Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Improvements in daytime sleepiness and disrupted nighttime sleep with once-nightly sodium oxybate in people with narcolepsy type 1 and type 2: 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 *Sleep*. Narcolepsy is a sleep condition that has 2 different subtypes: narcolepsy type 1 and narcolepsy type 2. These are called NT1 and NT2 for short.

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

Cataplexy: KAT-uh-plek-see
Narcolepsy: NAAR-kuh-lep-see
Sodium oxybate: SOH-dee-um AAK-see-bayt

Sodium oxybate (SXB) is approved to treat excessive daytime sleepiness (EDS) and cataplexy. People with NT1 and NT2 both have EDS, but cataplexy is only present in people with NT1. Limited information is available about how SXB works in people with NT2. This is because previous trials have included only people with NT1 or people with unspecified narcolepsy. For more than 20 years, the only available formulation of this medicine had to be given twice during the night. Many people with narcolepsy find that chronically waking up in the middle of the night for a second dose of SXB is disruptive to themselves or others in their household. People have also reported sleeping through alarm clocks, missing their second dose, and feeling worse the next day. Some people have accidentally taken the second dose too early, putting them at risk for serious adverse effects. These adverse effects may include slow breathing, low blood pressure, or sedation. The US Food and Drug Administration (FDA) approved a medicine called LUMRYZ™ (sodium oxybate) for extended-release oral suspension in May 2023. LUMRYZ is a once-nightly formulation of SXB (ON-SXB for short) and is taken as a single dose before bedtime. This medicine treats EDS and muscle weakness (also known as cataplexy) in people with narcolepsy.

A clinical trial called REST-ON studied ON-SXB to find out if it was better at treating narcolepsy symptoms than a medicine with no active ingredients (placebo). This summary describes a study that tested whether ON-SXB was better than placebo at treating narcolepsy symptoms in people with NT1 or NT2.

What were the results?

This study showed that compared to people who took placebo, people who took ON-SXB were able to stay awake longer during the day, felt less sleepy during the daytime, had less cataplexy, and had more improvements in their symptoms overall than people who took placebo.

What do the results mean?

ON-SXB has been proven effective for people with NT1 or NT2. Unlike prior formulations of SXB, ON-SXB is taken once at bedtime, without requiring waking up in the middle of the night for a second dose.

Becaris PUBLISHING

Who is this article for?

This summary is written to help people with narcolepsy, their families, their caregivers, and healthcare professionals understand how ON-SXB can be used to treat their symptoms.

Who sponsored this study?

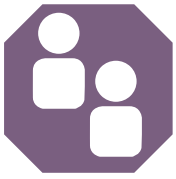
Avadel Pharmaceuticals supported this work.

What is narcolepsy?

Narcolepsy is a rare and long-term sleep condition

People with narcolepsy (PWN for short) feel **extreme sleepiness** during the day

Some individuals may have sudden muscle weakness called cataplexy



There are **two** types of narcolepsy

- People with narcolepsy type 1 (**NT1** for short) have cataplexy and people with narcolepsy type 2 (**NT2** for short) do not have cataplexy

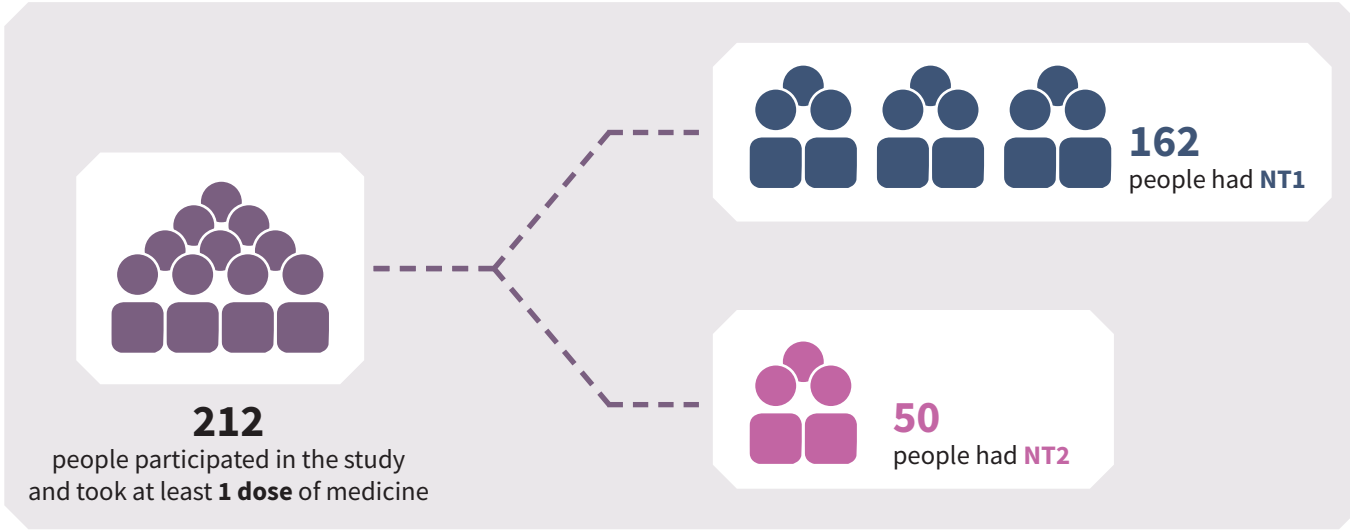
- People who have **NT1** do not have a chemical messenger in the brain called orexin or hypocretin
- Orexin/hypocretin helps control when a person is awake and asleep
- People who have **NT2** typically have normal levels of orexin/hypocretin

People may also have **difficulty sleeping** and have **paralysis** and/or **hallucinations** while falling asleep or waking up

Why was the study carried out?

- Sodium oxybate is a treatment option for narcolepsy.
- In the past, this medicine required a dose before bedtime and a dose 2.5 to 4 hours later.
- A formulation of sodium oxybate called LUMRYZ (ON-SXB for short) requires just 1 dose before bedtime.
- The REST-ON trial studied ON-SXB in people with NT1 or NT2.
  - The aim of the study was to see if ON-SXB improved narcolepsy symptoms compared to medicine with no active ingredients (placebo).
  - More people with NT1 than people with NT2 took part because a goal of the study was to understand how ON-SXB reduces cataplexy, which is only seen in NT1.
  - The study showed that people who took ON-SXB felt less sleepy during the day and had less cataplexy than people who took placebo.
- This summary looks at whether ON-SXB was better than placebo at treating symptoms of narcolepsy in people with NT1 and NT2.

Who took part in the study?



On average, people in the study were 31 years old

People with **NT1** were
31 years old
on average

People with **NT2** were
28 years old
on average

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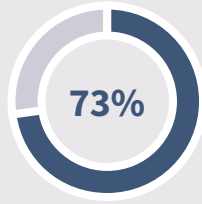
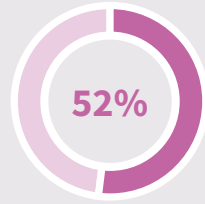
The majority of participants were **female**

Around three-quarters (**73%**) of the people with **NT1**

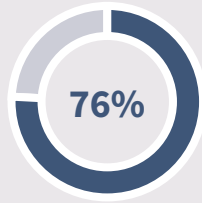


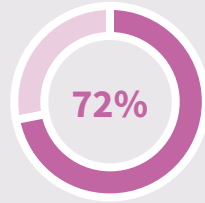


Around half (**52%**) of the people with **NT2**

Around three-quarters of the participants were **White**

76% of the people with **NT1**

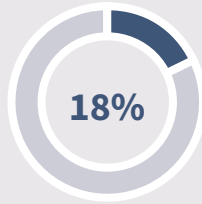


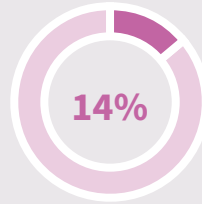


72% of the people with **NT2**

About 1 in 6 participants were **Black/African American**

18% of the people with **NT1**

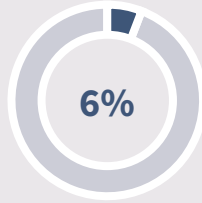


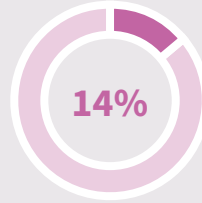


14% of the people with **NT2**

Almost 8% of the participants were **Asian or another race**

6% of the people with **NT1**

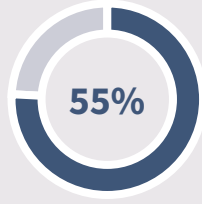


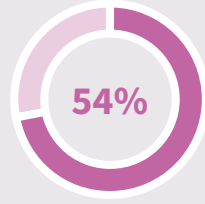


14% of the people with **NT2**

Just over half of the participants lived in the **United States**

55% of the people with **NT1**





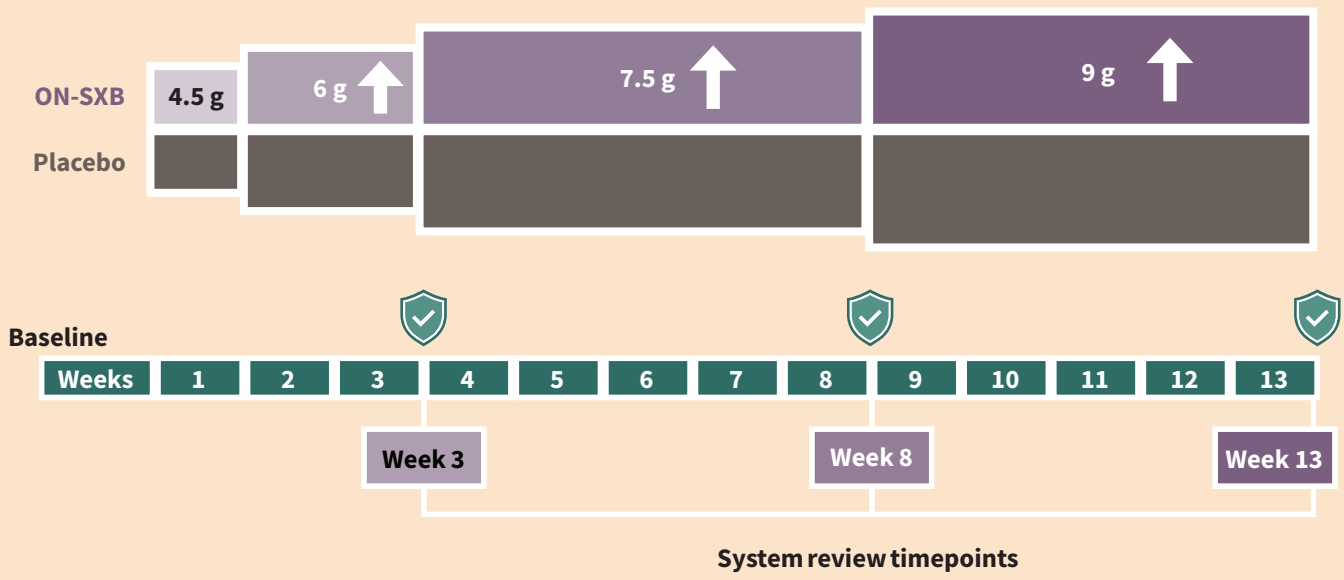
54% of the people with **NT2**

Other participants lived in Australia, Canada, Czech Republic, Denmark, Finland, France, Germany, The Netherlands, Switzerland or the United Kingdom

How was the study carried out?

- The REST-ON study was 13 weeks long. People in the study were randomly selected to take either ON-SXB or placebo. Neither the people in the study nor the researchers knew if they were taking ON-SXB or placebo. This is called a double-blind study design.
- About half of the people took ON-SXB and the other half took placebo. The dose of the study treatment was increased over the course of the study.
- People in the study took ON-SXB or placebo once per night at bedtime for 13 weeks.
- The researchers reviewed their narcolepsy symptoms at the start of the study (baseline) and at 3 timepoints during the study: week 3, week 8, and week 13.

People took the following doses once every night at bedtime:



The figure is taken from Kushida *et al. Sleep*. 2022;45(6):zsab200.

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- The researchers used different tests to find out if ON-SXB improved narcolepsy symptoms in people with NT1 or NT2 compared with placebo:

Maintenance of Wakefulness Test	Clinical Global Impression of Improvement
The average number of minutes a participant can stay awake while sitting quietly in a dark room	A study doctor rates the improvement of a participant's sleepiness on a scale of 1 (very much improved) to 7 (very much worse)

Epworth Sleepiness Scale

Participants rate their likelihood of falling asleep during 8 different activities on a scale from 0 (never) to 3 (high)

Number of Sleep Stage Shifts

An overnight test called polysomnography (PSG for short) that measures the number of sleep stage changes

- Sleep can be classified into five stages: wake, N1, N2, N3, and rapid eye movement (REM for short)
- For people without narcolepsy, sleep progresses through the night from light (N1) to deep sleep (N3) to REM sleep, which is when dreaming occurs
- PWN experience more frequent changes to light stages of sleep compared to people without narcolepsy
- This study measured the number of changes from light and deep sleep to waking up and from deeper stages of sleep to light sleep

Number of Nocturnal Arousals

An overnight PSG test that measures the number of times a participant experiences an abrupt change from deeper to lighter stages of sleep or from sleep to waking up during nighttime sleep

Sleep Quality	Refreshing Nature of Sleep
Participants record their sleep quality on a scale from 1 (did not sleep) to 100 (slept very well)	Participants record how refreshed they feel after waking on a scale from 1 (not refreshed) to 100 (refreshed)

What were the overall results of the study?

Maintenance of Wakefulness Test: standard test of ability to stay awake

- Before receiving any medicine (also called baseline), people with NT1 or NT2 stayed awake for a similar amount of time.
- People who took ON-SXB stayed awake longer than people who took placebo at each timepoint of the study.
- At each study timepoint:
  - People with NT1 who took ON-SXB stayed awake for a similar amount of time as people with NT2 who took ON-SXB.
  - People with NT1 who took placebo stayed awake for a similar amount of time as people with NT2 who took placebo.

Baseline | **Week 3** | **Week 8** | **Week 13**

NT1

On average, people with **NT1** who took **ON-SXB** were able to stay awake for **5 minutes**.

ON–SXB

People who took **placebo** were able to stay awake for **4.7 minutes** on average.

Placebo

NT2

On average, people with **NT2** who took **ON-SXB** were able to stay awake for **5 minutes**.

ON–SXB

People who took **placebo** were able to stay awake for **4.9 minutes** on average.

Placebo

Baseline | **Week 3: ON-SXB 6 grams** | **Week 8** | **Week 13**

NT1

People who took **ON-SXB** were able to **stay awake about 8 minutes longer** from baseline on average.

People who took **placebo** were able to **stay awake about 3 minutes longer** from baseline on average

NT2

People who took **ON-SXB** were able to **stay awake about 8 minutes longer** from baseline on average.

People who took **placebo** were able to **stay awake about 2 minutes longer** from baseline on average

Baseline | **Week 3** | **Week 8: ON-SXB 7.5 grams** | **Week 13**

NT1

People who took **ON-SXB** were able to **stay awake about 10 minutes longer** from baseline on average.

People who took **placebo** were able to **stay awake about 3 minutes longer** from baseline on average

NT2

People who took **ON-SXB** were able to **stay awake about 8 minutes longer** from baseline on average.

People who took **placebo** were able to **stay awake about 4 minutes longer** from baseline on average

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Baseline | Week 3 | Week 8 | **Week 13: ON-SXB 9 grams**

NT1	NT2
People who took **ON-SXB** were able to **stay awake about 11 minutes longer** from baseline on average.	People who took **ON-SXB** were able to **stay awake about 10 minutes longer** from baseline on average.
People who took **placebo** were able to **stay awake about 5 minutes longer** from baseline on average	People who took **placebo** were able to **stay awake about 3 minutes longer** from baseline on average

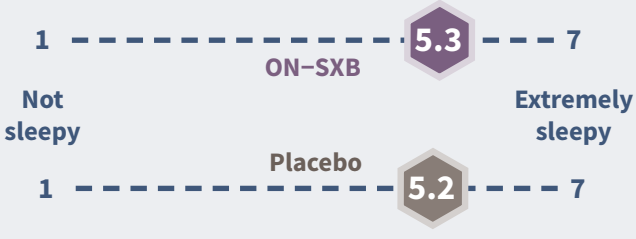
Most of these results are statistically significant. This means that it is likely that these results are due to ON-SXB treatment and not due to chance.

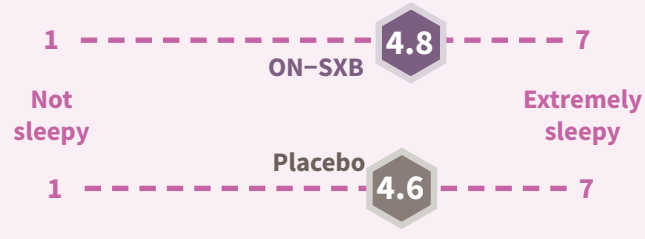
Clinical Global Impression of Improvement: standard test of disease severity

- At baseline, people with NT1 or NT2 who were taking ON-SXB or placebo had generally similar scores on the Clinical Global Impression of Severity scale.
  - The researchers then looked at the percentage of people whose scores on the scale were "much" or "very much" improved compared to their baseline score.
- A higher percentage of people who took ON-SXB were "much" or "very much" improved from baseline compared with people who took placebo.
- At weeks 8 and 13, a higher percentage of people with NT1 who took ON-SXB were "much" or "very much" improved from baseline compared with people with NT2 who took ON-SXB.
- At all study timepoints, a higher percentage of people with NT1 who took placebo were "much" or "very much" improved from baseline compared with people with NT2 who took placebo.

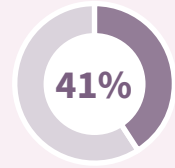
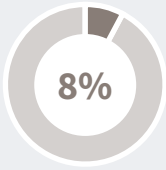
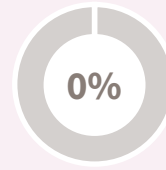
Baseline | Week 3 | Week 8 | Week 13

NT1	NT2
The average score of people with **NT1** who took **ON–SXB** was **5.3**. People who took **placebo** had an average score of **5.2**.	The average score of people with **NT2** who took **ON–SXB** was **4.8**. People who took **placebo** had an average score of **4.6**.

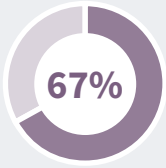
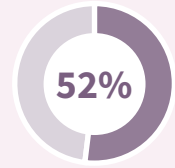
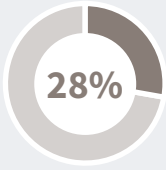
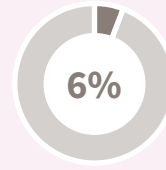




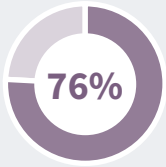
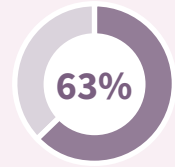
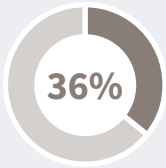
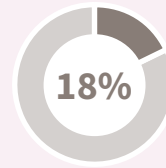
Baseline | **Week 3: ON-SXB 6 grams** | Week 8 | Week 13

NT1	NT2
 **40%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline	**41%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline 
 **8%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline	**0%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline 

Baseline | Week 3 | **Week 8: ON-SXB 7.5 grams** | Week 13

NT1	NT2
 **67%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline	**52%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline 
 **28%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline	**6%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline 

Baseline | Week 3 | Week 8 | **Week 13: ON-SXB 9 grams**

NT1	NT2
 **76%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline	**63%** of people who took **ON-SXB** were "**much**" or "**very much**" improved from baseline 
 **36%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline	**18%** of people who took **placebo** were "**much**" or "**very much**" improved from baseline 

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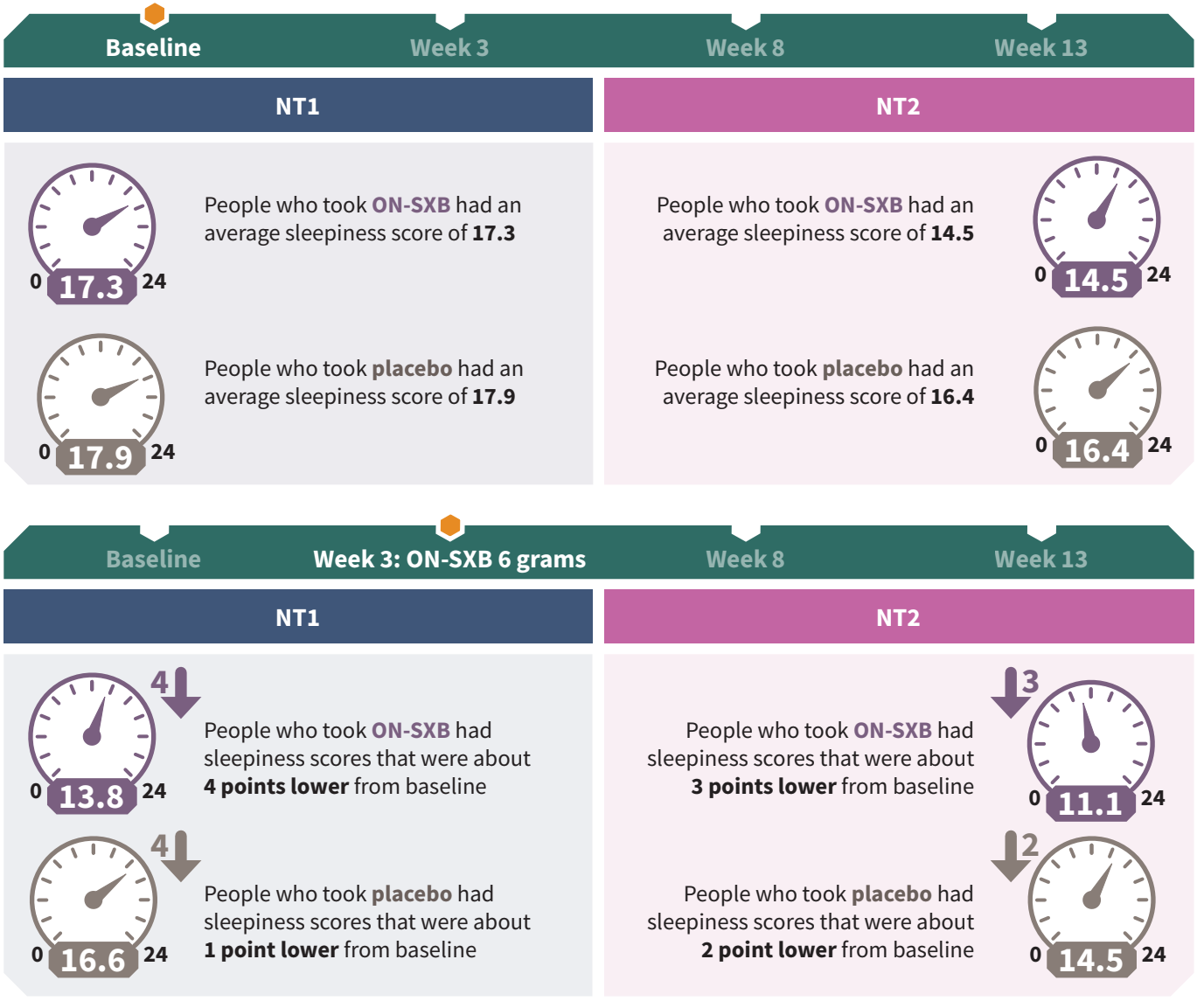
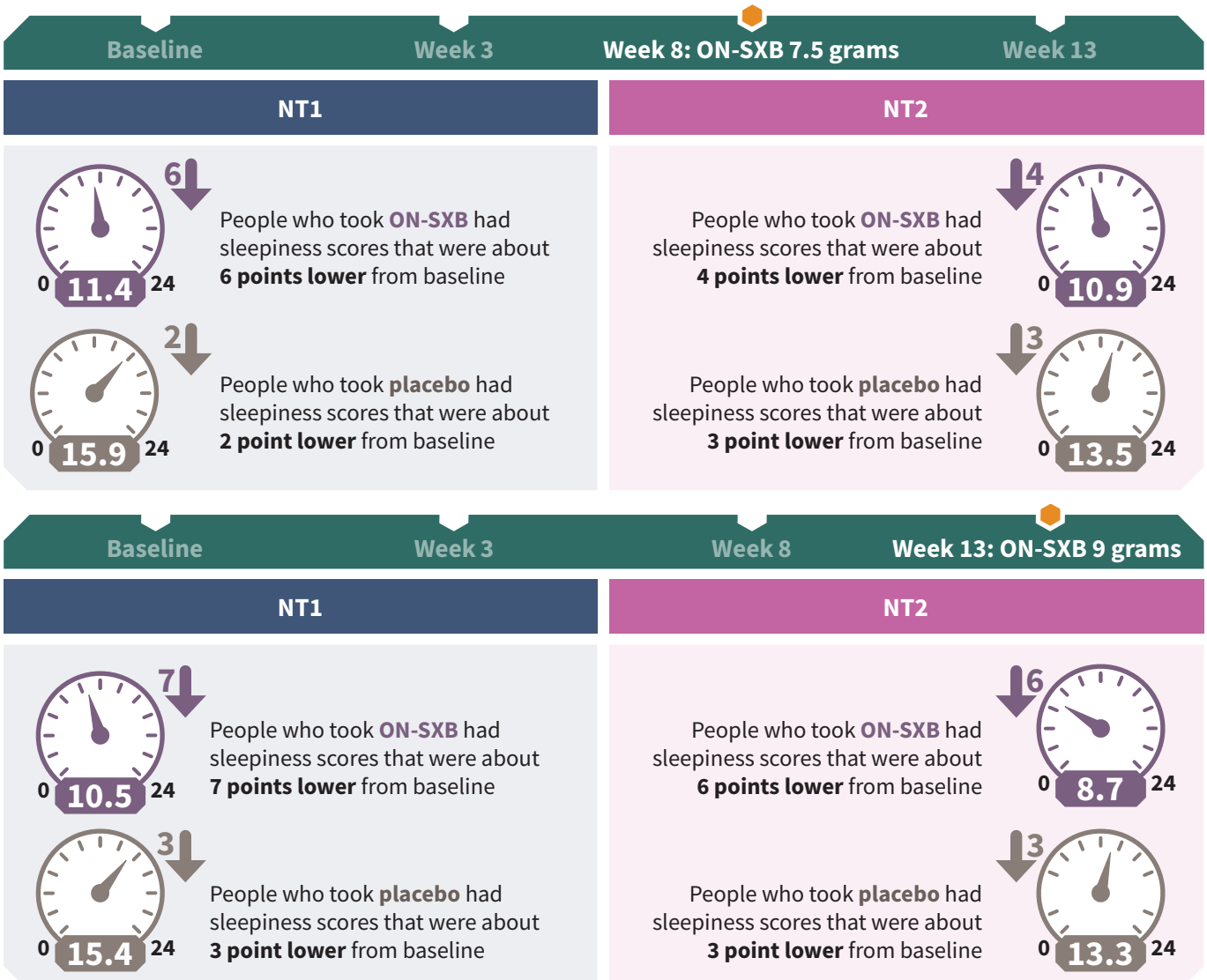
All these results are statistically significant for the NT1 group. This means that it is likely that these results are due to ON-SXB treatment and not due to chance. These results are not statistically significant for the NT2 group. This may be because there were fewer people in the NT2 group than the NT1 group.

Epworth Sleepiness Scale: standard test for sleepiness (tendency to fall asleep during activities of daily living)

- At baseline, people in the ON-SXB and placebo groups with NT1 or NT2 had generally similar ratings of sleepiness.
- Throughout the study, people who took ON-SXB had larger decreases in sleepiness score from baseline compared with people who took placebo.
- At each study timepoint:
  - People with NT1 who took ON-SXB had similar decreases from baseline in sleepiness score compared with people with NT2 who took ON-SXB.
  - People with NT1 who took placebo had similar decreases from baseline in sleepiness score compared with people with NT2 who took ON-SXB.





All results for people with NT1 were statistically significant. This means that it is likely that these results are due to ON-SXB treatment and not due to chance.

Similar improvements in sleepiness were seen in people with NT1 and NT2. However, these results were not statistically significant for the NT2 group. This is likely due to the low number of people in the NT2 group, which may have prevented researchers from seeing the true effect of ON-SXB.

Number of Sleep Stage Shifts: a measure of sleep stability

- At baseline, people in the ON-SXB and placebo groups with NT1 or NT2 had generally similar numbers of sleep stage shifts per night.
  - Fewer sleep stage shifts means individuals will have better quality of sleep
- People who took ON-SXB had more reductions in sleep stage shifts from baseline compared with people who took placebo.
- People with NT1 who took ON-SXB had a similar number of reductions in sleep stage shifts from baseline at weeks 3, 8, and 13 compared with people with NT2 who took ON-SXB.
- People with NT1 who took placebo had a similar number of reductions in sleep stage shifts from baseline at weeks 3 and 13 compared with people with NT2 who took placebo.

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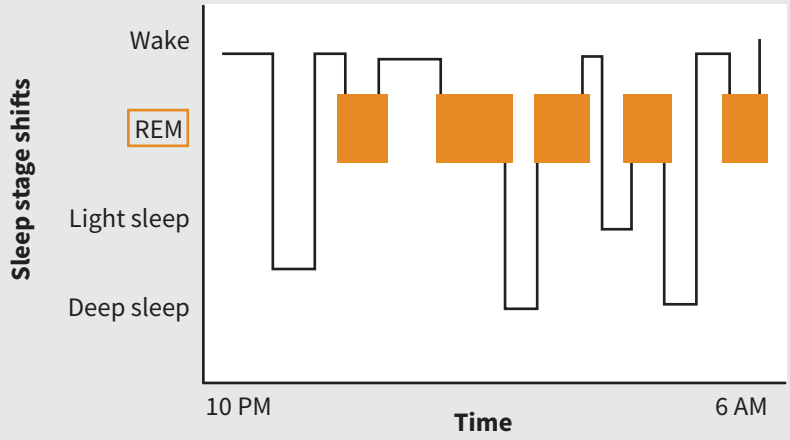
Baseline | **Week 3** | **Week 8** | **Week 13**

NT1

People who took **ON-SXB** had an average of **62.1** sleep stage shifts

People who took **placebo** had an average of **60.9** sleep stage shifts



NT2

People who took **ON-SXB** had an average of **53.9** sleep stage shifts

People who took **placebo** had an average of **58.0** sleep stage shifts

People shift between light and deep stages of sleep throughout the night, as shown in the above graph

Baseline | **Week 3: ON-SXB 6 grams** | **Week 8** | **Week 13**

NT1

10 People who took **ON-SXB** had **10 fewer** sleep stage shifts from baseline

1 People who took **placebo** had about **1 more** sleep stage shift from baseline

NT2

People who took **ON-SXB** had **10 fewer** sleep stage shifts from baseline 10

People who took **placebo** had about **2 more** sleep stage shift from baseline 2

Baseline | **Week 3** | **Week 8: ON-SXB 7.5 grams** | **Week 13**

NT1

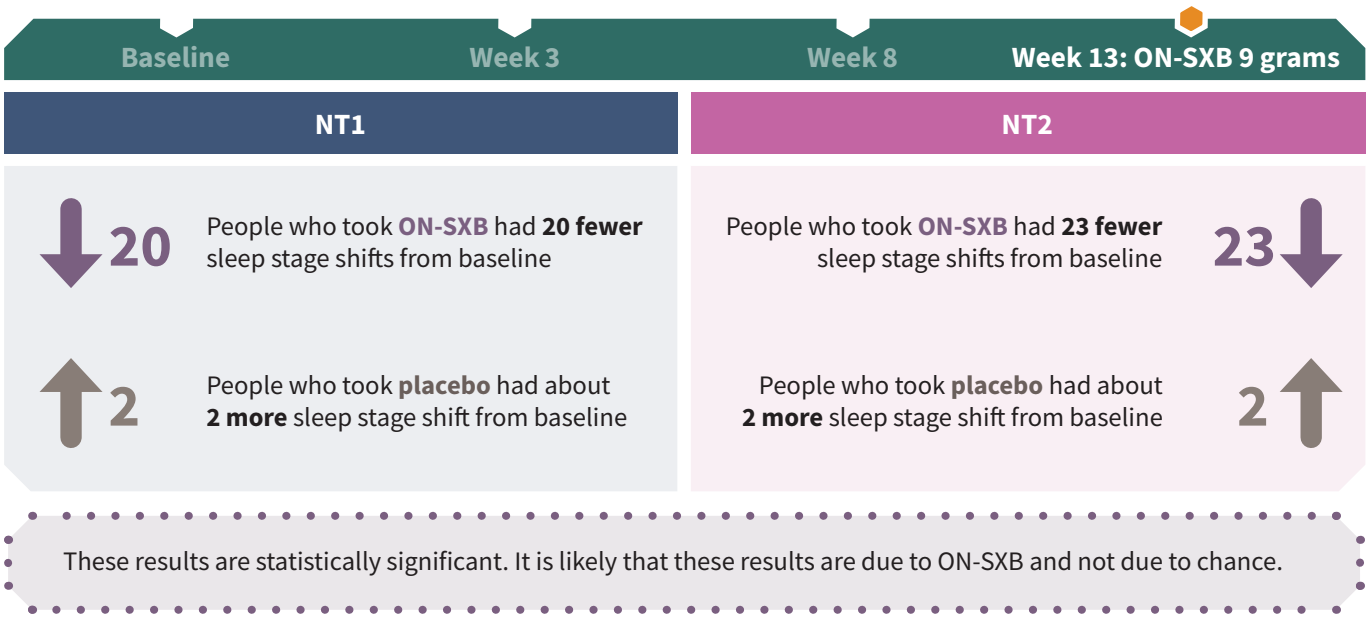
16 People who took **ON-SXB** had **16 fewer** sleep stage shifts from baseline

1 People who took **placebo** had about **1 more** sleep stage shift from baseline

NT2

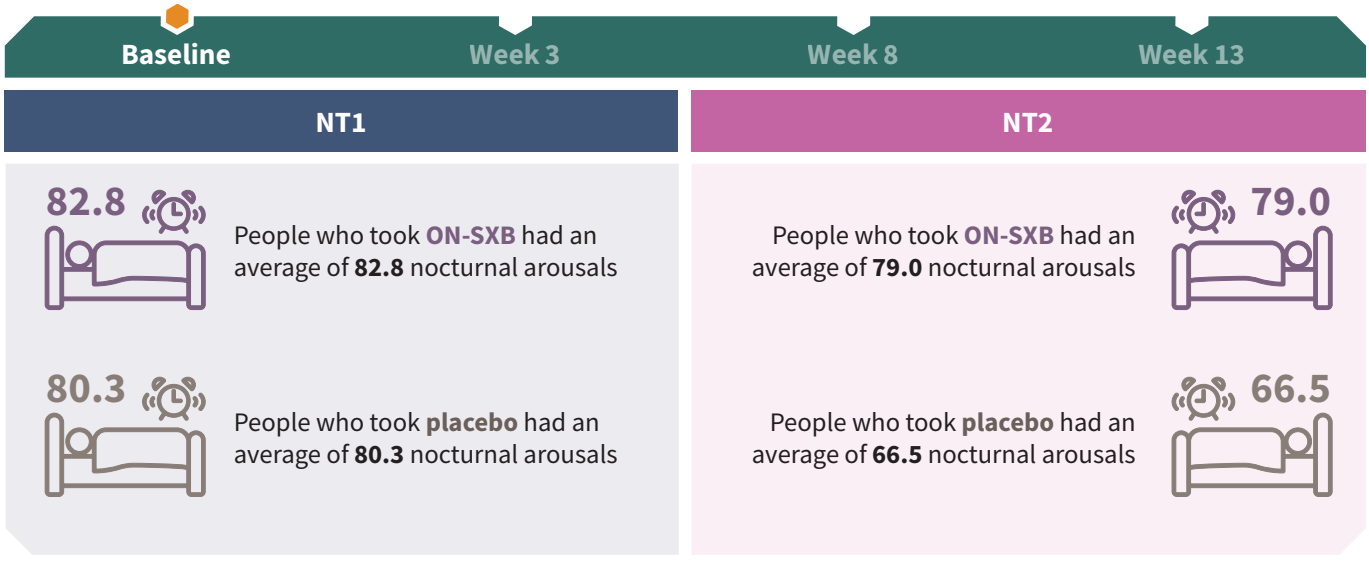
People who took **ON-SXB** had **13 fewer** sleep stage shifts from baseline 13

People who took **placebo** had about **8 more** sleep stage shift from baseline 8



Number of Nocturnal Arousals: test to measure changes from deep to light sleep

- At baseline, the average number of nocturnal arousals was generally similar between people in the ON-SXB or placebo groups with NT1 or NT2.
  - Fewer nocturnal arousals means individuals will have better sleep quality because PWN have more frequent nocturnal arousals compared with people who do not have narcolepsy.
- People who took ON-SXB had fewer nocturnal arousals compared with people who took placebo at weeks 3, 8, and 13.
- People with NT1 who took ON-SXB had a similar number of reductions from baseline in nocturnal arousals at weeks 3 and 8 compared with people with NT2 who took ON-SXB.
- People with NT1 who took placebo had a similar number of reductions from baseline in nocturnal arousals at week 8 compared with people with NT2 who took placebo.



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Baseline | **Week 3: ON-SXB 6 grams** | Week 8 | Week 13

NT1	NT2
People who took **ON-SXB** had about **31 fewer** nocturnal arousals from baseline	People who took **ON-SXB** had about **32 fewer** nocturnal arousals from baseline
People who took **placebo** had about **19 fewer** nocturnal arousals from baseline	People who took **placebo** had about **26 fewer** nocturnal arousals from baseline

Baseline | Week 3 | **Week 8: ON-SXB 7.5 grams** | Week 13

NT1	NT2
People who took **ON-SXB** had about **39 fewer** nocturnal arousals from baseline	People who took **ON-SXB** had about **38 fewer** nocturnal arousals from baseline
People who took **placebo** had about **20 fewer** nocturnal arousals from baseline	People who took **placebo** had about **21 fewer** nocturnal arousals from baseline

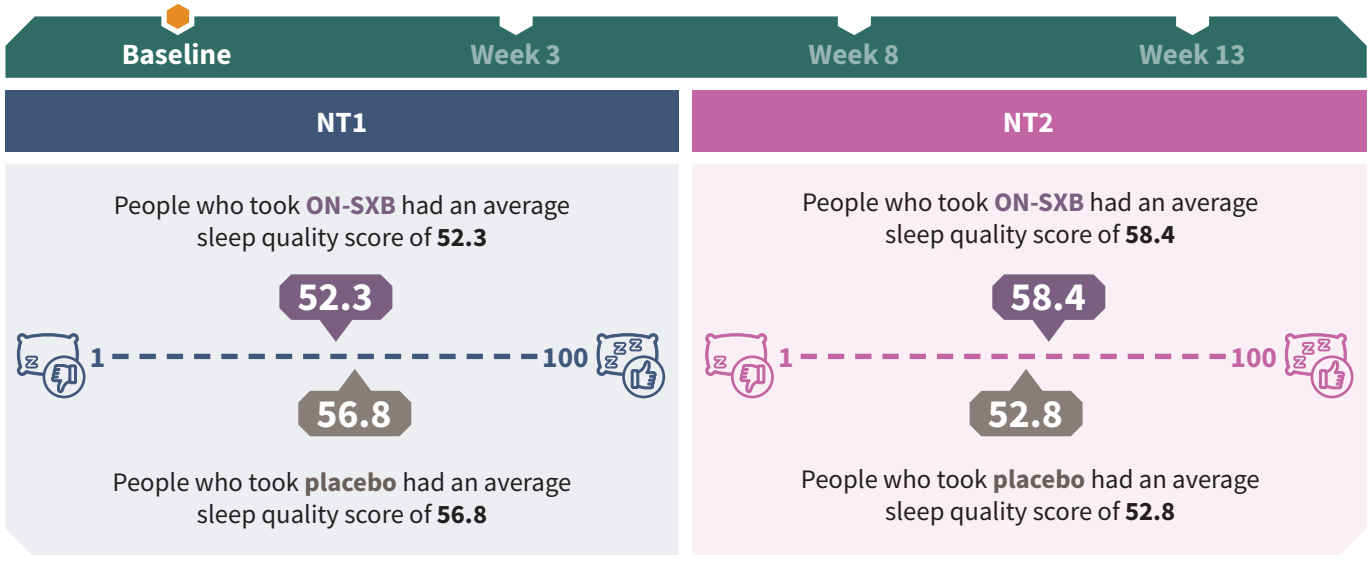
Baseline | Week 3 | Week 8 | **Week 13: ON-SXB 9 grams**

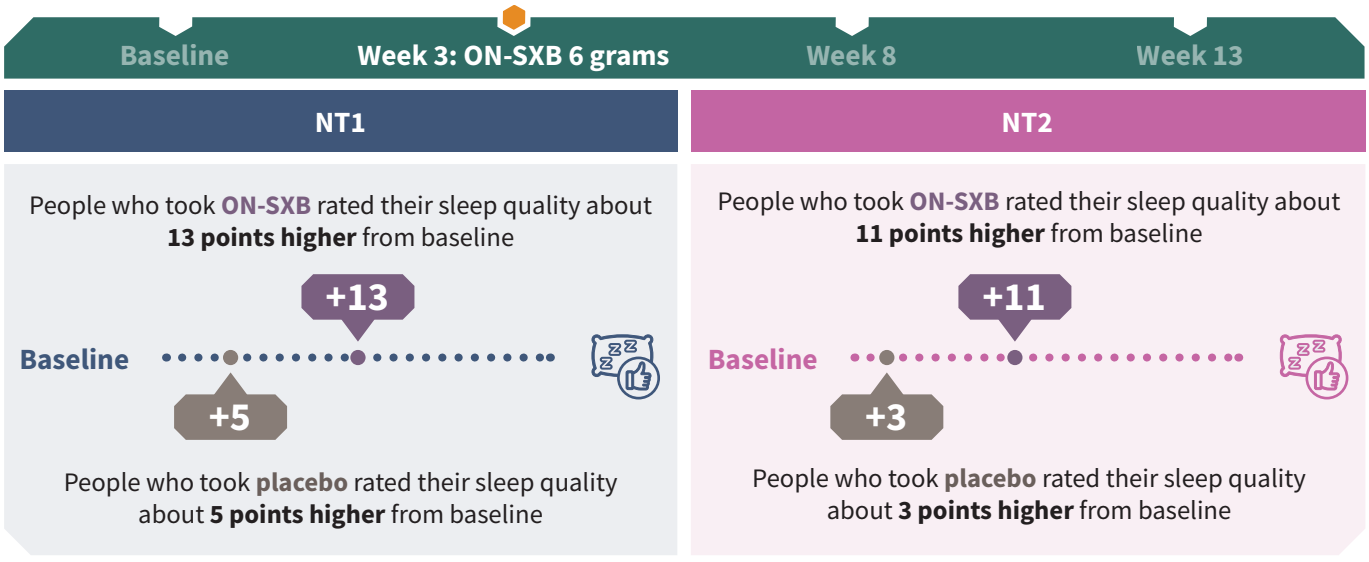
NT1	NT2
People who took **ON-SXB** had about **37 fewer** nocturnal arousals from baseline	People who took **ON-SXB** had about **45 fewer** nocturnal arousals from baseline
People who took **placebo** had about **14 fewer** nocturnal arousals from baseline	People who took **placebo** had about **25 fewer** nocturnal arousals from baseline

Most of these results are statistically significant. It is likely that these results are due to ON-SXB and not due to chance.

Sleep Quality: morning questionnaire completed by participants

- At baseline, people in the ON-SXB and placebo groups with NT1 or NT2 reported generally similar sleep quality scores.
- People who took ON-SXB rated their sleep quality higher than people who took placebo.
- People with NT1 who took ON-SXB had similar increases from baseline in sleep quality score compared with people with NT2 who took ON-SXB.
- People with NT1 who took placebo had similar increases from baseline in sleep quality scores compared with people with NT2 who took placebo.





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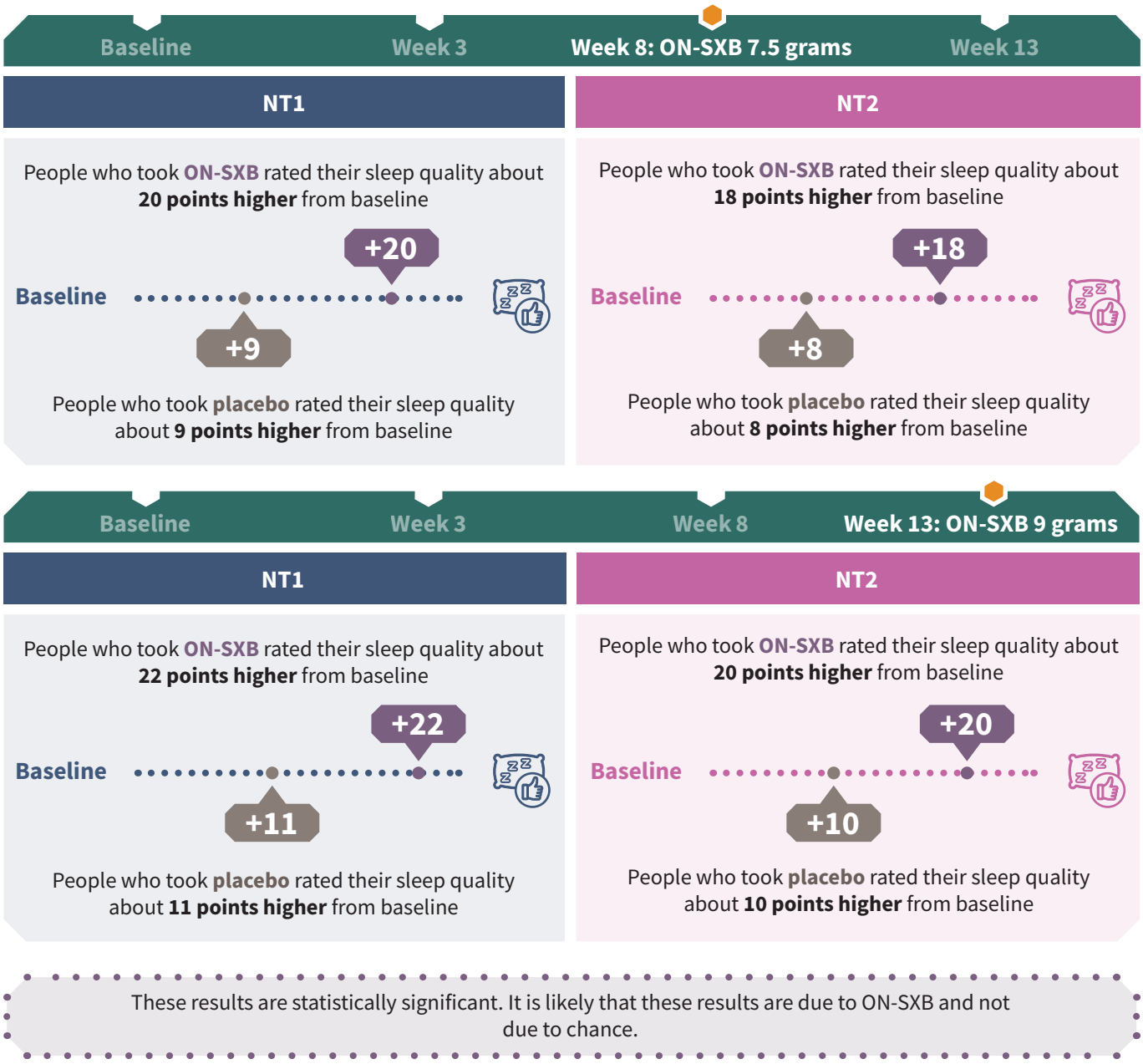


These results are statistically significant. It is likely that these results are due to ON-SXB and not due to chance.

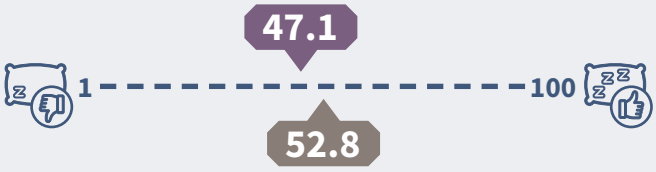
Refreshing Nature of Sleep: morning questionnaire completed by participants

- At baseline, people in the ON-SXB and placebo groups with NT1 or NT2 reported generally similar scores for the refreshing nature of their sleep.
- People who took ON-SXB rated their sleep as more refreshing compared with people who took placebo.
- People with NT1 who took ON-SXB had similar increases in the refreshing nature of their sleep from baseline at weeks 3, 8, and 13 compared with people with NT2 who took ON-SXB.
- People with NT1 who took placebo had similar increases in the refreshing nature of their sleep from baseline at weeks 3, 8, and 13 compared with people with NT2 who took placebo.

Baseline | Week 3 | Week 8 | Week 13

NT1

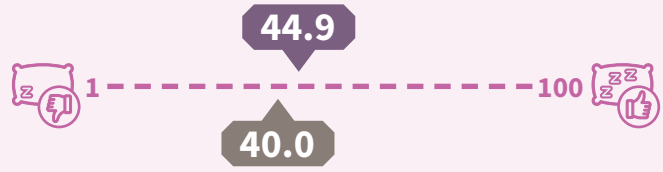
People who took **ON-SXB** had an average refreshing nature of sleep score of **47.1**



People who took **placebo** had an average refreshing nature of sleep score of **52.8**

NT2

People who took **ON-SXB** had an average refreshing nature of sleep score of **44.9**

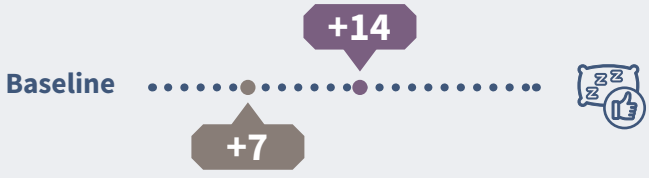


People who took **placebo** had an average refreshing nature of sleep score of **40.0**

Baseline | **Week 3: ON-SXB 6 grams** | Week 8 | Week 13

NT1

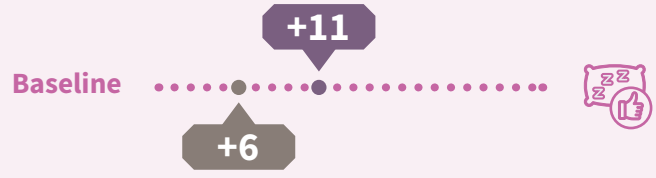
People who took **ON-SXB** rated their refreshing nature of sleep about **14 points higher** from baseline



People who took **placebo** rated their refreshing nature of sleep about **7 points higher** from baseline

NT2

People who took **ON-SXB** rated their refreshing nature of sleep about **11 points higher** from baseline

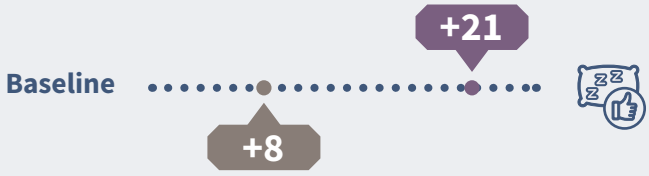


People who took **placebo** rated their refreshing nature of sleep about **6 points higher** from baseline

Baseline | Week 3 | **Week 8: ON-SXB 7.5 grams** | Week 13

NT1

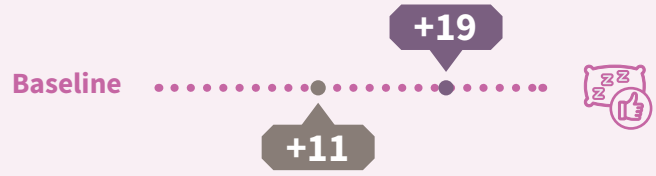
People who took **ON-SXB** rated their refreshing nature of sleep about **21 points higher** from baseline



People who took **placebo** rated their refreshing nature of sleep about **8 points higher** from baseline

NT2

People who took **ON-SXB** rated their refreshing nature of sleep about **19 points higher** from baseline



People who took **placebo** rated their refreshing nature of sleep about **11 points higher** from baseline

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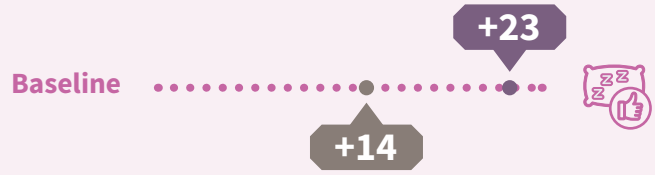
NT1

People who took **ON-SXB** rated their refreshing nature of sleep about **24 points higher** from baseline

People who took **placebo** rated their refreshing nature of sleep about **12 points higher** from baseline

NT2

People who took **ON-SXB** rated their refreshing nature of sleep about **23 points higher** from baseline



People who took **placebo** rated their refreshing nature of sleep about **14 points higher** from baseline

All results for NT1 were statistically significant. It is likely that these results are due to ON-SXB and not due to chance.

What were the most common side effects?

The most common side effects reported by people in the study were:

Side effect		Nausea	Vomiting	Bed-wetting	Dizziness	Headache	Decreased appetite	Anxiety	Weight loss	Drowsiness
Placebo		3%	2%	0%	0%	6%	0%	1%	0%	1%
ON-SXB dose	4.5 grams (week 1)	6%	3%	2%	6%	7%	4%	3%	1%	0%
	6 grams (weeks 2–3)	8%	3%	4%	4%	5%	4%	0%	0%	1%
	7.5 grams (weeks 4–9)	7%	6%	9%	6%	6%	3%	3%	0%	2%
	9 grams (weeks 9–13)	1%	5%	9%	5%	0%	3%	1%	4%	4%

Some people stopped the study early due to a side effect:

- 23 people who took ON-SXB stopped the study early
- 3 people who took placebo stopped the study early

What do the results of the study mean?

- Across all people in the study, those who took ON-SXB stayed awake longer, had fewer sleep stage shifts and nocturnal arousals, and had better sleep quality compared to people who took placebo.
- More people with NT1 who took ON-SXB were rated "much" or "very much" improved on the Clinical Global Impression of Improvement, reported more refreshing sleep, and reported less sleepiness compared to people with NT1 who took placebo.
- Because of the small number of people in the NT2 group, statistical significance was not reached for some of the tests in this study. This means that the results were more likely to be due to chance. However, these tests did show a trend that people with NT2 who took ON-SXB stayed awake longer, had less nocturnal arousals and sleepiness, and had more refreshing sleep compared to people with NT2 who took placebo.
- This study helps individuals with narcolepsy and their healthcare providers better understand how people with NT1 and NT2 respond to treatment with ON-SXB.

Where can readers find more information on this study?

The original article is titled "Efficacy of once-nightly sodium oxybate (FT218) in narcolepsy type 1 and type 2: post hoc analysis from the Phase 3 REST-ON Trial." It was published in *Sleep* in 2023. The article is free to access. You may read it at the link below:

- https://pubmed.ncbi.nlm.nih.gov/37246913/

You can read about 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" published in *Sleep* in 2022. A plain language summary of that article was published in *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/
- https://project-sleep.com/
- https://narcolepsynetwork.org/
- https://www.narcolepsydisrupts.com/ (website funded by Avadel Pharmaceuticals, Chesterfield, MO, USA)

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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