Oveporexton for Narcolepsy: Effectiveness and Value

Final Report

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Prepared for

ICER Staff and Consultants	The University of Washington Modeling Group
Grace A. Lin, MD Medical Director for Health Technology Assessment Institute for Clinical and Economic Review **Dmitriy Nikitin, MSPH** Senior Research Lead Institute for Clinical and Economic Review **Woojung Lee, PharmD, PhD** Associate Director of Health Economics and Decision Modeling Institute for Clinical and Economic Review **Marie Phillips, BA** Health Economics Research Assistant Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Senior Vice President of Research Institute for Clinical and Economic Review	**Josh J. Carlson, PhD** Professor University of Washington, School of Pharmacy **Linda Luu, MS** Research Scientist University of Washington, School of Pharmacy **Hui-Hsuan Chan, MHS** Research Assistant University of Washington, School of Pharmacy The role of the University of Washington is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Washington.

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Grace Lin served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Sol Sanchez. Josh Carlson, Linda Luu, and Hui-Hsuan Chan developed the cost-effectiveness model and authored the corresponding sections of the report. Woojung Lee and Marie Phillips conducted analyses for the budget impact model. Foluso Agboola provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Temiwunmi Shobanke, Chloe Fandetti, and Anna Geiger for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the initial draft evidence report:

Expert Reviewers

Tammy Anderson
Executive Director
Wake Up Narcolepsy

Kiran Maski, MD, MPH
Associate Professor, Neurology
Boston Children's Hospital

Katherine Sharkey, MD, PhD
Professor of Psychiatry and Behavioral Medicine and of Internal Medicine
Wake Forest University School of Medicine

Sonya J Snedecor, PhD
Chief Simplicity Officer
Science Clarity

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit: https://icer.org/assessment/narcolepsy-2026

Conflict of Interest Disclosures for the Report

Table 1. ICER Authors and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Foluso Agboola, MBBS, MPH	No conflicts to disclose.
Josh Carlson, PhD, MPH	Josh Carlson has received consulting fees from Takeda that are not related to Narcolepsy.
Hui-Hsuan Chan, MHS	No conflicts to disclose.
Woojung Lee, PharmD, PhD	No conflicts to disclose.
Grace Lin, MD, MAS	Grace Lin receives research grant funding from the National Institutes of Health, Mt. Zion Health Fund, GRAIL, Inc., and the California Health Benefits Research Program.
Linda Luu, MSc	No conflicts to disclose.
Dmitriy Nikitin, MSPH	No conflicts to disclose.
Marie Phillips, BA	No conflicts to disclose.
Sol Sanchez, BA	No conflicts to disclose.

Table 2. Expert Reviewers of the Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Tammy Anderson **Executive Director** **Wake Up Narcolepsy**	Tammy Anderson is a full-time employee of Wake Up Narcolepsy. Wake Up Narcolepsy receives grants/sponsorships from Jazz Pharmaceuticals, Harmony Biosciences, Avadel, and Takeda Pharmaceuticals to support patient programming. These grants represent approximately 80% of the funding received through pharmaceutical grants/sponsorships for the most recent year.
Kiran Maski, MD, MPH **Associate Professor, Neurology** **Boston Children's Hospital**	Dr. Maski has received consulting fees from Alkermes, Avadel Pharmaceuticals, Harmony Biosciences, Jazz Pharmaceuticals, Takeda Pharmaceuticals, Taysha Gene Therapies, Synchronicity, Eisai as well as grant funding from Jazz Pharmaceuticals and Harmony Biosciences. Dr. Maski also received compensation for serving as chair of a drug safety monitoring board chair (DSMB) for Idorsia. and serves on the Medical Advisory Board for Wake Up Narcolepsy and the Hypersomnia Foundation. Wake Up Narcolepsy and the Hypersomnia Foundation receive funding from health care companies including Takeda Pharmaceuticals, Avadel Pharmaceuticals, Harmony Biosciences, and Jazz Pharmaceuticals.

Expert Reviewer	Conflict of Interest
Katherine Sharkey, MD, PhD **Professor of Psychiatry and Behavioral Medicine and of Internal Medicine** **Wake Forest University School of Medicine**	Dr. Sharkey is on the Expert Advisory Board for Project Sleep. An estimated 80-95% of Project Sleep's annual revenue comes from charitable contributions from corporations including health care companies Takeda Pharmaceuticals, Avadel Pharmaceuticals, Harmony Biosciences, and Jazz Pharmaceuticals with whom Project Sleep has corporate partnerships.
Sonya J Snedecor, PhD **Chief Simplicity Officer** **Science Clarity**	Dr. Snedecor has no conflicts to disclose.

This page includes conflict of interest disclosures for ICER staff, external collaborators, and expert reviewers of the report. For all public meeting participant disclosures, please refer to Supplement I.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

AASM	American Academy of Sleep Medicine
AEs	Adverse events
AIAN	American Indian or Alaskan Native
BID	Twice daily
BMI	Body mass index
BOCF	Baseline observation carried forward
CDR	Clinical Diversity Rating
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CUP	Compassionate use program
DNS	Disturbed nocturnal sleep
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EIT	Extended intention-to-treat
ESS	Epworth Sleepiness Scale
evLYs	Equal-value life years
HIDI	Health Improvement Distribution Index
HRQoL	Health-related quality of life
IQR	Interquartile range
ITT	Intention-to-treat
LOCF	Last observation carried forward
LTE	Long-term extension
LYs	Life years
mg	Milligram
MID	Minimally important difference
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
N	Number of participants
NA	Not applicable
NC	Not calculated
NHPI	Native Hawaiian or Pacific Islander
NIM	Noninferiority margin
NMA	network meta-analysis
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1	Narcolepsy type 1
OR	Odds ratio
PDUFA	Prescription Drug User Fee Act
PP	Per protocol
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
REM	Rapid eye movement
RR	Relative risk
SAEs	Serious adverse events
SART	Sustained Attention to Response Task
SD	Standard deviation
SOC	Standard of care

SOREMP	Sleep-onset REM period
TEAEs	Treatment-emergent adverse events
VAS	Visual analogue scale
WCR	Weekly cataplexy rate

Executive Summary

Narcolepsy is a rare, chronic neurological disorder characterized by disruptions in the sleep-wake cycle. It affects approximately one in 2,000 people in the United States (US),[1] and the onset is usually in adolescence or young adulthood.[2] The main symptoms of narcolepsy are excessive daytime sleepiness (EDS), disrupted nighttime sleep, hallucinations while falling asleep or waking up, and sleep paralysis. People living with narcolepsy type 1 (NT1) also experience cataplexy - the sudden loss of muscle tone triggered by strong emotions - and have low levels of the neurotransmitter orexin.[3]

Narcolepsy symptoms can severely impact all aspects of a person's daily life, including work, education, social activities, travel, family planning, as well as everyday activities such as driving, grocery shopping, and exercise. We heard that there is also a large caregiver impact, including financial, as people living with NT1 may have difficulty finishing their education or working enough to support themselves. Additionally, people living with NT1 are also more likely to have comorbid conditions such as sleep apnea, obesity, high blood pressure, depression, anxiety, and heart disease.[3] Consequently, annual direct medical costs are approximately twice as much as those without the disorder;[4] and studies also show higher short-term disability rates.[5]

Treatment of NT1 focuses on increasing wakefulness and preventing cataplexy episodes. Daytime naps and a consistent sleep schedule can help people manage narcolepsy symptoms. Pharmacological treatment focuses on improving wakefulness and preventing cataplexy. Wake-promoting agents such as modafinil, methylphenidate, and solriamfetol are used to treat EDS, but have no direct effect on cataplexy symptoms. Antidepressants are often used off-label to prevent cataplexy, and sodium oxybates and pitolisant treat both EDS and cataplexy. We heard from persons living with NT1 that polypharmacy is commonly required to address symptoms; however, the efficacy of current treatments can wear off over time, do not restore normal function, and can have substantial side effects. Oveporexton is a first-in-class oral orexin receptor 2 agonist that addresses the orexin deficiency that underlies NT1. It is under consideration for approval by the US Food and Drug Administration (FDA), with a decision expected in the third quarter of 2026.

Oveporexton was compared with no pharmacological treatment in two Phase III and one Phase II randomized, controlled trials of participants with NT1. Participants in the trials were, on average, in their 30s, and over half were female. Baseline narcolepsy symptom measures (Epworth Sleepiness Scale [ESS] and Maintenance of Wakefulness Test [MWT]) were indicative of severe excessive daytime sleepiness, and participants experienced a median of over 20 weekly cataplexy attacks. A meta-analysis of the trials demonstrated that participants in the oveporexton arm saw statistically significant and clinically meaningful improvements on the MWT (mean difference 19.59 minutes; 95% CI: 17.3 to 21.88) and ESS (mean difference -9.84; 95% CI: -11.58 to -8.10) compared with those on no pharmacological treatment. Additionally, participants in the oveporexton group were

nearly six times as likely to have a treatment response, defined as an ESS ≤10 (relative risk 5.64; 95% CI: 3.45 to 9.23). Oveporexton also decreased weekly cataplexy rates by 62-75%, appeared to decrease symptoms such as sleep paralysis, hallucinations, and disrupted nighttime sleep, and improved health-related quality of life measures. A pooled safety review showed that oveporexton was tolerable, with low rates of serious adverse events and discontinuations.

A network meta-analysis comparing oveporexton to modafinil/armodafinil, sodium oxybates, and pitolisant showed that treatment with oveporexton resulted in statistically significant and clinically meaningful differences in MWT scores and ESS scores compared with all other treatments. Additionally, participants in the oveporexton arm were more likely to be treatment responders compared with modafinil/armodafinil and pitolisant. Treatment with oveporexton appeared to result in reductions in cataplexy similar to those with sodium oxybate and pitolisant, although there was greater uncertainty about how it compares on this outcome, due to differences in reporting and data availability across trials.

We have uncertainties about whether some patients treated with oveporexton may also require an additional agent to successfully manage symptoms of NT1. Additionally, we have limited data on long-term efficacy and safety, which may be particularly important for a drug that has a new mechanism of action. There is a lack of head-to-head studies that compare treatments; conclusions about oveporexton compared with active comparators are from indirect comparisons only. Finally, since NT1 is a heterogeneous disease, subgroup data are needed to understand which group of patients may benefit most from treatment; there is also a lack of data on important subgroups such as children and pregnant and lactating persons.

Oveporexton represents the first therapy for NT1 whose mechanism of action directly addresses the orexin pathway. It appears to be both effective in relieving multiple domains of NT1 symptoms and improving quality of life with a relatively benign side effect profile. Therefore, we judged oveporexton to have at least a small but more likely a substantial net health benefit compared with no pharmacological treatment, an ICER rating of B+. Compared with modafinil/armodafinil + venlafaxine, sodium oxybates, and pitolisant, oveporexton appeared to be more effective and tolerable than all comparators. However, due to the limitations of network meta-analysis and qualitative comparisons, we have more uncertainty for these comparisons and judged oveporexton to have at least comparable but more likely small to substantial net health benefit, an ICER rating of C++.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Narcolepsy Type 1		
Oveporexton	No pharmacological treatment	B+
	Modafinil/armodafinil with venlafaxine	C++
	Sodium oxybate	C++
	Pitolisant	C++

B+: "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit, C++: "Comparable or Better" – Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit

For the cost-effectiveness analysis, treatment with oveporexton monotherapy resulted in greater increases in QALYs (quality-adjusted life years) and evLYs (equal value life years) compared with modafinil + venlafaxine, sodium oxybate monotherapy, pitolisant monotherapy, and no pharmacological treatment. However, based on a placeholder price of $250,000, our analysis suggests that oveporexton would not meet traditional cost-effectiveness thresholds when compared to any of these treatment options. The actual cost-effectiveness of oveporexton will depend on its price. The Health Benefit Price Benchmark (HBPB) range for oveporexton was calculated relative to modafinil + venlafaxine and estimated to be between $50,400 and $59,400 annually.

Assuming a placeholder price for oveporexton of $250,000 per year, 25% of the eligible population could be treated before reaching the ICER potential budget impact threshold of $821 million. Under this assumed placeholder price, ICER is issuing an access and affordability alert for oveporexton. However, if priced within the ICER HBPB range (between $50,400 and $59,400 annually), all potentially eligible patients could be treated, and we would not issue an access and affordability alert.

Key policy recommendations include:

- Manufacturers have a responsibility to set prices at levels that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- If oveporexton is priced in line with value, there is no justification for payers to restrict access to oveporexton using step therapy. Additionally, payers should ensure that benefit designs developed in conjunction with plan sponsors minimize the cost-sharing impact for vulnerable patients.
- Stakeholders such as clinical specialty societies and patient organizations should work to increase awareness of NT1 and facilitate timely diagnosis of the disorder.

- Educational institutions and employers should recognize that persons with NT1 may need accommodations to successfully complete school work or job duties and offer appropriate accommodations, including, for example, providing designated rooms for short naps, flexible work schedules, and secure locations to store the controlled medications commonly prescribed to treat NT1.

- There are multiple high priority research areas for NT1 on which researchers and funders can focus attention to close gaps as soon as possible, including: conducting clinical trials in children, collecting safety data on pregnant and lactating women, conducting research that compares oveporexton to combination therapy, and developing better diagnostic tools and outcome measures for NT1.

1. Background

Narcolepsy is a rare, chronic neurological disorder characterized by disruptions in the sleep-wake cycle. It affects approximately one in 2,000 people in the United States (US),[1] and the onset is usually in adolescence or young adulthood.[2] One of the main symptoms of narcolepsy is excessive daytime sleepiness (EDS), which is described as an overwhelming urge to sleep during the day despite getting sufficient sleep at night, and onset of these symptoms is often sudden.[3] People living with narcolepsy also have dysregulated rapid-eye-movement (REM) sleep, which causes features of REM sleep (muscle atonia, dreamlike imagery) to emerge during sleep-wake transitions. Consequently, people with narcolepsy can have hallucinations while going to sleep or waking up, as well as sleep paralysis. Narcolepsy is often described as a 24-hour disorder because many people with narcolepsy have disrupted nighttime sleep, which includes frequent sleep/wake transitions, nightmares, and REM behavior disorder (dream enactment).[6] Finally, people living with narcolepsy may also experience cataplexy, which is a sudden loss of muscle tone. The loss of muscle tone usually starts in the face and neck and then can spread to the trunk and limbs, and in severe episodes, a person may slump to the ground and be immobile for up to one to two minutes.[3] Cataplexy is usually triggered by strong emotions, including laughter, surprise, or anger, or being overly tired.[7]

Narcolepsy has a substantial impact on daily life. In a survey of persons with narcolepsy, more than three-quarters of respondents felt that narcolepsy severely impacted their daily life, with more than 90% of people reporting difficulty with concentration, and more than 80% reporting that narcolepsy interferes with work, their social life, and makes it hard to do everyday activities, including exercise.[7] Furthermore, persons living with narcolepsy reported that the disease made them feel depressed and isolated, limited their education and/or career options, and limited their independence.[7,8] For example, persons with narcolepsy reported more difficulty at work with low productivity and accidents, and had higher costs associated with presenteeism and absenteeism.[9] People living with narcolepsy are also more likely to have comorbid conditions such as sleep apnea, depression, obesity, high blood pressure, and heart disease, among others.[3] Consequently, annual direct medical costs are approximately twice as much as those without the disorder;[4] and studies also show higher short-term disability rates.[5]

Diagnosis of narcolepsy is based on a history of three or more months of EDS plus one of the following: cataplexy, low orexin levels in cerebrospinal fluid, or a mean sleep latency time of eight minutes or less and two or more sleep-onset REM periods on a Multiple Sleep Latency Test (MSLT). There are two types of narcolepsy. Narcolepsy type 1 (NT1), or narcolepsy with cataplexy, is defined by the presence of cataplexy and by low levels of the neurotransmitter orexin, which regulates sleep and wakefulness.[3] Patients without cataplexy are diagnosed with Narcolepsy type 2 (NT2); they generally have less severe symptoms and normal orexin levels.[10] However, cataplexy can

develop after diagnosis, so patients can shift from being diagnosed with NT2 to NT1. There may also be some racial and ethnic differences in narcolepsy symptoms, with Black persons having earlier onset of symptoms and being less likely to manifest cataplexy despite having low orexin levels.[11] Finally, narcolepsy may be underdiagnosed in up to half of affected persons, and diagnosis of narcolepsy is often delayed, with nearly one-third of patients reporting 10 years or more from symptom onset before receiving a diagnosis.[3,7]

This review focuses on the treatment of individuals with NT1. Current management of NT1 is mainly symptomatic, with both non-pharmacological and pharmacological treatment. Daytime naps can help people with narcolepsy feel more alert, and a consistent sleep schedule is important because irregular and/or insufficient sleep can worsen symptoms. Pharmacological treatment focuses on improving wakefulness and preventing cataplexy in people with NT1. Clinical practice guidelines recommend individualized treatment based on factors such as age, reproductive planning, comorbidities, risk of substance use disorders, history of adverse events or side effects from prior treatments, and goals of care,[12] and treatment needs may evolve over time. Pharmacological treatments can treat EDS, cataplexy, or both. Wake-promoting agents such as modafinil/armodafinil, methylphenidate, and solriamfetol are commonly used to treat EDS, but have no direct effect on cataplexy symptoms. Antidepressants that suppress REM sleep are often used off-label to reduce or prevent cataplexy, though evidence for their effectiveness is limited. Sodium oxybates (including all three currently approved forms: twice-nightly, once-nightly, and mixed salts) and pitolisant are agents that treat both EDS and cataplexy and can be used as monotherapy; however, more than half of US patients with narcolepsy surveyed were taking combination therapy to treat their symptoms.[7] Furthermore, despite therapy, more than one-third of people with NT1 are not satisfied with their current treatment, and even those satisfied with treatment often have residual symptoms.[13]

Oveporexton (Takeda) is a first-in-class oral orexin receptor 2 agonist that treats both excessive daytime sleepiness and cataplexy and is under US Food and Drug Administration (FDA) consideration for approval for the treatment of NT1 as a breakthrough drug. The manufacturer announced its new drug application had been accepted in February 2026, with a target Prescription Drug User Fee Act (PDUFA) date in the third quarter of 2026.[14]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Oveporexton	Orexin receptor 2 agonist	Oral	1 mg or 2 mg twice daily*

mg: milligrams

*Drug not yet FDA approved, dosages used in the clinical trials

2. Patient and Other Stakeholder Input

This section was developed with input from diverse stakeholders, including patients, caregivers, a patient advocacy group, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. In response to public comments, we have made changes to the Draft Report, including: 1) clarifying that while oveporexton was studied as monotherapy and will likely be approved as monotherapy, patients and clinical experts commented on the possibility of combination therapy, and 2) clarifying the rationale for pooling data from the different sodium oxybate formulations. We have also added survey results from the ICER Share Your Story portal (see Supplement Section B). ICER appreciates the engagement with stakeholders throughout this review to help refine our understanding on the effectiveness and value of treatments for NT1.

2.1. Patient Community Insights

We heard that although symptoms and their severity vary amongst people living with narcolepsy, the disorder significantly affects daily life. People living with NT1 describe fighting to stay awake during the day – e.g., falling asleep frequently during sedentary activities such as lectures, movies, meetings, reading, and driving – as well as having disrupted nighttime sleep with nightmares and hallucinations. They describe having to carefully plan their day around how long they feel they can stay awake and feel limited in committing to activities because they are not sure how they will feel on any given day. For example, some routine activities, such as grocery shopping, become difficult, as individuals need to pace themselves and may not have enough energy to complete the task. We heard that students may need accommodations at school due to difficulty sitting for long periods of time and concentrating, and as the workload increases for older students, keeping up with studies can be challenging. People living with NT1 note that sedentary jobs (e.g., office work or jobs with multiple conference calls) can be particularly difficult to manage. One person living with narcolepsy described that the "brain fog" from narcolepsy makes it difficult to make decisions, resulting in many unfinished tasks. Naps are commonly needed throughout the day, also limiting activities outside the home.

We heard that cataplexy episodes can be embarrassing, particularly if those around aren't aware of the disorder and can cause people living with narcolepsy to miss out on "normal life experiences". Cataplexy episodes can also be unpredictable, leading people with narcolepsy to limit their activities due to safety reasons – both their own safety and the safety of others – during the episodes. For example, we heard that muscle weakness during cataplexy episodes can lead to dropping things; one person described that they do not use breakable cups or drink liquids around electronics due to the unpredictability of cataplexy episodes.

Narcolepsy affects the decision to have children, as medications may need to be changed and weaned off for pregnancy, and disrupted sleep can worsen symptoms. Since many medications used to treat narcolepsy are controlled substances, timing medication refills to make sure that one has enough medication can be challenging in the context of work, travel, or vacation. For college-aged persons living with narcolepsy, their options for treatment may be limited by safety and security concerns related to sodium oxybate being related to gamma-hydroxybutyrate (GHB), e.g., storing medications securely in a dormitory setting.

People living with narcolepsy describe difficulty getting a diagnosis, in part because the symptoms can be difficult to recognize. For example, many people with narcolepsy initially believe that their fatigue and sleepiness are mainly from life circumstances (being busy with school, work, activities, etc.) and do not necessarily recognize cataplexy symptoms. Even when they go and seek medical care for their symptoms, the symptoms are often brushed off, and thus, diagnosis can be delayed for years. We also heard that access to specialists with true expertise in treating narcolepsy is difficult to find, and some persons with NT1 traveled long distances to find that expertise.

We heard that caregiver impacts can be large, particularly since the onset of narcolepsy is in childhood. Family members often need to take on more tasks, particularly activities that may involve driving or leaving the home (e.g., shopping), increasing caregiver impact. Family caregivers describe needing to make accommodations for their family member with NT1, including shortening outings and altering travel plans. These accommodations also impact the lives of unaffected siblings. Finally, the financial burden on families can be large, as some persons with narcolepsy are not able to live on their own or hold a steady job, so they are dependent on their families for financial support.

We heard from people living with NT1 that current treatment usually involves juggling multiple medications. Many people are taking drugs to promote wakefulness, but those do not necessarily treat other symptoms like brain fog – one person described taking such medications as “how much less sleepy does this medication make me”, rather than feeling more awake. We also heard that medications constantly need to be adjusted and/or changed due to a change in symptoms, incomplete treatment of symptoms, intolerable side effects, or insurance coverage. For example, the dosing of sodium oxybate requires a dose in the middle of the night, which may be difficult for some people. However, despite being on medication, persons living with narcolepsy shared that they did not feel completely satisfied with treatment and wished for drugs that addressed the underlying pathophysiology rather than just treating symptoms.

Insurance coverage can be a substantial barrier to treatment. Many people struggle to get insurance coverage for newer drugs like solriamfetol and often do not have the energy to appeal denials. We heard that it also takes substantial effort to keep up with prior authorization requests. Treatments are also very expensive, particularly with high-deductible health plans; some families report spending tens of thousands of dollars on treatment per year.

We spoke with persons with NT1 who participated in one of the clinical trials of oveporexton. We heard that treatment with oveporexton was "life changing" and people felt like they were "normal" – more focused and awake - rather than less sleepy. We heard that those taking oveporexton were able to do activities they ordinarily would not be able to do, including driving long distances. However, some participants in the clinical trial said that they eventually felt like they needed additional medication to control their symptoms, including cataplexy.

2.2. Health Equity Considerations

The diagnosis of narcolepsy is difficult and delayed, even for those people who have good access to health care, and thus populations for whom access is challenging may be at risk for even further delays in diagnosis and care. Additionally, studies have shown that there are differences in narcolepsy presentation among different racial/ethnic groups. For example, African Americans with narcolepsy have earlier onset of disease, higher symptom burden, and are more likely to have low orexin levels, even without cataplexy.[11] Women with NT1 may also have more excessive daytime sleepiness compared to men.[15] Understanding differences in presentation may help with improving diagnostic rates and decrease diagnostic delays, as well as help identify populations in whom orexin receptor agonists may be particularly helpful.

2.3. Input from Other Stakeholders

Clinical experts concurred that the diagnosis of narcolepsy is often delayed, and that current treatments allow patients to maintain wakefulness but do not address the fatigue and cognitive symptoms that narcolepsy can result in. They were excited that there was a new drug in the pipeline that may address the underlying pathophysiology of narcolepsy and thought that if successful, specifically addressing orexin deficiency may change the paradigm of treatment for NT1. We heard from US-based clinical experts that they rarely order and are reluctant to recommend lumbar punctures to measure CSF orexin levels due to the potential risks of lumbar puncture, patient discomfort, the logistical difficulties of doing the procedure, and the limited number of labs in the US that can run the test. We also heard that this procedure is more commonly done in some centers in Europe, along with genotyping of human leukocyte antigen (HLA), to confirm the diagnosis. Finally, we heard from clinical experts and analysts that payer coverage for NT1 treatments is restrictive, prior authorization and step therapy are common, even with generic drugs available.

Finally, the manufacturer of oveporexton emphasized that since only NT1 patients have orexin deficiency, the drug at recommended doses is only effective in this population and would not be effective in NT2 patients. There are ongoing trials of orexin agonists at higher doses in the NT2 population; thus, accurate diagnosis is important.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

We conducted a systematic literature review in November 2025 with an updated search run in March 2026; detailed methodology can be found in Supplement Section D1. A research protocol was published on Open Science Framework and is registered with PROSPERO (CRD420251230999).

Scope of Review

We evaluated the clinical effectiveness and safety of oveporexton as a monotherapy for the treatment of adults with NT1 versus the following treatment options: (1) no pharmacological treatment, represented by the placebo arms evaluated in the clinical trials (2) a combination therapy of modafinil/armodafinil with venlafaxine, which we considered to be a representative comparator for concurrent use of a wake-promoting and anticataplectic agent, (3) sodium oxybate monotherapy; and (4) pitolisant monotherapy.

Our outcomes of interest included daytime symptoms (e.g., excessive daytime sleepiness, cataplexy), REM-related symptoms (e.g., sleep paralysis, sleep-related hallucinations), work or school performance, quality of life measures (e.g., cognitive and fatigue symptoms), and adverse events associated with treatment.

The full scope of the review is described in Supplement Section D1.

Evidence Base

Oveporexton versus No Pharmacological Treatment (Placebo)

We identified three clinical trials evaluating oveporexton versus placebo (no pharmacological treatment) in patients with NT1. Of the three, two were Phase III pivotal trials, FirstLight and RadiantLight, and the third is an earlier Phase II trial.[16,17] This review prioritized efficacy data from the 2 mg twice daily regimen study arms studied in all three trials. However, the 1 mg dose was considered in our examination of harms. At the time of this report, there are no peer-reviewed publications from the Phase III trials; data was accessed from presentations delivered by the manufacturer at the 2025 World Sleep Congress.

In the Phase III FirstLight and RadiantLight trials, individuals aged 16 to 70 with diagnosed NT1 and a minimum of four weekly cataplexy episodes were randomly assigned to oveporexton (1 mg or 2 mg twice daily in FirstLight, 2 mg only in RadiantLight) or placebo, for 12 weeks.[16] The primary endpoint of the studies was changes from baseline in the Maintenance of Wakefulness Test (MWT). The MWT is an objective measure of daytime alertness that assesses the number of minutes a patient can stay awake in non-stimulating conditions during four 40-minute test periods throughout the day. Scores (average of the number of minutes the patient was able to stay awake across all four test periods) below eight minutes are indicative of excessive daytime sleepiness, and a two-minute increase on the MWT is considered clinically meaningful.[12]

Other secondary outcomes evaluated include changes from baseline in the Epworth Sleepiness Scale (ESS) and changes in the weekly rate of cataplexy. The ESS is a subjective patient-reported outcome that measures the likelihood of dozing across eight activities of daily life. Scores above 10 indicate excessive daytime sleepiness; scores ≥16 are considered severe. A two-point decrease in the ESS is considered clinically meaningful, and a patient on treatment achieving an ESS score ≤10 is considered a responder with controlled excessive daytime sleepiness. See Supplement Section A1 for additional definitions.

At baseline, trial participants were, on average, in their 30s, and 56% were female (Table 3.1). The baseline ESS and MWT scores of participants were indicative of severe excessive daytime sleepiness. Participants experienced a median of over 20 cataplexy attacks at baseline. Oveporexton was studied as a monotherapy in all trials. In the Phase III FirstLight and RadiantLight trials, all participants underwent a washout period of previous medications for narcolepsy. Study participants across the three trials were permitted to roll over to an ongoing long-term extension (LTE) study, from which we currently have data available from a six-month follow-up from the Phase II study (See Supplement Section D4 for ongoing studies).[18]

Table 3.1. Baseline Characteristics of Oveporexton Trials[16]

Study	FirstLight		RadiantLight		Phase II	
Arm	**Placebo**	**OVE 2 mg BID**	**Placebo**	**OVE 2 mg BID**	**Placebo**	**OVE 2 mg BID**
n	41	66	35	70	22	21
Age, Mean (SD)	30.9 (12.7)	29.7 (9.6)	34 (13.1)	29.1 (9.6)	37.5 (11.9)	31.7 (11.3)
Female, n (%)	24 (58.5)	46 (69.7)	13 (37.1)	37 (52.9)	14 (64)	9 (43)
ESS, Mean (SD)	18.2 (3.6)	19 (3.2)	17.9 (3)	17.3 (3.4)	18.6 (2.7)	19 (3.1)
MWT, Mean (SD)	5.1 (6.8)	4.4 (5.5)	4.1 (4.9)	4.8 (4.9)	6.1 (8.8)	3.9 (6)
Weekly Cataplexy Rate, Median (IQR)	21.8 (10.5-37.5)	26.5 (14.5-52.8)	27 (19-66.5)	21.8 (10.5-37.5)	13.3 (5-100.9)	11.3 (12-130.5)

BID: twice daily, ESS: Epworth Sleepiness Scale, IQR: interquartile range, mg: milligrams, MWT: Maintenance of Wakefulness Test, n: number, OVE: oveporexton, SD: standard deviation
Note: FirstLight and Phase II studies include 1 mg study arms not shown in table.

Oveporexton versus Active Treatment

There were no active treatment comparisons in the oveporexton clinical trials. Thus, we identified trials of comparators of interest (modafinil/armodafinil, sodium oxybates, and pitolisant) relevant for our review. There are no randomized controlled trials (RCTs) that have directly examined modafinil or armodafinil combined with venlafaxine for the treatment of NT1, and no RCTs specifically evaluating venlafaxine for the reduction of cataplexy. Therefore, we relied on clinical evidence derived separately from trials of modafinil and armodafinil and an observational study of venlafaxine. Sodium oxybates are available in multiple formulations, including once and twice nightly formulations, and a low-sodium formulation. Our analysis for efficacy integrated data from clinical trials covering all formulations, acknowledging their comparable clinical efficacy.[19,20] We also pooled clinical evidence across daily dosages ranging from 3 to 9 grams due to data availability. For harms, we qualitatively analyzed data from the FDA labels of each product and our literature review, and highlighted differences where appropriate. Table 3.2 presents the key characteristics of these trials. When available, we supplemented our evidence base with prescribing labels and clinical reviews from the Food and Drug Administration (FDA) and European Medicines Agency (EMA), and other meta-analyses of the narcolepsy treatments.

Table 3.2. Key Trial Characteristics[21-32]

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics*
Modafinil/Armodafinil				
US 1998	Adults with narcolepsy with or without cataplexy N=283	Change from baseline in MWT and CGI-C	Treatment: 9 weeks	Female: 54.4% Mean age: 42 NT1: 88.3% Mean ESS: 17.8 Mean MWT: 6.1
US 2000	Adults with narcolepsy, an MSLT score ≤8 minutes, and ≥2 sleep-onset REM periods N=271	Change from baseline in MWT and CGI-S at week 9	Treatment: 9 weeks	Female: 54.2% Mean age: 41.7 NT1: 72.3 Mean ESS: 17.7 Mean MWT: 6
Harsh 2006	Adults with narcolepsy N=196	Change from baseline in MWT and proportion of patients with at least minimal improvement on CGI-C at week 12	Treatment: 12 weeks	Female: 56% Mean age: 38.2 NT1: 66.7% Mean ESS: 16.8 Mean MWT: 11.4

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics*
Venlafaxine				
Jin 2019	Adults with narcolepsy and treated with antidepressants N=148	Improvements in ESS and MWT scores before and after treatment	Follow-up: 1-6 years	Female: 28.4% Age range: 3-54 NT1: 81.1% Mean ESS: 16 Mean MWT: 6.5
Sodium Oxybate				
Cook 2002	Adults with narcolepsy and ≥3 cataplexy episodes per week N=136	Change from baseline in WCR at week 4	Treatment: 4 weeks	Female: 58.1% Mean age: 43.1 NT1: 100% Median ESS: 17.6[†]
Ahmed 2005	Participants aged ≥16 years with NT1 N=228	Change from baseline in ESS score at week 8	Treatment: 8 weeks	Female: 65.4% Mean age: 40.5 NT1: 100% Mean ESS: 18.4 Mean MWT: 8.7
Black 2006	Adults with narcolepsy taking 200-600 mg of modafinil daily N=222	Change from baseline in MWT at week 8	Treatment: 8 weeks	Female: 51.8% Mean age: 38.6 Mean ESS: 15 Mean MWT: 14
Bogan 2021	Adults with NT1 N=134	Change in WCR at 12 weeks	Treatment: 12 weeks	Female: 61.2% Mean age: 37.5 NT1: 100% Median ESS: 13.5
REST-ON	Participants aged ≥16 years with narcolepsy and ESS score >10 N=222	Change from baseline in MWT, CGI-I, and in WCR at week 13	Treatment: 13 weeks	Female: 68% Mean age: 31.3 NT1: 76.5% Mean ESS: 17.1 Mean MWT: 4.9
Pitolisant				
HARMONY 1	Adults with narcolepsy and ESS score ≥14 N=95	Change from baseline in ESS score at week 8	Treatment: 8 weeks	Female: 45.7% Mean age: 38.7 NT1: 81% Mean ESS: 18.4 Mean MWT: 8.2

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics*
HARMONY 1bis	Adults with narcolepsy and ESS score ≥14	Change from baseline in ESS score at week 8	Treatment: 8 weeks	Female: 53.3% Mean age: 42.7 NT1: 77.6% Mean ESS: 18.2 Mean MWT: 5
HARMONY CTP	Adults with NT1 and ESS score ≥12 N=106	Change from baseline in WCR at week 7	Treatment: 7 weeks	Female: 49.5% Mean age: 37.2 NT1: 100% Mean ESS: 17.2 Mean MWT: 7.4

ESS: Epworth Sleepiness Scale, CGI-C: Clinical Global Impression of Change, CGI-I: Clinical Global Impression of Improvement, CGI-S: Clinical Global Impression of Severity, mg: milligrams, MSLT: Multiple Sleep Latency Test, MWT: Maintenance of Wakefulness Test, N: number, NT1: narcolepsy type 1, REM: rapid eye movement, WCR: weekly cataplexy rate

*Key baseline characteristics were pooled and calculated if not reported.

†Data were digitized.

Using data from these trials and the three oveporexton trials presented above, we conducted an indirect treatment comparison via a network meta-analysis (NMA) to evaluate oveporexton versus three other therapies (modafinil/armodafinil, sodium oxybates, and pitolisant) on three available outcomes: MWT (mean difference), ESS (mean difference), and treatment response (ESS score 10 or less at study end). We included a total of 13 studies in our network (See Supplement Baseline Table D2.2 for baseline characteristics). Trial participants in the NMA were, on average, adults in their 30s or 40s, predominantly female, and mostly diagnosed with narcolepsy with cataplexy (NT1), with the remainder having narcolepsy without cataplexy (NT2). The patient population exhibited severe excessive daytime sleepiness, as indicated by baseline ESS scores between 16 and 24. All NMAs were conducted in a Bayesian framework with random effects models. Other information on NMA methodology and sensitivity analyses are provided in Supplement Section D2. A risk of bias assessment for studies within the network is shown in Supplement Tables D1.4 and D1.5.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the oveporexton pivotal trials (FirstLight and RadiantLight) using the ICER-developed Clinical trial Diversity Rating (CDR) Tool (Table 3.3).[33]

We were unable to locate prevalence data for the race/ethnicity of adults with narcolepsy in the US. In the absence of evidence indicating differential prevalence across racial or ethnic groups, consistent with input from clinical experts, we assumed that the racial and ethnic distribution of adults with narcolepsy was similar to the US population. Thus, we used the US census data for race and ethnicity prevalence estimates. FirstLight and RadiantLight were both multinational trials.

Both trials received a "poor" rating due the absence of data on the percentage of Hispanic participants in the trials, and an underrepresentation of Black participants. Race/ethnicity was reported as other or unknown for approximately 45% and 35% of participants in the FirstLight and RadiantLight trials, respectively.[16] Both trials achieved a "good" rating on the representation of males and females. The trials did not provide data by age groups, and as such, we did not assess the trials on the representation of older adults. See Supplement Section D1 for full details of CDR methods and results.

Table 3.3. Diversity Ratings on Race and Ethnicity, Sex, and Age

Trial	Race and Ethnicity	Sex	Age (Older Adults)
FirstLight	Poor	Good	Not Calculated
RadiantLight	Poor	Good	Not Calculated

3.2. Results

Clinical Benefits

Excessive Daytime Sleepiness

Oveporexton versus No Pharmacological Treatment (Placebo)

Participants treated with oveporexton showed significant improvements in both sleep latency and excessive daytime sleepiness compared with no pharmacological treatment (Table 3.4).

We conducted a fixed-effect meta-analysis of the three trials on the outcomes of excessive daytime sleepiness, including changes in the ESS and MWT, and the proportion of trial participants achieving a ≤10 on the ESS at the end of the study (See additional methodological details of the meta-analysis in Supplement Section D2).

The results of the meta-analyses are presented in Table 3.4. Participants treated with oveporexton saw an average increase of nearly 20 minutes on the MWT, greatly exceeding the clinically meaningful threshold of two minutes.[12] Likewise, patients on oveporexton saw an average decrease of almost 10 points on the ESS, well above a clinically meaningful drop of two points, and were five times more likely to achieve an ESS score of less than 10, indicative of treatment response.

Table 3.4. Meta-Analysis of Oveporexton Trials

Trial/ Outcome	FirstLight		RadiantLight		Phase II		Meta-Analysis Results OVE versus PBO
Arm (n)	OVE (n=125)	PBO (n=41)	OVE (n=70)	PBO (n=35)	OVE (n=21)	PBO (n=22)	
MWT, Mean Difference, Minutes (SE)	17.2 (1.80)		20.09 (1.80)		24.7 (2.96)		MD (95%CI) 19.59 (17.3 to 21.88)
ESS, Mean Difference, Points (SE)	-9.75 (0.94)		-9.53 (0.80)		-11.3 (1.58)		MD (95%CI) -9.84 (-11.58 to -8.10)
Treatment Response (ESS ≤10), n/N (%)	53/64 (82.8)	6/36 (16.7)	56/67 (83.6)	4/34 (11.8)	20/21 (95.2)	4/21 (19)	RR (95% CI): 5.64 (3.45 to 9.23)

CI: confidence interval, ESS: Epworth's Sleepiness Scale, MWT: Maintenance of Wakefulness Test, N: number, OVE: oveporexton, PBO: Placebo, MD: Mean Difference, RR: Risk Ratio, SE: standard error

An interim analysis of Phase II LTE trial participants showed a durable treatment effect by oveporexton across the MWT, ESS, and WCR outcomes compared to placebo, with efficacy maintained up to at least six months.[18]

Oveporexton versus Active Treatment

The results of the NMA showed that treatment with oveporexton resulted in statistically and clinically significant increases on the MWT of approximately 15 minutes versus sodium oxybate and modafinil/armodafinil, and 18 minutes versus pitolisant (Table 3.5). These effects were observed with a follow-up period ranging from 7 to 13 weeks.

Table 3.5. Mean Differences for Maintenance of Wakefulness Test (Minutes)

Oveporexton				
14.99 (10.04, 20.24)	Sodium Oxybate			
15.56 (11.07, 20.35)	0.6 (-3.73, 4.88)	Modafinil/Armodafinil		
18.48 (12.96, 23.92)	3.5 (-1.98, 8.48)	2.93 (-1.57, 6.97)	Pitolisant	
20.01 (16.32, 23.99)	**5.01 (1.63, 8.38)**	**4.43 (1.76, 7.15)**	1.51 (-2.22, 5.78)	Placebo

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random-effects model. N=11 studies. Ordering of therapies was made according to magnitude of benefit versus placebo.

Treatment with oveporexton also improved ESS scores by 6.5 to 7.5 points compared with its active comparators (Table 3.6). Patients treated with oveporexton were also about twice as likely to achieve an ESS score of ≤10 as compared to modafinil/armodafinil and pitolisant, although the risk ratios between oveporexton and modafinil/armodafinil were not statistically significant (Table 3.7).

At time of this review, there were no available ESS responder data from any of the sodium oxybate trials within our NMA. The REST-ON study reported that 56% of participants treated with the once-nightly sodium oxybate achieved an ESS score of ≤10 at 13 weeks of follow-up.[34] The data from this study could not be included in our NMA because the corresponding statistic for the placebo arm was not reported.

Table 3.6. Mean Differences for Epworth Sleepiness Scale (Points)

Oveporexton				
-6.68 (-8.51, -4.81)	**Modafinil/Armodafinil**			
-7.11 (-9.21, -5.05)	-0.44 (-2.01, 1.06)	**Pitolisant**		
-7.63 (-9.49, -5.66)	-0.97 (-2.46, 0.64)	-0.53 (-2.25, 1.37)	**Sodium Oxybate**	
-9.92 (-11.5, -8.4)	**-3.25 (-4.35, -2.25)**	**-2.82 (-4.19, -1.43)**	**-2.28 (-3.54, -1.24)**	**Placebo**

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random-effects model. N=13 studies. Ordering of therapies was made according to magnitude of benefit versus placebo.

Table 3.7. Risk Ratios for Treatment Responder (ESS ≤10) Outcome

Oveporexton			
2.01 (0.73 to 5.53)	**Modafinil/Armodafinil**		
2.54 (1.07 to 6.56)	1.26 (0.61 to 2.93)	**Pitolisant**	
5.06 (2.79 to 10.86)	**2.53 (1.27 to 5.75)**	**1.99 (1.11 to 3.79)**	**Placebo**

Note: Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random Effects model. Not adjusted for baseline risk. N=7 studies. Ordering of therapies was made according to magnitude of benefit versus placebo.

Other Patient Important Outcomes

We were unable to conduct NMAs on other patient-important outcomes (cataplexy, REM-related symptoms, quality of life, and harms) to compare oveporexton with other active comparators due to differences in reporting and data availability across trials. Instead, we qualitatively describe the findings on these outcomes for each treatment below. We did not identify any outcomes related to work or school performance.

Cataplexy

Oveporexton

Treatment with oveporexton resulted in a significant reduction in the weekly cataplexy rate (WCR) in both Phase III trials. In the FirstLight trial, the baseline median WCR was 26.3 and 28.5 in the oveporexton 2 mg and placebo arms, respectively.[16] Oveporexton demonstrated a 62% reduction in the WCR relative to placebo, with a calculated incidence rate ratio (IRR) of 0.38 (95% CI: 0.23 to 0.61) (Table 3.8). In the RadiantLight trial, there was a 75% reduction in WCR (IRR of 0.25 [95% CI: 0.15 to 0.42]). A reduction of 25% or greater in the daily/weekly cataplexy rate is clinically meaningful.[12]

Active Comparators

Pitolisant, sodium oxybate, and venlafaxine all reduced cataplexy events. Differences in outcome measures precluded indirect comparison across drugs. Venlafaxine was studied in a single-arm observational study. Table 3.8 presents a trial-by-trial overview of the cataplexy outcome.

Table 3.8. Narcolepsy Treatments Impact on Cataplexy Occurrence

Trial	Arms	Cataplexy Measure Study Findings
FirstLight (N=168)	2 mg OVE vs. Placebo	IRR 0.38 (95% CI: 0.23 to 0.61), p<0.001
RadiantLight (N=105)	2 mg OVE vs. Placebo	IRR 0.25 (95% CI: 0.15 to 0.42), p<0.001
Phase II (N=112)	2 mg OVE vs. Placebo	IRR 0.36 (95% CI: 0.16 to 0.79), p=0.03
Jin 2019 (N=148) Single-arm observational study	Venlafaxine	Median CFB WCR: 28 to 1 per week (p<0.001).[24]
Cook 2002 (N=136)	SXB 9 g twice nightly vs. Placebo	% CFB WCR: 69% reduction vs. 28% with placebo (p=0.0008).
Bogan 2021 (N=201) Withdrawal study	SXB (low sodium) vs. Placebo	Median CFB WCR: 0 in continued treatment group vs. 2.35 in group switched to placebo.[28]
Ahmed 2005 (N=228)	SXB 9 g twice nightly vs. Placebo	% CFB WCR: 84.7% reduction vs. 21.3% with placebo.[26]
REST-ON (N=222)	SXB (once nightly) vs. Placebo	Median CFB WCR: -11.5 vs. -4.9 with placebo.[35]
HARMONY CTP (N=106)	PIT 40 mg vs. Placebo	IRR 0.51 (95% CI: 0.44 to 0.60), p<0.0001
HARMONY 1 (N=95)	PIT 40 mg vs. Placebo	IRR 0.38 (95% CI: 0.16 to 0.93), p=0.034

CFB: Change from Baseline, CI: confidence interval, g: grams, IRR: incidence rate ratio, mg: milligram, NR: Not Reported, OVE: oveporexton, PIT: pitolisant, SXB: sodium oxybate, WCR: Weekly Cataplexy Rate
Note: All trials listed are parallel randomized controlled trials unless indicated otherwise.

REM-Related Symptoms

Oveporexton

The Narcolepsy Severity Scale for Clinical Trials (NSS-CT) is a self-administered measure of symptom severity and includes domains of sleepiness, cataplexy, sleep paralysis, hallucinations, and disrupted nocturnal sleep.[17] Oveporexton-treated patients saw an approximate 17-point drop on the NSS-CT versus placebo, exceeding the clinically meaningful threshold difference of eight points. Approximately 85% of treated patients had no hallucinations or sleep paralysis at end of 12-week follow-up; however, the baseline prevalence of these symptoms was not reported. An estimated 67% of treated patients showed meaningful improvement on disturbed nighttime sleep.

Combination Therapy (Modafinil/Armodafinil plus Venlafaxine)

In two US-based modafinil studies, nocturnal polysomnography measures did not find any clinically meaningful treatment differences on total sleep time, sleep and REM latency, between modafinil (200 and 400 mg) and placebo.[21,22] Modafinil 200 mg did improve the sleep efficiency percentage compared with placebo in one study.[22]

In the Harsh 2006 study, study participants underwent a nocturnal polysomnographic evaluation at baseline and final visits.[23] There were no significant effects on any sleep initiation, continuity, or sleep stage variables between armodafinil and placebo.

We did not identify any studies examining the impact of modafinil/armodafinil combined with venlafaxine or venlafaxine alone on nighttime symptoms.

Sodium Oxybate

In the Ahmed 2005 study, treatment with twice-nightly sodium oxybate did not significantly reduce the incidence of hypnagogic hallucinations or sleep paralysis compared with placebo.[26] In the REST-ON study, 13 weeks of treatment with once-nightly sodium oxybate resulted in significant improvements in disrupted nighttime sleep, as measured by sleep stage shifts and nocturnal arousals, compared with placebo.[35] The sodium oxybate group also had statistically significant improvements in patient-reported assessments of sleep quality and refreshing nature.

Pitolisant

In the HARMONY CTP trial, treatment with pitolisant reduced weekly episodes of hallucinations compared with placebo, with an estimated rate ratio of 0.50 (95% CI: 0.31 to 0.83; p=0.007).[31]

Quality of Life

Oveporexton

Oveporexton led to improvements in sustained attention through the day, as measured by the Psychomotor Vigilance Test, and activities of daily living, with more than 80% of treated participants reporting no problems with usual activities on the EQ-5D-5L compared to 30% in the placebo arm. A secondary analysis of the Phase II trial showed that treatment with oveporexton significantly improved memory and executive function after eight weeks.[36]

Combination Therapy (Modafinil/Armodafinil plus Venlafaxine)

We did not identify any studies of modafinil or armodafinil with or without venlafaxine that reported quality-of-life measures in patients with narcolepsy.

Sodium Oxybate

A post-hoc analysis of the Ahmed 2005 study compared twice-nightly sodium oxybates to placebo on the 36-item Short Form Health Status Survey.[37] After eight weeks, sodium oxybate 9 g/night produced significantly greater improvements than placebo on the Physical Component Summary (6.3 vs. 1.5; p=0.005), but not on the Mental Component Summary. Sodium oxybates significantly outperformed placebo in Physical Functioning, General Health, and Social Functioning scales, and all doses (4.5, 6, 9 g) improved Vitality versus placebo. No significant differences were found on the Physical, Emotional, or Mental Health scales.

Pitolisant

Pitolisant did not produce significant improvements on the European quality-of-life questionnaire EQ-5D over placebo in either the HARMONY 1 or HARMONY CTP trials.[30,31]

Harms

Oveporexton

A pooled safety review of the two pivotal trials provides an overview of the harms associated with the 1 mg and 2 mg twice daily of oveporexton against placebo (Table 3.9).[16] Oveporexton treatment resulted in a higher incidence of urinary frequency and urgency, insomnia, and salivary hypersecretion. The treatment was tolerable, with low rates of serious adverse events and discontinuations. An earlier orexin receptor 2 agonist studied by Takeda for the treatment of NT1, TAK-994, was withdrawn from further development after evidence of drug-induced liver injury in a Phase II trial.[38] The liver injury appeared to stem from effects of metabolites of TAK-994 on liver cells.[39] Based on currently available data from the Phase II trial and the two pivotal Phase III trials,

oveporexton does not appear to have a risk of severe liver toxicity.[17] An interim analysis of patients from the Phase II long-term extension study reported that oveporexton was well-tolerated and did not identify any new safety signals.[18]

Table 3.9. Pooled Harms of Oveporexton Trials[16]

Harms, n (%)		Pooled FirstLight and RadiantLight Trials	
		Oveporexton	Placebo
N		196	76
TEAE	Any	171 (87.2)	37 (48.7)
	Mild	98 (50)	23 (30.3)
	Moderate	67 (38.1)	12 (15.8)
	Severe	6 (3.1)	2 (2.6)
Serious TEAE		2 (1)	0
TEAEs Leading to Study Drug Discontinuation		5 (2.6)	1 (1.3)
Most Frequent TEAEs	Urinary Frequency	111 (56.6)	4 (5.3)
	Insomnia	110 (56.1)	1 (1.3)
	Urinary Urgency	31 (15.8)	1 (1.3)
	Nasopharyngitis	16 (8.2)	6 (7.9)
	Headache	17 (8.7)	7 (9.2)
	Salivary Hypersecretion	14 (7.1)	0

N: number, TEAE: Treatment-emergent adverse events
Note: Baseline characteristics were pooled across the pivotal phase III trials for oveporexton. In FirstLight, there were no significant differences in adverse events between oveporexton 1 mg BID and 2 mg BID arms.

Combination Therapy (Modafinil/Armodafinil plus Venlafaxine)

In a pooled safety review of two US-based modafinil RCTs, the most frequently reported adverse events occurring in at least 5% of modafinil-treated patients and at a rate at least twice that of placebo were nausea, diarrhea, dry mouth, anorexia, and pharyngitis.[21,22] The incidence of headache was more frequent (5% or greater difference) in the 400 mg/day group than 200 mg/day and placebo. Across the two RCTs, 1% and 15% of participants treated with modafinil discontinued treatment due to an adverse event, compared to 3% and 5% in the placebo group. The Harsh 2006 armodafinil trial reported similar findings of increased risk of headache, nausea, dizziness, decreased appetite, diarrhea, and dyspepsia.[23] In this study, the range of participants treated with armodafinil that discontinued the study due to adverse events was 3% to 8%, compared to 2% in the placebo group.

Modafinil and armodafinil are Schedule IV controlled substances, and there is the risk of serious adverse events such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), angioedema, anaphylaxis, multi-organ hypersensitivity reactions, and severe psychiatric symptoms.[40,41] Modafinil can also increase the risk of cardiovascular events, such as myocardial ischemia, stroke, and arrhythmias. Modafinil and armodafinil can decrease the efficacy of oral contraceptives and lead to an increased incidence of

unintended pregnancy; use during pregnancy is associated with increased risk of congenital abnormalities.[40,42]

Venlafaxine has not been studied in a placebo-controlled study in adults with narcolepsy.[43] When studied against placebo in other indications (e.g., major depressive disorder), the most common adverse reactions that occurred at ≥5% and at least twice the placebo rate were nausea, somnolence, dry mouth, sweating, abnormal ejaculation, anorexia, constipation, impotence, and decreased libido.

In the Chinese prospective study of patients taking venlafaxine to treat cataplexy, the most frequent adverse events were early awakenings (28%), irritability (22%), weight gain (22%), and dry mouth (17%).[24] Patients irregularly taking or abruptly withdrawing from venlafaxine are at risk of status cataplecticus, a rare occurrence of repeated cataplexy attacks for hours or days without a refractory period.[44]

Sodium Oxybate

We reviewed FDA prescribing labels of the three sodium oxybate formulations to identify common adverse effects associated with treatment (≥5% of treated patients).[45-47] These include nausea, dizziness, vomiting, somnolence, enuresis, tremor, headache, anxiety, insomnia, decreased appetite, hyperhidrosis, diarrhea, dry mouth, parasomnia, and fatigue. Discontinuation from adverse events ranged from 5 to 16% across the three forms of sodium oxybate, compared to 0-3% in the respective placebo arms.[45-48] The low sodium oxybate formulation demonstrated the lowest rate of discontinuation. A study of NT1/NT2 patients switching from high to low-sodium oxybates reported a reduction in 24-hour blood pressure.[49] Whether this reduction in blood pressure due to the switch in medication results in improved clinical outcomes such as lower rates of cardiovascular and kidney disease is not known.

All sodium oxybates carry two black box warnings. First, the drug is a central nervous depressant. Its use can cause respiratory depression even at recommended doses or when used in combination with other CNS depressants such as alcohol or opioid analgesics. Second, sodium oxybates are a sodium salt of gamma-hydroxybutyrate (GHB). Its abuse and misuse can cause seizures, respiratory depression, decreased consciousness, coma, and death. Oxybates are a Schedule III controlled substance and are administered through a Risk Evaluation and Mitigation Strategies (REMS) program. A review of post authorization safety data from approximately 26,000 patients between 2002 and 2008 confirmed that cases of abuse (0.039%), dependence (0.016%), overdoses with suicidal intent (0.031%), and deaths (0.08%) were extremely rare.[50]

Pitolisant

In a pooled safety review of the HARMONY trials, the most frequently reported adverse events occurring in ≥5% of pitolisant-treated patients and at a rate at least twice that of placebo were insomnia, nausea, and anxiety.[51] In the three RCTs, the rate of discontinuation due to adverse events ranged from 0-7% in both the pitolisant and placebo arms.

Beyond the clinical trial data, pitolisant poses several other risks, as identified in the FDA prescribing label.[51] Pitolisant can prolong the QT interval and its use should be avoided in patients with a history of cardiac arrhythmias and other cardiac conditions. Pitolisant can also have significant drug interactions with strong CYP2D6 inhibitors (e.g., paroxetine) and strong CYP3A4 inducers (e.g., hormonal contraceptives).

Subgroup Analyses and Heterogeneity

The oveporexton pivotal trials have not reported any clinical benefits or harms broken out by age, sex, and race/ethnicity subgroups. Specifically, we did not find any data for the pediatric subgroup.

Uncertainty and Controversies

- Uncertainty about potential real-world use of oveporexton: We reviewed oveporexton as a monotherapy and compared with no pharmacological treatment, as studied in clinical trials. While standard of care treatment for NT1 does not include no treatment, if oveporexton is approved, the comparison with no pharmacological treatment may be important for newly diagnosed patients with NT1 who are naïve to therapy. Additionally, since current treatment often requires combination therapy to address all the wake and sleep symptoms of NT1, we do not know yet whether some patients may require the addition of a nighttime agent such as sodium oxybate to have optimal treatment of all symptoms, as some patients and clinical experts have suggested may be the case. The efficacy and safety of oveporexton in combination requires further study.

- Uncertainty about oveporexton compared with combination therapy: We heard from patients and clinical experts that polypharmacy is common to treat NT1, as most patients do not get adequate relief of symptoms from one agent. However, in our analysis, other than our attempt to compare oveporexton to the combination of modafinil/armodafinil and venlafaxine, our comparators were assessed as monotherapy. Therefore, we do not know the comparative effectiveness of oveporexton to a multi-drug regimen.

- Limited evidence on modafinil/armodafinil and venlafaxine combination therapy: We did not find any randomized controlled trials examining the use of antidepressants to reduce and prevent cataplexy, despite its frequent use in practice. A more robust evidence base is needed to understand the relative magnitude of benefit of antidepressants on cataplexy, as well as in comparison to other anti-cataplexy treatments.

- Lack of head-to-head studies that compare oveporexton to other treatments for NT1: Our review relied on indirect treatment comparisons via NMA and qualitative review. Limitations to the NMA included that some trials enrolled both NT1 and NT2 patients, differences in baseline characteristics between trials, varying dosages and lengths of study follow-up for the comparator medications, and some trials permitted background therapy. Although the effect size of oveporexton is large enough that it is unlikely that these limitations would change our overall conclusions about oveporexton compared with other NT1 treatments, as more orexin-specific treatments are in the development pipeline, developers should consider head-to-head studies – particularly comparing combination therapy – to more precisely characterize relative clinical benefits and harms of the different drug treatments.

- Uncertainty around long term efficacy and safety: Data from clinical trials demonstrate that overall, oveporexton is well tolerated with few serious adverse events. However, trials of an earlier orexin receptor 2 agonist, TAK-994, were stopped due to participants suffering severe drug-induced liver injury, which was thought to be due to off-target effects. Although oveporexton is a more selective orexin 2 receptor agonist and there were no significant safety signals in the pivotal trials, these trials were short and thus long-term data confirming safety are needed; historical data demonstrate that almost one-third of drugs have safety issues that are only realized post-approval.[52] Additionally, the clinical trials for oveporexton were only 12 weeks and thus we do not have sufficient data on the durability of effect with oveporexton. Although results from the long-term extension of the Phase II study demonstrated durability of improvement for at least six months, narcolepsy requires lifelong treatment, and therefore, longer follow-up is needed to address questions of long-term efficacy and safety. Finally, more data on the impact of oveporexton on disrupted nighttime sleep is needed, as orexin agonists may cause insomnia.

- Uncaptured benefits of different formulations of sodium oxybate and time duration on oxybate: Although there are multiple formulations of sodium oxybate, for the NMA, we combined data, as the formulations have similar efficacy. However, in real-world practice, although the efficacy of the different formulations is similar, harms and compliance may differ. For example, mixed salts oxybate (low sodium form) has 92% less sodium than twice nightly sodium oxybate; over time, lower amounts of sodium may decrease the probability

of developing hypertension and cardiovascular disease. The once daily formulation may improve adherence to therapy, as the timing for the second dose of sodium oxybate can disrupt sleep and mis-timed doses have been documented to lead to severe side effects, emergency department visits, and hospitalizations.[53] Thus, there may be benefits and harms of different forms of sodium oxybate that were not fully captured in the NMA. Clinically, the maximal benefit of oxybate has been observed to occur four to five weeks after the goal dose is reached. This maximal benefit (e.g., change in ESS) may be underestimated in randomized withdrawal clinical trials or clinical trials lasting <8 weeks.

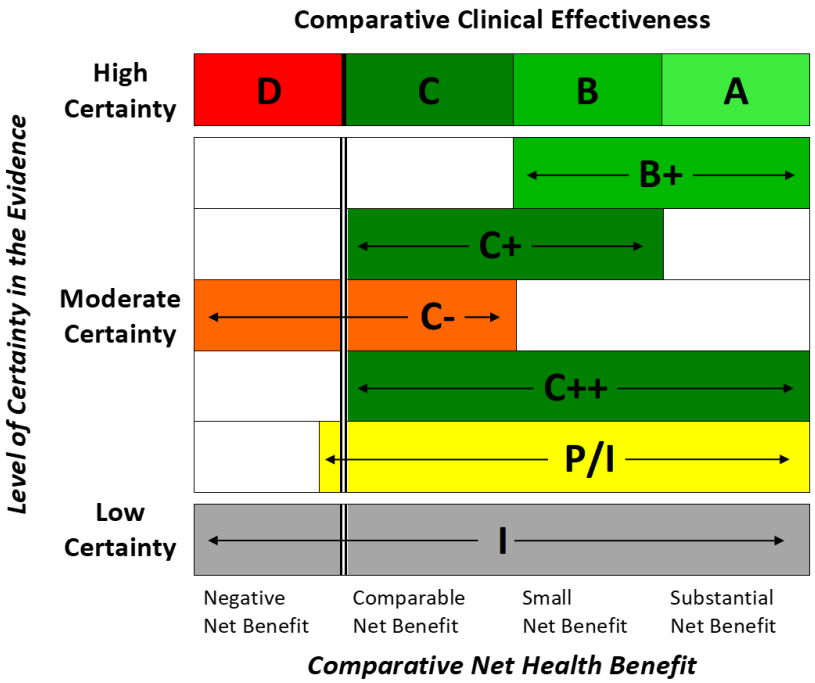
- Limitation of outcome measures: Although the outcomes measured in the clinical trials, such as ESS and MWT, are also standard tests in clinical practice, both outcomes have limitations. For example, the ESS is a subjective scale and has been found to have high variability and low reliability, and correlation with physiologic sleepiness is inconsistent.[54] The MWT is highly dependent on effort and is done in an artificial setting, so it can be an unreliable indicator of real-world daily functioning.[55] Thus, changes in ESS or MWT may not fully capture either the severity of disease or improvements from treatment.

- Lack of data on important subgroups: Finally, since NT1 is a heterogeneous disorder and affects each individual differently, subgroup data are needed to understand which group of patients may benefit most from treatment with oveporexton. Importantly, the onset of NT1 is often in childhood or adolescence, and there are currently no data on the efficacy and safety of oveporexton in children.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D= "Negative" *- High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Evidence Ratings Discussion

NT1 is a rare, chronic neurological disorder that has a large impact on daily life. Because disease onset is often in childhood or early adulthood, there can be lifelong impacts on education, work, and family planning, and caregiver impact can be high. Current treatments for NT1 are symptomatic and do not address the underlying orexin deficiency that is the hallmark of the disease, and persons living with narcolepsy and their caregivers describe the incomplete relief that current treatments provide, even with multiple medications. Thus, there is a large unmet need for additional, more effective therapies for NT1.

Oveporexton represents the first therapy for NT1 whose mechanism of action directly addresses the orexin pathway. In the pivotal Phase III trials, participants treated with oveporexton showed statistically and clinically significant improvements in MWT and ESS scores, as well as improvements in health-related quality of life (HRQoL) measures compared with no pharmacological treatment. Oveporexton was also well-tolerated, with no concerning safety signals and few serious adverse events. Although the results of the Phase III FirstLight and RadiantLight trials have not yet been published in a peer-reviewed journal, the magnitude of treatment benefits and the relatively benign safety profile seen in the currently available data suggest high certainty of at least a small overall net health benefit and likely substantial net health benefit over no pharmacological treatment. Therefore, we assigned an ICER rating of **B+ to the comparison of oveporexton and no pharmacological treatment.**

Although combination therapy is the norm for NT1 patients, we compared oveporexton as monotherapy to other recommended treatments for NT1. As there are no direct head-to-head trials, we conducted a network meta-analysis to compare the outcomes of change in ESS and MWT, and qualitatively evaluated differences in cataplexy reduction and harms.

- The ICER NMA found statistically significant and clinically meaningful improvements in ESS scores in the oveporexton arm compared with pitolisant (seven-point difference), sodium oxybate (seven-point difference) and modafinil/armodafinil (six-point difference). We also found substantial differences in MWT scores, with the oveporexton treatment arms having much longer wake periods compared with pitolisant (18 minutes), sodium oxybate (15 minutes), and modafinil (15 minutes).

- Oveporexton, pitolisant, sodium oxybate, and venlafaxine all reduced cataplexy events.

- Oveporexton appeared to have fewer serious harms than pitolisant, which can have cardiac and mental health side effects, and oxybates, which carry risks of abuse, respiratory depression, seizure, and central nervous system (CNS) depression.

Overall, because of the limitations of the NMA and qualitative comparisons, we have moderate certainty about the net health benefit of oveporexton compared with pitolisant, sodium oxybate, and the combination of modafinil/armodafinil plus venlafaxine. We judge that oveporexton has at least a comparable net health benefit, but more likely has a small to substantial net health benefit compared to the other treatments. Thus, we assigned an ICER rating of **C++ to the comparison of oveporexton to modafinil/venlafaxine, sodium oxybate, or pitolisant.**

Table 3.10. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Narcolepsy Type 1		
Oveporexton	No pharmacological treatment	B+
	Modafinil/armodafinil with venlafaxine	C++
	Sodium oxybate	C++
	Pitolisant	C++

B+: "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit, C++: "Comparable or Better" – Moderate certainty of a comparable, small, or substantial net health benefit

Midwest CEPAC Votes

Table 3.11. Midwest CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
For adults with narcolepsy type 1, is the current evidence adequate to demonstrate that the net health benefit of oveporexton is greater than that of no pharmacological treatment? *In discussion, one CEPAC member shared that he feels comfortable voting "yes" despite the unpublished nature of the Phase III data, but emphasized the short duration of the available trials and expressed a desire for additional long-term published evidence to further inform the assessment.*	13	0
For adults with narcolepsy type 1, is the current evidence adequate to demonstrate that the net health benefit of oveporexton is greater than that of modafinil with venlafaxine? *One CEPAC member explained that he voted "no", because, without at least an indirect treatment comparison evaluating the combination therapy, he did not believe the available evidence base was strong enough to support an affirmative vote.*	8	5
For adults with narcolepsy type 1, is the current evidence adequate to demonstrate that the net health benefit of oveporexton is greater than that of sodium oxybate? *One CEPAC member noted that the central issue underlying this question was whether voting members considered network meta-analysis (NMA) to be an appropriate and reliable method for generating comparable evidence, rather than focusing on the particulars of the medications themselves. In response, another CEPAC member stated that she viewed NMA as a valid approach and emphasized that her assessment of certainty was informed by the overall body of evidence, including large effect sizes from well-conducted trials that point to some added benefit.* *Another CEPAC member highlighted the methodological rigor underlying NMA, explaining that, in reviewing confidence intervals, substantial bias would likely be required to negate the results, which he considered highly unlikely.* *One CEPAC member further commented that his vote was influenced not only by the clinical trial evidence, but also by the strength of perspectives shared by patient experts and oral commenters during the public meeting.*	10	3
For adults with narcolepsy type 1, is the current evidence adequate to demonstrate that the net health benefit of oveporexton is greater than that of pitolisant?	11	2

4. Long-Term Cost Effectiveness

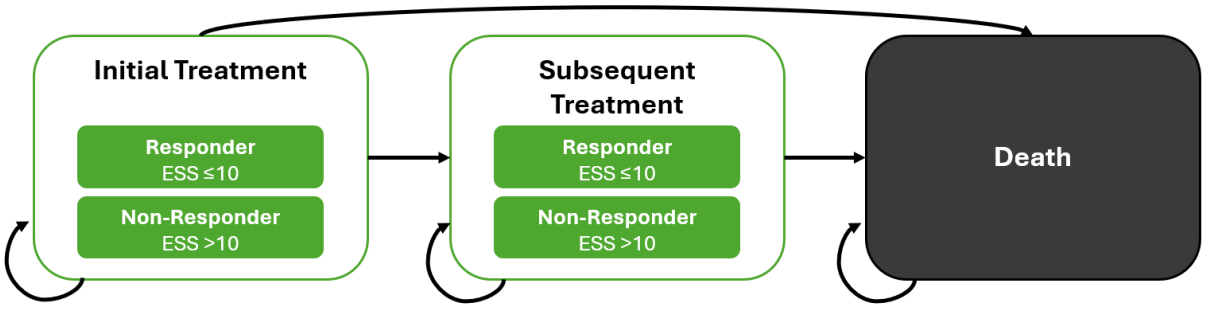
4.1. Methods Overview and Structure

The aim of this analysis was to estimate the cost-effectiveness of oveporexton compared to a combination of stimulant with cataplexy medication represented by modafinil combined with venlafaxine, sodium oxybate, pitolisant, or no pharmacological treatment for narcolepsy type 1 (NT1) in adults. We developed a *de novo* decision analytic model, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with NT1 being treated with oveporexton or comparators when entering the model. Cohort characteristics were based on the patient populations of the FirstLight and RadiantLight trials.[16] Model cycle length was three months, based on prior published economic models and clinical data.[16,56-60] Patients were modeled over a lifetime horizon with a half-cycle correction to account for the continuous nature of health state transitions.

The model followed a simple structure consistent with prior published economic models.[56-60] The model structure is displayed in Figure 4.1. and consists of three health states: initial treatment, subsequent treatment, and death. While on treatment, patients are classified as responders if Epworth Sleepiness Scale (ESS) scores are 10 or lower, and non-responders if ESS scores are greater than 10. Responders and non-responders were assigned differential costs. Patients are assumed to maintain their responder or non-responder status while remaining on the same treatment.

Figure 4.1. Model Structure



ESS: Epworth Sleepiness Scale
Health state utilities are treatment-based and not impacted by responder status.
Initial treatment may be oveporexton, modafinil + venlafaxine, sodium oxybate, pitolisant, or no pharmacological treatment.

Patients entering the model receive an initial treatment and could remain in this state or transition to subsequent treatment upon discontinuation due to adverse events (AEs) or lack of efficacy (LOE). Patients who begin with no pharmacological treatment do not transition to subsequent treatment and remain on no pharmacological treatment over their lifetime. When comparing oveporexton to no pharmacological treatment, patients who discontinue oveporexton transition to no pharmacological treatment in the subsequent treatment state. When comparing oveporexton to active comparators (modafinil + venlafaxine, sodium oxybate, pitolisant) patients who discontinue any active treatment are distributed across current therapies (modafinil + venlafaxine, sodium oxybate, pitolisant, no pharmacological treatment) using a treatment basket approach. The distribution of the basket is detailed in Table 4.2. All patients could transition to death from all causes from any of the alive health states.

The impact of treatments on NT1 symptoms, including excessive daytime sleepiness (EDS), cataplexy, and nighttime symptoms, was captured through impacts on health-related quality of life (HRQoL) obtained from the pivotal trials. Treatment specific health state utilities were derived from clinical trial data and represent the weighted average utility across responders and non-responders at the distribution observed in the respective clinical trials, as separate utility estimates for responders and non-responders were not available. Data was available to inform differential costs for responders and non-responders and is detailed in Section 4.2.

Changes to the economic evaluation between the draft evidence report and the revised evidence report include:

- Updated the placeholder price for oveporexton from $175,000 annually to $250,000 annually based on updated estimates from IPD Analytics.
- Modified the analysis to distinguish the oveporexton versus no treatment comparison from the oveporexton versus active treatment comparisons. In the no treatment comparison, patients who discontinue oveporexton will move to no treatment (rather than to a basket of current treatments). In comparison to active treatments, patients who discontinue oveporexton will still move to the subsequent treatment basket. This change corrects an asymmetry in the prior model structure, in which oveporexton discontinuers in the no-treatment comparison were assigned to a subsequent treatment pathway while patients who initiated on no treatment stayed there throughout the lifetime.
- Discontinuation rates in the draft report were calculated for 12 weeks. These have been updated to 13 weeks to align with the three-month time interval used for other model inputs.

- Pitolisant costs reported in the draft report were calculated for an average dose of 20.65 mg (annual net price of $162,912) and have been corrected to reflect the 28.69 mg dose used in the model (annual net price of $216,392). The dose was updated to reflect the average dose observed in the trials that informed the model's clinical inputs, ensuring greater consistency between efficacy and cost parameters. Note that this correction only applies to the costs in the report and does not affect model outputs or results, as the model in the draft report was applying the 28.69 mg dose.

- Added half-cycle correction to account for the continuous nature of transitions.

- Added two scenario analyses to better model real-world sodium oxybate utilization based on public comments received. As the generic is not the most used formulation, market share data across all sodium oxybate products was incorporated, and another applying clinician informed dose distributions that increases average dose from 7.5 g nightly to 8.25 g nightly.

- Added scenario analysis removing excess mortality from narcolepsy, informed by a sex- and age-matched, or sibling cohort study by Hsu et al. that found no significant excess mortality among patients with narcolepsy.[61]

- Recategorized treatment acquisition costs associated with retry of treatment after discontinuation from subsequent to initial treatment acquisition costs.

4.2. Key Model Assumptions and Inputs

Our model included several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Treatment effectiveness remained constant while on treatment.	There is limited long-term data on treatment effects. Clinical experts indicated patients on current narcolepsy medications maintain treatment response over extended durations.
Patients who discontinued initial treatment transitioned to a subsequent treatment basket.	Modeling all possible treatment pathways would substantially increase model complexity. There is no robust evidence to inform specific switching patterns. As a result, we used a basket approach informed by observed prescription patterns.
Patients who achieved ESS ≤10 had no EDS and incurred non-drug and productivity costs equivalent to controls without narcolepsy. Patients with ESS scores of 11 or higher had mild to severe EDS and incurred full narcolepsy related costs.	We expect patients to have reduced health care use and increased productivity when sleepiness is improved. There is insufficient evidence to model these costs by more granular disease severity categories.

Assumption	Rationale
Venlafaxine impacted cataplexy without additional effects on EDS; modafinil impacted EDS without additional effects on cataplexy and drove HRQoL changes.	There is no evidence available to model a combined effect of modafinil and antidepressants such as venlafaxine on EDS and cataplexy. The model applied modafinil's effects on EDS and HRQoL, while venlafaxine only contributed to treatment costs with no additional modeled effect on outcomes.
Treatments had no impact on mortality in the base case.	There is insufficient evidence that any narcolepsy treatment reduces the elevated mortality from the disease. While certain therapies such as stimulants or high-sodium oxybates have been associated with increased cardiovascular risks, narcolepsy itself has also been linked with adverse cardiometabolic outcomes.[62,63] Treatments may reduce risk by improving sleep disruptions while increasing risk due to direct pharmacological effects. Available data does not detangle these effects, nor quantify the impacts of these treatments on all-cause or cardiovascular mortality in patients with narcolepsy.
Treatments share long-term discontinuation rates from two years onwards from HARMONY 3.	Due to differing follow-up durations across extension trials for the different treatments (i.e., six months for oveporexton and five years for pitolisant),[18,57] extrapolation of treatment-specific rates may bias results. To ensure a fair comparison while using the available data, treatment-specific discontinuation rates obtained from trials and extension studies were only applied for the first two years. From two years onwards, we assumed uniform discontinuation rates across all treatments, informed by data with the longest follow-up of five years from HARMONY 3.[57]

EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, HRQoL: Health Related Quality of Life

Clinical Inputs

The clinical inputs in the model were derived from a review of the literature, ICER's network meta-analysis, and in consultation with experts. Key clinical inputs include transition probabilities to subsequent treatment, informed by discontinuation rates observed in the pivotal trials, the distribution of patients into the different therapies on subsequent treatment, and the proportion of patients who achieve an ESS score of ≤10. Key model inputs are displayed in Table 4.2.

Transitions to subsequent treatment were informed by treatment-specific discontinuation rates obtained from pivotal trials. Rates observed in pivotal trials were applied during the first 3-month cycle, with long-term rates obtained from long-term extension studies applied in subsequent cycles up to two years. Afterward, all initial treatments were assumed to have the same discontinuation rates obtained from HARMONY 3, as this represented the longest available follow-up data across the treatments.[57] Discontinuation due to lack of efficacy was only applied to patients who did not achieve an ESS score of ≤10, while discontinuation due to adverse events was applied to all patients

on initial treatment. Lack of efficacy rates were adjusted by dividing by one - proportion achieving ESS ≤10 to account for the fact that these rates were obtained from the full patient population in the trials but only applied to patients with mild to severe EDS in the model. Patients who were on no pharmacological treatment as their initial treatment stayed on no treatment throughout their lifetime, and patients on oveporexton in the no treatment comparison moved to no treatment upon discontinuation.

The subsequent treatment basket for comparison of oveporexton versus active comparators included a mixture of treatments used in current practice, with proportions obtained from published survey data by Ortiz et al.[7] Patients were able to retry the initial treatment in the subsequent treatment state, as patients may cycle to other doses or formulations of the same types of drugs, or resume the prior treatment after a period of discontinuation or exploring other treatment options. As most patients surveyed were on multiple treatments, we assumed the proportion on a stimulant + anti-cataplectic medication was the proportion of patients who were not on sodium oxybate, pitolisant, or no pharmacological treatment. Our subsequent treatment basket modeled a mixture of treatments; however, to limit uncertainty in our model, we assumed patients did not receive treatments in combination beyond the stimulant + antidepressant comparator (modafinil + venlafaxine), as data on efficacy on different combinations, as well as the distribution of combinations, are limited. All treatments were assumed to have the same effectiveness on subsequent treatment as initial treatment, as no clinical trial data was available to inform differential effectiveness following switching or re-initiation.

The proportion of patients who achieved an ESS score of ≤10 was obtained by adding absolute risk differences from an ICER NMA to the proportion observed to pass this threshold in the placebo arms of the FirstLight, RadiantLight, and Phase II oveporexton trials.[16,17] Due to lack of placebo data to incorporate estimates for sodium oxybate into the NMA, we applied the observed responder rate for patients who achieved ESS ≤10 from the sodium oxybate arm in the REST-ON trial directly.[34] Further information on the NMA can be found in Supplement Sections D2 and E2.

We applied age- and sex- specific mortality rates from Human Mortality Database US-specific tables, adjusted by sex-specific standardized mortality ratios (SMRs) for narcolepsy.[64] The elevated mortality rates were applied to all patients regardless of treatment in the base case. The removal of the elevated mortality, back to general population rates for patients with ESS ≤10 as well as for all patients, were explored in scenario analyses.

Adverse event (AE) related disutilities and costs were not incorporated into the model. AEs observed in the pivotal trials of all treatments were predominantly mild to moderate with low incidence of treatment-related serious adverse events (<4%).[16,21,31,65]

Cataplexy attack counts over the lifetime was included as a secondary outcome in the oveporexton versus no pharmacological treatment comparison. Cataplexy attacks were not comparable across studies for active comparators due to differing study populations, trial protocols and their allowance of background therapies, follow-up duration, and outcome reporting measurements, with some reporting median rates and others reporting means. As a result, we were unable to include cataplexy counts as a secondary outcome in the oveporexton versus active treatment comparisons.

See Supplement Section E2 for additional details.

Health State Utility Inputs

Health state utilities were composed of a no pharmacological treatment utility plus a treatment-specific increment. Utilities were not specific to response status and represent a weighted average across responders and non-responders at the distribution observed in the respective trials. Subsequent treatment utilities were calculated as a weighted average of the individual treatment utilities included in the subsequent treatment basket.

Age- and sex- based US population EQ-5D-5L values were adjusted with a disease-specific multiplier to reflect the utility decrements associated with NT1 with no pharmacological treatment, while preserving the underlying age-related trajectory. The multiplier was calculated by dividing the pooled placebo arm utility from the FirstLight and RadiantLight trials (0.76), by the population utility of 24-34 year olds, corresponding to our cohort's mean age at baseline.[16,66]

We explored two approaches for estimating treatment specific incremental utilities. In the base case, increments were derived from utility instruments used in the pivotal trials for each respective treatment. In a scenario analysis, treatment-specific changes in ESS scores were mapped to EQ-5D values using data from Cambron-Mellott et al.[67] Trial based utilities were chosen in the base case because NT1 has a larger impact on patient quality of life than what may be captured solely through looking at one symptom by proxy of ESS, which is known to be a subjective measure, to capture treatment impact on as many dimensions of disease as possible, rather than anchoring utility values on one factor with ESS. Additionally, the source for ESS based utilities were largely from patients with obstructive sleep apnea (n=2,277), with only a small proportion of patients having narcolepsy (n=48) or both (n=23), and the type of narcolepsy was not specified which introduces uncertainty in how well these value align with the modeled population.[67] Further details on the ESS based approach can be found in Supplement Sections E2 and E4.

For oveporexton, mean changes in EQ-5D-5L index scores from baseline versus placebo were pooled for the 2 mg BID arms of the FirstLight and RadiantLight trials.[16] SF-6D utilities were estimated using a published mapping algorithm for modafinil and sodium oxybate using SF-36 values published from the pivotal trials.[37,68,69] The utilities were based on SF-36 scores for the 200

mg arms, and 6 g and 9 g arms for modafinil and sodium oxybate, respectively. The incremental utility for these treatments was calculated using the difference-in-differences (DID) between the treatment arms and placebo arms of the respective trials. Modafinil was assumed to drive the change in HRQoL for the modafinil + venlafaxine comparator. This assumption was supported by literature examining determinants of HRQoL in narcolepsy populations as irresistible sleep episodes, disease duration, marital status, employment status, and mood were significant predictors of EQ-5D and SF-36 but not cataplexy.[70-72] EQ-5D Visual Analog Scale (VAS) scores were obtained from the HARMONY CTP trial for pitolisant, estimated using the DID between the treatment and placebo arms.[31] Although combining multiple different utility measures introduced uncertainties into our results, incorporating trial-based utilities allowed modeling a more complete picture of the patient experience by indirectly capturing the impact on all symptoms, including EDS, cataplexy, and nighttime symptoms.

Cost Inputs

All costs used in the model were updated to 2025 dollars.

Drug Costs

Based on estimates from IPD Analytics, we used an annual placeholder price of $250,000 for oveporexton, as neither list nor net prices are available. For modafinil, venlafaxine, and sodium oxybate, we used the median price of all the generic options in RedBook. Costs for sodium oxybate were calculated with a dose of 3.75 g twice nightly (7.5 g nightly) based on the trials that informed our utilities and response rates.[34,37] For venlafaxine, prices per dose were calculated using the most common dose of 75 mg/day.[24] An average dose of 28.69 mg for pitolisant was calculated from the stable dose of HARMONY 1.[30] A discount of 17.6% for pitolisant was obtained from SSR Health and applied to the list price from RedBook. Drug costs for subsequent treatments were calculated by weighing each treatment's cost by its proportions within the basket. See Supplement Table E2.3 for detailed drug acquisition cost calculations.

Health Care Utilization Costs

Non-drug health care costs included costs associated with outpatient care, emergency room visits, and hospitalizations. Available evidence from the literature compared costs between patients with narcolepsy and controls without narcolepsy, with limited evidence comparing costs across varying disease severities. Given this limitation, we assumed all patients experiencing any EDS symptoms (ESS >10) incurred all narcolepsy-related health care costs, and patients with no EDS (ESS ≤10) incurred the costs of the control population.

See Supplement Section E2 for additional information on costs, including costs associated with productivity.

Table 4.2. Key Model Inputs

Parameter		Input	Source
Mean (SD) Age, Years		30.4 (10.9)	2 mg twice daily arms of the FirstLight and RadiantLight trials[16]
Female, %		56.6	
Clinical Inputs			
Weekly Cataplexy Rate – Oveporexton		4.5	FirstLight and RadiantLight[16]
Weekly Cataplexy Rate – No Pharmacological Treatment		17	
Proportion Achieving ESS ≤10 On No Pharmacological Treatment		0.1503	ICER NMA (See Supplement Table D2.3 for detailed results)
Proportion Achieving ESS ≤10 On Sodium Oxybate		0.56	REST-ON [34]
Absolute Risk Difference – Response (ESS ≤10) Compared to No Pharmacological Treatment*			
Oveporexton		0.66 (95% CrI 0.31-0.87)	ICER NMA (See Supplement Table D2.3 for detailed results)
Modafinil + Venlafaxine		0.25 (95% CrI 0.05-0.69)	
Pitolisant		0.17 (95% CrI 0.02-0.40)	
Transition Probabilities to Subsequent Treatment: 3-Month Discontinuation Rates†			
Oveporexton	**AE 1st Cycle**	2.76%	FirstLight and RadiantLight[16]
	LOE 1st Cycle	0%	
	AE Up To 2 Years	1.09%	Phase II LTE[18]
	LOE Up To 2 Years	0%	
Modafinil + Venlafaxine	**AE 1st Cycle**	5.66%	US Modafinil in Narcolepsy Multicenter Study Group 1998 and 2000[21,22]
	LOE 1st Cycle	2.20%	
	AE Up To 2 Years	2.64%	Mitler 2000 and Moldofsky 2000[73,74]
	LOE Up To 2 Years	3.85%	
Sodium Oxybate	**AE 1st Cycle**	21.19%	Ahmed 2005 (6g and 9g arms), Black 2006 and REST-ON[26,65,87,34]
	LOE 1st Cycle	1.87%	REST-ON [34]
	AE Up To 2 Years	1.45%	Mayer 2018, Bogan 2023, and Roy 2024[75-77]
	LOE Up To 2 Years	0.43%	Mayer 2018 and Bogan 2023[75,76]
Pitolisant	**AE 1st Cycle**	2.17%	HARMONY 1 and CTP[30,31]
	LOE 1st Cycle	9.86%	
	AE Up To 2 Years	2.80%	HARMONY 3[57]
	LOE Up To 2 Years	5.29%	
All Treatments	**AE 2 Years +**	0.39%	HARMONY 3[57]
	LOE 2 Years +	0.39%	
Subsequent Treatment Basket Composition			
Modafinil + Venlafaxine		0.38	Ortiz 2025[7]
Sodium Oxybate		0.32	
Pitolisant		0.11	
No Pharmacological Treatment		0.19	

Parameter	Input	Source
Health State Utilities		
General US Population Utilities	Age-dependent	Jiang 2021[66]
Narcolepsy Utility Multiplier for No Pharmacological Treatment	0.834	Placebo arms of the FirstLight and RadiantLight trials[16] + Jiang 2021[66]
Incremental Utility – Oveporexton	0.20	The FirstLight and RadiantLight 2 mg/2 mg arms[16]
Incremental Utility – Modafinil + Venlafaxine	0.021	Beusterien 1999[69] and Ara 2009[68]
Incremental Utility – Sodium Oxybate	0.016	Bogan 2016[37] and Ara 2009[68]
Incremental Utility – Pitolisant	0.011	Szakacs 2017[31]
Mortality		
SMR For Narcolepsy - Male	1.57 (95% CI: 1.43, 1.72)	Ohayon 2014[64]
SMR For Narcolepsy - Female	1.43 (95% CI: 1.31, 1.57)	
All-Cause Mortality	Age- and sex-dependent	US Life Tables
Costs		
Annual Net Drug Acquisition Costs		
Oveporexton	$250,000‡	IPD Analytics
Modafinil	$460.22§	RedBook
Venlafaxine	$164.36§	
Sodium Oxybate	$160,363§	
Pitolisant (Wakix®)	$216,392	RedBook with 17.6% discount from SSR Health
Annual Health Care Utilization Costs for Mild to Severe EDS - Mean (SD)		
Outpatient Care	$9,245 (14,854)	Doane 2025[78]
Emergency Room	$2,822 (7,916)	
Hospitalization	$25,749 (72,889)	
Annual Health Care Utilization Costs for No EDS - Mean (SD)		
Outpatient Care	$4,934 (8,686)	Doane 2025[78]
Emergency Room	$1,742 (6,215)	
Hospitalization	$16,647 (76,399)	

AE: adverse event, CrI: credible interval, CI: confidence interval, EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, LOE: lack of efficacy, NMA: Network-Meta Analysis, RR: relative risk, SD: standard deviation, SMR: Standardized Mortality Ratio, US: United States

*The proportion of patients achieving ESS ≤10 is estimated as the sum of the proportion achieving this threshold on no pharmacological treatment, and the absolute risk difference for each treatment. Where this sum exceeds 1, the value is capped at 1.

†Discontinuation rates from pivotal trials are applied for the first three-month cycle, followed by discontinuation observed in long-term extension trials for subsequent cycles up to two years. All initial treatments were then assumed to have the same discontinuation rates from two years onwards.

‡Placeholder Price

§Represents the median price of all available generics

4.3. Results

Base-Case Results

Under the base-case assumption that no treatments impact mortality, life years are equal across all strategies, and equal value of life years (evLYs) are equivalent to quality-adjusted life years (QALYs). Further information on how evLYs are calculated can be found in Supplement Section E1. Discounted acquisition costs for initial and subsequent treatments, total costs, QALYs, and evLYs are detailed in Table 4.3. Incremental cost-effectiveness ratios for oveporexton relative to active comparators are displayed in Table 4.4, and ratios relative to no pharmacological treatment are displayed in Table 4.5. These include cost per QALY gained, cost per evLY gained, and cost per life year gained for the base case.

Table 4.3. Results for the Base Case

Oveporexton vs. Active Comparators						
Treatment	**Initial Treatment Acquisition Costs**	**Subsequent Treatment Acquisition Costs**	**Total Costs**	**QALYs**	**evLYs**	**Life Years**
Oveporexton	$3,884,000*	$649,000	$5,192,000*	20.11	20.11	24.05
Modafinil + Venlafaxine	$9,600	$1,055,000	$1,809,000	17.29	17.29	24.05
Sodium Oxybate	$2,456,000	$318,000	$3,503,000	17.25	17.25	24.05
Pitolisant	$2,268,000	$791,000	$3,816,000	17.20	17.20	24.05
Oveporexton vs. No Pharmacological Treatment						
Treatment	**Initial Treatment Acquisition Costs**	**Total Costs**	**QALYs**	**evLYs**	**Life Years**	**Cataplexy Attacks†**
Oveporexton	$3,884,000*	$4,574,000*	19.99	19.99	24.05	23,093
No Pharmacological Treatment	$0	$857,000	16.88	16.88	24.05	39,832

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

†Cataplexy attacks are not discounted

Table 4.4. Base Case Incremental Cost-Effectiveness Ratios versus Active Comparators

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	Modafinil + Venlafaxine	$1,201,000	$1,201,000	No difference in life years
	Sodium Oxybate	$589,000	$589,000	No difference in life years
	Pitolisant	$472,000	$472,000	No difference in life years

evLYs: equal value of life years gained, QALY: quality-adjusted life year
*Based on placeholder price for oveporexton of $250,000 annually

Table 4.5. Base Case Incremental Cost-Effectiveness Ratios versus No Pharmacological Treatment

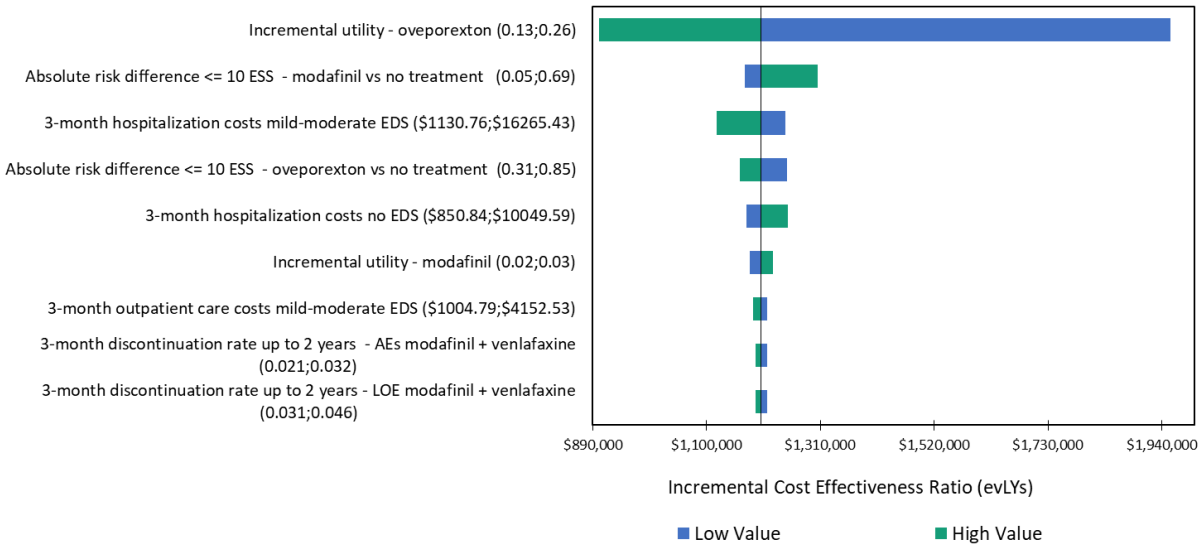
Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	No Pharmacological Treatment	$1,196,000	$1,196,000	No difference in life years

evLYs: equal value of life years gained, QALY: quality-adjusted life year
*Based on placeholder price for oveporexton of $250,000 annually

Sensitivity Analyses

Results for QALYs were equivalent to evLYs in all sensitivity analyses. One-way sensitivity analysis was conducted to evaluate the impact of parameter uncertainty and identify key drivers to model outcomes. Figure 4.2. shows how cost per evLY varies as parameters change in the health care sector perspective for oveporexton compared to modafinil + venlafaxine. The incremental utility of oveporexton had the largest impact on these results, followed by the probability of achieving response on treatments, and hospitalization costs. When compared to other treatments, key parameters were similar with the addition of discontinuation rates. Additional tornado diagrams for the other comparators can be found in Supplement Section E4.

Figure 4.2. Tornado Diagram – Oveporexton versus Modafinil + Venlafaxine*



AEs: adverse events, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, evLY: equal value life year, LOE: lack of efficacy

*Based on placeholder price for oveporexton of $250,000 annually

Probabilistic Sensitivity analyses were conducted by varying all parameters over 1,000 simulations to calculate the proportion of simulations oveporexton was cost-effective at the standard cost-effectiveness thresholds relative to each comparator. At a placeholder price of $250,000, oveporexton was not cost-effective relative to any comparator in any simulation. Results are detailed in Table 4.6 with simulation means and credible intervals detailed in Supplement Section E4.

Table 4.6. Probabilistic Sensitivity Analysis: Cost per evLY Gained Results

Comparator	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Oveporexton vs. Active Comparators				
Modafinil + Venlafaxine	0%	0%	0%	0%
Sodium Oxybate	0%	0%	0%	0%
Pitolisant	0%	0%	0%	0%
Oveporexton vs. No Pharmacological Treatment				
No Pharmacological Treatment	0%	0%	0%	0%

evLY: equal value of life year

*Based on placeholder price for oveporexton of $250,000 annually

Scenario Analyses

We conducted scenario analyses to examine the uncertainty and potential variations in our results.

1. Modified societal perspective, including costs associated with patient productivity.
2. ICER reference case removing unrelated health care costs.
3. Applying ESS based utilities.
4. Sodium oxybate costs weighted by market share across all available products.
5. Sodium oxybate dose reflecting the real-world distribution.
6. Removal of elevated mortality for patients who reach ESS ≤10.
7. No excess all-cause mortality attributed to narcolepsy.

Applying ESS based utilities resulted in the largest deviation from the base case incremental cost-effectiveness ratios across all scenarios explored, with incremental outcomes detailed in Table 4.7 and Table 4.8. Although ESS based utilities offer the advantage of applying a uniform instrument across treatments, values are obtained from a population of predominantly obstructive sleep apnea patients and are only based on changes in ESS, accounting for one factor of disease when narcolepsy is multi-dimensional. Conversely, trial-derived utilities, while more specific to the narcolepsy population, may reflect treatment-specific measurement contexts and instrument specific measurement properties that limit comparability across products. Incremental cost-effectiveness ratios increased in this scenario by approximately 8% to 150% from the base case across the comparators. The sensitivity of incremental cost-effectiveness ratios to utility measurement methodology reflects the broader uncertainty in instrument selection for this condition, where no single approach is without limitations. Other scenarios did not result in substantial changes. Additional details and results are presented in the Supplement Section E5.

Table 4.7. Scenario Analysis Results 3 – Incremental Outcomes for ESS Based Utilities versus Active Comparators

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	Modafinil + Venlafaxine	$3,202,000	$3,202,000	No difference in life years
	Sodium Oxybate	$1,599,000	$1,599,000	No difference in life years
	Pitolisant	$1,303,000	$1,303,000	No difference in life years

ESS: Epworth Sleepiness Scale, evLYs: equal value of life years, QALY: quality-adjusted life year
*Based on placeholder price for oveporexton of $250,000 annually

Table 4.8. Scenario Analysis Results 3 – Incremental Outcomes for ESS Based Utilities versus No Pharmacological Treatment

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	No Pharmacological Treatment	$1,574,000	$1,574,000	No difference in life years

ESS: Epworth Sleepiness Scale, evLYs: equal value of life years, QALY: quality-adjusted life year
*Based on placeholder price for oveporexton of $250,000 annually

Threshold Analyses

Threshold analyses were conducted for oveporexton to estimate the annual price needed to meet common cost-effectiveness thresholds for QALYs and evLYs versus comparators. Results are displayed in Table 4.9 and Table 4.10.

Table 4.9. QALY-Based Threshold Analysis Results

Comparator Treatment	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Oveporexton vs. Active Comparators				
Modafinil + Venlafaxine	$41,300	$50,400	$59,400	$68,500
Sodium Oxybate	$150,000	$160,000	$169,000	$178,000
Pitolisant	$171,000	$180,000	$190,000	$199,000
Oveporexton vs. No Pharmacological Treatment				
No Pharmacological Treatment	$20,800	$30,800	$40,800	$50,800

QALY: quality-adjusted life year
Note: Anticipated annual price for oveporexton is $250,000 annually.

Table 4.10. evLY-Based Threshold Analysis Results

Comparator Treatment	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Oveporexton vs. Active Comparators				
Modafinil + Venlafaxine	$41,300	$50,400	$59,400	$68,500
Sodium Oxybate	$150,000	$160,000	$169,000	$178,000
Pitolisant	$171,000	$180,000	$190,000	$199,000
Oveporexton vs. No Pharmacological Treatment				
No Pharmacological Treatment	$20,800	$30,800	$40,800	$50,800

evLY: equal value of life year

Note: Anticipated annual price for oveporexton is $250,000 annually.

Model Validation

Model validation followed standard practices in the field. All model inputs and mathematical functions were reviewed to ensure consistency with the report and supplemental appendix materials. Stress testing using null input values confirmed that the model produced results aligned with expectations. An independent modeler also verified the mathematical functions, inputs, and outputs. Validation also included comparisons with findings from similar models identified in the literature, focusing on those with comparable populations, settings, perspectives, and treatments. Specifically, we compared our model's outcomes, inputs, and assumptions with other published models to evaluate face validity and identify key similarities and differences (please find more details in "Prior Economic Models" section in Supplement Section E7). Additionally, the model analysis plan and/or draft evidence report were reviewed by multiple stakeholders—including manufacturers and clinical and economic experts—and changes were made based on their feedback.

Uncertainty and Controversies

There are several limitations and uncertainties in our model:

- Uncertainty Around Utility Estimates: Large data gaps exist on how clinical outcomes, such as those related to cataplexy, nighttime sleep, and cognitive symptoms, can be translated into impacts on HRQoL. Trial-based utilities were used in the base case to incorporate these dimensions of NT1, rather than relying on ESS based utilities, which reflect only excessive daytime sleepiness. However, utility increments for modafinil + venlafaxine and sodium oxybate were derived via a SF-36 to SF-6D mapping algorithm, and for pitolisant from EQ-5D-VAS scores. As different instruments capture different dimensions of health with different evaluation methods, they may respond differently to the same clinical change. This

introduces uncertainty when comparing incremental utilities across treatments, however the impact on magnitude and direction is unknown. In a scenario analysis using uniform utility estimates based solely on ESS, incremental QALYs for oveporexton versus all comparators decreased, resulting in higher incremental cost-effectiveness ratios across all pairwise comparisons. Another limitation around utilities is that conventional measures such as the EQ-5D may not be able to adequately capture all dimensions related to NT1, resulting in potentially conservative utility estimates. However, these were the best estimates available when developing the model.

- Data Gaps in Disease Burden: Downstream and broader life course consequences of uncontrolled NT1 such as cardiovascular disease, mental health comorbidities, caregiver burden and educational and professional impacts could not be explicitly modeled due to limited evidence directly linking treatment to reductions in these outcomes. Due to these gaps, model results may underestimate the full burden of NT1 and value of effective treatment – particularly in comparison to no treatment.

- Differences in Trial Protocols and Outcomes: Pivotal trials for different treatments had varying protocols and reported measures in their results, increasing uncertainty when comparing treatments. Oveporexton trials required washout of all previous therapy, with the baseline and placebo values associated with no pharmacological treatment. However, trials for sodium oxybate and pitolisant allowed patients to remain on either stable stimulant or anti-cataplectic medications, depending on the trial. This resulted in different baseline measures, and continued background therapies may have reduced the opportunity for changes in the clinical outcomes when compared to oveporexton. Although we performed NMAs to produce more comparable results, differences in trial protocol still introduce uncertainties in our comparisons and should be kept in mind while viewing the model's results.

- Uncaptured Benefits of Combination Treatments: In the current treatment space, patients with NT1 tend to rely on multiple pharmacological treatments to manage their symptoms. While a combination of a stimulant + anti-cataplectic medication, such as modafinil + venlafaxine, tends to be the first-line treatment for most NT1 patients, no trials have been conducted to evaluate this combination. Trials examining these treatments as monotherapies show that they may have an impact on both excessive daytime sleepiness and cataplexy, although in practice stimulants like modafinil are used to treat sleepiness, and anti-depressants like venlafaxine are used to treat cataplexy, there was no data to model a synergistic effect of these treatments and large uncertainties around this combination exist.[21,22,24] Due to these limitations, utilities in the model were based solely on the effect of modafinil and may underestimate the clinical impact of the combination.

- Lack of Granularity in Health Care Utilization Costs and Productivity Estimates: Non-drug costs and productivity estimates in the literature have only been reported for controls without narcolepsy, and for patients with narcolepsy of varying severity and type. There is currently a gap in the literature on how these estimates may vary across disease severity and treatments. Due to this, we were limited in differentiating these costs between treatments and were only able to assume that patients with no EDS would assume the costs of the controls. This may underestimate costs for patients who achieve no EDS, while overestimating costs for patients on treatment who don't reach that threshold.

4.4. Summary and Comment

Over a lifetime horizon, patients on oveporexton experienced gains in QALYs and evLYs relative to all comparators in the base case. At a placeholder price of $250,000, our analysis estimates oveporexton to exceed commonly used cost-effectiveness thresholds relative to all comparators. The actual cost-effectiveness of oveporexton will depend on its price. Results were most influenced by the incremental utilities for treatments (especially for oveporexton), treatment response rates, costs associated with hospitalizations, and discontinuation rates.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	Although multiple drugs exist for the treatment of NT1, current treatments do not address the underlying cause of orexin deficiency, provide incomplete symptom relief, may have significant side effects, and may have inconvenient dosing. Thus, there is a need for better treatments for NT1. Oveporexton is the first treatment for NT1 that addresses the underlying orexin deficiency that is the hallmark of the disease. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled population below. Individuals who manage NT1 with modafinil + venlafaxine were used as a reference group. evLY shortfalls: Absolute shortfall: 10.4 Proportional shortfall: 24.5% QALY shortfalls: Absolute shortfall: 9.4 Proportional shortfall: 22.7% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	We did not find any evidence that NT1 disproportionately affects those from racial/ethnic groups that have not been equitably served by the health care system.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.	None identified.
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Caregiver impact is high for NT1, as persons with NT1 often have significant limitations to their daily activities even with treatment. A more effective treatment for NT1 could lessen caregiver impact by allowing persons with NT1 to participate more fully in daily activities. This would likely result in improved caregiver quality of life, as well as improved ability of caregivers to pursue their own education, work, and family life.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.	Some treatments for NT1 are controlled substances and/or require enrollment in a REMS program for access, which can present barriers to treatment. It is not known how oveporexton will be classified if approved by the US FDA. However, if oveporexton does not have any of the above restrictions placed, access to treatment may be improved.

ICER did not calculate the Health Improvement Distribution Index (HIDI) due to a lack of available race/ethnicity data of US adults with NT1.

Midwest CEPAC Votes

At the public meeting, the Midwest CEPAC deliberated and voted on the relevance of benefits beyond health and special ethical priorities to inform judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please answer the following questions:

Table 5.2. Midwest CEPAC Votes on Special Ethical Priorities - Narcolepsy

Special Ethical Priorities	Typical Obligations	Some Added Obligations	Substantial Added Obligations
Are there particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies? *Patient and clinical experts emphasized the unmet need that persists despite currently available therapies. One clinical expert, who also lives with NT1, shared that even with the latest medications, many patients still feel as though their life is "on hold" while waiting for more effective treatment options. Drawing from his own experience, he described feeling limited in his ability to accomplish personal and professional goals because of his condition. One patient expert reinforced patient perspectives shared during the oral comment session, noting that while many individuals with NT1 are getting by, they still feel unable to fully live their lives, particularly with challenges associated with cataplexy and excessive daytime sleepiness.*	1	6	6
Are there particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the healthcare system?	10	2	1
Apart from issues around disease severity/unmet need and race/ethnicity, are there other particular obligations to people with this condition? *Patient experts described NT1 as an "invisible" condition that is frequently misunderstood by employers, peers, and the broader public, contributing to stigma and social challenges for individuals living with NT1. Drawing on perspectives shared during the oral comments, as well as discussion of insurance coverage barriers and the stigma associated with stimulant medications, one CEPAC member noted that, while these concerns may not fall within traditional racial/ethnic disparities, they nonetheless represent important societal obligations that voting members should consider.*	1	12	0

Table 5.3. Midwest CEPAC Votes on Benefits Beyond Health - Oveporexton

Benefits Beyond Health	No	Yes: Small Improvement	Yes: Substantial Improvement
Is oveporexton likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life? *One patient expert emphasized the important role of caregivers for adults with NT1, including assistance with activities such as driving or communication during doctor appointments. Another patient expert described the broader family burden of NT1 and noted that a new treatment could help reduce time spent managing the condition, allowing the family to redirect time toward other priorities and community engagement.*	0	4	9
If payment/cost were not an issue, would oveporexton be likely to improve access to treatment because of its method of delivery and/or treatment setting? *In discussion, this question was interpreted to include oral formulation and storage with oveporexton's 'method of delivery and/or treatment setting,' given their relevance to potential impacts on access. With expanding this framing, several CEPAC members indicated that they would consider those additional factors and be more inclined to vote yes.* *One clinical expert noted that oveporexton may broaden the range of providers comfortable with managing NT1 care following diagnosis, as it is unlikely to be a controlled substance and is therefore unlikely to carry the same abuse potential concerns as other therapies. ICER staff also noted that some existing treatment options require middle-of-the-night dosing or present storage challenges, whereas these issues would not be expected with oveporexton.*	1	10	2

6. Health Benefit Price Benchmark

The threshold prices for oveporexton from the health care sector perspective, based on both evLYs and QALYs gained relative to the common first-line and generic treatment option, modafinil + venlafaxine, are presented in Table 6.1 below. The Health Benefit Price Benchmark (HBPB) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. The HBPB for oveporexton is $50,400 to $59,400.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Oveporexton

Annual Prices Using…	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
QALYs Gained	$50,400	$59,400
evLYs Gained	$50,400	$59,400

evLY: equal value life year, QALY: quality-adjusted life year

Midwest CEPAC Votes

Long-term value for money votes were not taken at the public meeting because a net price for oveporexton was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to calculate the total potential budgetary impact of oveporexton for the population of adults with NT1. Potential budget impact is defined as the total differential cost of using the new therapy rather than a relevant existing therapy for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. At baseline, we assumed 38% of the eligible population was treated with modafinil + venlafaxine, 32% was treated with sodium oxybate, 11% was treated with pitolisant, and 19% received no pharmacological treatment, as per available market share data.[7] All costs were undiscounted and estimated over a five-year time horizon. We used the oveporexton annual placeholder price of $250,000 and the threshold prices (at $50,000, $100,000, $150,000, and $200,000 per evLY) when compared to modafinil + venlafaxine to estimate the percentage of the eligible population that could be treated before reaching the ICER potential budget impact threshold of $821 million. Further details on ICER's approach to the budget impact analysis are available in Supplement Section F.

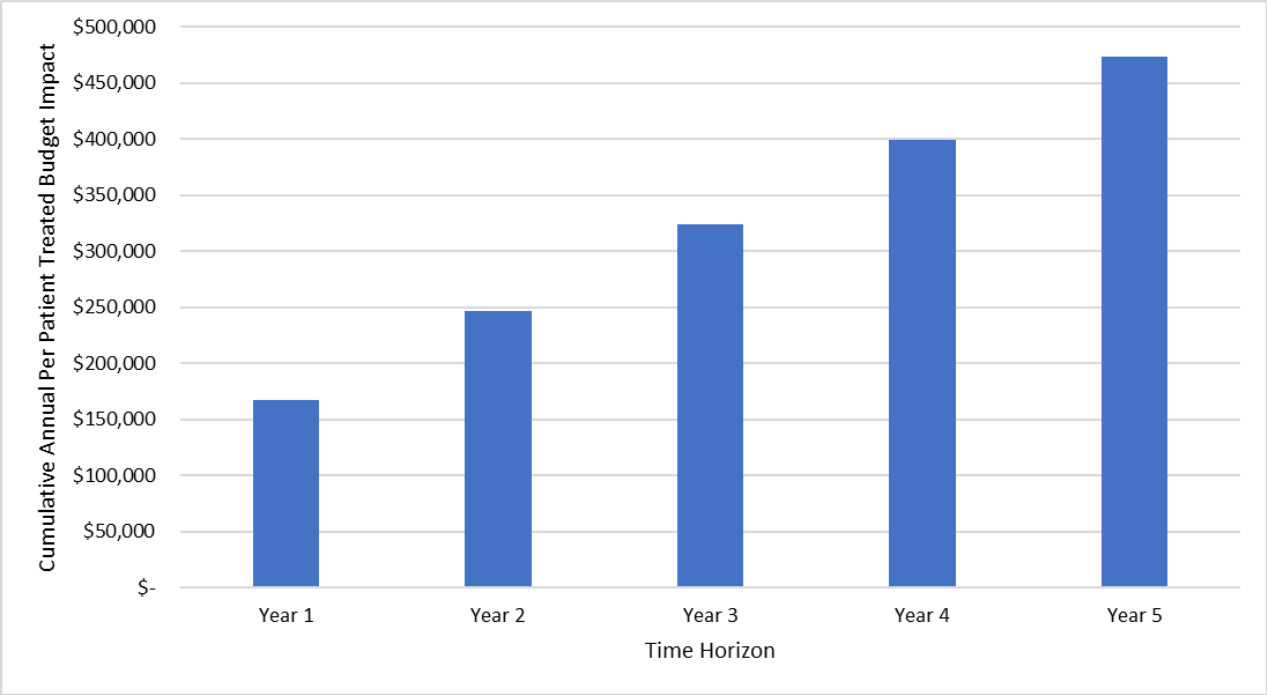
This budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with oveporexton. To estimate the size of the potential candidate population, we used inputs for the prevalence of NT1 in the US (12.6 per 100,000 individuals) and the total US adult population averaged over the next five years (approximately 272,700,000).[1,79] Applying these sources results in estimates of approximately 34,000 eligible patients in the US. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, approximately 6,900 patients per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for oveporexton compared to baseline (split market share between modafinil + venlafaxine, sodium oxybate, pitolisant, and no pharmacological treatment). The cumulative per patient budget impact represents the incremental costs of oveporexton compared to the baseline per patient across all patients treated within a time horizon (including those who initiated oveporexton in previous years), assuming oveporexton is used with 20% uptake each year over five years.

At oveporexton's placeholder price of $250,000 annually, the cumulative annual budget impact per patient was approximately $167,000 in the first year, and increased to approximately $473,000 by year five.

Figure 7.1. Cumulative Annual Per Patient Budget Impact of Oveporexton at a Placeholder Price



Results showed that 25% of eligible patients could be treated with oveporexton at the annual placeholder price of $250,000 before reaching the potential budget impact threshold of $821 million per year. At the $50,000, $100,000, $150,000, and $200,000 per evLY threshold prices for oveporexton compared with modafinil + venlafaxine ($41,300, $50,400, $59,400, and $68,500), all patients could be treated before reaching the potential budget impact threshold.

Access and Affordability Alert

The goal of the Access and Affordability alert is to signal that the additional health care costs introduced by a new intervention may be difficult for the health care system to absorb over the short term. In this situation, other needed services may be displaced, or health care insurance costs may rapidly rise, which would threaten sustainable access to high-value care for all patients.

Assuming a placeholder price for oveporexton of $250,000 per year, 25% of the eligible population could be treated before reaching the ICER potential budget impact threshold of $821 million. Under this assumed placeholder price, ICER is issuing an access and affordability alert for oveporexton. However, if priced within the ICER HBPB range ($100,000 per QALY to $150,000 per evLY), all potentially eligible patients could be treated, and we would not issue an access and affordability alert. Pricing according to value is one policy lever to manage access and affordability concerns for new treatments.

8. Policy Recommendations

Following the Midwest CEPAC's deliberation on the evidence, a policy roundtable discussion was moderated by Sarah Emond, President and Chief Executive Officer at ICER, around how best to apply the evidence on the use of oveporexton for the treatment of NT1. The policy roundtable members included two patient representatives, two clinical experts, two payers, and one representative from the drug maker. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with narcolepsy type 1 (NT1) are introduced in a way that will help reduce health inequities.

Although current therapies for NT1 treat symptoms such as excessive daytime sleepiness (EDS) and cataplexy, the majority of persons living with NT1 are not satisfied with their current treatment.[7] Clinical experts and patient representatives highlighted that the approval of oveporexton would shift the paradigm of treatment for NT1, as it would be the first therapy aimed directly at the underlying orexin deficiency characteristic of the disorder. However, efforts are needed to ensure that new therapies for NT1 such as oveporexton improve the health of patients and families and do not aggravate existing health inequities. For example, the high cost of new therapies may worsen disparities in accessing care. This may be due to a lack of health insurance that limits access to specialists and the new therapies that they may prescribe, or high-deductible health insurance plans that can result in steep out of pocket costs, rendering treatments unaffordable. This is particularly relevant for persons living with NT1, as they may not be able to hold full-time employment due to the severity of their symptoms. Furthermore, the cost of care is not the only factor that may contribute to health inequities. Our clinical and patient experts noted that diagnosis can be severely delayed due to under-recognition of symptoms related to NT1, and that those with poor access to care may be particularly vulnerable to missed or delayed diagnosis.

To address these concerns:

Manufacturer actions:

- Set the price for new treatments for NT1 in fair alignment with added benefits for patients. This is particularly important for first-in-class medications that may shift the treatment paradigm – setting prices in line with value can broaden and expedite access.

- Take steps necessary to expeditiously test oveporexton in areas of high clinical need. In the case of NT1, conducting trials of oveporexton in children and collecting data on safety in pregnancy and lactation is of high priority in order for these populations to have equitable access. In addition, head-to-head trials of oveporexton compared with other treatments, as well as in combination with other treatments, are needed to develop a robust evidence base.

Payer actions:

- Allow for telemedicine consultation with sleep medicine specialists, including across state lines if necessary, given the shortage of sleep medicine providers, particularly in rural areas.

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients.

Educational institution and employer action:

- Provide appropriate accommodations (e.g., designated rooms for short naps, flexible work schedules, secure locations to keep controlled medications) for people living with NT1. Successful accommodation of persons with NT1 could increase work productivity and school achievement.

Clinical specialty society actions:

- Develop and disseminate educational materials to primary care physicians, including pediatricians, about the symptoms and diagnosis of NT1, to heighten awareness and decrease delays in diagnosis.

- Seek ways to increase access to sleep specialists, including advocating for expansion of telemedicine and expanding the sleep medicine workforce.

Policymaker action:

- Ensure affordable access to non-employer-based health insurance programs, such as Medicaid and health insurance exchange plans, given that full-time employment can be challenging for persons living with NT1.

Payers

Recommendation 1

In conjunction with other stakeholders (e.g., manufacturers and clinicians), work to find innovative ways to ensure access for all appropriate patients to therapy given the apparent advantage in efficacy of oveporexton over current treatments.

NT1 is a chronic disorder and persons diagnosed with NT1 generally require lifelong therapy. A survey of patients with NT1 suggested that treatment satisfaction with current therapies is low, likely because, in part, current therapies treat symptoms but do not address the underlying etiology of NT1. Oveporexton is the first drug to correct the underlying orexin deficiency characteristic of NT1. Data from pivotal trials of oveporexton show large improvements in measures of excessive daytime sleepiness, cataplexy, and other patient-important measures, including health-related quality of life, and participants who had taken part in the clinical trials confirmed the substantial difference in efficacy between oveporexton and current standard of care therapies. Given oveporexton's efficacy and relatively benign safety profile, if approved, clinical experts predicted that oveporexton would be considered first-line therapy. Thus, it is critical that payers, manufacturers, and other stakeholders work together to find innovative solutions to ensure access to all NT1 patients who may benefit from treatment with oveporexton. Payers have a role to play in encouraging pricing aligned to value – for example, payers could reduce or eliminate utilization management and cost-sharing for new drugs for manufacturers who pick value-based launch prices. Conversely, if oveporexton is priced beyond its expected value, payers will likely seek to restrict its use, limiting access for patients. Payers could consider outcomes-based agreements in case there are patients who do not respond to or do not tolerate the drug, or a financial-risk based contracts that reimburse the payer if financial outcomes, such as treatment at a lower cost than current standard of care drugs, are not met. Finally, given that NT1 is a chronic disorder requiring lifelong treatment, payers and manufacturers could consider implementing a subscription model, where payers could negotiate a set price for unlimited access to oveporexton for a set period of time.

Recommendation 2

For new therapies that have demonstrated safety and efficacy, particularly where there is substantial unmet need, develop coverage policies in advance of Food and Drug Administration (FDA) approval and avoid new-to-market blocks so that patients can access new treatments as soon as possible after launch.

Many payers now employ new-to-market blocks for nearly all newly approved drugs, lasting up to 180 days, in order to have time to assess the evidence and develop coverage policies. However, these new-to-market blocks pose a significant barrier to access, as clinicians and patients then need to appeal to the health plan for exceptions to have access to the drug during this period of time. For the majority of newly approved drugs, data from pivotal trials are available prior to drug approval and launch. Payers should develop mechanisms to more rapidly craft coverage policies, ideally having coverage policies available at or shortly following the launch of a new drug; the delay in coverage policy development should not exceed the standard set by the Centers for Medicare and Medicaid (review of a new treatment within 90 days, coverage decision within 180 days).

Manufacturers

Recommendation 1

Manufacturers have a responsibility to set prices at levels that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Pricing novel treatments in accordance with the demonstrated benefits to patients as determined through independent analyses would contribute to fair, affordable access for patients with NT1.

Recommendation 2

Conduct research that directly compares real-world treatment options and effectiveness of combination therapy.

Multiple stakeholders expressed concerns about the lack of information directly comparing treatments and the need for active comparator trials. With combination therapy the norm for treatment of NT1, there is an urgent need to understand both the efficacy of oveporexton compared with combination treatment with existing therapies, and whether some NT1 patients

treated with oveporexton may require combination therapy for optimal treatment of NT1 symptoms. Appropriate head-to-head trials would inform decision making by patients and clinicians.

Recommendation 3

Support the development of improved diagnostic tests to support timely diagnosis of NT1.

Clinical experts and patients highlighted that there are multiple barriers to getting a diagnosis of NT1, ranging from low awareness of the disorder to the high burden of diagnostic tests such as the Multiple Sleep Latency Test or a lumbar puncture to test orexin levels. This has led to lengthy diagnostic delays, with surveys showing that the mean time to diagnosis is almost 9 years.[80] Clinical experts mentioned that the development of more accessible diagnostic tests such as blood-based biomarkers tests could potentially help increase the accuracy of diagnosis and decrease diagnostic delay.

Clinicians and Clinical Societies

Recommendation 1

Develop a process to rapidly update treatment guidelines for patients with NT1 when new treatment options are approved in a form that is easy to interpret and use by clinicians, patients, and payers.

Although the American Academy of Sleep Medicine issued an updated clinical practice guidelines in 2025, the approval of new drugs can cause guidelines to be out-of-date quickly. Since payers often base their coverage decisions on clinical guidelines, it is imperative for clinical specialty societies to have processes to rapidly update treatment guidelines when new treatment options emerge, particularly if they substantially change clinical practice. The approach of the National Comprehensive Cancer Network (NCCN), which updates their clinical practice guidelines at least annually and when needed with the approval of a new treatment, is a helpful model.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to raise awareness of NT1 and its impact on patients. In particular, patient organizations are well-positioned to advocate to policymakers, educators, and employers to ensure that the needs of the community are being met.

Patient-led efforts can raise awareness of NT1 in order to decrease diagnostic delays, decrease stigma related to having a diagnosis of NT1, ensure reasonable accommodations from educators as

well as employers, and educate patients about the potential risks and benefits of new therapies, including the development and dissemination of evidence-based, balanced materials that are accessible to all patients, including those with limited health literacy.

Recommendation 2

Patient organizations have a powerful voice to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Patient groups have a large role to play in publicly promoting access and fair pricing of new therapies, particularly when a therapy like oveporexton represents a substantial improvement over current standard of care treatments. This can be done both through advocacy (e.g., releasing public statements calling for manufacturers to price new treatments according to expected value, and encouraging patients and families to write to Congress, state legislatures, and state regulators to advocate for fair pricing and broader access of new treatments), and through direct engagement with stakeholders (e.g., payers, pharmacy benefit managers, employers) to craft patient-centered coverage policies promoting fair access.

Researchers/Regulators

Recommendation 1

There are multiple high priority research areas for NT1 on which researchers and funders can focus attention to close gaps as quickly as possible.

As previously discussed, there can be lengthy delays in receiving a diagnosis of NT1, in part due to the fact that diagnosis generally requires a clinician trained in sleep disorders and either a sleep study and/or a lumbar puncture. Given the potential consequences of untreated NT1, more streamlined diagnostic tests are needed. This could be in the form of blood-based biomarkers, or testing the use of an orexin agonist as a diagnostic tool.

Current outcome measures for NT1 may be subject to bias and may not fully capture all aspects of NT1. For example, the Epworth Sleepiness Scale (ESS) score has been criticized for its inconsistent association with physiologic sleepiness.[81] Persons living with NT1 have described suffering from "brain fog" and other cognitive symptoms that may not be well-captured by the ESS, MWT, or other commonly used measures in NT1 trials. Thus, researchers have an opportunity to develop more comprehensive patient-centered scales to measure the impact of NT1.

Finally, combination therapy is the norm for treatment of NT1; however, oveporexton was studied as a monotherapy. We heard from clinical and patient experts that it is likely that some patients will require combination therapy to satisfactorily address all their symptoms. This is a key area of future research on which researchers and funders can focus.

Recommendation 2

Regulators have a role in promoting trials comparing new agents with current standard of care prior to approval, rather than placebo-controlled trials for conditions that have existing therapies.

There are currently no head-to-head trials of oveporexton compared with the current standard of care therapies and thus clinicians and patients do not have all the information needed to make informed and shared decisions about treatment. The FDA has an opportunity to encourage manufacturers to design and conduct trials that reflect real-world treatment of NT1.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Cataplexy: The hallmark symptom of narcolepsy type 1. Defined as sudden muscle weakness or full paralysis triggered by strong, often positive, emotions (i.e., laughing, joking). The cause of cataplexy remains unknown, but it has been tied to the loss of orexin signaling. The muscle weakness/paralysis of cataplexy often begins in the face and neck before spreading to the trunk and limbs. In severe episodes, the individual may fall to the ground and be unable to move or speak for a couple of minutes.[10]

Epworth Sleepiness Scale (ESS): A self-administered eight-item measure of daytime sleepiness. The questions are related to specific activities of daily life, and scored on a four-point Likert scale with zero indicating "would never doze" and three indicating a "high chance of dozing". The total score range is 0–24, and a two-point decrease in the total score is deemed clinically significant. In clinical trials, a total score of ≤10 is recognized as a normal level of daytime sleepiness.[12,17,82]

Excessive daytime sleepiness (EDS): An overwhelming urge to sleep during the day despite getting sufficient sleep at night. It is one of the hallmark symptoms of narcolepsy types 1 and 2.[10]

Hypnagogic/hypnopompic hallucinations: Vivid, often disturbing, dream-like hallucinations that occur when falling asleep (hypnagogic) or waking up (hypnopompic). These hallucinations likely occur during non-REM sleep, unlike nightmares that occur during REM sleep.

Multiple Sleep Latency Test (MSLT): The MSLT assesses excessive daytime sleepiness by measuring the time to fall asleep (i.e., sleep latency) during the day under controlled conditions. The test consists of five scheduled 20-minute nap opportunities at two-hour intervals in which the patient is instructed to attempt to fall asleep. The MSLT result is the average of the sleep latencies across all five nap opportunities reported in minutes. A one-minute increase in sleep latency is recognized as the clinically significant threshold.[12,83]

Maintenance of Wakefulness Test (MWT): The MWT assesses daytime alertness by measuring the ability to stay awake in nonstimulating conditions during four 40-minute periods throughout the day. The MWT result is the average of the sleep latencies across all four test periods reported in minutes. A two-minute increase in sustained wakefulness is considered clinically significant.[12,84]

Narcolepsy Severity Scale for Clinical Trials (NSS-CT): A 15-item measure that assesses the frequency, severity, and effect of five key symptoms of narcolepsy type 1: EDS, cataplexy, hallucinations, sleep paralysis, and disturbed nighttime sleep. Scores range from 0-57, with higher scores indicating greater severity. A difference of eight points between treated and untreated participants is considered clinically significant.[17]

Narcolepsy Type 1 (NT1): NT1, also called "narcolepsy with cataplexy", is defined by the presence of cataplexy, excessive daytime sleepiness, and low levels of the neurotransmitter orexin in cerebrospinal fluid. The low/undetectable levels of orexin are attributed to severe orexin neuron loss.[10]

Narcolepsy Type 2 (NT2): NT2, also called "narcolepsy without cataplexy", is defined by excessive daytime sleepiness with an absence of cataplexy. Individuals with NT2 typically have normal orexin levels.[10]

Orexin: Orexin (or "hypocretin") is a neurotransmitter produced in the hypothalamus that regulates the sleep-wake cycle, as well as other autonomic functions. Orexin signaling stimulates other neurons that maintain wakefulness and suppresses rapid eye movement (REM) sleep during the day. Thus, a loss of orexin signaling (necessary for a NT1 diagnosis) is linked to the dysregulation of one's sleep-wake cycle.[10]

Rapid Eye Movement (REM): A stage of sleep when most dreaming occurs, characterized by rapid eye movements and temporary muscle paralysis. Most individuals with narcolepsy exhibit symptoms of abnormal REM sleep, with REM sleep occurring during wake and manifesting as hypnopompic/hypnagogic hallucinations or sleep paralysis.[10]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[85] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[86,87] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often

arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and, therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans, whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

ICER did not calculate the Health Improvement Distribution Index (HIDI) due to lack of available race/ethnicity data of US adults with narcolepsy type 1.

A2. Potential Cost-Saving Measures in Narcolepsy

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by oveporexton (e.g., emergency care for narcolepsy-related accident injuries), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of narcolepsy beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with narcolepsy that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients.

ICER did not receive any feedback on this inquiry.

B. Stakeholder Input: Supplemental Information

B1. Clinical Expert Input: Methods

We spoke with six sleep medicine experts from academic centers around the United States, and one international clinical expert from Europe. The clinical experts were trained in sleep medicine, as well as internal medicine, neurology (adult and pediatric), pulmonology (adult and pediatric), psychiatry, and pediatrics. Two clinical experts were participants on writing committees for clinical practice guidelines on the management of narcolepsy.

B2. Patient Community Insights: Methods

We spoke with one patient advocacy organization, five persons diagnosed with narcolepsy, and five caregivers of persons with NT1.

We also reviewed submissions from the ICER Share Your Story Form. The form included five questions to better understand the experience of living with narcolepsy, described below:

1. How has your disease/condition affected your day-to-day life (physical, emotional, or otherwise)?
2. What is your experience with previous and/or current treatments?
3. What is your experience with accessing and affording care for your disease/condition?
4. What are your hopes for a new treatment?
5. How has your disease/condition impacted your family and caregivers?

ICER received a total of 37 responses on the Share Your Story Form and are grateful to members of the narcolepsy community for their contributions. In Section B3, we report on the qualitative, thematic analysis of the responses supplemented with direct quotes from patients/caregivers. Insights from the patient organizations, patient discussions, and survey responses directly informed the patient community insights section of our report (see Section 2).

B3. Patient Community Insights: Results

Participant Type: Among the 37 responses, five self-identified as caregivers with the remainder as persons with narcolepsy.

Condition Type: Among the 32 self-responders, 15 (47%) identified as having NT1, 5 (16%) had NT2, and three responders (9%) had idiopathic hypersomnia. Nine (28%) of the survey cohort did not specify their narcolepsy type.

Four of the five caregivers noted they provided care to a person with NT1.

Impact on Daily Life

Physical and Cognitive Challenges: Patients experience extreme daytime sleepiness with unpredictable sleep attacks, sudden muscle weakness (cataplexy), significant brain fog and memory issues, and reduced ability to perform daily activities like driving or exercising.

- *"Narcolepsy dramatically affects my daily life. Imagine living 72 hours without sleep, and the rest of the world still expects you to perform as if you got 8 hours of sleep. That is what narcolepsy is like living with."*

- *"I often experience cataplexy; I will often drop things, or my legs will collapse beneath me. I do my best to avoid high stress situations and environments because of the risk of cataplexy."*

Emotional and Psychological Toll: The condition creates profound isolation, depression, and anxiety due to unpredictable symptoms and lack of understanding from others.

- *My social life is limited to occasional daytime activities that are close to home, and often I have to cancel plans if I feel that I might not have the alertness to get back home safely.*

- *It creates divides in my relationships, affects my mental health and what I want to do moving forward as goals. It's hard to accept that this is something I will always have to deal with and grieve the things I won't be able to do.*

- *Cataplexy is not only dangerous, but humiliating. When I should be laughing with my friends at night, I slump over as I loss complete muscle tone, it takes immense focus not to panic because my diaphragm lost muscle tone to. I gasp for air, as I try to stay calm. It is immensely uncomfortable.*

Disrupted Life Functioning: Narcolepsy severely impacts work, careers, social relationships, and education, forcing patients to reduce work hours, avoid social activities, make major lifestyle adjustments, and depend heavily on support systems and medication schedules. Several respondents shared their decision not to have children because of the impact of narcolepsy on their lives, while others highlighted the difficulty of parenting with the disorder.

- *"Maintaining consistent employment has been difficult due to sleep inertia, fatigue, and the need for daytime rest periods."*

- *"Narcolepsy has always shaped every part of my life—my career, family, dating, friendships, hobbies, security, and nutrition. Managing this condition requires so much physical and emotional energy that I've had to reconsider what responsibilities I can realistically take on; while many of my friends are starting families, I have chosen not to have children."*

Experience with Treatment

Many patients reported a trial-and-error approach to finding an effective treatment, often trying combinations of medications and modifying dosages to best address the excessive daytime sleepiness and cataplexy.

Durability and Side Effects: Even when a medication initially provides a benefit, it can be short-lived, with diminishing efficacy over time or the development of new side effects. A recurring sentiment is the feeling that treatments are merely managing symptoms rather than addressing the root cause of narcolepsy. Patients often grapple with the choice between tolerating unpleasant side effects to maintain some level of functionality versus trying medications with potentially more severe or unpredictable consequences.

- *"My current treatment is titrating intense nighttime medications in combination with daytime stimulants and chasing side effects like bouncy balls. These treatments manage pieces of this disease, but they don't restore normal alertness. And at what cost? Over time, the stress on my heart, dulling of my mind, and ongoing side effects weigh heavily on me."*

- *"Even though I'm only in my 20s, I cannot drink alcohol because of the side effects it causes with the sedative I take in order to get an adequate amount of sleep, equating to about 5 or 6 hours so that I'm not falling asleep during the day at work or with my friends. It lowers my heart rate into the 40s, makes me feel blackout drunk, and makes my limbs feel like molasses so much to the point that I can't move them 5 minutes after taking the medication."*

Access and Affordability

Specialist Access and Diagnostic Barriers: Patients face significant delays in finding qualified narcolepsy specialists, often requiring consultations with multiple providers before correct diagnosis. Diagnostic testing like the Multiple Sleep Latency Test (MSLT) creates additional barriers due to time off work requirements and substantial out-of-pocket costs. Healthcare providers often lack understanding of narcolepsy's severity, and patients must engage in self-advocacy to secure coverage.

- *"It took me 3 years from being trapped on the couch with sleep attacks, severe brain fog where I couldn't work, and tremors, to finally getting a diagnosis. That's considered a fairly fast timeline for narcolepsy."*

- *"I was lucky to meet someone else with narcolepsy who referred me to her neurologist. Before that, doctors would tell me I was tired because I was depressed or overweight, even after I lost 60 pounds without improvement to my tiredness. I had to pay out of pocket for one of the tests that allowed my neurologist to prove I had narcolepsy because insurance would not approve it despite him appealing twice."*

Medication Costs and Insurance Obstacles: Narcolepsy medications can be very expensive, compounded by frequent insurance denials and prior authorization delays. Many patients depend on manufacturer assistance programs to afford treatment, while navigating complex and exhausting insurance approval processes.

- *"A large part of the little "free" time I have is dedicated to accessing my prescribed medications, and it's exhausting."*

- *"I cannot afford medication that insurance doesn't approve. They always require a prior authorization and then deny because I "haven't had symptoms for at least 3 months" even though this has been a 9 year long journey."*

Systemic Gaps and Limited Support: Limited clinical trial accessibility and dependence on specialty pharmacies further complicate patients' ability to access consistent, affordable care.

- *"While I am grateful for the life-changing experience of participating in an orexin agonist trial, the compensation did not fully reflect the time, travel, and disruption required. Between travel logistics, patient support errors, and misunderstandings about symptom severity, the experience left me in a more difficult financial position than when I started. Patients who help advance these treatments should be compensated more fairly for the sacrifices involved."*

Hopes for New Treatment

Reclaiming a "Normal" Life: Patients expressed the desire for new treatments that would help them restore basic functionality and independence, such as waking up alert, ability to work or pursue an education, and engaging socially. Eliminating cataplexy, reducing dependence on stimulants (which carry significant side effects), and improving cognitive clarity were also noted priorities.

- *"I'd like to be myself again. In a group I attend, people talk about the idea of mourning the person you were before your disease worsened. I'd like to have the energy to live for something, instead of spending each day fighting to make it to the end."*

Targeted Medical Solutions: Patients hope for treatments that address narcolepsy at its root. There is enthusiasm about orexin receptor agonist medications such as oveporexton for their ability to restore orexin neurons in the brain and improve wakefulness in persons with NT1.

- *"My personal experience in the orexin agonist trial showed me that meaningful improvement is possible. For the first time, I experienced what it felt like to function with clarity and reliable wakefulness."*

- *"I'm hoping that medications that actually target the source of my illness, like oveporexton, will allow me to live a normal life again where I can shower daily, eat a meal without battling falling asleep during it, play piano/guitar, and be the husband/father that my family deserves."*

Impact on Caregiver/Family

Caregiving Burden: Patients expressed gratitude for people in their life who help them live with narcolepsy. However, the dependence on their caregivers for physical, emotional, and financial support leads to significant strain on relationships. Caregivers shared that the burden related to the managing a partner's or child's narcolepsy can negatively impact their own personal well-being, social lives, and financial stability.

- *"My attempts to hide symptoms and maintain a facade of independence and stability created distance in my relationships. Over time, this may have damaged trust, understanding, and openness in my most valued connections. Family members have often perceived me navigating my fluctuating symptoms as "chaotic" or "irresponsible" as I did everything in my power to keep up the appearance of being easy and unbothered."*

- *"I'm the parent of a 27 year old PWN. I've felt an enormous responsibility to provide everything for her financially (while moving into retirement age), including her living with us, all of her primary expenses (housing, food, healthcare, etc.). I also have spent years seeking medical providers, new medications, providing intense emotional support, and connecting her with therapists for support, cooking meals, and assisting her in managing daily living."*

Awareness and Empathy: A key frustration is the lack of understanding and empathy from family members or friends, who may not fully grasp the severity of the condition or the impact it has on daily life.

- *"My health has put a huge strain on my relationship with my wife, and since I don't have any energy to keep up with friends/family they've become very distant. I've had family insult me and cut ties because they don't understand my disease, or care to learn about it. Not being able to help much with caring for our son has taken a big toll on my wife, who struggles with her own health issues as well."*

- *"My partner never really understood how sleepy I was and what that meant -- how I could be totally unfunctional when it was bad. It caused a lot of strife in our relationship."*

C. Clinical Guidelines

We found clinical practice guidelines for the management of narcolepsy from the American Academy of Sleep Medicine and the European Academy of Neurology/European Sleep Research Society/European Narcolepsy Network. We summarized the guidelines below.

American Academy of Sleep Medicine (2021)[12]

The American Academy of Sleep Medicine published a clinical practice guideline on the treatment of central disorders of hypersomnolence, including narcolepsy, in 2021. The guideline was developed based on a systematic review done by the guideline task force, and included nonpharmacological and pharmacological interventions. The resultant guideline focuses on drug treatment of narcolepsy. It does not explicitly distinguish between NT1 and NT2 in its recommendations; however, cataplexy is one of the critical outcomes evaluated for each drug. For adult patients, the guideline strongly recommends using modafinil, pitolisant, sodium oxybate, and solriamfetol on the basis of data showing clinically significant improvement in excessive daytime sleepiness and disease severity. For cataplexy, the guidelines strongly recommend using pitolisant and sodium oxybate. Armodafinil, dextroamphetamine, and methylphenidate have conditional recommendations for the treatment of narcolepsy. The guidelines also include recommendations for the pediatric population with narcolepsy; in the pediatric population, modafinil and sodium oxybate both receive conditional recommendations for the treatment of narcolepsy. Finally, the guideline does not address treatment in pregnant or lactating women due to a lack of relevant data.

European Guideline and Expert Statements (2021)[88]

The European Academy of Neurology (EAN), European Sleep Research Society (ESRS), and European Narcolepsy Network (EU-NN) jointly released a clinical practice guideline around key areas of management of narcolepsy in 2021. The guidelines were based on a systematic review of the literature and the expert opinion of a nominated task force of 18 narcolepsy specialists. The guideline has recommendations for both pharmacological and non-pharmacological interventions for narcolepsy. For pharmacological management, recommendations are made based on the predominant symptoms (excessive daytime sleepiness, excessive daytime sleepiness/cataplexy, and excessive daytime sleepiness/cataplexy/disturbed nighttime sleep) and include both recommendations for monotherapy and combination therapies. The main recommendations for excessive daytime sleepiness in adults include scheduled naps, modafinil, pitolisant, sodium oxybate, and solriamfetol (all strong); methylphenidate and amphetamine derivatives (both weak). For adults with cataplexy, guideline recommendations include sodium oxybate, venlafaxine, and clomipramine (all strong), and pitolisant (weak). For children with excessive daytime sleepiness, scheduled naps and sodium oxybate are recommended (both strong); modafinil, methylphenidate,

pitolisant, and amphetamine derivatives constitute second-line therapy. Finally, for children with cataplexy, the guidelines strongly recommend sodium oxybates; antidepressants can be used but are a weak recommendation. Finally, the guideline recommends that treatment choices be tailored to each patient's symptoms, comorbidities, tolerance and risk of potential drug interactions.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is adults living with NT1. Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors including age, sex, and race/ethnicity

Interventions

Oveporexton (Takeda Development Center Americas)

Comparators

We compared the intervention to the following comparators:

- No pharmacological treatment (represented as placebo arms in clinical trials)
- Data permitting, we will compare oveporexton to other treatments for NT1 for EDS and cataplexy, including pitolisant (WAKIX®), sodium oxybate in all formulations (XYREM, XYWAV®, or LUMRYZ™), and combination regimens that pair a wake-promoting agent such as modafinil with an anti-cataplexy medication such as venlafaxine.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Daytime Symptoms
        - Cataplexy events
        - Excessive Daytime Sleepiness as measured by various tests including Maintenance of Wakefulness Test (MWT), the Epworth Sleepiness Scale (ESS), and the Karolinska Sleepiness Scale (KSS)
        - Cognitive Symptoms

        - Fatigue Symptoms
    - Nighttime Symptoms (e.g., disturbed nighttime sleep, dreams, hallucinations, sleep paralysis)
    - Symptoms and Daily Function
        - Work/school performance/attendance
    - Quality of Life and Treatment Satisfaction (e.g., SF-36, EQ-5D-5L)
    - Adverse events including but not limited to:
        - Insomnia, nausea, anxiety, urinary frequency, cardiovascular or hepatic injury
- Other Outcomes
    - Biomarkers such as levels of orexin (also known as hypocretin) in cerebrospinal fluid

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered.

Table D1.1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From : Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for narcolepsy followed established best research methods.[89,90] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[91] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews

1	exp narcolepsy/
2	("Gelineau Syndrome" OR "Syndrome, Gelineau" OR "Gelineau's Syndrome" OR "Gelineaus Syndrome" OR "Gelineau's Syndromes" OR "Syndrome, Gelineau's" OR "Syndromes, Gelineau's" OR "Narcoleptic Syndrome" OR "Narcoleptic Syndromes" OR "Syndrome, Narcoleptic" OR "Syndromes, Narcoleptic" OR "Paroxysmal Sleep" OR "Sleep, Paroxysmal" OR "Narcolepsy-Cataplexy Syndrome" OR "Narcolepsy Cataplexy Syndrome" OR "Narcolepsy-Cataplexy Syndromes" OR "Syndrome, Narcolepsy-Cataplexy" OR "Syndromes, Narcolepsy-Cataplexy" OR "Narcoleptic Syndrome 1" OR "Cataplexy" OR "NRCLP1").ti,ab.
3	1 OR 2
4	(“tak 861” OR “tak861” OR “oveporexton”).ti,ab.
5	("Sodium oxybate" OR "Oxybate, Sodium" OR "4-Hydroxybutyrate Sodium" OR "4 Hydroxybutyrate Sodium" OR "Oxybate Sodium" OR "Sodium gamma-Hydroxybutyrate" OR "Sodium gamma Hydroxybutyrate" OR "Sodium Oxybutyrate" OR "Oxybutyrate, Sodium" OR "gamma-Hydroxybutyrate" OR "gamma Hydroxybutyrate" OR "Somsanit" OR "Xyrem" or “xywav” or “lumryz”).ti,ab.
6	(“Pitolisant” OR “BF2.649” OR “tiprolisant” OR “Wakix”).ti,ab.
7	("solriamfetol" OR "JZP-110" OR "ADX-N05" OR "Sunosi" OR "modafinil" OR "provigil" OR "armodafinil" OR "nuvigil" OR "methylphenidate" OR "methylphenidate hydrochloride" OR "ritalin" OR "ritalin LA" OR "concerta" OR "amphetamine" OR "amphetamine sulfate" OR "adzenys" OR "dyanavel" OR "evekeo" OR "dextroamphetamine" OR "dextroamphetamine sulfate" OR "dexedrine spansule" OR "procentra" OR "zenzedi" OR "adderall" OR "adderall XR" OR "mydayis" OR “venlafaxine” OR “Effexor”).ti,ab.

8	4 OR 5 OR 6 OR 7
9	3 and 8
10	9 NOT (animals not (humans and animals)).sh.
11	10 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
12	limit 11 to English language
13	Remove duplicates from 12

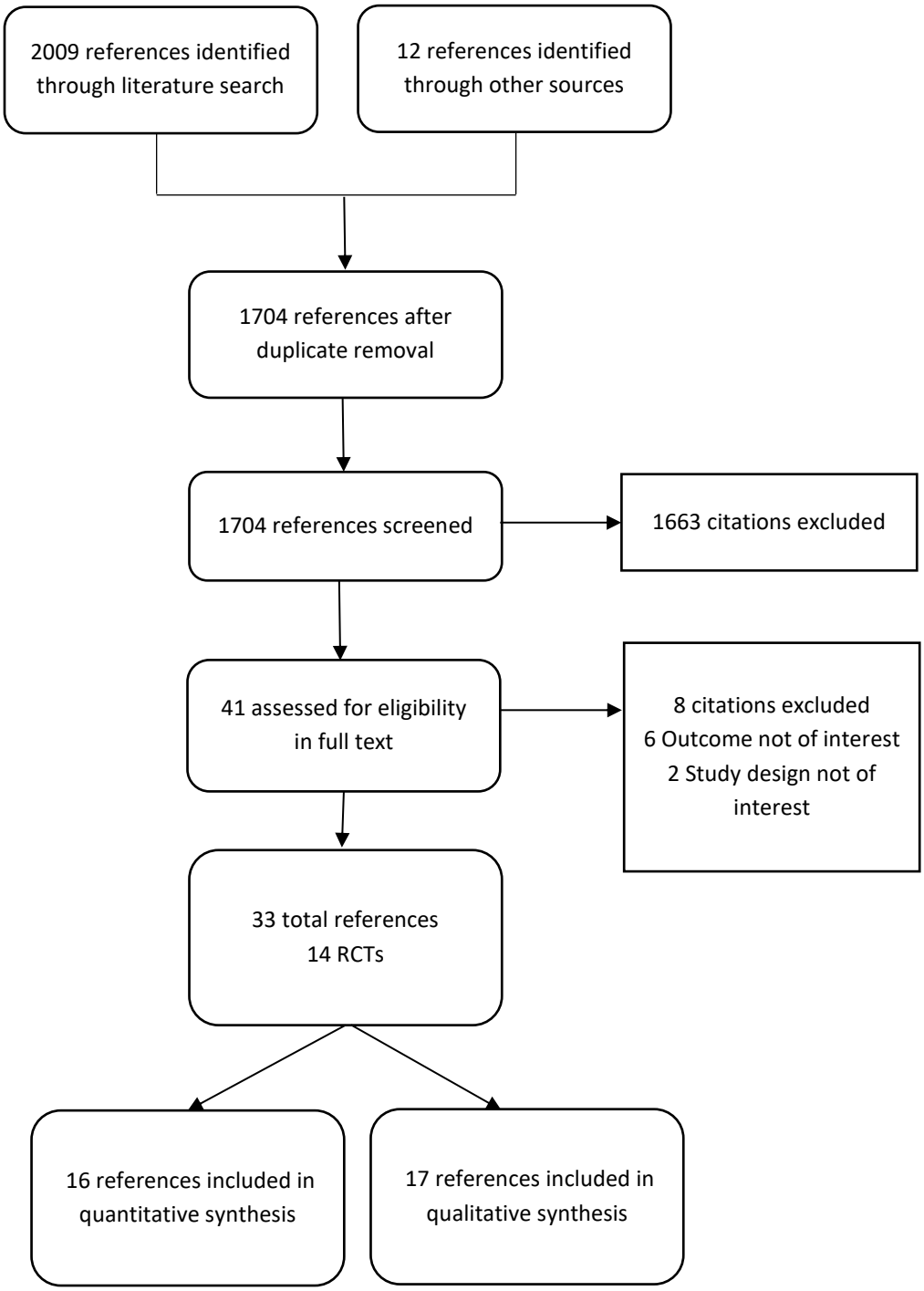
Updated search: 3/30/2026

Table D1.3. Search Strategy of EMBASE SEARCH

1	'narcolepsy'/exp
2	('cataplexy and narcolepsy' OR 'Gelineau disease' OR 'Gelineau syndrome' OR 'Gelineau`s disease' OR 'Gelineau`s syndrome' OR 'narcolepsy type 1' OR 'narcolepsy-cataplexy' OR 'narcolepsy-cataplexy syndrome' OR 'type 1 narcolepsy' OR 'narcolepsy with cataplexy' OR 'epilepsy, sleep' OR 'narcolepsies' OR 'narcolepsis' OR 'narcoleptic syndrome' OR 'narcoleptic syndromes' OR 'neurolepsy' OR 'paroxysmal sleep' OR 'rapid eye movement narcolepsy' OR 'REM narcolepsy' OR 'sleep epilepsies' OR 'sleep epilepsy' OR 'sleep, paroxysmal'):ti,ab
3	#1 OR #2
4	('oveporexton' OR 'tak 861' OR 'tak861'):ti,ab
5	('sodium oxybate' OR 'sodium oxybutyrate' OR 'somsanit' OR 'wy 3478' OR 'wy3478' OR 'xyrem' OR 'oxybate sodium' OR 'lumryz' OR 'xywav' OR GHB OR 'gamma-hydroxybutyrate' OR 'gamma hydroxybutyrate'):ti,ab
6	('pitolisant' OR 'wakix' OR 'bf 2.649' OR 'bf 2649' OR 'bf2.649' OR 'bf2649' OR 'hbs 101' OR 'hbs101' OR 'ozawade' OR 'pitolisant hydrochloride' OR 'tiprolisant' OR 'tiprolisant hydrochloride'):ti,ab
7	('solriamfetol' OR 'JZP-110' OR 'ADX-N05' OR 'Sunosi' OR 'modafinil' OR 'provigil' OR 'armodafinil' OR 'nuvigil' OR 'methylphenidate' OR 'methylphenidate hydrochloride' OR 'ritalin' OR 'ritalin LA' OR 'concerta' OR 'amphetamine' OR 'amphetamine sulfate' OR 'adzenys' OR 'dyanavel' OR 'evekeo' OR 'dextroamphetamine' OR 'dextroamphetamine sulfate' OR 'dexedrine spansule' OR 'procentra' OR 'zenzedi' OR 'adderall' OR 'adderall XR' OR 'mydayis' OR 'venlafaxine' OR 'effexor'):ti,ab
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
11	#9 NOT #10
12	#11 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
13	#12 AND [english]/lim
14	#13 NOT [medline]/lim

Updated search: 3/30/2026

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for NT1



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also reviewed FDA, EMA, and CADTH documents for clinical trial data associated with our comparators of interest, as well as peer-reviewed published meta-analyses.

Data Extraction

Data were extracted into Microsoft Word and Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[90,92] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: Epworth Sleepiness Scale (ESS) and Maintenance of Wakefulness Test (MWT). See Tables D1.4 and D1.5.

Table D1.4. Risk of Bias Assessment for the Epworth Sleepiness Scale (ESS)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Oveporexton						
Phase II	Low	Low	Low	Low	Low	Low
FirstLight	--	--	--	--	--	--
	Comment: No peer-reviewed publication available at time of review.					
RadiantLight	--	--	--	--	--	--
	Comment: No peer-reviewed publication available at time of review.					
Armodafinil/Modafinil						
Harsh 2006	Low	Low	Some Concerns	Low	Low	Some Concerns
	Comment: Some concerns regarding insufficient information on missing outcome data and prespecified analyses. Some risk of attrition bias: Only 75% of randomized patients in the 150 mg/day arm completed the study (84% and 86% in the 250 mg/day and placebo arms, respectively. The study enrolled fewer patients than estimated in the protocol due to review of variability in blinded data.					
USA 1998	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses. Some concern surrounding missing outcome data due to greater discontinuation from adverse effects seen in 400 mg study arm (12%) compared to placebo (0%).					
USA 2000	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses and on missing data.					
Sodium Oxybate						
Cook 2002	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses, outcome data and trial design.					
Ahmed 2005	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
	Comment: Some concerns regarding insufficient information on prespecified analyses, outcome data and trial design.					
Black 2006	Some Concerns	Some Concerns	Low	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analysis plan, trial design and deviations from intended interventions. The trial enrolled participants already being treated with modafinil for ≥3 months, which could increase risk of unblinding among participants subsequently assigned to placebo arm.					
REST-ON	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on trial design, specifically randomization and blinding, and missing outcome data. The rate of premature study discontinuation was high; overall, 64 (30.2%) subjects discontinued study prematurely, 38 (35.5%) in treatment group and 26 (24.8%) in the placebo group. Additionally, analyses for secondary endpoints (i.e., ESS) were not prespecified. A placebo effect was noted, likely influenced by expectations from escalating dose and previous known effects of sodium oxybates.					
Pitolisant						
HARMONY 1	Low	Low	Some Concerns	High	Some Concerns	Some Concerns
	Comment: Risk of unblinding due to prior-exposed modafinil participants' possibility able to detect allocated intervention, thus impacting ESS results.					
HARMONY CTP	Low	Low	Low	Low	Some Concerns	Some Concerns
	Comment: Secondary endpoints were not pre-specified in the study protocol.					
HARMONY 1bis	Low	Low	Some Concerns	High	High	High
	Comment: High risk due to no peer-reviewed publication, insufficient information, particularly on missing outcome data and measurement of outcome data for the ESS.					

ESS: Epworth Sleepiness Scale, mg: milligrams

Table D1.5. Risk of Bias Assessment for the Maintenance of Wakefulness Test (MWT)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Oveporexton						
Phase II	Low	Low	Low	Low	Low	Low
FirstLight	--	--	--	--	--	--
	Comment: No peer-reviewed publication available at time of review.					
RadiantLight	--	--	--	--	--	--
	Comment: No peer-reviewed publication available at time of review.					
Armodafinil/Modafinil						
Harsh 2006	Low	Low	Some Concerns	Low	Low	Some Concerns
	Comment: Some risk of attrition bias: Only 75% of randomized patients in the 150 mg/day arm completed the study (84% and 86% in the 250 mg/day and placebo arms, respectively.					
USA 1998	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses. Some concern surrounding missing outcome data due to greater discontinuation from adverse effects seen in 400 mg study arm (12%) compared to placebo (0%).					
USA 2000	Low	Low	Low	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses and on missing data.					
Sodium Oxybate						
Ahmed 2005	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analyses, outcome data and trial design.					
Black 2006	Some Concerns	Some Concerns	Low	Low	Some Concerns	Some Concerns
	Comment: Some concerns regarding insufficient information on prespecified analysis plan, trial design and deviations from intended interventions. The trial enrolled participants already being treated with modafinil for ≥3 months, which could increase risk of unblinding among participants subsequently assigned to placebo arm.					
REST-ON	Some Concerns	Some Concerns	Some Concerns	Low	Low	Some Concerns
	Comment: Some concerns regarding insufficient information on trial design, specifically randomization and blinding, and missing outcome data. The rate of premature study discontinuation was high; overall, 64 (30.2%) subjects discontinued study prematurely, 38 (35.5%) in treatment group and 26 (24.8%) in the placebo group. A placebo effect was noted, likely influenced by expectations from escalating dose and previously known effects of sodium oxybates.					

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Pitolisant						
HARMONY 1	Low	Low	Some Concerns	Some Concerns	Some Concerns	Some Concerns
	Comment: Risk of unblinding due to prior-exposed modafinil participants' possibility able to detect allocated intervention, thus impacting MWT results. Some concerns regarding insufficient information on missing data and prespecified analysis plan.					
HARMONY CTP	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Secondary endpoints were not pre-specified in the study protocol.					
HARMONY 1bis	Low	Low	Some Concerns	Some Concerns	High	High
	Comment: High risk due to no peer-reviewed publication, insufficient information, and report of a different analysis of MWT data that was not prespecified. When results of the MWT were analyzed using the statistical test that was prespecified in the analysis plan, the results were not significant.					

mg: milligrams, MSLT: Multiple Sleep Latency Test, MWT: Maintenance of Wakefulness Test

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[33] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.6. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates,[1] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.7 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.8.

Table D1.6. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.7. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.8. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

We identified prevalence data for sex among adults with narcolepsy type 1 in the United States.[1] We were unable to locate prevalence data for the race/ethnicity of adults with narcolepsy in the US In the absence of evidence indicating differential prevalence across racial or ethnic groups, consistent with input from clinical experts, we assumed that the racial and ethnic distribution of adults with narcolepsy was similar to the US population. Thus, we used the US census data for race and ethnicity prevalence estimates. The trials did not provide data by age groups, and as such we did not assess the trials on representation of older adults.

Results

Table D1.9. Diversity Ratings on Race and Ethnicity, Sex, and Age

Trial	Race and Ethnicity	Sex	Age (Older Adults)
FirstLight	Poor	Good	Not Calculated
RadiantLight	Poor	Good	Not Calculated

Table D1.10. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence[1]	75.5%	13.8%	6.3%	19.1%	1.3%	0.3%	-	-
FirstLight[16]	35.12%	4.17%	15.48%	NR	NR	NR	-	-
PDRR	0.47	0.30	2.46	NC	NC	NC	-	-
Score	1	1	3	NC	NC	NC	5	Poor
RadiantLight[16]	44.76%	0.00%	20.00%	NR	NR	NR	-	-
PDRR	0.59	0.00	3.17	NC	NC	NC	-	-
Score	2	0	3	NC	NC	NC	5	Poor

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Race and Ethnicity: Both trials received a "poor" rating due the absence of data on the percentage of Hispanic participants in the trials, and an underrepresentation of Black participants. Race/ethnicity was reported as other or unknown for approximately 45% and 35% of participants in the FirstLight and RadiantLight trials, respectively.[16] Thus, we were unable to rate those participants. It is important to note that the trials were conducted across North America, Asia, Europe and Australia.

Table D1.11. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 Years)	Score	Rating
Prevalence[1]	52.0%	48.0%	-	-	16.6%	-	-
FirstLight[16]	41.67%	58.33%	-	-	NR	-	-
PDRR	0.8	1.22	-	-	NC	-	-
Score	3	3	6	Good	NC		
RadiantLight[16]	52.38%	47.62%	-	-	NR	-	-
PDRR	1.01	0.99	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC

NA: Not Applicable, NC: Not Calculated, NR: Not reported, PDRR: Participant to Disease-prevalence Representation Ratio

Sex: Both trials achieved a "good" rating on the representation of males and females.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[93,94]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for oveporexton and other therapies in our scope using ClinicalTrials.gov. Search terms included therapies identified in lines four to seven of Tables D1.2 and D1.3 of the literature search (e.g., oveporexton, pitolisant, sodium oxybate).

The pitolisant HARMONY 1bis trial is completed but their results have not been published in a peer-reviewed journal. Evidence from this trial was collected using FDA, CADTH, and EMA documents. In this study, changes in MWT and cataplexy were not statistically significant between pitolisant and placebo.

D2. Data Synthesis and Statistical Analyses

Feasibility of Conducting Meta-Analysis and/or Network Meta-Analysis

We first examined the feasibility of meta-analyzing the three oveporexton trials. The two Phase III trials, FirstLight and RadiantLight, had identical trial designs, and the earlier Phase II trial was sufficiently similar to these two. Additionally, the 2 mg twice daily study arm was evaluated in all three trials. Given the similarities across study designs and outcome measures, we conducted fixed-effect meta-analyses (see details below).

Due to the lack of head-to-head trials comparing oveporexton to pitolisant, sodium oxybates, and combination therapy (modafinil/armodafinil plus venlafaxine), we evaluated the feasibility of conducting network meta-analyses. We assessed 13 trials associated with these interventions and examined differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality/risk of bias. We deemed these trials sufficiently similar for EDS outcomes(see details below). However, NMA of cataplexy events was not feasible due to inconsistent reporting. Studies differed in reporting outcomes using means versus medians, as well as daily versus weekly rates. There were also data gaps on baseline cataplexy rates. The inclusion of NT2 patients in some trials of our network further prevented meaningful comparisons between interventions.

An independent research team member validated all data analyses. This process included reviewing and confirming the data analysis methods, data format, and analysis code. The member also re-ran the analysis, validated the results, and confirmed the appropriateness of the reported data.

MA/NMA Methods

Meta-analysis: Oveporexton versus No Pharmacological Treatment

We performed a fixed-effect meta-analyses using evidence from three oveporexton trials on the outcomes of MWT, ESS, and ESS Responder (≤10). We reported the first two outcomes as the mean difference between oveporexton and placebo, and the third as a pooled risk ratio. All three-point estimates were reported with associated 95% confidence intervals in the main report (Table 3.4). Meta-analyses were conducted using R Statistical Software (version 4.2.1) with the meta package.

Network Meta-analysis: Oveporexton versus Active Treatment

Oveporexton was compared against pitolisant, sodium oxybates, and combination therapy of modafinil/armodafinil with venlafaxine. The dosage of each intervention, including in-trial and FDA label, is outlined in Table D2.1.

Table D2.1. Interventions in Network Meta-Analysis

Intervention	Detail
Oveporexton	2 mg tablet taken twice daily (BID) for 12 weeks
Armodafinil/Modafinil Plus Venlafaxine	Clinical trial dosage: Armodafinil: 150, 250 mg per day Modafinil: 100 to 400 mg per day Venlafaxine: 37.5 to 150 mg per day FDA label recommended dosage: Armodafinil: 150 to 250 mg per day Modafinil: 200 mg per day Venlafaxine: No labeled indication for narcolepsy but clinical guidelines recommend 37.5 to 150 mg per day
Sodium Oxybate	Clinical trial dosage: 3, 4.5, 6, 7.5, 9 grams per night FDA label recommended dosage: Initiate 4.5 g per night, titrate to 6 to 9 g per night across one or two doses
Pitolisant	Clinical trial dosage: 5 to 40 mg per day FDA label recommended dosage: Initiate 8.9 mg once daily, titrate to 17.8 mg per day at week 2 to a maximum of 35.6 mg per day at week 3
Placebo/ No Pharmacological Treatment	Note: Some trials allowed continuation of wake-promoting and/or anti-cataplectic medication if dosing stable

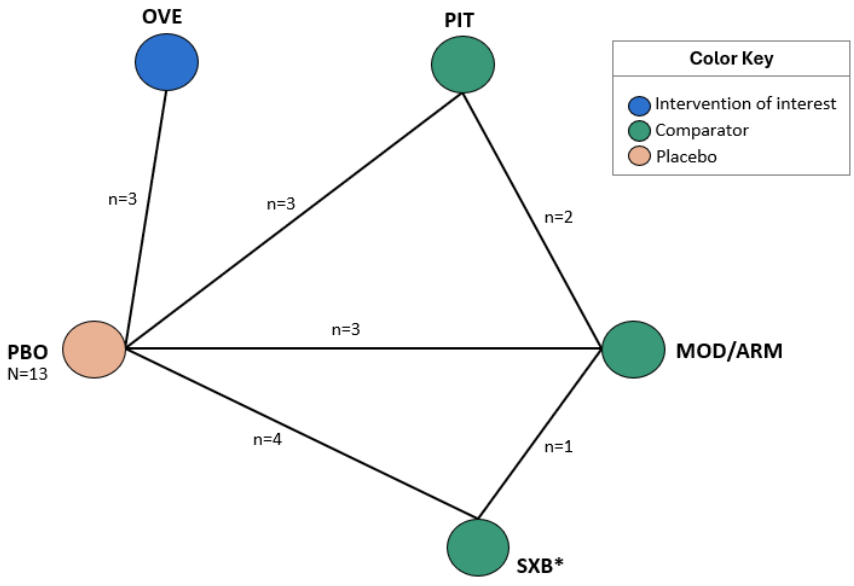
g: grams, mg: milligrams

We included RCTs in the NMA that were aligned with the inclusion/exclusion criteria of the Light trials. Eligible studies were RCTs that recruited adults diagnosed with narcolepsy. We excluded single-arm, open-label, and crossover trials. We did not apply a minimum follow-up length, and the study duration in the network ranged from four to 13 weeks.

A total of 13 RCTs met our inclusion criteria (See Figure D2.1 and Table D2.2). Not all trials contributed to every NMA outcome; data availability for each trial is noted in the "NMA Contribution" column. Across the study arms, participants were predominantly middle-aged adults (30s or 40s), largely female, and had severe excessive daytime sleepiness, indicated by baseline ESS scores between 16 and 24.

NMAs were conducted using R Statistical Software (version 4.2.1) and indiRect NMA platform (EVERSANA). Our outcomes of interest were the change from baseline in ESS and MWT, as well as the proportion of study participants who had a final ESS score of less than 10, deemed to be a treatment responder. The first two outcomes are continuous (mean difference) and the third a dichotomous outcome (risk ratio and absolute risk difference). The ESS and MWT scores were analyzed with a normal likelihood and identity link, and the ESS responder NMA was analyzed with a binomial likelihood with a log and identity link. Analyses were based on burn-in and sampling of 40,000 iterations. All were analyzed using a random-effects Bayesian NMA. We conducted fixed-effects models to confirm model choice. In the ESS Responder NMA, we also explored baseline risk adjustment as an additional component in a sensitivity analysis due to some observable differences in the placebo response. However, our assessment of the model fit, presented in Table D2.10, showed that the unadjusted model provided a better fit.

Figure D2.1. NMA Network Diagram



MOD/ARM: modafinil/armodafinil, N: number, OVE: oveporexton, PBO: placebo, PIT: pitolisant, SXB: sodium oxybates

*Studies in our network included the once and twice nightly formulations, but not the mixed salts/low-sodium formulation.

Table D2.2. Narcolepsy NMA Trial Baseline Characteristics (N=13)

Study	Arm	n	Age, Mean (SD or Range)	Female, n (%)	ESS, Mean (SD)	MWT, Mean (SD)	Cataplexy, n (%) or NT1	Concomitant Medication Used, n (%)	NMA Contribution
Oveporexton									
FirstLight[16]	Placebo	41	30.9 (12.7)	24 (58.5)	18.2 (3.6)	5.1 (6.8)	41 (100)	0 (wash-out)	All
	OVE 1 mg BID	61	33.5 (11.8)	28 (45.9)	18.2 (2.6)	5.5 (7.7)	61 (100)	0 (wash-out)	
	OVE 2 mg BID	66	29.7 (9.6)	46 (69.7)	19 (3.2)	4.4 (5.5)	66 (100)	0 (wash-out)	
RadiantLight[16]	Placebo	35	34 (13.1)	13 (37.1)	17.9 (3)	4.1 (4.9)	35 (100)	0 (wash-out)	All
	OVE 2 mg BID	70	29.1 (9.6)	37 (52.9)	17.3 (3.4)	4.8 (4.9)	70 (100)	0 (wash-out)	
Phase II[17]	Placebo	22	37.5 (11.9)	14 (64)	18.6 (2.7)	6.1 (8.8)	22 (100)	0 (wash-out)	All
	OVE 2 mg BID	21	31.7 (11.3)	9 (43)	19 (3.1)	3.9 (6)	21 (100)	0 (wash-out)	
Armodafinil/Modafinil									
USA 1998[21]	Placebo	92	42 (18-68)	50 (54)	18.3 (3.3)	5.8 (4.7)	83 (90)	NR	ESS MD and MWT MD
	MOD 200 mg	96	40 (18-67)	52 (54)	17.9 (3.8)	5.8 (5)	86 (90)	NR	
	MOD 400 mg	95	44 (19-67)	52 (55)	17.1 (4.2)	6.6 (5.2)	81 (85)	NR	
USA 2000[22]	Placebo	93	41 (17-66)	50 (54)	17.6 (4) [n=86]	6 (5) [n=88]	70 (75)	NR	ESS MD and MWT MD
	MOD 200 mg	89	42 (18-67)	52 (58)	17.4 (3.8) [n=83]	6.1 (4.9) [n=83]	63 (71)	NR	
	MOD 400 mg	89	42 (18-66)	45 (51)	18 (3.4) [n=85]	5.9 (4.4) [n=86]	63 (71)	NR	
Harsh 2006[23]	Placebo	63	39.2 (12)	31 (49)	17.5 (3.9)	12.5 (6.6)	41 (65)	NR	All
	ARM 150 mg	64	40.4 (12.5)	36 (56)	17.3 (3.4)	12.1 (6.6)	44 (69)	NR	

Study	Arm	n	Age, Mean (SD or Range)	Female, n (%)	ESS, Mean (SD)	MWT, Mean (SD)	Cataplexy, n (%) or NT1	Concomitant Medication Used, n (%)	NMA Contribution
	ARM 250 mg	67	35 (12.5)	42 (63)	15.7 (4.7)	9.5 (6.1)	44 (66)		
Sodium Oxybate									
Cook 2002[25]	Placebo	34	43.1	79 (58.1)	*19**	NR	34 (100)	0 (wash-out)	ESS MD
	SXB 3 g	34			*17**	NR	34 (100)	0 (wash-out)	
	SXB 6 g	33			*17.5**	NR	33 (100)	0 (wash-out)	
	SXB 9 g	35			*17**	NR	35 (100)	0 (wash-out)	
Ahmed 2005[65]	Placebo	59	40.5 (16-75)	149 (65.4)	17.5* [n=58]	9.5*	59 (100)	0 (wash-out)	ESS and MWT MD
	SXB 4.5 g	64			18* [n=61]	8.53* [n=62]	64 (100)	0 (wash-out)	
	SXB 6 g	58			19*	9* [n=57]	58 (100)	0 (wash-out)	
	SXB 9 g	47			19*	7.63*	47 (100)	0 (wash-out)	
Black 2006[27,95]	Placebo	55	41 (13.4)	31 (56.4)	16* [n=54]	9.74 (6.57)	32 (58.2)	NR†	ESS MD and MWT MD
	SXB	50	35.1 (12.9)	24 (48)	15* [n=48]	11.29 (6.4)[n=49]	14 (28)	NR†	
	MOD	63	38.9 (15.6)	31 (49.2)	14* [n=61]	10.48 (6.03)	26 (41.3)	NR†	
	SXB + MOD	54	38.9 (15.6)	29 (53.7)	15*	10.43 (6.77)	23 (42.6)	NR†	
REST-ON[29]	Placebo	105	31.6 (16-69)	75 (71.4)	17.5	4.7	82 (78.1)	Modafinil: 21.0%, Armodafinil: 6.7%, Amphetamine: 5.7%, Methylphenidate: 6.7%	ESS MD and MWT MD
	ON-SXB	107	30.9 (16-72)	69 (64.5)	16.6	5	80 (74.8)	Modafinil: 21.5%, Armodafinil: 12.1%, Amphetamine: 10.3% Methylphenidate: 10.3%	

Study	Arm	n	Age, Mean (SD or Range)	Female, n (%)	ESS, Mean (SD)	MWT, Mean (SD)	Cataplexy, n (%) or NT1	Concomitant Medication Used, n (%)	NMA Contribution
Pitolisant									
HARMONY 1[30,32]	Placebo	30	41.3 (14.8)	17 (56.7)	18.9 (2.5)	11.5 (2)	24 (80)	Sodium oxybate: 4 (13.3)	All
	PIT	31	35.7 (14.6)	11 (35.5)	17.8 (2.5)	12.5 (1.9)	25 (81)	Sodium oxybate: 2 (6.5)	
	MOD	33	39.2 (14.6)	15 (45.5)	18.5 (2.7)	11.6 (2)	27 (82)	Sodium oxybate: 2 (6.1)	
HARMONY CTP[31,32]	Placebo	51	38.5 (12.9)	24 (47.1)	17.1 (3.4)	7.8 (7.8)	51 (100)	Sodium oxybate: 1 (2)	All
	PIT	54	35.8 (12.1)	28 (51.9)	17.3 (3.3)	6.9 (7.7)	54 (100)	Sodium oxybate: 1 (2)	
HARMONY 1bis[32]	Placebo	33	43.4 (17.9)	18 (53.1)	18.2 (2.3) [n=32]	8.3‡ [n=32]	26 (81.3) [n=32]	Sodium oxybate: 2 (6)	ESS MD, ESS Responder
	PIT	67	40.7 (15.7)	35 (52.2)	18.2 (2.4)	7.4‡	50 (74.6)	22 (32.8)	
	MOD	65	44.1 (14.7)	35 (53.8)	18.1 (2.8)	7‡	50 (76.9)	20 (30.8)	

ARM: armodafinil, BID: twice daily, ESS: Epworth Sleepiness Scale, g: grams, MD: mean difference, mg: milligrams, MOD: modafinil, MWT: Maintenance of Wakefulness Test, n: number, NMA: network meta-analysis, NR: not reported, NT1: Narcolepsy Type 1, OVE: oveporexton, PIT: pitolisant, SD: standard deviation, SXB: sodium oxybate

Note: Italicized data has been calculated or digitized. Weekly or daily cataplexy rates (WCR/DCR) are reported as median (IQR), unless specified otherwise.

*Median (IQR or range).

†Inclusion criteria: patients were treated with stimulant medication for EDS for ≥3 months and were on a stable modafinil dose (200–600 mg/day) for ≥1 month or ≥6 weeks prior to trial entry.

‡Geometric mean.

Results

Results of the NMA are presented in Section 3.2 of the main report. Table D2.3 presents results of the ESS Responder NMA as risk differences.

Table D2.3. Risk Difference for Treatment Responder (ESS ≤10) Outcome

Oveporexton			
0.40 (-0.16 to 0.76)	Modafinil/Armodafinil		
0.49 (0.04 to 0.79)	0.08 (-0.18 to 0.48)	Pitolisant	
0.66 (0.31 to 0.87)	**0.25 (0.05 to 0.69)**	**0.17 (0.02 to 0.40)**	Placebo

ESS: Epworth Sleepiness Scale

Note: Each box represents the estimated risk differences and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random Effects model. Not adjusted for baseline risk. N=7 studies. Ordering of therapies was made according to magnitude of benefit versus placebo.

Assessing Model Fit

Oveporexton versus No Pharmacological Treatment

Random-Effects versus Fixed-Effects Model

Given the small number of trials and similar study designs, we reported the fixed-effects results in the main report. A comparison between the fixed-effects and random-effects models are provided in Table D2.4, demonstrating no significant difference in point estimates.

Table D2.4. Fixed and Random Effects Meta-Analysis Results, Oveporexton versus Placebo

Outcomes	Mean Difference (95% CI) Fixed-Effects Model	Mean Difference (95% CI) Random-Effects Model	I^2, p-value
MWT	19.59 (17.30 to 21.88)	20.12 (11.34 to 28.90)	58.5%, p=0.09
ESS	-9.84 (-10.95 to -8.73)	-9.84 (-11.58 to -8.10)	0%, p=0.60
	Rate Ratio (95% CI)	**Rate Ratio (95% CI)**	
ESS Responder	5.64 (3.45 to 9.23)	5.49 (3.39 to 8.88)	0%, p=0.81

CI: Confidence Interval, ESS: Epworth Sleepiness Scale, I^2: Measure of heterogeneity, MWT: Maintenance of Wakefulness Test

Oveporexton versus Active Treatment

Random-Effects versus Fixed-Effects Model

Given the heterogeneity across the trials with regards to the above patient characteristics, we decided a priori that random-effects model would be more appropriate. To validate this decision, we assessed model fit between the random-effects and fixed effect model for our three NMA outcomes. Model fit in terms of the posterior distribution for the deviance (Dbar), the deviance information criterion (DIC), and heterogeneity (I^2) confirmed the use of the random-effects models. The comparison between the random-effects and fixed effect model for the ESS responder outcome yielded similar results.

Table D2.5. Random versus Fixed Effect Model Fit Assessment

Outcome	Data Points	Random Effects Model			Fixed Effects Model		
		Dbar	DIC	I^2	Dbar	DIC	I^2
MWT	12	12.31	22.33	11%	42.87	46.88	74%
ESS	15	14.71	23.79	5%	21.42	25.41	35%
ESS Responder	15	13.54	24.74	0%	13.55	23.09	0%

DIC: Deviance information criterion, ESS: Epworth Sleepiness Scale, I^2: Measure of heterogeneity, MWT: Maintenance of Wakefulness Test

We present league tables of sensitivity analyses below. As expected, the fixed-effects model presented comparisons with narrower credible intervals and, in some cases, the comparison was significant in fixed-effects model but non-significant in the base case NMAs presented in the main report.

Table D2.6. Mean Differences for Maintenance of Wakefulness Test (Minutes) (Random Effects – Base Case)

Oveporexton				
14.99 (10.04, 20.24)	**Sodium Oxybate**			
15.56 (11.07, 20.35)	0.6 (-3.73, 4.88)	**Modafinil/Armodafinil**		
18.48 (12.96, 23.92)	3.5 (-1.98, 8.48)	2.93 (-1.57, 6.97)	**Pitolisant**	
20.01 (16.32, 23.99)	**5.01 (1.63, 8.38)**	**4.43 (1.76, 7.15)**	1.51 (-2.22, 5.78)	**Placebo**

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random-effects model. N=11 studies.

Table D2.7. Mean Differences for Maintenance of Wakefulness Test (Minutes) (Fixed Effect – Sensitivity Analysis)

Oveporexton				
14.58 (11.84, 17.32)	Sodium Oxybate			
15.35 (12.95, 17.74)	0.77 (-0.92, 2.44)	Modafinil/Armodafinil		
18.94 (16.32, 21.54)	**4.36 (2.39, 6.31)**	**3.59 (2.33, 4.86)**	Pitolisant	
19.59 (17.30, 21.89)	**5.01 (3.50, 6.53)**	**4.25 (3.53, 4.97)**	0.66 (-0.60, 1.92)	Placebo

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Fixed-effects model. N=11 studies.

Table D2.8. Mean Differences for Epworth Sleepiness Scale (Points)(Random Effects - Base Case)

Oveporexton				
-6.68 (-8.51, -4.81)	Modafinil/Armodafinil			
-7.11 (-9.21, -5.05)	-0.44 (-2.01, 1.06)	Pitolisant		
-7.63 (-9.49, -5.66)	-0.97 (-2.46, 0.64)	-0.53 (-2.25, 1.37)	Sodium Oxybate	
-9.92 (-11.5, -8.4)	**-3.25 (-4.35, -2.25)**	**-2.82 (-4.19, -1.43)**	**-2.28 (-3.54, -1.24)**	Placebo

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random-effects model. N=13 studies.

Table D2.9. Mean Differences for Epworth Sleepiness Scale (Points)(Fixed Effect – Sensitivity Analysis)

Oveporexton				
-6.69 (-7.98 to -5.39)	Modafinil/Armodafinil			
-7.02 (-8.51 to -5.52)	-0.32 (-1.45 to 0.80)	Pitolisant		
-7.78 (-9.07 to -6.48)	**-1.09 (-2.05 to -0.13)**	-0.77(-1.98 to 0.45)	Sodium Oxybate	
-9.84 (-10.94 to -8.73)	**-3.15 (-3.83 to -2.47)**	**-2.83 (-3.83 to -1.81)**	**-2.06 (-2.74 to -1.38)**	Placebo

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Fixed-effect model. N = 13 studies.

Table D2.10. Risk Ratios for ESS Responder [≤10] Outcome (Random Effects - Base Case)

Oveporexton			
2.01 (0.73 to 5.53)	Modafinil/Armodafinil		
2.54 (1.07 to 6.56)	1.26 (0.61 to 2.93)	Pitolisant	
5.06 (2.79 to 10.86)	**2.53 (1.27 to 5.75)**	**1.99 (1.11 to 3.79)**	Placebo

ESS: Epworth Sleepiness Scale

Note: Significant results are in bold. Random Effects model. Not adjusted for baseline risk. N=7 studies

Table D2.11. Risk Ratios for ESS Responder [≤10] Outcome) (Fixed Effect - Sensitivity Analysis)

Oveporexton			
2.06 (1.05 to 4.22)	Modafinil/Armodafinil		
2.5 (1.35 to 4.93)	1.21 (0.74 to 2.01)	Pitolisant	
4.99 (3.24 to 8.64)	**2.44 (1.5 to 4.07)**	**2 (1.33 to 3.11)**	Placebo

ESS: Epworth Sleepiness Scale

Note: Significant results are in bold. Fixed Effect model. Not adjusted for baseline risk. N=7 studies

In the ESS Responder NMA, we explored baseline risk/placebo risk adjustment as an additional component of the sensitivity analysis.

Table D2.12. Assessment of Model Fit, Unadjusted versus Baseline-Risk Adjusted NMA

Parameter	Unadjusted NMA (RE)	Baseline Risk Adjusted NMA (RE)	Note
ESS Responder			
Regression Coefficient (β) (95% CrI)	NA	-0.89 (-1.72 to 0.02)	Regression coefficient credible interval for baseline risk adjusted model contains 0
Heterogeneity SD (95% CrI)	0.21 (0.01 to 0.98)	0.11 (0.01 to 0.65)	Between-study SD reduced for baseline risk adjusted model
Total Residual Deviance (vs. 15 Data Points)	15.36	15.19	Similar values
Deviance Information Criterion (DIC)	82.68	82.98	Similar values

CrI: credible interval, ESS: Epworth Sleepiness Scale, NA: not applicable, NMA: network meta-analysis, RE: Random Effects, SD: Standard Deviation

Tables D2.13 and D2.14 demonstrate the impact of adjustment for cross-trial differences. The point estimate between oveporexton and modafinil/armodafinil became significant.

Table D2.13. NMA Results (Rate Ratio [95% CrI) on ESS Responder [≤10] Outcome) (Random Effects - Base Case)

Oveporexton			
2.01 (0.73 to 5.53)	Modafinil/Armodafinil		
2.54 (1.07 to 6.56)	1.26 (0.61 to 2.93)	Pitolisant	
5.06 (2.79 to 10.86)	**2.53 (1.27 to 5.75)**	**1.99 (1.11 to 3.79)**	Placebo

ESS: Epworth Sleepiness Scale

Note: Significant results are in bold. Random Effects model. Not adjusted for baseline risk. N = 7 studies

Table D2.14. NMA Results (Relative Risk on ESS Responder [≤10] Outcome)(Random Effects – Baseline Risk Adjusted)

Oveporexton			
2.4 (1.25 to 4.55)	Modafinil/Armodafinil		
2.4 (1.49 to 4.2)	1.01 (0.55 to 1.87)	Pitolisant	
4.96 (3.54 to 7.38)	**2.08 (1.21 to 3.58)**	**2.06 (1.39 to 2.97)**	Placebo

ESS: Epworth Sleepiness Scale

Note: Significant results are in bold. Random Effects model. Adjusted for baseline risk. N = 7 studies

There were three studies (Harsh 2006, Black 2006, and HARMONY 1) that had baseline MWT values that were higher than other studies in the network. We ran a sensitivity analysis to explore what impact the exclusion of these trials had on the MWT NMA. There were several changes in the magnitude of the point estimates and 95% credible intervals. The most notable change was the modafinil/armodafinil versus placebo treatment difference no longer being statistically credible.

Table D2.15. Mean Differences for Maintenance Wakefulness Test (Minutes) (Random Effects – Exclusion of High Baseline MWT Studies)

Oveporexton				
14.82 (9.01 to 21.88)	Sodium Oxybate			
16.92 (11.07 to 23.77)	2.10 (-4.49 to 8.79)	Modafinil/Armodafinil		
15.52 (7.18 to 24.80)	0.66 (-8.39 to 9.65)	-1.45 (-10.28 to 7.40)	Pitolisant	
19.84 (16.03 to 24.58)	**4.99 (0.18 to 9.71)**	2.90 (-1.58 to 7.48)	4.35 (-3.43 to 11.97)	Placebo

Note: Each box represents the estimated mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. Random-effects model. N=8 studies.

NMA Input Data

The inputs abstracted and used in the NMA are provided in Tables D2.16 through D2.18.

Table D2.16. Input Data for NMA: Change from Baseline in Maintenance of Wakefulness Test (N=11)

Study	Treatment	Treatment Effect	Standard Error	MWT Measurement	Source
FirstLight	OVE	17.2	1.8	4 sessions, 40 mins	Takeda's World Sleep Congress Presentation, 2025
	PBO	NA	NA		
RadiantLight	OVE	20.09	1.8	4 sessions, 40 mins	Takeda's World Sleep Congress Presentation, 2025
	PBO	NA	NA		
Phase II	OVE	24.7	2.96	4 sessions, 40 mins	Table 2: Dauvilliers et al., 2025
	PBO	NA	NA		
USA 1998	MOD	3.39	0.66	4 sessions, 20 mins	Figure S7: Maski et al., 2021
	PBO	NA	NA		
USA 2000	MOD	2.4	0.66		

Study	Treatment	Treatment Effect	Standard Error	MWT Measurement	Source
	PBO	NA	NA	4 sessions, 20 mins	Figure S7: Maski et al., 2021
Harsh 2006	ARM	3.8	1.07	6 sessions, 20 mins	Table 4: Australian PBS 2015
	PBO	NA	NA		
Ahmed 2005	SXB	3.8	1.35	4 sessions, 20 mins	Figure S22: Maski et al., 2021
	PBO	NA	NA		
Black 2006	SXB	5.1	1.34	4 sessions, 20 mins	Figure S23: Maski et al., 2021
	PBO	NA	NA		
REST-ON	SXB	6.13	1.33	5 sessions, 30 mins	Kushida et al., 2021
	PBO	NA	NA		
HARMONY 1	PIT	2.1	0.74	4 sessions, 40 mins	Calculated using end of MWT scores from Table 2: Dauvilliers et al., 2013
	MOD	7.5	0.72		
	PBO	NA	0.52		
HARMONY CTP	PIT	4.3	2.42	4 sessions, 40 mins	Figure S15: Maski et al., 2021
	PBO	NA	NA		

ARM: armodafinil, mins: minutes, MOD: modafinil, MWT: Maintenance of Wakefulness Test, n: number, OVE: oveporexton, PBO: placebo, PIT: pitolisant, SXB: sodium oxybate

Table D2.17. Input Data for NMA: Change from Baseline in Epworth Sleepiness Scale (N=13)

Study	Treatment	Treatment Effect	Standard Error	Source
FirstLight	OVE	-9.75	0.94	Takeda's World Sleep Congress Presentation, 2025
	PBO	NA	NA	
RadiantLight	OVE	-9.53	0.80	Takeda's World Sleep Congress Presentation, 2025
	PBO	NA	NA	
Phase II	OVE	-11.3	1.58	Table 2: Dauvilliers et al., 2025
	PBO	NA	NA	
USA 1998	MOD	-3.4	0.66	Figure S6: Maski et al., 2021
	PBO	NA	NA	
USA 2000	MOD	-3.16	0.66	Figure S6: Maski et al., 2021
	PBO	NA	NA	
Harsh 2006	ARM	-2.00	0.68	Table 4: Australian PBS 2015
	PBO	NA	NA	
Cook 2002	SXB	-2.05	0.68	Figure S20: Maski et al., 2021
	PBO	NA	NA	
Ahmed 2005	SXB	-1.1	0.51	Figure S20: Maski et al., 2021
	PBO	NA	NA	
Black 2006	SXB	-3.3	1.09	Figure S19: Maski et al., 2021
	PBO	NA	NA	
REST-ON	SXB	-3.86	0.82	Kushida et al., 2021
	PBO	NA	NA	
HARMONY 1	PIT	-3.7	1.16	Table 12: FDA Clinical Review of Wakix (Pitolisant), 2020
	MOD	-4.36	1.14	
	PBO	NA	0.81	
HARMONY CTP	PIT	-3.48	0.79	Table 2: Szakacs et al., 2017
	PBO	NA	NA	

Study	Treatment	Treatment Effect	Standard Error	Source
HARMONY 1bis	PIT	-2.19	1.01	Table 3: FDA Clinical Review of Wakix (Pitolisant), 2020
	MOD	-4.1	1.28	Table 2 and text on page 16: CADTH Pitolisant Review, 2023
	PBO	NA	0.8	Calculated using R meta with differences between MOD and PBO ESS scores at end of follow-up.

ARM: armodafinil, MOD: modafinil, n: number, OVE: oveporexton, PBO: placebo, PIT: pitolisant, SXB: sodium oxybate

Table D2.18. Input Data for NMA: Epworth Sleepiness Scale Responders (N=7)

Study	Treatment Arm	Responders	Sample Size	Source:
FirstLight	OVE 2 mg BID	53	64	Page 46: Takeda's World Sleep Congress Presentation, 2025
	PBO	6	36	
RadiantLight	OVE 2 mg BID	56	67	Page 59: Takeda's World Sleep Congress Presentation, 2025
	PBO	4	34	
Phase II	OVE 2 mg BID	20	21	Table 2: Dauvilliers et al., 2025
	PBO	4	21	
Harsh 2006	ARM 250 mg	17	60	In-text page 767: Harsh et al., 2006 Note: Responder definition was ESS <10
	PBO	4	58	
HARMONY 1	PIT	14	31	Table 2: Dauvilliers et al., 2013
	MOD	15	33	
	PBO	4	30	
HARMONY CTP	PIT	20	51	Table 2: Szakacs et al., 2017
	PBO	9	50	
HARMONY 1bis	PIT	20	67	Table 18: European Medicines Agency's Report on Wakix, 2015
	MOD	NR	65	
	PBO	7	33	

ARM: armodafinil, BID: twice daily, mg: milligrams, MOD: modafinil, n: number, OVE: oveporexton, PBO: placebo PIT: pitolisant

NMA Limitations

- There were cross-trial differences within our NMA that merit careful interpretation of results.
    - The pivotal trials of oveporexton included 12-weeks of treatment; other trials in our network were as short as four weeks (Cook 2002) and up to 13 weeks (REST-ON). Studies with shorter follow-up may underestimate the magnitude of treatment effect. However, the shortest trial in our network only contributed data to the ESS mean difference NMA, with a similar magnitude of benefit as other sodium oxybate studies. We also note that a change in ESS score can occur as early as two weeks between active treatment and placebo, as seen in the HARMONY 1 (pitolisant vs. placebo) and Dauvilliers et al. 2025 Phase II studies (oveporexton vs. placebo).
    - Our population of interest was adults with narcolepsy with cataplexy (NT1). Some studies in our network allowed patients with narcolepsy without cataplexy (NT2). However, a subgroup analysis of results between NT1 and NT2 showed similar treatment differences versus placebo on ESS and MWT in at least two sodium oxybate trials in our network, Black 2006 and the REST-ON study.[95,96] This may be due to the fact that current narcolepsy treatments do not directly address orexin signaling, which is the hallmark of NT1. Oveporexton has not been shown to be clinically effective in a NT2 population, likely due to this population largely having normal orexin levels.[97]

    - Oveporexton was studied as a monotherapy, with a washout period of other narcolepsy treatments. Numerous studies in the NMA network allowed for concomitant use of stimulants and other wake-promoting agents, which could impact treatments effects due to unknown interaction effects. Polypharmacy is common in the treatment of narcolepsy.

    - When possible, we included data from dosages that reflect FDA prescribing recommendations. However, this was not always possible due to data gaps. In instances where data was not available, we opted to include data from pooled doses, such as sodium oxybate pooling of three-, six-, and nine-gram arms, when a calculated treatment effect and standard error was reported.

    - To account for these differences, we opted to present outputs from the random-effects model as our base-case results.

- Over time, the implementation of the MWT in clinical trials has changed. Oveporexton trials measured MWT across four sessions of 40 minutes each. Other trials in the network used five or six sessions, varying from 20 to 40 minutes.

D3. Evidence Tables

Table D3.1. Study Design for All Studies

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
Oveporexton				
FirstLight[16] **NCT06470828**	Phase III, double-blind, randomized, placebo-controlled study. N=168	All arms were administered BID and orally for 12 weeks. - 1 mg TAK-861 (n=61) - 2 mg TAK-861 (n=66) - Placebo (n=41)	Inclusion - Ages 18-70 (16-70 in Japan). - ICSD Diagnosis of NT1. - ≥4 partial/complete cataplexy episodes per week (WCR). - Positive for genotype HLA-DQB1*06:02 or CSF orexin/hypocretin-1 concentration ≤110 pg/mL Exclusion - Diagnosis of a current medical disorder, other than NT1, associated with EDS.	Primary - CFB to week 12 in mean sleep latency from the 4 MWT wake trials. Secondary - CFB to week 12 in ESS total score. - WCR at week 12. - Number of participants with ≥1 TEAE.
RadiantLight[16] **NCT06505031**	Phase III, double-blind, randomized, placebo-controlled study. N=105	All arms were administered BID and orally for 12 weeks. - 2 mg TAK-861 (n=70) - Placebo (n=35)		
Phase II[17] **NCT05687903**	Phase II, double-blind, randomized, placebo-controlled study. N=112	All arms were administered BID and orally for 12 weeks. - 0.5 mg TAK-861 (n=23) - 2 mg TAK-861 (n=21) - 2 mg and 5 mg TAK-861 (n=23) - 7 mg TAK-861 QD (n=23) - Placebo (n=22)		Primary - CFB to week 8 in mean sleep latency from the 4 MWT wake trials. Secondary - CFB to week 8 in ESS total score. - WCR at week 8. - Number of participants with ≥1 TEAE.
Armodafinil/Modafinil				
Harsh 2006[23] **NCT00078377**	Phase III, double-blind, randomized, placebo-controlled, parallel-group study. N=196	All arms were administered once daily for 12 weeks. - Armodafinil 150 mg (n=65) - Armodafinil 250 mg (n=67) - Placebo (n=64)	Inclusion - Adults with a current ICSD diagnosis of narcolepsy and complaints of excessive sleepiness. - MSLT score ≤6 minutes.	Primary - CFB to week 12 in mean sleep latency from the 4 MWT wake trials. - CFB to week 12 in CGI-C Score.

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
			- CGI-S rating of ≥4 - No medical or psychiatric disorders that could account for the excessive daytime sleepiness. Exclusion - Used any unauthorized prescription drugs or clinically significant use of over the-counter drugs 7 days before second screening visit.	Secondary - CFB to week 12 in ESS total score. - Safety
USA 1998[21]	Double-blind, randomized, parallel-group study. N=281	All arms were administered once daily for 9 weeks. - Modafinil 200 mg (n=94) - Modafinil 400 mg (n=95) - Placebo (n=92)	Inclusion - Adults with a current ICSD diagnosis of narcolepsy, but who required more stringent criteria for EDS. - Recurrent daytime naps or sleep lapses almost daily for ≥3 months, cataplexy, and <8 minutes on MSLT. - Alternatively, adults who complain of excessive somnolence or sudden muscle weakness with an MSLT of <5 minutes. Exclusion - Prior reaction to stimulants.	- Subjective sleepiness at week 9 (ESS) - Objective sleepiness and wakefulness at week 9 (MSLT and MWT) - Level of illness at week 9 (CGI-C)
USA 2000[22]	Double-blind, randomized, placebo-controlled study.	All arms were administered once daily for 9 weeks. - Modafinil 200 mg (n=89)	Inclusion - Ages 17 to 67 years. - ICSD diagnosis of narcolepsy.	- Subjective sleepiness at week 9 (ESS)

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
	N=271	- Modafinil 400 mg (n=89) - Placebo (n=93) All patients randomized to modafinil treatment received modafinil 100 mg for the first 7 days of therapy and 200 mg on the eighth day. Starting on day 9, patients received modafinil 200 mg or 400 mg per day for the remaining 8 weeks.	- MSLT of ≤8 minutes. - ≥2 sleep-onset REM periods. Exclusion - Prior treatment with Modafinil. - Use of any stimulating/ sedating medication, or any psychoactive agents within 3 weeks of study.	- Objective sleepiness and wakefulness at week 9 (MSLT and MWT) - Level of illness at week 9 (CGI-C) - Safety
Sodium Oxybate				
Cook 2002[25]	Double-blind, randomized, placebo-controlled study. N=136	All arms were administered in equally divided doses immediately upon retiring to bed and 2.5-4 hours later, without titration, for 4 weeks. - Sodium oxybate 3 g (n=34) - Sodium oxybate 6 g 9n=33) - Sodium oxybate 9 g (n=35) - Placebo (n=34) Prior to randomization, patients completed a five-day washout period.	Inclusion - Adults diagnosed with narcolepsy for ≥6 months according to American Sleep Disorders Association's criteria. - Valid polysomnogram (PSG) within previous 5 years. Exclusion - Diagnosed with sleep apnea or had coexisting causes of daytime sleepiness.	- Subjective sleepiness at week 4 (ESS) - Overall severity of disease at week 4 (CGI-S) - Level of illness at week 4 (CGI-C) - Safety
Ahmed 2005[26,65] **NCT00049803**	Phase III, double-blind, randomized, placebo-controlled study. N=228	All arms were administered for 8 weeks. 6 and 9 g doses were titrated in weekly 1.5-g increments. Placebo arm underwent a mock dose-titration schedule. - Sodium oxybate 4.5 g (n=64)	Inclusion - Ages ≥16 years. - Prior diagnosis of narcolepsy based on an overnight PSG and MSLT performed within 5 years. - Current symptoms of	- Excessive daytime sleepiness at week 8 (ESS and MWT) - Changes in disease severity at week 8 (CGI-S) - Safety

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
		- Sodium oxybate 6 g 9 (n=58) - Sodium oxybate 9 g (n=47) - Placebo (n=59) Prior to randomization, patients completed a five-day washout period.	narcolepsy (EDS, cataplexy, recurrent sleep attacks) almost daily for ≥3 months. Exclusion - Use of sodium oxybate 30 days prior to trial entry.	
Black 2006[27] **NCT00066170**	Phase III, double-blind, randomized, placebo-controlled study. N=222	All participants entered a two-week baseline period of single-blind modafinil 200 to 600 mg per day and nightly placebo sodium-oxybate solution (volume equivalent to 6 g) prior to randomization into the 8-week double-blind phase. - Group 1: placebo (n=55) - Group 2: sodium oxybate 6 g for first 4 weeks, titrated to 9 g for remaining 4 weeks (n =50) - Group 3: modafinil 200 to 600 mg per day (n=63) - Group 4: sodium oxybate 6 g titrated to 9 g after 4 weeks + modafinil 200 mg (n=54) Sodium oxybate was administered in 2 equally divided doses at bedtime and again 2.5 to 4 hours later.	Inclusion - Adults with ICSD diagnosis of narcolepsy. - Taking stable doses of modafinil (200 to 600 mg/day) for EDS for ≥3 months, with dose stable for ≥1 month prior to trial entry. Exclusion - Use of sodium oxybate within 30 days prior to enrollment.	Primary - MWT at 8 weeks Secondary - ESS at 8 weeks - CGI-C and CGI-S at 8 weeks - Safety
Bogan 2021[28] **NCT03030599**	Phase III, double-blind, randomized-withdrawal, placebo-controlled	Of 201 participants enrolled and treated (safety population), 134 were randomized in the 2-week double-blind randomized	Inclusion - Adults diagnosed with NT1, and currently untreated or treated with	Primary - CFB to week 2 of double-blind randomized withdrawal period in WCR

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
	trial. N=201	withdrawal period (efficacy population). - Sodium oxybate 0.5 g/mL orally (n=69) - Placebo (n=67)	or without anticataplectics. - If applicable, treatment with stimulant at unchanged doses for ≥ 2 months, or not treated with a stimulant. Exclusion - Narcolepsy secondary to another medical condition. - Treatment with CNS sedating agents, or antidepressants for cataplexy.	Secondary - CFB to week 2 of double-blind randomized withdrawal period in ESS score - Number of patients with worsening PGI-C and CGI-C at week 2 of double-blind randomized withdrawal period
REST-ON[29] **NCT02720744**	Phase III, double-blind, randomized, placebo-controlled study. N=212	All arms were administered once nightly for 13 weeks. - Sodium oxybate 4.5 g for week 1, titrated to 6 g for weeks 2-3, 7.5 g for weeks 4-8, and 9 g for weeks 9 -13 (n=107) - Placebo (n=105)	Inclusion - Ages ≥16 years. - Diagnosis of narcolepsy, determined by an overnight PSG and MSLT <8 minutes. - ≥2 sleep-onset REM periods. - Current continuing presence of EDS for last 3 months. - ESS >10. - For NT1, presence of cataplexy for last 3 months. - For concomitant stimulant use: stable dose of stimulants for ≥3 weeks prior to screening and continuation of regimen throughout study.	Primary - CFB to week 14 in mean sleep latency from the 5 MWT wake trials - CFB to week 14 in number of cataplexy attacks Secondary - CFB to week 14 in ESS total score - Safety

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
			Exclusion - Prior sodium oxybate dosing must have been ≤4.5g per night for ≤2 weeks and not within the last year prior to trial entry.	
Pitolisant				
HARMONY 1[30] **NCT01067222**	Phase III, double-blind, randomized, parallel-group, placebo-controlled study. N=95	All arms were administered daily for 8 weeks: 3 weeks of flexible dosing followed by 5 weeks of stable dosing. - Pitolisant, escalating dose of 10, 20 or 40 mg (n=32) - Modafinil 100, 200 or 400 mg (n=33) - Placebo (n=30) All patients completed a washout period, took a low dose (10 mg of pitolisant, 100 mg modafinil or placebo) in week 1, then a medium dose (20 mg pitolisant, 200 mg modafinil or placebo) in week 2 prior to randomization.	Inclusion - Diagnosis of narcolepsy, with or without cataplexy. - No psychostimulant medications for ≥14 days; patients with severe cataplexy could remain on anticataplectic medications at stable doses. Exclusion - Other conditions that could cause EDS.	Primary - CFB to week 8 in ESS Secondary - CFB to week 8 in MWT
HARMONY CTP[31] **NCT01800045**	Phase III, double-blind, randomized study. N=106	All arms were administered once daily. All participants completed a one-week washout period prior to randomization. - Pitolisant at 5, 10, 20 or 40 mg (n=54) - Placebo (n=52)	Inclusion - Narcoleptic with cataplexy; ≥3 weekly cataplexy attacks - ESS ≥12 Exclusion - Other conditions that could cause EDS.	Primary - WCR at week 7 Secondary - ESS at week 7 - Safety

Trial (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
HARMONY 1bis[32] **NCT01638403**	Phase III, double-blind, randomized, parallel-group, placebo and comparator-controlled study N=180	All arms were administered once daily for 8 weeks. - Pitolisant 5, 10 or 20 mg (n=67) - Modafinil 100, 200 or 400 mg (n=65) - Placebo (n=33) All participants completed a two-week washout period prior to randomization.	Inclusion - Adults with ICSD diagnosis of narcolepsy, with or without cataplexy, - No psychostimulant medications for ≥14 days prior to baseline. - Patients with severe cataplexy could remain on anticataplectic medications at stable doses. - ESS of ≥14. Exclusion - Use of pitolisant within 30 days prior to screening.	Primary - ESS at week 10 Secondary - MWT at week 10

BID: twice daily, CFB: change from baseline, CGI-C: Clinical Global Impression of Change, CGI-S: Clinical Global Impression of Severity, CSF: cerebrospinal fluid, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, g: grams, g/mL: grams per milliliters, HLA: human leukocyte antigen, ICSD: International Classification of Sleep Disorders, mg: milligrams, n: number, MSLT: Multiple Sleep Latency Test, MWT: Maintenance of Wakefulness Test, NT1: narcolepsy type 1, PGI-C: Patient Global Impression of Change, pg/mL: picograms per milliliters, QD: once daily, TEAE: treatment-emergent adverse event, WCR: weekly cataplexy rate

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Trial, NCT, and Trial Sponsor	Study Design	Arms	Inclusion Criteria and Patient Population	Primary Outcome(s)	Estimated Completion Date
TAK-861-2003 **NCT05816382** **Takeda Pharmaceuticals**	Phase II/III long-term extension study assessing the safety and tolerability of TAK-861 (oveporexton) in patients with NT1. N=500	Participants will continue to receive the dose assigned to them in their parent study for up to five years: • 1 mg TAK-861 BID • 2 mg TAK-861 BID	• Diagnosis of NT1. • Participation and completion of FirstLight or RadiantLight.	Number of participants with at least 1 TEAE through five years.	February 2028

BID: twice daily, mg: milligrams, n: number, NT1: narcolepsy type 1, TEAE: treatment-emergent adverse events

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D5. Previous Systematic Reviews and Technology Assessments

We identified several systematic reviews that have made indirect comparisons between narcolepsy treatments.

Zhan 2023[98]

A frequentist fixed-effect model NMA of 17 trials in patients with narcolepsy found that modafinil/armodafinil, sodium oxybate, pitolisant, solriamfetol, and lower-sodium oxybate all improved narcolepsy symptoms more than placebo. Solriamfetol produced the largest gains on the MWT, ESS, and Patient Global Impression of Change, while lower-sodium oxybate showed the greatest Clinical Global Impression of Change benefit. Lower-sodium oxybate also carried the lowest risk of overall, serious, and discontinuation-related adverse events. All agents demonstrated acceptable safety.

Chien 2022[99]

In a NMA of 19 trials (2504 patients with narcolepsy), solriamfetol ranked first for reducing ESS scores and prolonging MWT times, outperforming pitolisant and sodium oxybate on the former and pitolisant and modafinil on the latter. However, clustered ranking showed that pitolisant, sodium oxybate, and modafinil offer more balanced efficacy-safety profiles.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type Of Impact (Add Additional Domains, As Relevant)	Included In This Analysis From […] Perspective?		Notes On Sources (If Quantified), Likely Magnitude and Impact (If Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[100]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[101]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of this economic evaluation was based on the patient population in the 2 mg twice a day dose and placebo arms of the RadiantLight and FirstLight trials; two 12-week studies comparing treatment with oveporexton to placebo.[16] Baseline characteristics summarized in Table 4.2. and below in Table E1.2. reflect weighted averages across both trials.

Table E1.2. Baseline Population Characteristics

Characteristics	Value
Mean (SD) Age, Years	30.4 (10.9)
Female, %	56.6
Mean (SD) ESS Score	18.1 (3.3)

ESS: Epworth Sleepiness Scale, SD: Standard Deviation

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Oveporexton (Takeda Pharmaceuticals)

Comparators

The Comparators for these interventions were:

- Combination of a wake-promoting agent represented by modafinil (generic; originally Provigil®, Cephalon/Teva) plus anti-cataplexy medication represented by venlafaxine (generic; originally Effexor®, Pfizer).
    - Modafinil was chosen as it is the most common first-line therapy for wakefulness in patients with NT1. Venlafaxine was chosen as the anti-depressant to use in combination with modafinil as it is the most widely used antidepressant for treating cataplexy.[102]
- Sodium oxybate (generic; originally Xyrem®, Jazz Pharmaceuticals)
    - Branded single dose and low-sodium oxybate products have comparable clinical efficacy to the twice nightly. Applying a distribution of all sodium oxybate products following their market share was explored in a scenario analysis.
- Pitolisant (WAKIX®, Harmony Biosciences)
- No pharmacological treatment

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

Excessive Daytime Sleepiness

The proportion of patients achieving ESS ≤10 on each treatment was obtained from an internal network meta-analysis (NMA). These patients were assumed to have no excessive daytime sleepiness and received non-drug and productivity costs of controls without narcolepsy. Response data for sodium oxybate was obtained directly from REST-ON, which did not specify the proportion in placebo that achieved a response and therefore not included in the network.[34] Due to modafinil trials not reporting the proportion of patients who achieved this response, we used a trial for armodafinil to inform the modafinil response, assuming the two treatments have comparable efficacy.[23]

We used mean changes in ESS scores from an NMA to base health state utilities in a scenario analysis. More details including change in ESS can be found in Supplement Section E5. Venlafaxine was assumed to have no impact on EDS.

Pivotal clinical trials that were included in any of the mentioned NMAs are detailed in Table E2.1. below.

Table E2.1. Studies Included in NMA

Treatment	Studies Contributing Evidence
Oveporexton	FirstLight (NCT06470828) RadiantLight (NCT06505031) Phase II Study (NCT05687903)
Modafinil	US Modafinil in Narcolepsy Multicenter Study Group 1998 US Modafinil in Narcolepsy Multicenter Study Group 2000 Harsh 2006 (NCT00078377)
Sodium Oxybate	XYREM Study Group/Cook 2002 Ahmed 2005 (NCT00049803) Black 2006 (NCT00066170) REST-ON (NCT02720744)
Pitolisant	HARMONY 1 (NCT01067222) HARMONY 1bis (NCT01638403) HARMONY CTP (NCT01800045)

Cataplexy

Cataplexy is a major symptom of NT1; however, there was insufficient evidence to support modeling its direct impacts on HRQoL and health care costs. Instead, the impact of cataplexy on HRQoL was captured indirectly through trial-based utilities in our base case which reflected the overall disease burden patients experienced during the trial. Consultations with patients and clinicians indicated that cataplexy attacks rarely resulted in health care system contact or required medical intervention beyond pharmacological treatment, and therefore, no direct cataplexy-related costs were included. Some costs may be indirectly captured in the difference in utilization costs between patients with narcolepsy and controls.

Cataplexy attacks were not comparable across studies due to differing study populations, trial protocols and their allowance of background therapies, follow-up duration, and outcome reporting measurements, with some reporting median rates and others reporting means. As a result, we were unable to include cataplexy counts as a secondary outcome in the oveporexton versus active treatment comparisons.

Transition Probabilities - Discontinuation

While real-world treatment persistence rates were available for some comparators, data on oveporexton was limited to trial-based observations. To maintain consistency across treatments, we derived discontinuation rates from data observed in trials.

Rates were converted to 13-weeks to align with the three-month cycles, and rates within treatments were pooled based on the number of patients in each trial. Trials with longer follow-up were observed to have more patients.

Mortality

We applied age- and sex- specific mortality rates from Human Mortality Database US-specific tables, adjusted by standardized mortality ratios (SMRs) of 1.57 for males and 1.43 for females with narcolepsy.[64] The elevated mortality rates were applied to all patients regardless of treatment, as current evidence did not support a differential mortality rate for any narcolepsy treatment. This is consistent with prior published models, that have either assumed elevated mortality rates with no differential between treatments or that it was a nonfatal disease.[56-60] Narcolepsy being a nonfatal disease was explored in a scenario analysis, where patients were assumed to have the same mortality rate as the general population and is detailed in Section E5.

Economic Inputs

Drug Acquisition Costs

The following inputs were used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen

Table E2.2. Treatment Regimen Recommended Dosage

Generic Name	Oveporexton	Modafinil	Venlafaxine	Sodium Oxybate	Pitolisant
Brand Name	NA	Generic (originally Provigil®, Cephalon/Teva)	Generic (originally Effexor®, Pfizer)	Generic (originally Xyrem®, Jazz Pharmaceuticals)	WAKIX®
Manufacturer	Takeda Pharmaceuticals	Various	Various	Various	Harmony Biosciences
Route of Administration	oral	oral	oral	oral	oral
Dosing	2 mg twice daily	200 mg/day	37.5-150 mg/day	2.25 g twice nightly, titrated to 3 - 4.5 g twice nightly in weekly increments of 0.75 g per dose	Week 1: 8.9 mg daily Week 2: 17.8 mg daily Week 3: May increase to maximum dose 35.6 mg daily

g: gram, mg: milligram, NA: not available

Table E2.3. Drug Cost Inputs

Drug	WAC	Discount from WAC	Net Price per Dose	Net Price per Year
Oveporexton	$171.12/mg*	Not applicable	$342.23*	$250,000*
Modafinil (Generic)	$0.0063/mg†	Not applicable	$1.26†	$460.22†
Venlafaxine (Generic)	$0.0060/mg†	Not applicable	$0.45†	$164.36†
Sodium Oxybate (Generic)	$58.54/g†	Not applicable	$219.53†	$160,363†
Pitolisant (Wakix®)	$25.06/mg	17.6%	$592.45	$216,392

g: grams, mg: milligram, WAC: wholesale acquisition cost

*Placeholder price

†Represents the median price of all available generics

Productivity Costs

Literature compared productivity costs between narcolepsy patients and controls with no evidence across varying disease severities. We included patient productivity costs displayed in Table E2.4 and applied narcolepsy related productivity estimates to all patients experiencing any EDS (ESS >10) and control estimates to patients with no EDS (ESS ≤10). These costs were incorporated in a scenario analysis for a modified societal perspective and obtained from the same source as the non-drug costs.

Table E2.4. Annual Patient Productivity Costs

Parameter	Narcolepsy Mean Costs (SD)	Controls Mean Costs (SD)	Source
Absenteeism	$12,267 (19,314)	$6,191 (12,048)	Doane 2025[78]
Presenteeism	$18,814 (16,460)	$11,913 (13,971)	
Total Indirect Costs	$30,075 (24,741)	$17,222 (20,251)	

SD: standard deviation

E3. Results

Base case results are displayed in the main report Section 4.3.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per addition QALY/evLY.

Table E4.1. Tornado Diagram Inputs and Results for Oveporexton versus Modafinil + Venlafaxine

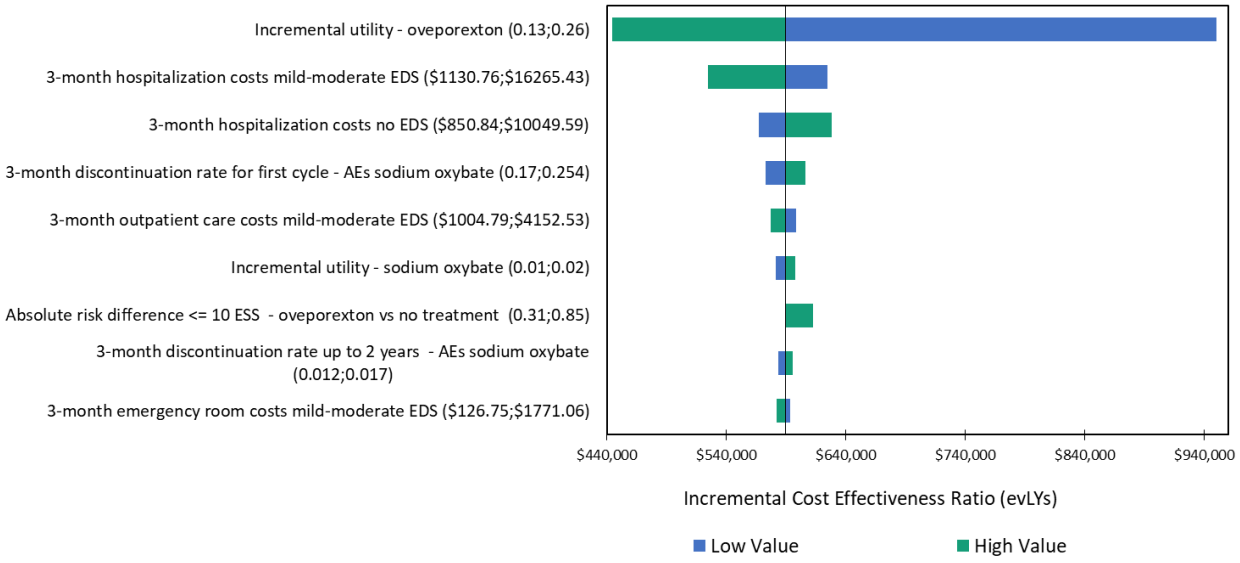
	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton	$1,956,000	$902,000	0.13	0.26
Absolute Risk Difference ESS ≤10 - Modafinil vs. No Treatment	$1,171,000	$1,305,000	0.05	0.69
3-Month Hospitalization Costs Mild-Moderate EDS	$1,245,000	$1,119,000	$1,131	$16,265
Absolute Risk Difference ESS ≤10 - Oveporexton vs. No Treatment	$1,249,000	$1,162,000	0.31	0.85
3-Month Hospitalization Costs No EDS	$1,173,000	$1,250,000	$851	$10,050
Incremental Utility - Modafinil	$1,179,000	$1,223,000	0.02	0.03
3-Month Outpatient Care Costs Mild-Moderate EDS	$1,212,000	$1,186,000	$1,005	$4,153

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
3-Month Discontinuation Rate Up To 2 Years - AEs Modafinil + Venlafaxine	$1,212,000	$1,190,000	0.021	0.032
3-Month Discontinuation Rate Up To 2 Years - LOE Modafinil + Venlafaxine	$1,212,000	$1,191,000	0.031	0.046

AEs: adverse events, CE: cost-effectiveness, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, LOE: lack of efficacy

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratios value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Figure E4.1. Tornado Diagram – Oveporexton Versus Sodium Oxybate



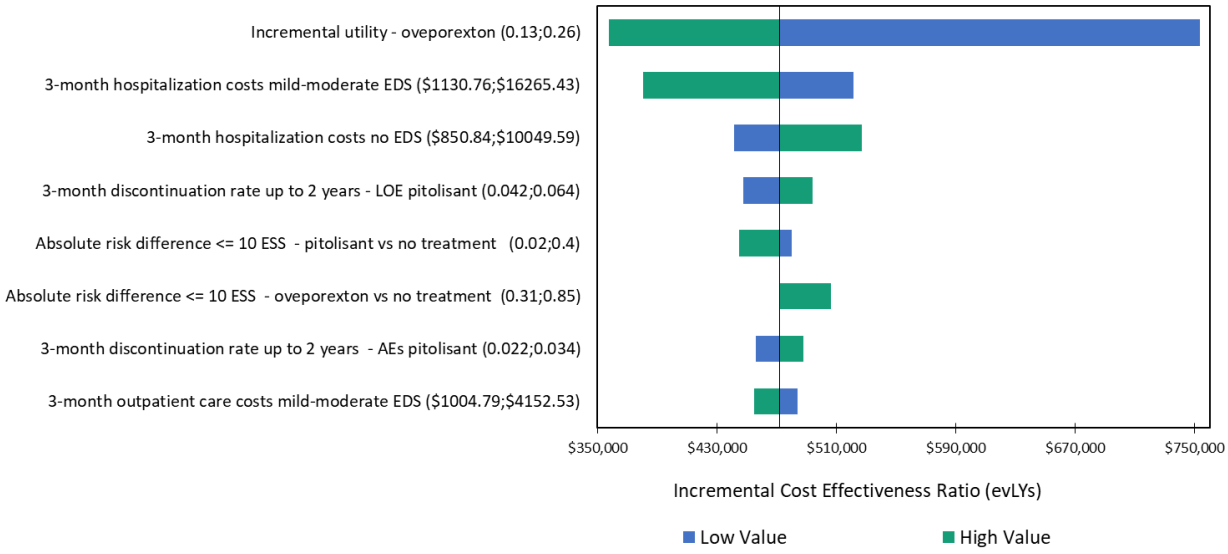
AEs: adverse events, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, evLY: equal-value life year

Table E4.2. Tornado Diagram Inputs and Results for Oveporexton versus Sodium Oxybate

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton	$950,000	$445,000	0.13	0.26
3-Month Hospitalization Costs Mild-Moderate EDS	$625,000	$524,000	$1,131	$16,265
3-Month Hospitalization Costs No EDS	$568,000	$629,000	$851	$10,050
3-Month Discontinuation Rate for First Cycle - AEs Sodium Oxybate	$573,000	$606,000	0.17	0.254
3-Month Outpatient Care Costs Mild-Moderate EDS	$598,000	$577,000	$1,005	$4,153
Incremental Utility - Sodium Oxybate	$581,000	$598,000	0.01	0.02
Absolute Risk Difference ESS ≤10 - Oveporexton vs. No Treatment	$597,000	$612,000	0.31	0.85
3-Month Discontinuation Rate Up To 2 Years - AEs Sodium Oxybate	$584,000	$595,000	0.012	0.017
3-Month Emergency Room Costs Mild-Moderate EDS	$593,000	$582,000	$127	$1,771

AEs: adverse events, CE: cost-effectiveness, EDS: excessive daytime sleepiness ESS: Epworth Sleepiness Scale
*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Figure E4.2. Tornado Diagram – Oveporexton versus Pitolisant



AEs: adverse events, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, evLY: equal-value life year, LOE: lack of efficacy

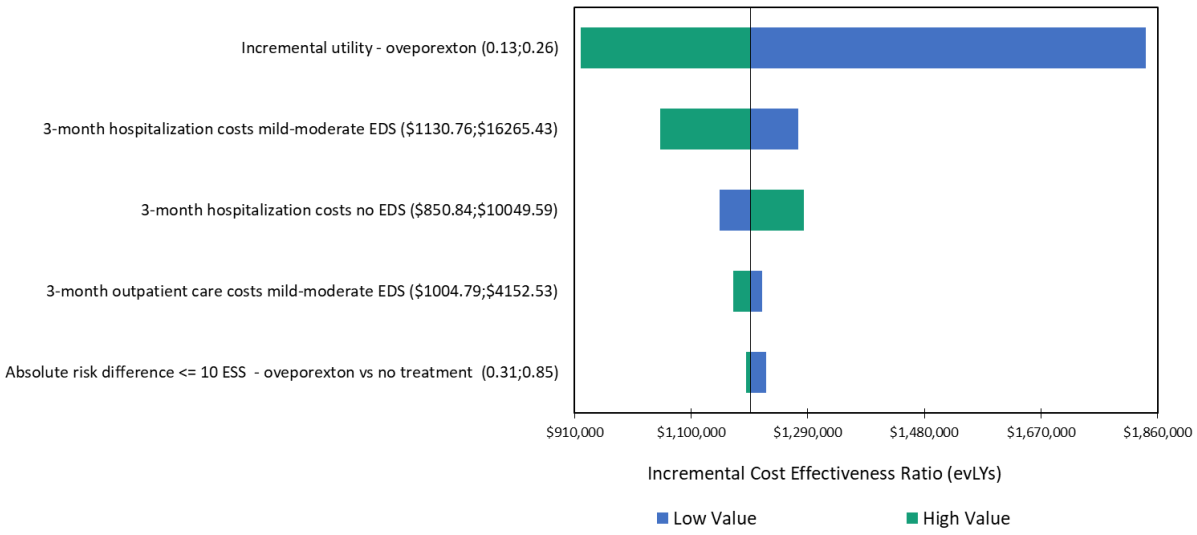
Table E4.3. Tornado Diagram Inputs and Results for Oveporexton versus Pitolisant

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton	$753,000	$358,000	0.13	0.26
3-Month Hospitalization Costs Mild-Moderate EDS	$521,000	$381,000	$1,131	$16,265
3-Month Hospitalization Costs No EDS	$441,000	$527,000	$851	$10,050
3-Month Discontinuation Rate Up to 2 Years - LOE Pitolisant	$448,000	$494,000	0.042	0.064
Absolute Risk Difference ESS ≤10 - Pitolisant vs. No Treatment	$480,000	$445,000	0.02	0.4
Absolute Risk Difference ESS ≤10 - Oveporexton vs. No Treatment	$472,000	$506,000	0.31	0.85
3-Month Discontinuation Rate Up to 2 Years - AEs Pitolisant	$456,000	$488,000	0.022	0.034
3-Month Outpatient Care Costs Mild-Moderate EDS	$484,000	$455,000	$1,005	$4,153

AEs: adverse events, CE: cost-effectiveness, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, LOE: lack of efficacy

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Figure E4.3. Tornado Diagram – Oveporexton versus No Pharmacological Treatment



EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, evLY: equal-value life year

Table E4.4. Tornado Diagram Inputs and Results for Oveporexton versus No Pharmacological Treatment

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton	$1,840,000	$920,000	0.13	0.26
3-Month Hospitalization Costs Mild-Moderate EDS	$1,275,000	$1,050,000	$1,131	$16,265
3-Month Hospitalization Costs No EDS	$1,147,000	$1,284,000	$851	$10,050
3-Month Outpatient Care Costs Mild-Moderate EDS	$1,216,000	$1,169,000	$1,005	$4,153
Absolute Risk Difference ESS ≤10 - Oveporexton vs. No Treatment	$1,222,000	$1,189,000	0.31	0.85

CE: cost-effectiveness, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table E4.5. Results of Probabilistic Sensitivity Analysis for Oveporexton versus Modafinil + Venlafaxine

	Oveporexton Mean	Modafinil + Venlafaxine Mean	Incremental
Costs*	$5,219,000	$1,796,000	$3,423,000
QALYs	20.12 (16.14, 23.20)	17.29 (13.37, 20.22)	2.83 (2.77, 2.98)
evLYs	20.12 (16.14, 23.20)	17.29 (13.37, 20.22)	2.83 (2.77, 2.98)
Incremental CE Ratio*			$1,200,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

Table E4.6. Results of Probabilistic Sensitivity Analysis for Oveporexton versus Sodium Oxybate

	Oveporexton Mean	Sodium Oxybate Mean	Incremental
Costs*	$5,241,000	$3,507,000	$1,734,000
QALYs	20.19 (16.08, 23.52)	17.28 (13.40, 20.22)	2.91 (2.68, 3.30)
evLYs	20.19 (16.08, 23.52)	17.28 (13.40, 20.22)	2.91 (2.68, 3.30)
Incremental CE Ratio*			$596,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

Table E4.7. Results of Probabilistic Sensitivity Analysis for Oveporexton versus Pitolisant

	Oveporexton Mean	Pitolisant Mean	Incremental
Costs*	$5,224,000	$3,810,000	$1,414,000
QALYs	20.18 (16.42, 23.49)	17.22 (13.59, 20.17)	2.96 (2.83, 3.32)
evLYs	20.18 (16.42, 23.49)	17.22 (13.59, 20.17)	2.96 (2.83, 3.32)
Incremental CE Ratio*			$478,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

Table E4.8. Results of Probabilistic Sensitivity Analysis for Oveporexton versus No Pharmacological Treatment

	Oveporexton Mean	No Pharmacological Treatment Mean	Incremental
Costs*	$4,637,000	$865,000	$3,772,000
QALYs	19.98 (16.03, 23.03)	16.81 (13.00, 19.65)	3.17 (3.03, 3.38)
evLYs	19.98 (16.03, 23.03)	16.81 (13.00, 19.65)	3.17 (3.03, 3.38)
Incremental CE Ratio*			$1,200,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

E5. Scenario Analyses

Scenario Analysis 1 – Modified Societal Perspective

Our modified societal perspective analysis incorporated patient productivity cost estimates detailed in Table E2.4. All patients with mild to moderate EDS accrued costs related to patients with narcolepsy, and patients who achieved ESS ≤10 were assumed to have no EDS and accrued costs of patients with no narcolepsy.

Scenario Analysis 2 – Exclusion of Unrelated Health Care Costs

Unrelated health care costs were excluded by subtracting the costs related to control patients (no EDS) from patients with narcolepsy (mild to severe EDS) in Table 4.2.

Scenario Analysis 3 – ESS Based Utilities

In this scenario, HRQoL measures were based on the Epworth Sleepiness Scale (ESS) to allow methodological consistency in utility estimates across treatments. While the Maintenance of Wakefulness Test (MWT) is a more objective measure of sleepiness than patient-reported scales such as the ESS, there was no published data linking MWT measures to HRQoL utilities. As a result, we referenced Cambron-Mellott et al., who used data from the European National Health and Wellness Survey from 2016/2017 of 2,348 patients with obstructive sleep apnea (n=2,277),

narcolepsy (n=48) or both (n=23).[67] Despite allowing for a consistent measure across treatments, these utilities introduce their own uncertainties by being elicited largely from an obstructive sleep apnea population, and only focus on one symptom of NT1.

The utility for no pharmacological treatment was kept the same as the base case. ESS based treatment-specific utility increments were calculated by taking the difference between utilities displayed in Table E5.2. of EDS severities of the category treatment fell into, to our cohort's baseline severity. Changes in ESS for each treatment are detailed in Table E5.1; these were applied to the baseline ESS (18.1) for our cohort to obtain the treatment specific ESS values. The resulting post-treatment ESS score determined the treatments mean EDS severity and the difference between the treatment and baseline severity utilities were taken as the treatment-specific increment. For example, our baseline ESS fell within the severe EDS categorization corresponding to a utility of 0.559. If a treatment reduced the mean ESS to fall within the moderate category (utility 0.643), the incremental utility for that treatment would be 0.084 (0.643 – 0.559).

Table E5.1. Epworth Sleepiness Scale Scores

Treatment	Difference in ESS	Incremental Utility
Oveporexton	-9.92 (95% CrI: -11.5; -8.4)	0.152
Modafinil + Venlafaxine	-3.25 (95% CrI: -4.35; -2.25)	0.084
Sodium Oxybate	-2.28 (95% CrI: -3.54; -1.24)	0.084
Pitolisant	-2.82 (95% CrI: -4.19, -1.43)	0.084

CI: credible interval, ESS: Epworth Sleepiness Scale

Table E5.2. Health State Utilities by EDS Severity

Treatment	Mean (SD)	Source
No EDS (ESS ≤10)	0.711 (0.251)	Cambron-Mellot 2022[67]
Mild EDS (ESS 11-12)	0.685 (0.261)	
Moderate EDS (ESS 13-15)	0.643 (0.268)	
Severe EDS (ESS 16-24)	0.559 (0.323)	

EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, SD: Standard Deviation

Scenario Analysis 4 – Distribution of Sodium Oxybate Products Based on Market Share

In this scenario, sodium oxybate is represented by a distribution of all available products, weighted according to their market share.[103] Based on clinical expert opinion, all sodium oxybate products have comparable clinical efficacy and could be treated as interchangeable in the model. While differences in long-term risks and adherence may exist across products due to sodium content and dosing schedules, these could not be modeled due to lack of available data and were not included in the base case nor in this scenario. Table E5.3. presents wholesale acquisition costs, net prices and market share for each product, with costs calculated based on an average dose of 7.5 g nightly. Discounts for Xyrem and Xywav were obtained from SSR Health, and Lumryz from IPD Analytics Rebate Monitor.

Table E5.3. Wholesale Acquisition Costs, Net Prices and Market Share for Sodium Oxybate Products

Sodium Oxybate Product	WAC/g	Discount from WAC	Net Price per Year	Market Share
Generic	$58.54	--	$160,363	29%
XYREM®	$82.88	29.7%	$159,595	8%
XYWAV®	$78.33	29.7%	$150,846	52%
LUMRYZ™	$76.98	42.5%	$121,254	11%

g: grams, WAC: wholesale acquisition cost

Scenario Analysis 5 – Dosing of Sodium Oxybate Reflecting Real-World Utilization

In this scenario, sodium-oxybate dosing was adjusted to better reflect real-world utilization based on clinical expert consultation. Two-thirds of patients were assumed to be on 9 g nightly, with the remaining third split between 6 g and 7.5 g, resulting in higher treatment costs relative to the base case (annual net cost of $176,399 vs. $160,363 in the base case). While this dosing better reflects real-world utilization, treatment effects were held constant from the base case. If higher doses are associated with better treatment benefit, this scenario may underestimate the true effects of sodium oxybate at real-world doses and result in oveporexton looking more cost-effective.

Scenario Analysis 6 – Removal of Elevated Mortality in Patients with No EDS

Patients who achieved an ESS score of 10 or lower received the mortality rates of the general population, regardless of which treatment they were on. This scenario is based off the assumption that returning excessive daytime sleepiness to normal levels would return mortality back to the general population. However, it does not account for any increases in mortality due to the

treatments themselves such as stimulants and sodium oxybate due to lack of data. evLYs were calculated in respect to modafinil + venlafaxine.

Scenario Analysis 7 – Removal of Elevated Mortality

In this scenario, excess mortality associated with narcolepsy was removed, such that patients were assumed to experience the same all-cause mortality rate as the general population. This assumption is supported by Hsu et al. which found no statistically significant difference in all-cause or cause-specific mortality between patients with narcolepsy and age- and sex-matched controls, or sibling controls in a large Taiwanese cohort.[61] However, authors note that longer-term follow up may be required to detect mortality differences that emerge later in life, and that modest increases in risk cannot be fully excluded.

Table E5.4. Scenario Analysis Results – Total Outcomes for Oveporexton versus Active Comparators

Treatment	Initial Treatment Acquisition Cost*	Subsequent Treatment Acquisition Cost	Total Cost*	QALYs	evLYs	LYs
Scenario Analysis 1: Modified Societal Perspective						
Oveporexton	$3,884,000	$649,000	$5,716,000	20.11	20.11	24.05
Modafinil + Venlafaxine	$9,600	$1,055,000	$2,410,000	17.29	17.29	24.05
Sodium Oxybate	$2,456,000	$318,000	$4,088,000	17.25	17.25	24.05
Pitolisant	$2,268,000	$791,000	$4,428,000	17.20	17.20	24.05
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs						
Oveporexton	$3,884,000	$649,000	$4,631,000	20.11	20.11	24.05
Modafinil + Venlafaxine	$9,600	$1,055,000	$1,248,000	17.29	17.29	24.05
Sodium Oxybate	$2,456,000	$318,000	$2,942,000	17.25	17.25	24.05
Pitolisant	$2,268,000	$791,000	$3,256,000	17.20	17.20	24.05
Scenario Analysis 3: ESS Based Utilities						
Oveporexton	$3,884,000	$649,000	$5,192,000	19.96	19.96	24.05
Modafinil + Venlafaxine	$9,600	$1,055,000	$1,809,000	18.90	18.90	24.05
Sodium Oxybate	$2,456,000	$318,000	$3,503,000	18.90	18.90	24.05
Pitolisant	$2,268,000	$791,000	$3,816,000	18.90	18.90	24.05
Scenario Analysis 4: Weighted Distribution of Sodium Oxybate Products						
Oveporexton	$3,884,000	$623,000	$5,167,000	20.11	20.11	24.05
Modafinil + Venlafaxine	$9,600	$1,013,000	$1,768,000	17.29	17.29	24.05
Sodium Oxybate	$2,314,000	$318,000	$3,360,000	17.25	17.25	24.05
Pitolisant	$2,268,000	$745,000	$3,771,000	17.20	17.20	24.05

Treatment	Initial Treatment Acquisition Cost*	Subsequent Treatment Acquisition Cost	Total Cost*	QALYs	evLYs	LYs
Scenario Analysis 5: Sodium Oxybate Dose Adjusted to Reflect Real-World Utilization						
Oveporexton	$3,884,000	$692,000	$5,236,000	20.11	20.11	24.05
Modafinil + Venlafaxine	$9,600	$1,126,000	$1,881,000	17.29	17.29	24.05
Sodium Oxybate	$2,702,000	$318,000	$3,748,000	17.25	17.25	24.05
Pitolisant	$2,268,000	$869,000	$3,895,000	17.20	17.20	24.05
Scenario Analysis 6: Removal of Excess Mortality from Responders						
Oveporexton	$4,010,000	$674,000	$5,364,000	20.79	20.80	24.89
Modafinil + Venlafaxine	$9,800	$1,083,000	$1,852,000	17.70	17.70	24.64
Sodium Oxybate	$2,518,000	$327,000	$3,589,000	17.69	17.70	24.69
Pitolisant	$2,312,000	$811,000	$3,894,000	17.58	17.58	24.60
Scenario Analysis 7: Removal of All Excess Mortality from Narcolepsy						
Oveporexton	$4,015,000	$704,000	$5,414,000	21.08	21.08	25.30
Modafinil + Venlafaxine	$10,000	$1,127,000	$1,920,000	18.17	18.17	25.30
Sodium Oxybate	$2,557,000	$341,000	$3,664,000	18.11	18.11	25.30
Pitolisant	$2,347,000	$842,000	$3,986,000	18.07	18.07	25.30

ESS: Epworth Sleepiness Scale, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $250,000 annually

Table E5.5. Scenario Analysis Results – Total Outcomes for Oveporexton versus No Pharmacological Treatment

Treatment	Initial Treatment Acquisition Costs*	Total Costs*	QALYs	evLYs	Life Years	Cataplexy Attacks†
Scenario Analysis 1: Modified Societal Perspective						
Oveporexton	$3,884,000	$5,125,000	19.99	19.99	24.05	23,093
No Pharmacological Treatment	$0	$1,558,000	16.88	16.88	24.05	39,832
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs						
Oveporexton	$3,884,000	$4,013,000	19.99	19.99	24.05	23,093
No Pharmacological Treatment	$0	$296,000	16.88	16.88	24.05	39,832
Scenario Analysis 3: ESS Based Utilities						
Oveporexton	$3,884,000	$4,574,000	19.24	19.24	24.05	23,093
No Pharmacological Treatment	$0	$857,000	16.88	16.88	24.05	39,832

Treatment	Initial Treatment Acquisition Costs*	Total Costs*	QALYs	evLYs	Life Years	Cataplexy Attacks†
Scenario Analysis 6: Removal of Excess Mortality from Responders						
Oveporexton	$4,010,000	$4,717,000	20.56	20.60	24.74	24,095
No Pharmacological Treatment	$0	$862,000	17.01	17.01	24.24	40,441
Scenario Analysis 7: Removal of All Excess Mortality from Narcolepsy						
Oveporexton	$4,015,000	$4,743,000	20.94	20.94	25.30	26,036
No Pharmacological Treatment	$0	$902,000	17.73	17.73	25.30	43,893

ESS: Epworth Sleepiness Scale, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year
Scenario analysis 4 and 5 did not impact results for this comparison and were not included in this table.
*Based on placeholder price for oveporexton of $250,000 annually
†Cataplexy attacks are not discounted

Table E5.6. Scenario Analysis Results – Incremental Outcomes versus Active Comparators

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Scenario Analysis 1: Modified Societal Perspective				
Oveporexton	Modafinil + Venlafaxine	$1,174,000	$1,174,000	No difference in life years
	Sodium Oxybate	$568,000	$568,000	No difference in life years
	Pitolisant	$442,000	$442,000	No difference in life years
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs				
Oveporexton	Modafinil + Venlafaxine	$1,201,000	$1,201,000	No difference in life years
	Sodium Oxybate	$589,000	$589,000	No difference in life years
	Pitolisant	$472,000	$472,000	No difference in life years
Scenario Analysis 4: Weighted Distribution of Sodium Oxybate Products				
Oveporexton	Modafinil + Venlafaxine	$1,207,000	$1,207,000	No difference in life years
	Sodium Oxybate	$631,000	$631,000	No difference in life years
	Pitolisant	$479,000	$479,000	No difference in life years
Scenario Analysis 5: Sodium Oxybate Dose Adjusted to Reflect Real-World Utilization				
Oveporexton	Modafinil + Venlafaxine	$1,191,000	$1,191,000	No difference in life years
	Sodium Oxybate	$519,000	$519,000	No difference in life years

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
	Pitolisant	$460,000	$460,000	No difference in life years
Scenario Analysis 6: Removal of Excess Mortality from Responders				
Oveporexton	Modafinil + Venlafaxine	$1,139,000	$1,139,000	$14,082,000
	Sodium Oxybate	$573,000	$573,000	$8,902,000
	Pitolisant	$458,000	$458,000	$5,112,000
Scenario Analysis 7: Removal of All Excess Mortality from Narcolepsy				
Oveporexton	Modafinil + Venlafaxine	$1,200,000	$1,200,000	No difference in life years
	Sodium Oxybate	$591,000	$591,000	No difference in life years
	Pitolisant	$474,000	$474,000	No difference in life years

evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year

Note: Incremental outcomes for scenario analysis 3 can be found in the main report Table 4.6.

*Based on placeholder price for oveporexton of $250,000 annually

Table E5.7. Scenario Analysis Results – Incremental Outcomes versus No Treatment

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Scenario Analysis 1: Modified Societal Perspective				
Oveporexton	No Pharmacological Treatment	$1,148,000	$1,148,000	No difference in life years
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs				
Oveporexton	No Pharmacological Treatment	$1,196,000	$1,196,000	No difference in life years
Scenario Analysis 6: Removal of Excess Mortality from Responders				
Oveporexton	No Pharmacological Treatment	$1,086,000	$1,086,000	$7,707,000
Scenario Analysis 7: Removal of All Excess Mortality from Narcolepsy				
Oveporexton	No Pharmacological Treatment	$1,196,000	$1,196,000	No difference in life years

evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year

Note: Incremental outcomes for scenario analysis 3 can be found in the main report Table 4.6. Scenario analysis 4 and 5 did not impact results for this comparison and were not included in this table.

*Based on placeholder price for oveporexton of $250,000 annually

E6. Heterogeneity and Subgroups

There were no pre-specified heterogeneity or subgroup analyses.

E7. Model Validation

Prior Economic Models

Several prior published economic models evaluating treatments for narcolepsy were identified and compared to our current analysis. All identified models share a similar structure, with a cohort of patients starting on an initial treatment phase, who may transition to a subsequent treatment due to adverse events, lack of efficacy or non-response, and death. Despite this common framework, models differed considerably in major factors such as time horizons, treatment comparators, standard care, and response definitions that limit direct comparisons of results.

The Canadian Drug Agency (formerly CADTH) evaluated a sponsor submitted model for pitolisant with a lifetime time horizon that also employed a basket approach for standard of care.[57] Patients initiated treatment, and could transition to subsequent treatment by discontinuation due to adverse events or lack of efficacy. Discontinuation rates were informed by key trials and long-term extensions, similar to in our model. However, their standard of care basket consisted of stimulants combined with off-label anticataplectic agents, while ours had a mixture of pitolisant, sodium oxybate, modafinil with venlafaxine, and no treatment. Response was defined using CGI-C rather than the ESS threshold used in our model, and the initial treatment evaluation period was eight weeks compared to three months. Utilities were specific to non-responders and responders, with responder utilities from the general population, whereas a mean utility from the trial was used for all patients on treatment in our model. Total discounted life years were 32.4 in the CADTH model, compared to 24.05 in ours, with the discrepancy due to difference in discount rates (1.5% vs. 3%), mortality assumptions (no elevated mortality due to narcolepsy vs. elevated mortality) and cohort starting age (38 vs. 30). Total discounted QALYs were similarly higher in the CADTH model at 21.29 for no treatment and 22.25 for pitolisant, compared to 16.91 and 17.22 in the current model.

In an evaluation of solriamfetol for narcolepsy by the National Institute for Health and Care Excellence (NICE), response was defined as an improvement in ESS of three or greater, and utilities were derived using an NHWS mapping algorithm applied to ESS scores from obstructive sleep apnea and narcolepsy patients.[56] This utility approach is comparable to the approach used to obtain incremental utilities in our scenario analysis. Despite both models' applying excess mortality from Ohayon et al. and the NICE cohort having an older mean age of 38, total life years gained were higher in the NICE model (42) compared to ours (24). The source for this discrepancy is unclear and may reflect differences in background mortality assumptions.

Lanting et al. evaluated sodium oxybate as an add-on to standard of care comprised of stimulants and anti-depressants, for patients with narcolepsy with cataplexy.[58] A short, five-year time horizon was modeled for their cohort with a mean age of 20 years. Due to limited data, they assumed 75% of patients discontinued sodium oxybate at three months due to non-response or adverse events –

a very high discontinuation assumption relative to current evidence. Utilities were derived indirectly from ESS changes mapped to EQ-5D using a regression from an obstructive sleep apnea population. No excess mortality associated with narcolepsy was applied.

Bolin et al. evaluated sodium oxybate with methylphenidate compared to standard treatment of methylphenidate with venlafaxine using a 10-year time horizon.[60] This model is very structurally similar to ours, with patients transitioning to standard care starting at three months; however, our definitions of standard care vary greatly with our basket approach. Additionally, patients in their model were only able to transition within the first three months, while our model applied cycle-by-cycle discontinuation rates throughout the lifetime. Utilities in their model were based on SF-36 scores from a published study, and they found their results to be sensitive to the duration of quality-of-life improvements, and sodium oxybate unit costs – factors we did not vary in our model.

In subsequent analysis, Bolin et al. evaluated pitolisant over a 50-year horizon for a 20-year-old cohort assuming standard treatment was modafinil/venlafaxine, and non-responders transitioned up to 6 months.[59] In both models, no excess mortality was applied, and utilization costs were informed by Danish registry data.

Across all the identified models, common limitations included relying on proxy utility estimates based on ESS or limited trial quality of life data, and exclusion of productivity losses. Our model tries to address these gaps by incorporating trials-based utilities along with ESS based mapping in a scenario analysis, and by including productivity estimates in a modified societal perspective analysis.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

This budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with oveporexton. To estimate the size of the potential candidate population, we used inputs for the prevalence of NT1 in the US (12.6 per 100,000 individuals) and the total US adult population averaged over the next five years (approximately 272,700,000).[1,79] Applying these sources results in estimates of approximately 34,000 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, approximately 6,900 patients per year. At baseline, we assumed 38% of the eligible population was treated with modafinil + venlafaxine, 32% was treated with sodium oxybate, 11% was treated with pitolisant, and 19% received no pharmacological treatment, as per available market share data.[7]

ICER's methods for estimating potential budget impact are described in detail in the Value Assessment Framework. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility.

As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2025-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $821 million per year for new drugs.

G. Supplemental Policy Recommendations

Payers

Prior Authorization

Given that some uncertainty remains about the efficacy of oveporexton over current combination treatments and longer-term safety and effectiveness, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policy are discussed below. Relevant Fair Access Design Criteria set out in ICER's previous work are included.

Cost Sharing

Patient cost sharing should be based on the net price to the plan sponsor, not the unnegotiated list price.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: see **Cornerstones of "Fair" Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals.**

Drug-Specific Coverage Criteria: Oveporexton

If the price for oveporexton is out of line with value, and given the uncertainty of durability of effect and potential need for combination therapy, payers may develop prior authorization criteria and consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[104] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for oveporexton.

Coverage Criteria

- **Age**: Age criteria are likely to follow the FDA label for oveporexton. However, given that NT1 can have a severe detrimental effect on children's lives and the relatively benign safety profile of oveporexton, payers should have efficient mechanisms for clinicians to seek coverage exceptions for younger patients with serious unmet need.

- **Clinical eligibility**: Payers are likely to require a diagnosis of NT1 to be eligible for treatment. Diagnostic criteria include ≥3 months of excessive daytime sleepiness and at least one of the following: (1) presence of cataplexy and either a mean sleep latency of ≤8 minutes and ≥2 sleep-onset rapid eye movement (REM) periods (SOREMPs) on a Multiple Sleep Latency Test or a SOREMP on nocturnal polysomnogram, or (2) cerebrospinal fluid orexin or hypocretin level of ≤110 pg/mL.

    - We heard from clinical experts that given the potential logistical challenges of obtaining a lumbar puncture in the United States (US), it is not reasonable for payers to require lumbar puncture prior to approving therapy.

- **Exclusion criteria**: Oveporexton is not currently indicated for treatment of narcolepsy type 2.

- **Dose:** Consistent with dosages tested in clinical trials, 1 mg or 2 mg twice daily.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for dose titration, assessment of side effects, or disorder progression. Clinician attestation of efficacy is reasonable to require prior to renewal.

- **Provider restrictions**: Given the complexity of diagnosing NT1, it is reasonable to restrict initial prescriptions of oveporexton to sleep medicine specialists (e.g., neurologist or pulmonologist), or by generalist clinicians in consultation with sleep medicine specialists. Once a patient is stable on treatment, given the safety profile of oveporexton and the potential difficulty in accessing specialty care, it is reasonable for prescription renewals to be done by non-specialist prescribers such as primary care physicians.

Step Therapy

If oveporexton is priced in line with its value, because it has a novel mechanism of action that directly addresses the underlying cause of NT1, it would not be appropriate for payers to restrict access to oveporexton using step therapy.

- Clinical experts highlighted that the approval of oveporexton would potentially represent a paradigm shift in the treatment of NT1, in that there would finally be a treatment that addresses the underlying etiology of NT1. Available data from pivotal clinical trials demonstrated large improvements in outcomes compared with placebo, and indirect evidence also suggests improvement over current therapies. Additionally, oveporexton has a favorable safety profile. Given the evidence, clinical experts suggested that oveporexton should become a first-line therapy, and if that were the case, step therapy would inappropriately delay access to an effective drug and cause harm to patients.

If oveporexton is priced beyond its expected value, the principles of fair access require that step therapy be used only if the policies are implemented in a patient-centered manner, providing adequate flexibility to meet the needs of diverse patients transparently and efficiently, for example by allowing patients and clinicians to choose from multiple options rather than requiring patients to try multiple options. Utilization management is also reasonable for combination therapy with oveporexton (if required), given the high cost of most of the treatments for NT1.

- Clinical and patient experts stated that medication failures and polypharmacy are common for NT1 patients, which raises the concern that inappropriate step therapy requirements could delay and restrict access to treatment. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients.

- Currently available specialty society guidelines recommend multiple options for treatment for NT1, depending on patient symptoms. Clinical experts and patients stated since symptoms of NT1 differ from patient to patient, individualized treatment is necessary. Additionally, some medications can lose efficacy over time, as patients develop medication tolerance, or side effects become intolerable. Finally, because no current treatment addresses all NT1 symptoms, patients often require multiple medications for adequate symptom relief. Thus, there is no justification to require patients to attempt trials with all options prior to obtaining coverage for a newer, more expensive agent. This kind of policy does not meet ICER's Fair Access Criteria. Additionally, some patients may require combination therapy with an additional agent and given the high cost of most of the drugs for NT1, utilization management is reasonable for combination therapy.

H. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on May 14th, 2026, including the manufacturer feedback on economic modeling. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit summaries of their public comments.

A video recording of all comments can be found here beginning at minute 00:12:15. Conflict of interest disclosures for all public commenters can be found in Supplement I.

Emily Clegg Barker, PhD, Freelance Medical Communicator; Person with Narcolepsy; Patient Advocate

Greetings and thank you for this opportunity. Soon after my 20th birthday, I had my first experiences with strange neurological weakness, seemingly triggered by laughter and the emotion of amusement - my knees buckling while dancing in the kitchen with my family, or my entire body going limp and collapsing from a bar stool after a very clever wordplay delivered by my older brother. "What is happening?!" We all wondered. I was fortunate among individuals presenting with elusive symptoms – Thanks to access to resources and a supportive network of family and friends that included knowledgeable medical experts, we put the pieces together. Within weeks, we discovered that the muscle weakness and collapsing was not disconnected from the daily fight to stay awake through college lectures, nor from the nights disrupted by frequent awakenings. All of these disjointed symptoms ended up forming a textbook diagnosis of "Narcolepsy with Cataplexy," commonly referred to today as "Type 1 Narcolepsy."
Early trials of therapy included stimulants that got me by for needed spurts of alertness in class or driving. Unfortunately, antidepressants like venlafaxine were ineffective for cataplexy and involved titration to the highest dose (still ineffective) followed by many months of painfully slow down titration in an attempt to avoid intrusive withdrawal effects and rebound cataplexy. With these disappointments, sodium oxybate became a lifesaver roughly one year into my diagnosis and has made possible a stable and independent adulthood that has gratefully included opportunities like marriage, children, and a fulfilling career, a career that includes important flexibility to accommodate symptoms of narcolepsy.

Despite the powerful difference, oxybate therapies still come up short on my daytime sleepiness and cataplexy, even in combination with the older stimulants or the newest wake promoting and anti-cataplexy agents. Just ask my siblings who still stand by to stabilize me when they see me gearing up on a clever punchline.

So in late 2024, My neurologist suggested I enroll on the phase 3 clinical trial with a new orexin 2 agonist, oveporexton, when I had come to her yet again with complaints related to residual

cataplexy and sleepiness disrupting day-to-day functionality. Following a challenging washout and initiation on the study drug, it was immediately apparent that I had been randomized to active treatment. Even the sleep techs were stunned when my Maintenance of Wakefulness Test went from 4 minutes at baseline to 40 minutes on treatment, but what did this look like in real life? This looked like going from years reliant on a midday nap to spending most days nap free. I went from avoiding drives beyond 30 minutes to being the primary driver on a 9-hour family road trip. I went from carefully rationing social energy to hosting regular weekend gatherings in my home. I went from reacting irrationally out of sheer exhaustion as a parent to more even-keeled and productive interactions with my kids. And aside from improved alertness and mood, I had an unexpected stability during both amusing and frustrating interactions that usually made me slump over and melt with cataplexy.

I wish there was a word more remarkable than “normal” to describe the wakefulness I experienced with this medication that lifted me out of the narcoleptic fog I had been slogging through for decades. It was different from traditional wake-promoting agents. It was more than just getting by with my eyes open while my brain feels cognitively exhausted. Instead, it was

functioning with a calm clarity where the idea of sleepiness hardly entered my consciousness, except to notice that I wasn’t experiencing it.

Despite this amazing experience with improved daytime alertness, oveporexton monotherapy did come up short on my evening and nighttime symptoms, an experience that I believe signifies a continued expectation for polytherapy to address the 24-hour disorder of narcolepsy.

Before closing, I want to acknowledge that I am likely not representative of the typical person with narcolepsy. I recognize that access to insurance, healthcare, and health literacy have helped to place me in a position where I have the energy and feel the responsibility to advocate for peers with narcolepsy who face barriers to optimal care and more severe day-to-day struggles.

Knowing their struggles, when I consider the potential impact of oveporexton in a treatment regimen, I anticipate seeing friends experience life-changing improvements, such as: freedom from fears about safety, stable housing and employment, opportunities to pursue education or family life that once seemed out of reach, and the confidence to contribute meaningfully to society.

Thank you for your time and I am glad to elaborate more on any of these topics during our afternoon roundtable.

Anne Samarawickrama, Trustee
Wake Up Narcolepsy

I, Anne Samarawickrama, am thankful to submit this response on this public forum on behalf of people who have narcolepsy or has a loved one with narcolepsy. I have been an advocate for better awareness, education, continued research, and better therapies at reasonable prices for narcolepsy. I am a trustee at Wake Up Narcolepsy for the last 10 years and a narcolepsy support group facilitator for the last 3 years.

Narcolepsy has been a poly-therapy managed disease. Oveporexton, manufactured by Takeda and reviewed by ICER, is a medication, pending FDA approval to enhance daytime wakefulness and functioning for people with narcolepsy. Upon review of the draft ICER summary and then the final report recently released, there was an increase from $175,000 to $250,000 (assumed annual market price). This price was not a higher recommended value by ICER. Their actual recommended value-based price in the final report was approximately $50,000–$60,000 annually (Table 6.1 Annual Cost-Effectiveness Threshold Prices for Oveporexton). This benchmark is based on comparison to modafinil + venlafaxine, a relatively inexpensive generic treatment combination. This methodology does not seems precise as Oveporexton directly addresses the underlying orexin deficiency while the others manages symptoms mildly.

Oveporexton as said by Dr. Scammel, is a medication like insulin to treat diabetes, and clinical trials indicate that is has a strong effect on reducing excessive daytime sleepiness and cataplexy. Participants who were in the Takeda clinical trials described the treatment as “life changing” and said they felt “normal” for the first time. The changes includes being mentally alert and not needing scheduled naps to function during the day. Most people with narcolepsy limit their extra activities as they are too tired. With Oveporexton during the day, they can socialize, travel and exercise without overwhelming exhaustion. By day-end the drug wears off as it’s a mono-therapy clinical trial. Most people would need additional medication to manage their nighttime sleep and those experiences are yet to be seen after the medication is approved.
From my involvement with narcolepsy support groups, I know of people who were made homeless because of their symptoms, lack of medication and lack of support and inability to work. There are many who are not able to take current therapies due to severe side effects. I know of women who bravely have their babies knowing how hard parenthood with narcolepsy would be for her and the whole family. A high percentage of people with narcolepsy experience anxiety and depression. There is no model to fully capture the burden of living with narcolepsy. A new therapy like Oveporexton which can strongly alleviate symptoms along with other medications to help to sleep properly is vital for families.

Based on peoples experiences with the clinical trials, this medication may give the freedom to come closer to normal, not to feel guilty about having to reply on their families, not have to make excuses for not taking part in activities due to exhaustion and reduce the anxiety of planning the day. It represents the possibility of greater independence, productivity, and quality of life.
Because assessments such as ICER's can influence future insurance coverage decisions, it is important that evaluations remain balanced, objective, and reflective of the full patient experience, without creating barriers that could limit access to potentially transformative treatments. Preliminary reviews can shape public perception, insurance expectations, and access decisions before the full clinical evidence and patient experience are fully understood.

People with narcolepsy matter. Therapies that improve their lives matter. Thank you.
Anne

Audelia Wittbrodt, Patient; Peer Support Volunteer
Wake Up Narcolepsy and Dysautonomia International

Hi, I'm Audelia. I'm 37, and I have Narcolepsy Type 1. Onset was at age 13, triggered by a mono infection. My pediatrician said I'd be sleepy for up to six months. We waited. Over time my symptoms got normalized. I went to countless specialists, but it took an astounding 15 years for me to get diagnosed. That was 8 years ago. And it's been a struggle. It was a struggle pre-diagnosis, and it has been a struggle since diagnosis.

I've tried 23 different medications, averaging two different therapeutic doses per medication, to try to treat my Narcolepsy symptoms. I've had side effects on almost all of them. Nevertheless, I've felt stable on medications three times since diagnosis, with my longest stable period lasting two and a half years. I'm currently on a combination of medications where I do feel stable. However, I still do not feel awake. I won't necessarily fall asleep during the day, but I spend all day feeling like I am fighting to stay awake.

Moment-to-moment, I am so sleepy that I have to consciously focus my eyes and actively merge both images from my eyes into one. If I relax, I see double and everything is blurry. I am continually expending energy trying to stay awake. Frustratingly, if I try to lay down and nap, I won't necessarily fall asleep. There is no relief.

My first sleep doctor described Narcolepsy as "Inability to stay awake during the day, and inability to stay asleep at night: the worst of both worlds." That resonates with my experience.

I want to emphasize the distinction between "not falling asleep" and "feeling awake", as well as the profound contrast between "feeling sleepy" and "feeling awake" in talking with other people that have been on Orexin Agonists. Not only do they "feel awake", but I get the impression that they feel *alive.* Not just normal, but actually alive!

I didn't even know that was a bar I could strive for! I genuinely expected my treatment to max out at it “not hurting as bad trying to stay awake all day”. And that’s telling. I think that once more people get on Orexin Agonists and see the extent to which Narcolepsy affects them, we will be able to change the language of how we describe Narcolepsy. I don't think I myself am fully aware of all the Narcolepsy-related symptoms I experience, partly because I've spent decades accommodating my deficiencies in a state of “half-asleep”, but also because I’ve come to realize I don’t have a clue what “normal” feels like. So this medication is extremely exciting.

I have to pause because I am symptomatic right now. Brain fog means that I frequently lose my train of thought. Although I spent the past two weeks trying to write a script out ahead of time, it was just a mess of rambling ideas, and I couldn't manage to get those ideas into a coherent … “thing that made sense”.

Brain fog is probably the most difficult aspect of Narcolepsy for me. It's not just feeling sleepy. It's forgetting things. I get mixed up a lot. I do not expect to remember anything that I said here. It is likely I will forget having even been at this meeting.

And that's the part I feel is lost when explaining Narcolepsy: the forgetting. How do you keep a full accounting of the things you’ve forgotten? I know I’ve forgotten parts of my personal history, I forget conversations, I often have no idea what people are talking about even if we were just talking about it, I get lost in familiar places, I’ve forgotten entire people, I’ve confused people I know with completely different people. It’s extremely disorienting and embarrassing.

Switching gears to what I have given up because of Narcolepsy. I had to drop out of my PhD program in Applied Physics. I took the maximum permitted medical semesters off and was not able to continue. That is probably my biggest personal loss because I really loved it.

I am also not able to work. Three years ago, I went from struggling to work full-time to struggling to work 3-6 hours a week. Indeed, the variability in symptoms can be extreme from year to year, and from day to day.

In the end, Orexin Agonists offer not only a hope for stability in symptoms, but the hope for a full life. Thank you for your time.

Phil Naughten, PharmD, Takeda
Head of US Value and Evidence Generation

Takeda appreciates the opportunity to provide feedback while ICER takes on the difficult task of modelling narcolepsy type 1 (NT1), also known as narcolepsy with cataplexy. Through more than 20 years of dedicated orexin research and deep NT1 expertise, Takeda understands that NT1 is more than sleepiness. NT1 is a rare, chronic neurological disease caused by a loss of orexin. Due to the 24-hour cycle of excessive daytime sleepiness, cataplexy (sudden loss of muscle tone), cognitive symptoms and disrupted nighttime sleep, NT1 can have a debilitating impact on many aspects of a person's life, including work, education and social interactions.[1,2,3,4,5] Despite existing therapies, the majority of patients continue to experience symptoms and are forced to cope with the continued impact of NT1. ICER appropriately highlights these patient realities in their clinical comparative effectiveness assessment. Other key areas of alignment throughout the report include:

- Oveporexton is an investigational orexin 2 receptor agonist designed to address the underlying cause of NT1 by restoring orexin signaling. ICER notes that currently approved drugs generally manage symptoms rather than addressing underlying orexin deficiency,[6 (Background)] positioning oveporexton as potentially the first drug to treat NT1 holistically by restoring orexin signaling.[6 (Executive Summary)] This difference matters to patients who hope to reclaim their life,[6 (Stakeholder Input: Supplemental Information: Section B3)] rather than simply feeling "less sleepy."[6 (Patient and Other Stakeholder Input)]
- Many patients currently treated for NT1 are unsatisfied with their therapy and most have residual symptoms.[6 (Background)]
- ICER assigns oveporexton a net health benefit rating of B+ versus placebo and C++ versus active comparators,[6 (Comparative Clinical Effectiveness: Section 3.3)] supporting that it may set a new bar for efficacy in key clinical outcomes.
- ICER leveraged trial-based quality-of-life measures in the economic model to make progress towards accounting for benefits beyond sleepiness associated with oveporexton.[6 (Long Term Effectiveness: Section 4.2)]

We appreciate that ICER's assessment of long-term value does not reduce NT1 to a single outcome, and that it reflects patient testimony that oveporexton treatment can impart "meaningful improvement….to function with clarity and reliable wakefulness."[6 (Stakeholder Input: Supplemental Information – Section B3)] However, even with a thoughtful discussion throughout the report, ICER's economic model can only account for benefits that are translated into quality-adjusted life years (QALYs) and costs. As such, the economic results should be interpreted in the context of unavoidable modeling limitations because, as constructed, the model undervalues oveporexton treatment benefits.

ICER states that the purpose of their assessment is to "support deliberation on medical policies related to health services and delivery system interventions" for populations.[7 (Introduction: Section 1.3)]

Economic analyses are conducted from the healthcare sector perspective in the base case.[7. (Incremental Cost Effectiveness, Section 3.5)] The assessment objectives and perspective are at odds with capturing holistic patient benefits that cannot be quantified by their impact on the health care system or patient quality of life.

As noted earlier, no single measure captures change across the broad range of NT1 symptoms or related functional burdens. Different measures assess different disease symptoms; they are related but are not interchangeable and a model that privileges one endpoint will necessarily miss other treatment benefits. In ICER's assessment, statistically significant and patient-important improvements in objective wakefulness (MWT) and cataplexy[6 (Comparative Clinical Effectiveness: Section 3.2)] are not incorporated into the economic analysis in a way that impacts economic value.

Patient-important outcomes like tiredness and fatigue, cognition, and daily function are not directly modeled. Although ICER recognizes these burdens and reports improvement on related measures in oveporexton studies,[6 (Comparative Clinical Effectiveness: Section 3.2)] they are not explicitly modeled beyond what may (or may not) be reflected in generic quality-of-life measures. ICER also notes that generic instruments such as EQ-5D may miss NT1-specific impacts,[6 (Long Term Effectiveness: Section 4.3)] which increases the likelihood that modeled QALY gains undervalues the true oveporexton benefits.

These model gaps matter because the model is a simplification of patient reality, and symptom management is not the same as restoring function. Improvements in ESS from symptom-based strategies are not guaranteed to restore alertness, cognitive clarity, stamina, or function in everyday life. These outcomes often define whether patients can sustain school, work, parenting, social life, and independence. For a disease that begins early and can shape an entire life course, the difference between "less sleepy"[6 (Patient and other Stakeholder Input: Section 2.1)] and "function with clarity"[6 (Stakeholder Input: Supplemental Information – Section B3)] is not a nuance, it is the outcome many patients are seeking.

We recognize ICER must choose comparators. However, anchoring the health benefit price benchmark analysis to modafinil + venlafaxine, despite weak evidence supporting use in NT1,[6 (Long Term Effectiveness: Section 4.3)] creates an uneven evidence standard when compared to a rigorously studied therapy and may negatively bias long-term value. It can also imply an easy substitute in real-world practice, even though symptom-based treatments are not designed to address the underlying disease or the broader outcomes patients associate with treating orexin deficiency.

Relatedly, the report could improve clarity regarding the benchmark price result interpretation for patients and clinicians. When several benefits are not translated into QALYs or cost offsets, the benchmark reflects what the model can measure, not the full benefit patients experience.

Finally, we acknowledge ICER's concerns about remaining uncertainties, especially long-term durability, long-term safety, and real-world treatment patterns for a first-in-class therapy. Takeda is committed to continued evidence generation after regulatory approval and launch and looks forward to further characterizing the full impact of oveporexton on patients, communities and society.

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I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the May 14, 2026 Public meeting of Narcolepsy. You can find any conflicts reported by the authors of the report, or expert reviewers, on page v.

Table I1. Midwest CEPAC Panel Member Participants and Conflict of Interest Disclosures

Midwest CEPAC Member	Conflict of Interest
Eric Armbrecht, PhD Professor and Associate Provost, Saint Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health & Social Justice	No conflicts to disclose.
Bijan Borah, PhD Professor of Health Services Research, Mayo Clinic College of Medicine and Science Consultant, Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic Joint Appointment as a Consultant, Department of Obstetrics and Gynecology, Mayo Clinic	No conflicts to disclose.
Donald E. Casey Jr., MD, MPH, MBA, MACP, FAHA, DFACMQ, DFAAPL, CPE Associate Professor of Internal Medicine, Rush Medical College; Adjunct Professor of Healthcare Quality & Safety and Population Health, Thomas Jefferson University College of Population Health; Affiliate Faculty, Institute for Healthcare Informatics, University of Minnesota; Faculty, Artificial Intelligence in Cardiology Program (ATRIA)	No conflicts to disclose.
Yngve Falck-Ytter, MD, AGAF Professor of Medicine, Case Western Reserve University; Chief, Gastroenterology and Hepatology VA Northeast Ohio Healthcare System, Cleveland	No conflicts to disclose.
Jayani Jayawardhana, PhD Associate Professor, Department of Health Management and Policy, University of Kentucky College of Public Health	No conflicts to disclose.
Jill Johnson, PharmD Professor, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy	No conflicts to disclose.
Bradley Martin, PharmD, PhD Professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences College of Pharmacy	No conflicts to disclose.

Midwest CEPAC Member	Conflict of Interest
Timothy McBride, PhD School of Public Health, Washington University in St. Louis Co-Director, Center for Advancing Health Services, Policy & Economics Research (CAHSPER)	No conflicts to disclose.
Reem Mustafa, MD, MPH, PhD Professor of Medicine, Division of Nephrology and Hypertension Director, Evidence Based Practice Center (EPC), University of Kansas	No conflicts to disclose.
Jimi Olaghere Sickle Cell Disease Advocate Entrepreneur, Sugarloaf Capital	No conflicts to disclose.
Rachel Sachs, JD, MPH Professor of Law, Washington University in St. Louis	No conflicts to disclose.
Kurt Vanden Bosch, PharmD Pharmacist, St. Luke's Health System, Idaho	No conflicts to disclose.
Stuart A. Winston, DO Cardiologist in the Sub-Specialty of Cardiac Electrophysiology, Trinity Health IHA Medical Group, Ann Arbor, MI Physician Lead, Professional Enhancement Program, Trinity Health IHA Medical Group, Ann Arbor, MI	No conflicts to disclose.

Table I2. Clinical and Patient Experts and Conflict of Interest Disclosures

Clinical and Patient Experts	Conflict of Interest
Tammy Anderson Executive Director, Wake Up Narcolepsy	Tammy Anderson is a full-time employee of Wake Up Narcolepsy. Wake Up Narcolepsy receives grants/sponsorships from Jazz Pharmaceuticals, Harmony Biosciences, Avadel, and Takeda Pharmaceuticals to support patient programming. These grants represent approximately 80% of the funding received through pharmaceutical grants/sponsorships for the most recent year.
Emily Clegg Barker, PhD Freelance Medical Communicator; Person with Narcolepsy; Patient Advocate	Emily Clegg Barker has received honoraria from Jazz Pharmaceuticals and compensation for supporting advisory boards by Jazz Pharmaceuticals and Centessa Pharmaceuticals. She volunteers with Wake Up Narcolepsy as a peer support facilitator.
Luis Ortiz, MD Sleep Medicine Physician, John Hopkins All Children's Hospital Assistant Professor of Pediatrics, John Hopkins University School of Medicine	Luis Ortiz has received fees from serving on advisory boards for Harmony Biosciences, Jazz Pharmaceuticals, and Avadel regarding pitolisant and Oxybate products.
Thomas Scammell, MD Professor of Neurology, Harvard Medical School	Over the last three years, Thomas Scammell has received consulting fees from Takeda, Jazz Pharmaceutical, Harmony Biosciences, Avadel Pharmaceuticals, and Merck.

Table I3. Health Care Companies and Conflict of Interest Disclosures

Health Care Company Representatives	Conflict of Interest
Becky Faustgen, PharmD Manager, Clinical Pharmacy, UnitedHealthcare	Becky Faustgen is a full-time employee of UnitedHealthcare.
Phil Naughten, PharmD Head of US Value and Evidence Generation, Takeda Pharmaceuticals	Phil Naughten is a full-time employee of Takeda Pharmaceuticals.
Emily Tsiao, PharmD, BCPS Senior Clinical Pharmacist, Trend Management Strategies and Programs, Premera Blue Cross	Emily Tsiao is a full-time employee of Premera Blue Cross.

Table I4. All Other Participants and Conflict of Interest Disclosures

All Other Participants	Conflict of Interest
Matthew Horsnell Patient Advocate, Wake Up Narcolepsy	Matthew Horsnell has received consulting fees from Avadel Pharmaceuticals and honoraria from Harmony Biosciences. Matthew Horsnell is a patient volunteer for the Hypersomnia Foundation, Project Sleep, and Wake Up Narcolepsy.
Anne Samarawickrama Trustee, Wake Up Narcolepsy	Wake Up Narcolepsy receives grants/sponsorships from Jazz Pharmaceuticals, Harmony Biosciences, Avadel, and Takeda Pharmaceuticals to support patient programming. These grants represent approximately 80% of the funding received through pharmaceutical grants/sponsorships for the most recent year.
Audelia Wittbrodt Patient; Peer Support Volunteer, Wake Up Narcolepsy and Dysautonomia International	Audelia Wittbrodt is a patient volunteer for the Dysautonomia International and Wake Up Narcolepsy.