after shaking, is called an “oral suspension.”



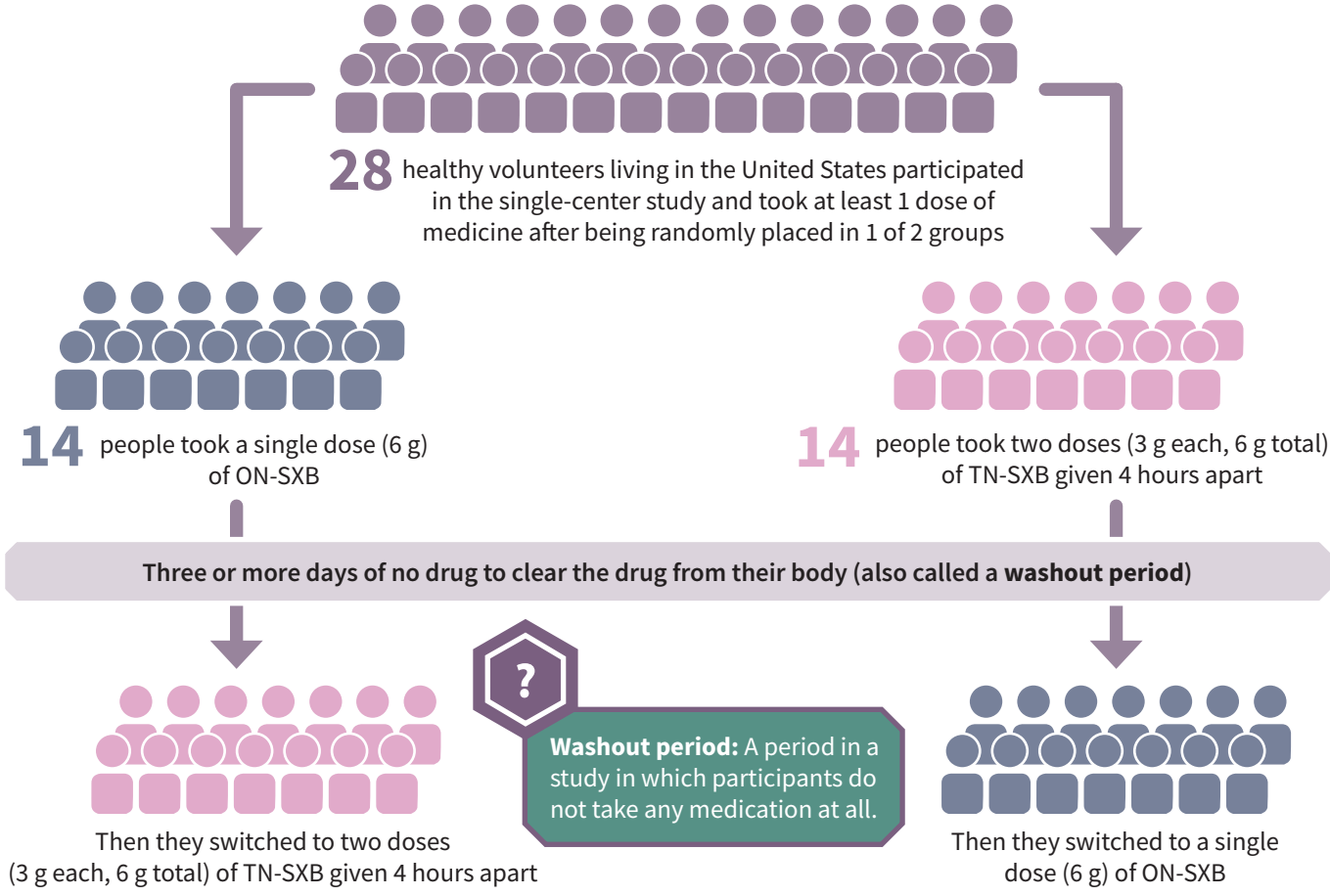
10.57264/cer-2024-0243

What did this study look at?

- This study was a **phase 1 study**, which tested the drug in people who did not have narcolepsy to see how their bodies processed the drug (known as pharmacokinetics). These people volunteered to take part in the study.
  - The goal of a phase 1 study is to learn if a new drug is safe and what doses people should take.
  - Phase 1 studies usually include small numbers of healthy volunteers. Companies carry out these studies after a medicine is tested in laboratory or animal research (also called preclinical research).
  - If the new medication appears safe in the phase 1 study, it is then tested in a phase 2 trial, which looks at whether the medicine improves symptoms and is safe in patients who have the condition the medicine was developed to treat.
- This study looked at whether the participants had the same overall amount of SXB in their body after taking ON-SXB as they did after taking TN-SXB.
- Researchers looked at when SXB reached the maximum amount in the body after both forms were taken by measuring the amount of SXB in the blood at different times after they took the medicine.
- They also looked to see how much SXB remained in the body 8 hours after taking the first dose.
- Lastly, researchers wanted to see if ON-SXB enters the body at the same speed and at the same amount as TN-SXB because this would mean that the medications would start working at about the same time.

Phase 1 study: The goal of a phase 1 study is to learn if a new drug is safe and what doses people should take.

Who took part in the study?

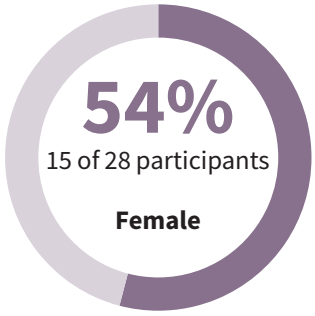


Washout period: A period in a study in which participants do not take any medication at all.

Age

- Average age of participants was 40 years old
- Age ranged from 19 to 60 years old

Sex



Race (physical trait)

Ethnicity (cultural identity)

How was the study carried out?

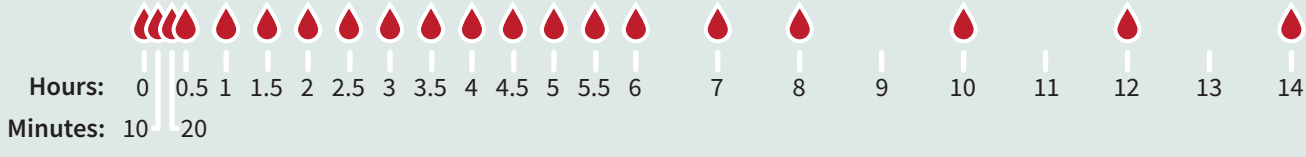
- Participants in the study were randomly selected to take ON-SXB and TN-SXB at different times.
- This was an **open-label study**.
- This study had a **crossover design**.
- Half of the participants took ON-SXB first, and blood samples were collected.
  - After their washout period of 3 or more days, they took TN-SXB, and more blood samples were collected.
- The other half of the participants took TN-SXB first, and blood samples were collected.
  - After their washout period, they took ON-SXB, and more blood samples were collected.
- The doses of ON-SXB and TN-SXB were given 2 hours after the participants ate dinner because food can affect how medicines enter, travel through, and exit the body. Food is usually fully digested within 1-2 hours following a meal.

Open-label study: A study in which participants and the researchers know which medicine the participants were taking.

Crossover design: A study in which participants start by taking 1 medication and then, after a washout period, switch to the other medication being tested in the study.

- Blood samples were taken at many different time points to measure the levels of the drug in the participants' bodies. People who take the medicine as treatment for narcolepsy typically do not need blood samples taken.
  - Before dosing
  - 10, 20, and 30 minutes after dosing
  - 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, and 14 hours after dosing

Blood collection schedule



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- The researchers compared the blood samples from the participants after taking both versions of SXB to see how their bodies processed the 2 medications.
- Researchers looked at the following:

Highest amount of SXB in the blood, also called **C_{max}**

Total amount of SXB in the blood, also called the area under the curve or **AUC** for short

Amount of SXB in the blood 8 hours after taking the medicine, also called **C_{8h}**

Time it takes to reach the highest amount of SXB in the blood, also called **T_{max}**

- C_{max} and C_{8h} were measured in micrograms per milliliter (also called mcg/ml)
- AUC was measured in micrograms per hour per milliliter to measure the amount of medicine in the blood over time (also called mcg·h/ml).
- T_{max} was measured in hours.
- Next, researchers wanted to know if ON-SXB circulates in the body at the same levels as TN-SXB. This comparison is known as bioequivalence.

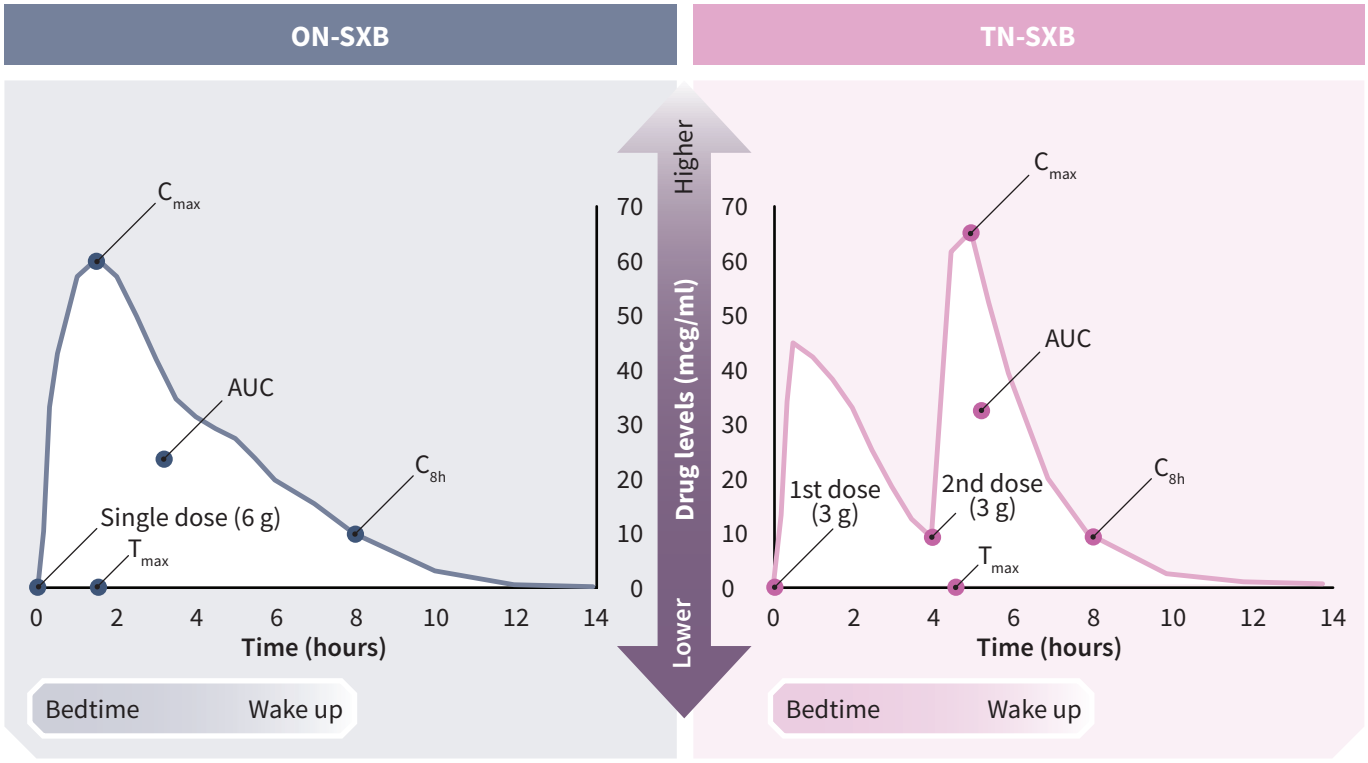
Does 1 dose of ON-SXB equal 2 doses of TN-SXB?

ON-SXB		TN-SXB		
Only 1 dose: taken at bedtime	=	**Dose 1:** taken at bedtime	+	**Dose 2:** taken in the middle of the night

- Lastly, researchers measured the side effects. Side effects are problems that a medicine can cause when a person takes it. Stomach aches, sleepiness, and headaches are examples of side effects.
  - Participants reported any side effects they had during the study and 2 to 4 days after taking the medicine.
  - The researchers who conducted the study also asked the participants questions about how they were feeling after they took the medicine. The researchers then decided if it was likely that the medicine caused the side effects.

What were the overall results of the study?

Average drug levels of SXB in participants over time



- With ON-SXB, the highest levels of the drug were reached around 1.5 hours after taking the single dose, and then drug levels slowly and gradually declined.
  - With TN-SXB, drug levels rapidly increased and then decreased after taking the first dose.
  - After the second dose, drug levels rapidly increased and were slightly higher in the middle of the night compared with the first peak.
    - The highest level of TN-SXB was reached about 5 hours after taking the first bedtime dose.

Highest amount of SXB in the blood

The highest amount of SXB in the blood after participants took one dose (6 g) of ON-SXB was 63 mcg/ml

63 mcg/ml

71 mcg/ml

The highest amount of SXB in the blood after participants took two doses (3 g each) of TN-SXB was 71 mcg/ml

- With both ON-SXB and TN-SXB, the highest amount of SXB in the blood was about the same. This means that whether patients take 2 doses of TN-SXB (3 g each) or 1 dose of ON-SXB (6 g), they will have about the same amount of SXB in their blood.

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Total amount of SXB in the blood from the time SXB was taken until it completely left the body

The total amount of SXB in the blood from the time one dose (6 g) of ON-SXB was taken until it completely left the body was 242 mcg·h/ml

The total amount of SXB in the blood from the time the first of the two doses (3 g each) of TN-SXB was taken until it completely left the body was 235 mcg·h/ml

- The total amount of SXB that enters the blood per night was about the same with ON-SXB and TN-SXB. This means that people who take ON-SXB are likely to experience similar effects as those who take the same dose of TN-SXB.

Amount of SXB in the blood 8 hours after taking the medicine

The amount of SXB in the blood 8 hours after participants took one dose (6 g) of ON-SXB was 2.3 mcg/ml

The amount of SXB in the blood 8 hours after participants took the first of the two doses (3 g each) of TN-SXB was 3.7 mcg/ml

- ON-SXB was in the body in the same amounts as TN-SXB, which means that the 2 medications are bioequivalent.
- 8 hours after taking SXB, the amount of SXB in the blood was significantly lower with ON-SXB compared with TN-SXB. This means that ON-SXB could lead to less sleepiness or grogginess the next day after waking up.

What were the most common side effects?

- The most common side effect reported after taking ON-SXB was feeling sick to one's stomach, also known as nausea.
- The most common side effects reported by participants after taking ON-SXB or TN-SXB in the study were the following:

Side effect		One dose of ON-SXB (6 g)	Two doses of TN-SXB (3 g each)
	Nausea	29%	11%
	Dizziness	25%	25%
	Feeling sleepy (somnolence)	11%	14%
	Throwing up (vomiting)	11%	11%
	Headache	7%	7%
	Feeling like you are spinning (vertigo)	4%	4%
	Feeling hot	4%	4%
	Unclear speech (dysarthria)	4%	4%
	Feeling low energy (lethargy)	4%	4%
	Disrupted breathing during sleep (apnea)	4%	4%

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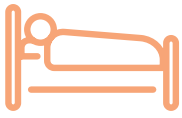
What do the results of this study mean?

ON-SXB is processed in the body of healthy volunteers the same way as TN-SXB.

People with narcolepsy will receive approximately the same amount of SXB whether they take 1 dose of ON-SXB 6 g or 2 doses of TN-SXB 3 g taken 4 hours apart.



ON-SXB helps people sleep in a way that is closer to natural sleep patterns because people do not need to wake up to take the medication in the middle of the night. This may improve quality of life.

Eight hours after taking the bedtime dose, the amount of medicine in the blood was lower with ON-SXB compared with TN-SXB, which could lead to less sleepiness or grogginess the next day after waking up.

Some side effects in this study of healthy volunteers were found at different rates than studies of SXB in people with narcolepsy (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf). It is important to speak with your doctor about potential side effects of medications if you are considering treatment.

ON-SXB provides an option for people with narcolepsy to take their medicine once at bedtime without the need for a middle-of-the-night dose.

Where can readers find more information on this study?

The original article is titled "Randomized, crossover, open-label study of the relative bioavailability and safety of FT218, a once-nightly sodium oxybate formulation: Phase 1 study in healthy volunteers." It was published in *Sleep Medicine* in 2022. The article is free to access at the following link: https://pubmed.ncbi.nlm.nih.gov/36252412/

Results from a study called REST-ON have already been published. REST-ON was a clinical study that looked at whether ON-SXB was better than a substitute that had no medicine in it (called a placebo). The main results from the REST-ON study in the article titled "Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy" were published in *Sleep* in 2022. A plain language summary of that article was published in the journal *Future Neurology* in 2022. The articles are free to access at the links below:

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

You can find more information about narcolepsy at the websites below:

- https://www.ninds.nih.gov/health-information/disorders/narcolepsy
- https://project-sleep.com/
- https://narcolepsynetwork.org/
- https://www.narcolepsydisrupts.com/ (website funded by Avadel Pharmaceuticals, Chesterfield, MO, USA)

Financial disclosure

Avadel Pharmaceuticals funded the study and provided the medication.

Competing interests disclosure

R Bogan is a shareholder in WaterMark Medical and Healthy Humming, LLC; serves on the board of directors for WaterMark Medical; is a consultant for Jazz Pharmaceuticals, Takeda Pharmaceutical Co., Avadel Pharmaceuticals, and Oventus; has received industry-funded research from Avadel Pharmaceuticals, BresoTec, Bayer, Idorsia, Suven Life Sciences Ltd., Jazz Pharmaceuticals, Balance, Vanda, Merck & Co., Eisai, Philips, FRESCA Medical, Takeda Pharmaceutical Co., LivaNova, Roche, and Sommetrics; and has served on speakers bureaus for Jazz Pharmaceuticals, Eisai, and Harmony Biosciences. M Thorpy has served as a consultant or on advisory boards for Axsome Therapeutics, Balance Therapeutics, Eisai, Avadel Pharmaceuticals, Harmony Biosciences, Jazz Pharmaceuticals, NLS Pharmaceuticals, Suven Life Sciences Ltd., and Takeda Pharmaceutical Co. S Berkowitz is a person with narcolepsy who has personal experience with both ON-SXB and TN-SXB and has received compensation from Avadel Pharmaceuticals as a LUMRYZ™ ambassador. J Gudeman is an employee of Avadel Pharmaceuticals.

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Writing disclosure

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