Oveporexton for Narcolepsy: Effectiveness and Value

Draft Evidence Report

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Prepared for

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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 draft evidence report:

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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 of the draft 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

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

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Table of Contents

Conflict of Interest Disclosures for the Report v
Executive Summary ES1
1. Background 1
2. Patient and Other Stakeholder Input 3
2.1. Patient Community Insights 3
2.2. Health Equity Considerations 5
2.3. Input from Other Stakeholders 5
3. Comparative Clinical Effectiveness 6
3.1. Methods Overview 6
Scope of Review 6
Evidence Base 6
3.2. Results 11
Clinical Benefits 11
Harms 16
Subgroup Analyses and Heterogeneity 19
Uncertainty and Controversies 19
3.3. Summary and Comment 22
4. Long-Term Cost Effectiveness 25
4.1. Methods Overview and Structure 25
4.2. Key Model Assumptions and Inputs 26
Clinical Inputs 27
Health State Utility Inputs 28
Cost Inputs 29
4.3. Results 32
Base-Case Results 32
Sensitivity Analyses 33
Scenario Analyses 34
Threshold Analyses 35
Model Validation 36

Uncertainty and Controversies 36
4.4. Summary and Comment 38
5. Benefits Beyond Health and Special Ethical Priorities 39
6. Health Benefit Price Benchmark 41
7. Potential Budget Impact 42
7.1. Overview of Key Assumptions 42
7.2. Results 42
References 44
A. Background: Supplemental Information A1
A1. Definitions A1
A2. Potential Cost-Saving Measures in Narcolepsy A3
A3. Patient Input on Clinical Trial Design A4
B. Stakeholder Input: Supplemental Information B1
B1. Patient Community Insights: Methods B1
B2. Clinical Expert Input: Methods B1
C. Clinical Guidelines C1
American Academy of Sleep Medicine (2021)[12] C1
European Guideline and Expert Statements (2021)[80] C1
D. Comparative Clinical Effectiveness: Supplemental Information D1
D1. Detailed Methods D1
PICOTS D1
Data Sources and Searches D6
Study Selection D9
Data Extraction D9
Evaluation of Clinical Trial Diversity D15
Assessment of Level of Certainty in Evidence D17
Assessment of Bias D18
D2. Data Synthesis and Statistical Analyses D18
Feasibility of Conducting Meta-Analysis and/or Network Meta-Analysis D18
MA/NMA Methods D19

NMA Limitations D30
D3. Evidence Tables D32
D4. Ongoing Studies D39
D5. Previous Systematic Reviews and Technology Assessments D40
Zhan 2023[90] D40
Chien 2022[91] D40
E. Long-Term Cost-Effectiveness: Supplemental Information E1
E1. Detailed Methods E1
Description of evLY Calculations E2
Target Population E2
Treatment Strategies E3
Comparators E3
E2. Model Inputs and Assumptions E3
Model Inputs E3
E3. Results E8
E4. Sensitivity Analyses E8
E5. Scenario Analyses E13
Scenario Analysis 1 – Modified Societal Perspective E13
Scenario Analysis 2 – Exclusion of Unrelated Health Care Costs E13
Scenario Analysis 3 – ESS Based Utilities E14
Scenario Analysis 4 – Removal of Elevated Mortality in Patients with No EDS E15
Scenario Analysis 5 – Inclusion of Cataplexy Attacks & Discontinuation to No Treatment E15
E6. Heterogeneity and Subgroups E18
E7. Model Validation E18
Prior Economic Models E18
F. Potential Budget Impact: Supplemental Information F1
Methods F1

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 expansion
LYs	Life years
mg	Milligram
MID	Minimally important difference
MLST	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 2000 people in the 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, hypnagogic or hypnopompic hallucinations, 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 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 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 the effects of oveporexton as part of combination therapy, particularly because we heard that combination therapy is the norm to address the various 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 are 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 is 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.

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 likely 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

We conducted a cost-effectiveness analysis of oveporexton as monotherapy compared with a combination of modafinil + venlafaxine, sodium oxybate, pitolisant, and no pharmacological treatment for the treatment of NT1 in adults. Treatment with oveporexton resulted in greater increases in QALYs (quality-adjusted life years) and evLYs (equal value life years) compared with all other treatments in the model. Based on a placeholder price of $175,000, treatment with oveporexton as monotherapy did not meet traditional cost-effectiveness thresholds compared with no pharmacological treatment or modafinil + venlafaxine (cost per QALY gained of over $700,000 for both). However, treatment with oveporexton as monotherapy was cost-effective compared with sodium oxybates and pitolisant.

Overall, we found treatment with oveporexton resulted in statistically significant and clinically meaningful improvements in NT1 symptoms, as well as health-related quality of life, with few serious harms. The cost-effectiveness of oveporexton compared with no pharmacological therapy or other active treatments will depend on its actual price.

1. Background

Narcolepsy is a rare, chronic neurological disorder characterized by disruptions in the sleep-wake cycle. It affects approximately one in 2000 people in the 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 this 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 commonly have hypnagogic or hypnopompic hallucinations and 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. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments for Narcolepsy type 1 (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 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; detailed methodology can be found in Supplement 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 anticataleptic 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 draft 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 ages 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 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. 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[19-30]

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
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	Change from baseline in WCR at week 4	Treatment: 4 weeks	Female: 58.1% Mean age: 43.1 NT1: 100%

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics*
	cataplexy episodes per week N=136			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
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 was 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).[31]

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 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 vs. PBO Mean Difference (95% CI)
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)		19.59 (17.3 to 21.88)
ESS, Mean Difference, Points (SE)	-9.75 (0.94)		-9.53 (0.80)		-11.3 (1.58)		-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, 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.[32] 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 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 comparable treatment effect, with an 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]

Comparators

Pitolisant, sodium oxybate, and venlafaxine all reduced cataplexy events. Table 3.8 presents a qualitative trial-by-trial overview of comparator's impact on cataplexy occurrence.

Table 3.8. Narcolepsy Treatments Impact on Cataplexy Occurrence

Trial	Arms	Cataplexy Measure Study Findings
FirstLight	**2 mg OVE vs. Placebo**	IRR 0.38 (95% CI: 0.23 to 0.61), p<0.001
RadiantLight	**2 mg OVE vs. Placebo**	IRR 0.25 (95% CI: 0.15 to 0.42), p<0.001
Phase II	**2 mg OVE vs. Placebo**	IRR 0.36 (95% CI: 0.16 to 0.79), p = 0.03
Jin 2019	**Venlafaxine**	Median cataplexy episodes declined from 28 to 1 per week (p<0.001) and cataplexy-like episodes dropped from 56 to 7 per week (p<0.005).[22]
Cook 2002	**SXB 9 g twice nightly vs. Placebo**	69% reduction in WCR from baseline, compared to a reduction of 28% with placebo (p = 0.0008).
Bogan 2021	**SXB (low sodium) vs. Placebo**	Withdrawal study; median increase of 2.35 (interquartile range [IQR], 0.00 to 11.61) weekly cataplexy attacks in group switching to placebo vs 0 (IQR, -0.49 to 1.75) in the group that continued treatment.[26]
Ahmed 2005	**SXB 9 g twice nightly vs. Placebo**	Median decreases in weekly cataplexy attacks of 84.7% versus a 21.3% drop by placebo.[24]
REST-ON	**SXB (once nightly) Placebo**	Reduced weekly cataplexy attacks by 6.65 attacks (95% CI: -9.32 to -3.98), p <0.001.[33]
HARMONY CTP	**PIT 40 mg vs. Placebo**	IRR 0.51 (95% CI: 0.44 to 0.60), p<0.0001
HARMONY 1	**PIT 40 mg vs. Placebo**	IRR 0.38 (95% CI: 0.16 to 0.93), p=0.034
HARMONY 1bis*	**PIT 20 mg vs. Placebo**	Pitolisant/placebo fraction −1.00 (95% CI: −2.12 to 0.128), p =0.077 (daily)

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

*No peer-reviewed study available; data drawn from European Medicines Agency report.

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 and 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.[19,20] Modafinil 200 mg did improve the sleep efficiency percentage compared with placebo in one study.[20]

In the Harsh 2006 study, study participants underwent a nocturnal polysomnographic evaluation at baseline and final visits.[21] 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.[24] 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.[33] 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).[29]

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.[34]

Combination Therapy (Modafinil/armodafinil and 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.[35] 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.[28,29]

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).[28] 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.[36] The liver injury appeared to stem from effects of metabolites of TAK-994 on liver cells.[37] 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 and 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.[19,20] 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, 1-15% 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.[21] In this study, the range of participants treated with armodafinil that discontinued the study due to adverse events was 3-8%, 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.[38,39] 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.[38,40]

Venlafaxine has not been studied in a placebo-controlled study in adults with narcolepsy.[41] 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%).[22] 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.[42]

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).[43-45] 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.[43-46] The low sodium oxybate formulation demonstrated the lowest rate of discontinuation.

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.[47]

Pitolisant

In a pooled safety review of the HARMONY trials, the most frequently reported adverse events occurring in at least 5% of pitolisant-treated patients and at a rate at least twice that of placebo were insomnia, nausea, and anxiety.[48] 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.[48] 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 as a part of a combination therapy: We reviewed oveporexton as a monotherapy, as studied in clinical trials. However, since current treatment often requires combination therapy, we do not know whether oveporexton can replace multiple medications or if combination treatment will still be necessary. It is possible, for example, that patients may require oveporexton and a nighttime agent such as sodium oxybate to adequately address all wake and sleep symptoms of NT1. 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.[49] 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 6 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.[50] 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 4-5 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.

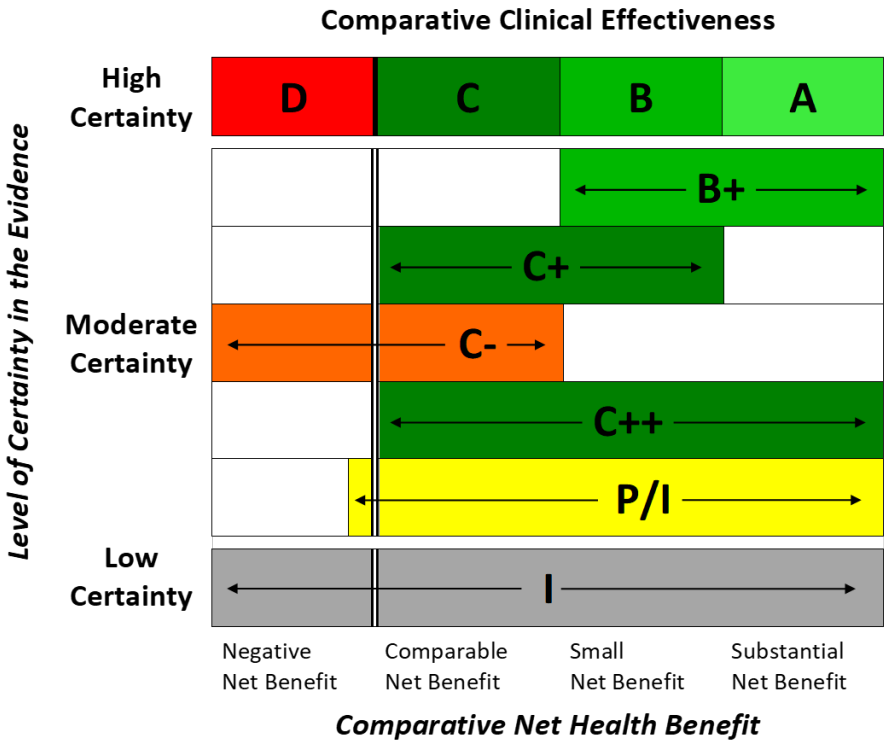
- Limitation of outcome measures: Although the outcomes measured in the clinical trials, such as ESS and MWT, are also standard tests in clinical practice, both outcomes have limitations. For example, the ESS is a subjective scale and has been found to have high variability and low reliability, and correlation with physiologic sleepiness is inconsistent.[51] 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.[52] 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, we have moderate certainty about the net health benefit of oveporexton compared with pitolisant, sodium oxybate, and the combination of modafinil/armodafinil and 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 to **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, with high certainty of at least a comparable net health benefit

4. Long-Term Cost Effectiveness

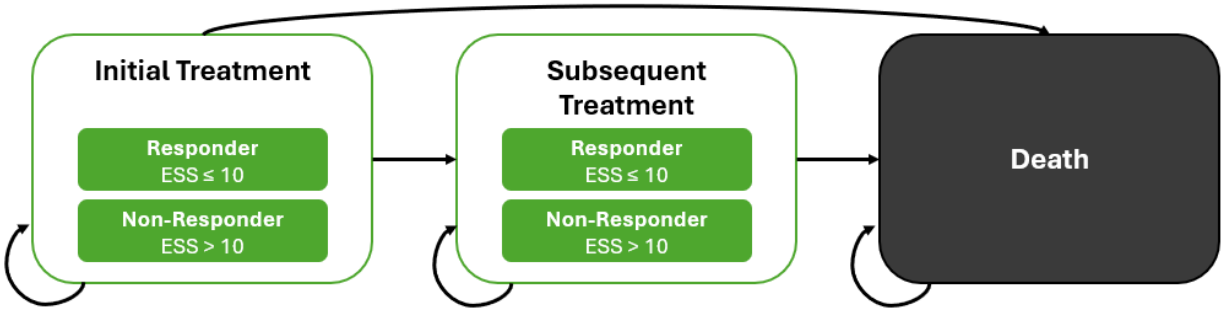
4.1. Methods Overview and Structure

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, and 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.[16,53-57] Patients were modeled over a lifetime horizon.

The model followed a simple structure consistent with prior published economic models.[53-57] 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.

Figure 4.1. Model Structure



ESS: Epworth Sleepiness Score
Initial treatment may be oveporexton, modafinil + venlafaxine, sodium oxybate, pitolisant, or no pharmacological treatment. Subsequent treatment consists of a weighted basket of all treatments excluding oveporexton. Patients who begin with no pharmacological treatment stay with no treatment while alive and do not transition to subsequent 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), where they are distributed across current therapies using a treatment basket approach. The basket includes all comparators and excludes oveporexton. The distribution across treatments in the basket is detailed in Table 4.2. Patients who begin with no pharmacological treatment remain on no pharmacological treatment over their lifetime and do not discontinue subsequent treatment. 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. Separate utility estimates for responders and non-responders were not available. 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. Data was available to inform differential costs for responders and non-responders, and is detailed in Section 4.2.

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 ≤10 ESS 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.
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, and only the costs associated with venlafaxine.
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

Assumption	Rationale
	also been linked with adverse cardiometabolic outcomes.[58,59] 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),[18,54] 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.[54]

EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Score, 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.[54] 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 were applied to all patients on initial treatment. Lack of efficacy rates were adjusted by dividing by 1 – 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.

Subsequent treatment baskets 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 were 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 ≤10 ESS from the sodium oxybate arm in the REST-ON trial directly.[32] 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.[60] 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 ≤10 ESS, was explored in a scenario analysis.

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%).[16,19,29,61]

See Supplement E2 for additional details.

Health State Utility Inputs

Health state utilities were composed of a no pharmacological treatment utility plus a treatment-specific increment.

A multiplier was applied to reduce age-based US population EQ-5D-5L values for NT1 in the absence of pharmacological treatment while maintaining the impact of age. This 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.[16,62]

Treatment-specific increments were derived from the pivotal trials for each treatment. Trial based utilities were chosen to capture treatment impact on as many dimensions of disease as possible. 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.[35,63,64] 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. 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.[29] Utilities for subsequent treatment were calculated as a weighted average of the individual treatment utilities within each basket, weighted by basket proportions. 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.

Cost Inputs

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

Drug Costs

Based on estimates from AInvest, we used an annual placeholder price of $175,000 for oveporexton, as neither list nor net prices are available.[65] For modafinil, venlafaxine, and sodium oxybate, we used the median price of all the generic options in RedBook. Costs for sodium oxybate were calculated using the middle of the recommended range for 3.75 g twice nightly. For venlafaxine, prices per dose were calculated using the most common dose of 75 mg/day.[22] An average dose of 28.69 mg for pitolisant was calculated from the stable dose of HARMONY 1.[28] 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 E2.7 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 & RadiantLight[16]
Female, %		56.6	
Clinical Inputs			
Proportion Achieving ≤10 ESS On No Pharmacological Treatment		0.1503	ICER NMA (See Supplement Table D2.3 for detailed results)
Proportion Achieving ≤10 ESS On Sodium Oxybate		0.56	REST-ON [32]
Absolute Risk Difference – Response (≤10 ESS) 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**	2.55%	FirstLight & RadiantLight[16]
	LOE 1st Cycle	0%	
	AE Up To 2 Years	1.01%	Phase II LTE[18]
	LOE Up To 2 Years	0%	
Modafinil + Venlafaxine	**AE 1st Cycle**	5.24%	US Modafinil in Narcolepsy Multicenter Study Group 1998 & 2000[19,20]
	LOE 1st Cycle	2.03%	
	AE Up To 2 Years	2.44%	Milter 2000 & Moldofsky 2000[66,67]
	LOE Up To 2 Years	3.56%	
Sodium Oxybate	**AE 1st Cycle**	15.46%	Ahmed 2005 & Black 2006[24,25,61,87]
	LOE 1st Cycle	0%	
	AE Up To 2 Years	1.34%	Mayer 2018, Bogan 2023, & Roy 2024[68-70]
	LOE Up To 2 Years	0.40%	Mayer 2018 & Bogan 2023[68,69]
Pitolisant	**AE 1st Cycle**	2.00%	HARMONY 1 & CTP[28,29]
	LOE 1st Cycle	9.14%	
	AE Up To 2 Years	2.60%	HARMONY 3[54]
	LOE Up To 2 Years	4.91%	
All Treatments	**AE Long Term**	0.36%	HARMONY 3[54]
	LOE Long Term	0.36%	
Subsequent Treatment Basket Composition			
Modafinil + Venlafaxine		0.38	Ortiz 2025[7]
Sodium Oxybate		0.32	
Pitolisant		0.11	
No Pharmacological Treatment		0.19	
Health State Utilities			
General US Population Utilities		Age-dependent	Jiang 2021[62]
Narcolepsy Utility Multiplier For No Pharmacological Treatment		0.834	Placebo arms of The FirstLight and The RadiantLight[16] + Jiang 2021[62]
Incremental Utility – Oveporexton		0.20	The FirstLight & The RadiantLight 2 mg/2 mg arms[16]

Parameter	Input	Source
Incremental Utility – Modafinil + Venlafaxine	0.021	Beusterien 1999[64] & Ara 2009[63]
Incremental Utility – Sodium Oxybate	0.016	Bogan 2016[35] & Ara 2009[63]
Incremental Utility – Pitolisant	0.011	Szakacs 2017[29]
Mortality		
SMR For Narcolepsy - Male	1.57 (95% CI: 1.43, 1.72)	Ohayon 2014[60]
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	$175,000‡	AInvest[71]
Modafinil	$460.22§	RedBook
Venlafaxine	$164.36§	
Sodium Oxybate	$160,366§	
Pitolisant (Wakix®)	$162,912	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[72]
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[72]
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 comparators are displayed in Table 4.4. 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

Treatment	Initial Treatment Acquisition Costs	Subsequent Treatment Acquisition Costs	Total Costs	QALYs	evLYs	Life Years
Oveporexton	$2,800,000*	$616,000	$4,075,000*	20.22	20.22	24.09
Modafinil + Venlafaxine	$6,800	$1,011,000	$1,765,000	17.32	17.32	24.09
Sodium Oxybate	$2,043,000	$864,000	$3,633,000	17.27	17.27	24.09
Pitolisant	$2,038,000	$1,117,000	$3,916,000	17.22	17.22	24.09
No Pharmacological Treatment	$0	$0	$859,000	16.91	16.91	24.09

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

*Based on placeholder price for oveporexton of $175,000 annually

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	Modafinil + Venlafaxine	$797,000	$797,000	No difference in life years
	Sodium Oxybate	$150,000	$150,000	No difference in life years
	Pitolisant	$53,000	$53,000	No difference in life years
	No Pharmacological Treatment	$970,000	$970,000	No difference in life years

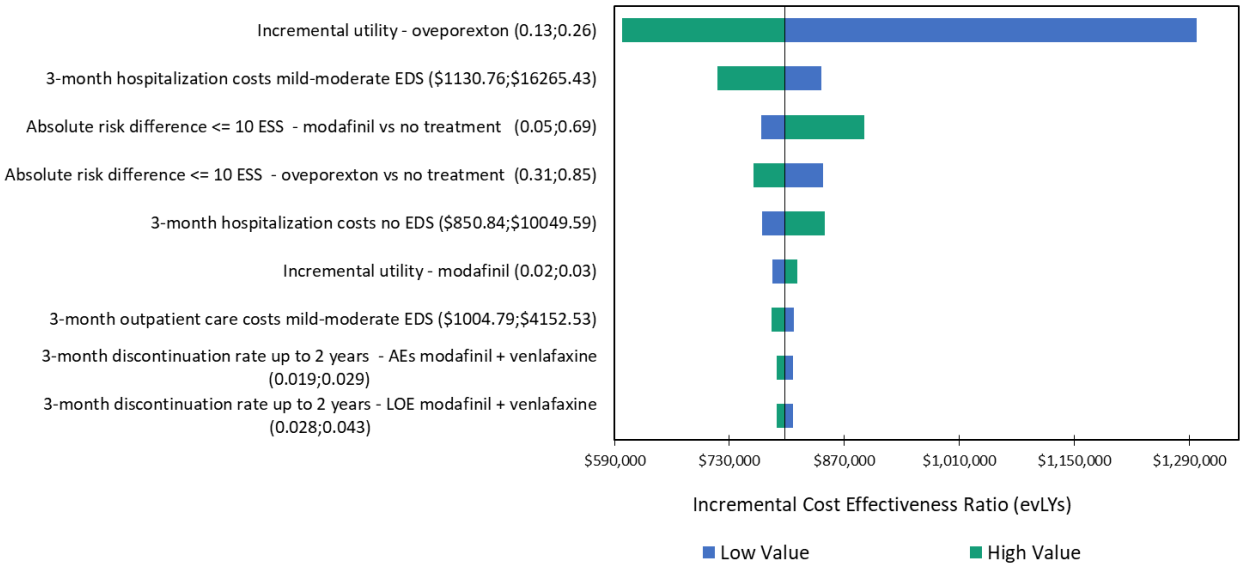
evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on placeholder price for oveporexton of $175,000 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 hospitalization costs and the probability of response to treatments. 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 vs. Modafinil + Venlafaxine*



evLY: equal value life year, EDS: excessive daytime sleepiness, ESS: Epworth Sleepiness Scale, AEs: adverse events, LOE: lack of efficacy
*Based on placeholder price for oveporexton of $175,000 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. Results are detailed in Table 4.5 with simulation means and credible intervals detailed in Supplement Section E4.

Table 4.5. Probabilistic Sensitivity Analysis Cost per evLY Gained Results

Treatment	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	Modafinil + Venlafaxine	0%	0%	0%	0%
	Sodium Oxybate	1%	8%	43%	84%
	Pitolisant	44%	82%	96%	99%
	No Pharmacological Treatment	0%	0%	0%	0%

evLY: equal value of life year

*Based on placeholder price for oveporexton of $175,000 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 productivity.
2. ICER reference case removing unrelated health care costs.
3. Applying ESS based utilities.
4. Removal of elevated mortality for patients who reach ≤10 ESS.
5. Patients on oveporexton discontinue to no pharmacological treatment to include cataplexy counts over the lifetime for oveporexton and no pharmacological treatment.

Applying ESS based utilities resulted in the largest difference in the incremental cost-effectiveness ratios compared to the base case, with incremental outcomes detailed in Table 4.6. Incremental cost-effectiveness ratios for sodium oxybate and pitolisant increased past commonly used cost-effectiveness thresholds that were met in the base case and inflated above $2,000,000 per evLY gained when compared to modafinil + venlafaxine. Other scenarios did not result in substantial changes. Additional details and results are presented in the Supplement Section E5.

Table 4.6. Scenario Analysis Results 3 – Incremental Outcomes for ESS Based Utilities

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Oveporexton	Modafinil + Venlafaxine	$2,100,000	$2,100,000	No difference in life years
	Sodium Oxybate	$407,000	$407,000	No difference in life years
	Pitolisant	$147,000	$147,000	No difference in life years
	No Pharmacological Treatment	$1,000,000	$1,000,000	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 $175,000 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 modafinil + venlafaxine. Results are displayed in Table 4.7 and Table 4.8.

Table 4.7. QALY-Based Threshold Analysis Results Versus Modafinil + Venlafaxine

	Anticipated Annual Price*	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	$175,000	$39,600	$48,700	$57,700	$66,800

QALY: quality-adjusted life year

*Based on placeholder price for oveporexton of $175,000 annually

Table 4.8 evLY-Based Threshold Analysis Results Versus Modafinil + Venlafaxine

	Anticipated Annual Price*	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	$175,000	$39,600	$48,700	$57,700	$66,800

evLY: equal value of life year

*Based on placeholder price for oveporexton of $175,000 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 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, 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.

- Differences in Trial Protocols & 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.[19,20,22] 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 $175,000, our analysis estimates oveporexton to exceed commonly used cost-effectiveness thresholds relative to modafinil + venlafaxine, and no pharmacological treatment, but reached some common cost-effectiveness thresholds when compared to sodium oxybate and most thresholds when compared to pitolisant. Oveporexton did not reach common cost-effectiveness thresholds when compared to modafinil + venlafaxine or no pharmacological treatment in probabilistic analyses but reached almost all thresholds in majority of simulations when compared to pitolisant. When compared to sodium oxybate, it was cost-effective at $150,00 per QALY/evLY at under half the simulations, and most simulations at $200,000 per QALY/evLY. Results were most influenced by the treatment response rates, the incremental utility of oveporexton, costs associated with hospitalizations, and discontinuation rates, as well as the utility source.

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: 10.3 Proportional shortfall: 24.3% QALY shortfalls: Absolute shortfall: 9.3 Proportional shortfall: 22.5% 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.
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.

6. Health Benefit Price Benchmark

ICER does not provide a Health Benefit Price Benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report. We plan to estimate the health benefit price benchmark for oveporexton against the common first-line and generic treatment option, modafinil + venlafaxine.

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 $175,000 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 Section F of the Supplement.

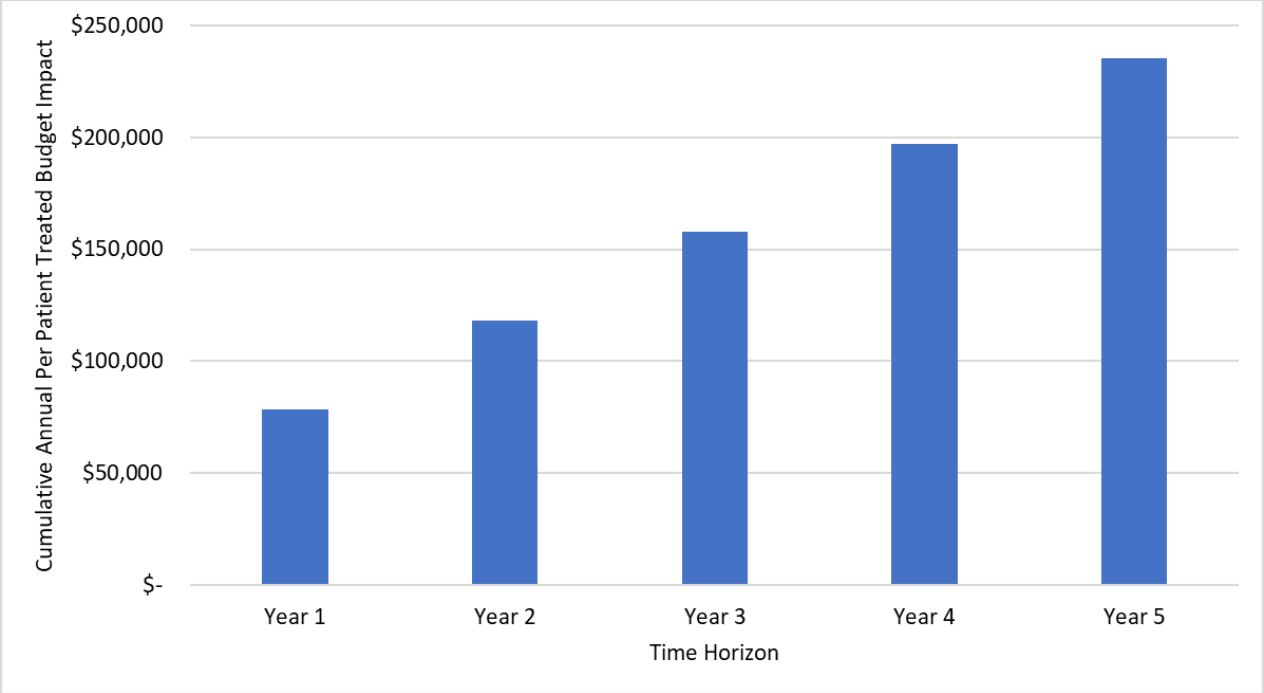
This budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with oveporexton. To estimate the size of the potential candidate population, we used inputs for the prevalence of NT1 in the US (12.6 per 100,000 individuals) and the total US adult population averaged over the next five years (approximately 272,700,000).[1,73] 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 $175,000 annually, the cumulative annual budget impact per patient was approximately $78,000 in the first year, and increased to approximately $235,000 by year five.

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



Results showed that 51% of eligible patients could be treated with oveporexton at the annual placeholder price of $175,000 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 ($39,600, $48,700, $57,700, and $66,800), all patients could be treated before reaching the potential budget impact threshold.

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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.[12,17,74]

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.[12,75]

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.[12,76]

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.[77] 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.[78,79] 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. 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 received 32 written comments via ICER's "Share Your Story" portal.

B2. 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.

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)[80]

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 intend to compare 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.[81,82] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[83] 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

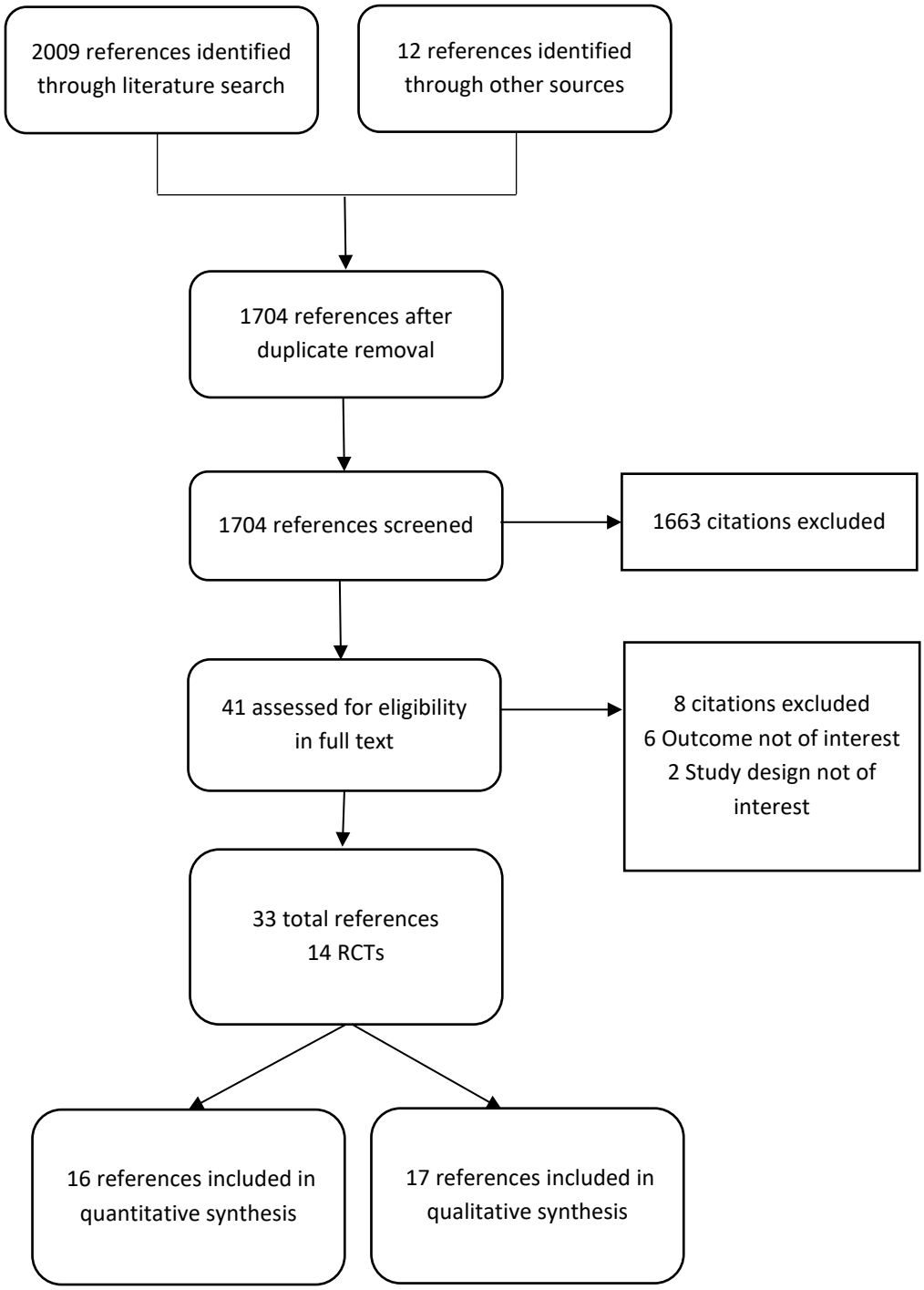
1	exp narcolepsy/
2	("Gelineau Syndrome" OR "Syndrome, Gelineau" OR "Gelineau's Syndrome" OR "Gelineaus Syndrome" OR "Gelineau's Syndromes" OR "Syndrome, Gelineau's" OR "Syndromes, Gelineau's" OR "Narcoleptic Syndrome" OR "Narcoleptic Syndromes" OR "Syndrome, Narcoleptic" OR "Syndromes, Narcoleptic" 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

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

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.[82,84] 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: TBD, no peer-reviewed publication available.					
RadiantLight	--	--	--	--	--	--
	Comment: TBD, no peer-reviewed publication available.					
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, TBD: to be determined

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: TBD, waiting on peer-reviewed publication.					
RadiantLight	--	--	--	--	--	--
	Comment: TBD, waiting on peer-reviewed publication.					
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.					

MSLT: Multiple Sleep Latency Test, MWT: Maintenance of Wakefulness Test, TBD: to be determined

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[31] 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 & 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.[85,86]

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 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 and 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

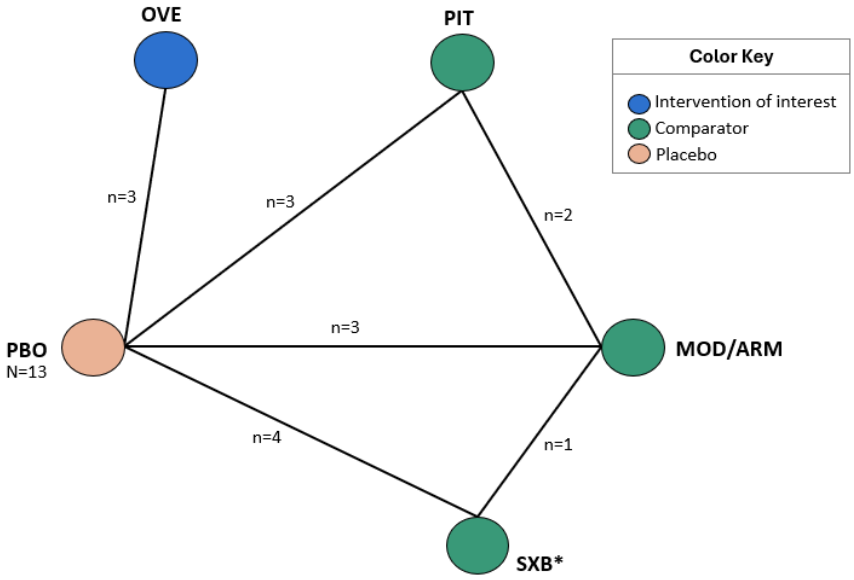
g: grams, mg: milligrams

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[19]	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[20]	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[21]	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[23]	Placebo	34	43.1	79 (58.1)	*19**	NR	34 (100)	0 (wash-out)	ESS MD
	SXB 3 mg	34			*17**	NR	34 (100)	0 (wash-out)	
	SXB 6 mg	33			*17.5**	NR	33 (100)	0 (wash-out)	
	SXB 9 mg	35			*17**	NR	35 (100)	0 (wash-out)	
Ahmed 2005[61]	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 mg	64			18* [n=61]	8.53* [n=62]	64 (100)	0 (wash-out)	
	SXB 6 mg	58			19*	9* [n=57]	58 (100)	0 (wash-out)	
	SXB 9 mg	47			19*	7.63*	47 (100)	0 (wash-out)	
Black 2006[25,87]	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[27]	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[28,30]	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[29,30]	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[30]	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, 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 2.3 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 be. tween 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, 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	4 sessions, 20 mins	Figure S7: Maski et al., 2021
	PBO	NA	NA		
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	
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	

Study	Treatment Arm	Responders	Sample Size	Source:
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.[87,88] 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.[89]

- 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 & 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] **NCT05687916**	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[21] **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 & 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[19]	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[20]	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 & 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[23]	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[24,61] **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 & 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[25] **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[26] **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 & 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 anticataleptics. - 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[27] **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 & 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[28] **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 anticataleptic 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[29] **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 & Dosing Regimen	Key Inclusion / Exclusion Criteria	Key Outcomes
HARMONY 1bis[30] **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 anticataleptic 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, & Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcome(s)	Estimated Completion Date
TAK-861-2003 **NCT0581638** **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[90]

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[91]

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 & 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[92]

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.[93]
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 or 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. 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, MWT: Maintenance of Wakefulness Test, 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.[94]
- Sodium oxybate (generic; originally Xyrem®, Jazz Pharmaceuticals)
    - Branded single dose and low-sodium oxybate products have comparable clinical efficacy to the twice nightly. As data informing real-world distributions of oxybate product use was not available, we followed ICER's reference case using the generic version for the base-case.
- Pitolisant (WAKIX®, Harmony Biosciences)
- No pharmacological treatment

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

Utilities

In the base case, utilities were sourced from pivotal trials and consisted of a mixture of different measures across treatments. This included EuroQol 5 Dimension (EQ-5D) index scores for oveporexton from the FirstLight and RadiantLight Trials, visual analog scale (VAS) scores for pitolisant from HARMONY CTP, and the 36-Item Short Form Health Survey (SF-36) converted into Short Form 6-Dimension (SF-6D) values following a mapping algorithm for sodium oxybate and modafinil + venlafaxine comparators from Bogan et al and Mitler et al, respectively.[16,29,35,63,66]

Utilities for sodium oxybate were calculated using the 6 g and 9 g treatment arms to match the recommended dose. Modafinil utilities were not separated by dose and included a mixture of 200 mg, 300 mg, and 400 mg arms.

Although combining multiple different utility measures introduced uncertainties into our results, incorporating trial-based utilities allowed for modeling a complete picture of the patient experience by indirectly capturing the impact of all symptoms, including EDS, cataplexy, and nighttime symptoms. We believe this was the better approach for 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. The sources of 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.[95] As a result, we decided the base case should use the trial-based utilities despite their limitations, and explored applying the uniform EQ-5D ESS based utilities to all treatments in a scenario analysis.

Modafinil was assumed to be the main driver of HRQoL in the combination treatment of modafinil + venlafaxine. 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.[96-98]

Excessive Daytime Sleepiness

The proportion of patients achieving ≤10 ESS 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.[32] 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.[21]

We used mean changes in ESS scores from an NMA to base health state utilities in a scenario analysis. 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 E2.3.

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, including cataplexy. 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 reduction of non-drug costs to those of patients without narcolepsy for the proportion who achieve an ESS score of 10 or lower.

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. However, we conducted a scenario analysis to evaluate the impact of oveporexton on cataplexy attacks compared to no pharmacological treatment following the rates detailed in Table E2.4. More information on this analysis is presented in Section E5.

Table E2.2. Weekly Cataplexy Rates

Treatment	Weekly Cataplexy Rate	Source
Oveporexton	4.5	FirstLight & RadiantLight[16]
No Pharmacological Treatment	17	

* Trial allowed patients to maintain stable background anti-cataplectic medication

Transition Probabilities - Discontinuation

Discontinuation rates in the model reflected discontinuation due to treatment-emergent adverse events (TEAE) or lack of efficacy observed in the pivotal trials and long-term extension studies.

The model applied discontinuation rates observed in the pivotal trials for the first cycle, and rates from long-term extensions for the remainder of the lifetime. Adverse event rates were applied to all patients on initial treatment, regardless of EDS status, whereas discontinuation due to lack of efficacy was only applied to patients with mild to severe EDS. Since trial-observed rates included all patients regardless of EDS severity, LOE was inflated to compensate for the inclusion of patients with no EDS. 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 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.[60] 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.[53-57]

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 E2.3. Treatment Regimen Recommended Dosage

Generic Name	Oveporexton	Modafinil	Venlafaxine	Sodium Oxybate	Pitolisant
Brand Name	n/a	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, n/a: not available

Table E2.4. Drug Cost Inputs

Drug	WAC	Discount from WAC	Net Price per Dose	Net Price per Year
Oveporexton	$119.78/mg*	Not applicable	$239.56*	$175,000*
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†	$160,366†
Pitolisant (Wakix®)	$25.06/mg	17.6%	$446.03	$162,912

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 productivity costs displayed in Table E2.9 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 E2.5. Annual Productivity Costs

Parameter	Narcolepsy Mean Costs (SD)	Controls Mean Costs (SD)	Source
Absenteeism	$12,267 (19,314)	$6,191 (12,048)	Doane 2025[72]
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.

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.

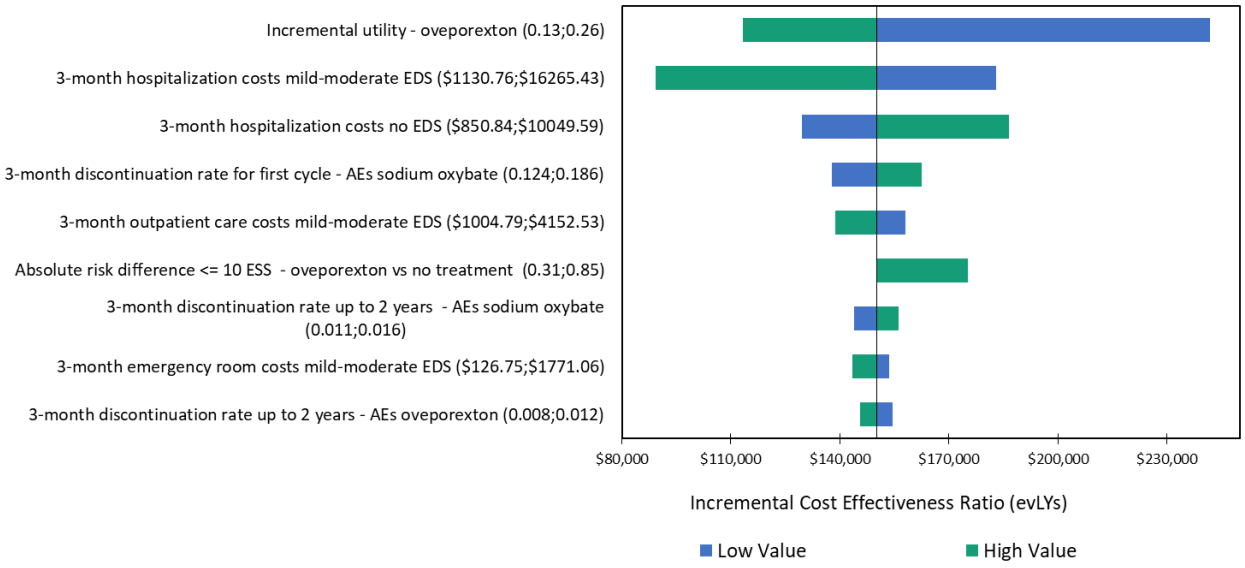
Table E4.1. Tornado Diagram Inputs and Results for Oveporexton versus Modafinil + Venlafaxine

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton (0.13;0.26)	$1,300,000	$599,000	0.13	0.26
3-Month Hospitalization Costs - Mild-Moderate EDS ($1130.76;$16265.43)	$842,000	$715,000	$1,131	$16,265
Absolute Risk Difference ≤10 ESS - Modafinil vs. No Treatment (0.05;0.69)	$769,000	$895,000	0.05	0.69
Absolute Risk Difference ≤10 ESS - Oveporexton vs. No Treatment (0.31;0.85)	$844,000	$759,000	0.31	0.85
3-Month Hospitalization Costs - No EDS ($850.84;$10049.59)	$770,000	$846,000	$851	$10,050
Incremental Utility - Modafinil (0.02;0.03)	$783,000	$812,000	0.02	0.03
3-Month Outpatient Care Costs - Mild-Moderate EDS ($1004.79;$4152.53)	$808,000	$782,000	$1,005	$4,153
3-Month Discontinuation Rate Up to 2 years - AEs Modafinil + Venlafaxine (0.019;0.029)	$808,000	$787,000	0.019	0.029
3-Month Discontinuation Rate Up to 2 years - LOE Modafinil + Venlafaxine (0.028;0.043)	$807,000	$788,000	0.028	0.043

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

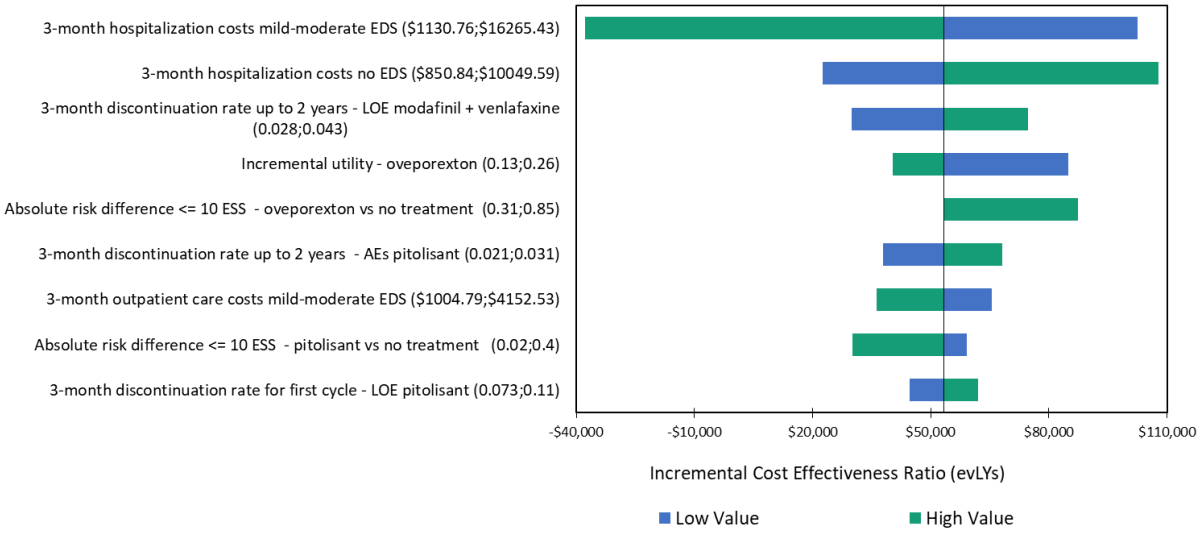
Table E4.2. Tornado Diagram Inputs and Results for Oveporexton versus Sodium Oxybate

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Incremental Utility - Oveporexton (0.13;0.26)	$242,000	$113,000	0.13	0.26
3-Month Hospitalization Costs - Mild-Moderate EDS ($1130.76;$16265.43)	$183,000	$89,000	$1,131	$16,265
3-Month Hospitalization Costs - No EDS ($850.84;$10049.59)	$130,000	$187,000	$851	$10,050
3-Month Discontinuation Rate for First Cycle - AEs Sodium Oxybate (0.124;0.186)	$138,000	$163,000	0.124	0.186
3-Month Outpatient Care Costs - Mild-Moderate EDS ($1004.79;$4152.53)	$158,000	$139,000	$1,005	$4,153
Absolute Risk Difference ≤10 ESS - Oveporexton vs. No Treatment (0.31;0.85)	$158,000	$175,000	0.31	0.85
3-Month Discontinuation Rate Up to 2 Years - AEs Sodium Oxybate (0.011;0.016)	$144,000	$156,000	0.011	0.016
3-Month Emergency Room Costs - Mild-Moderate EDS ($126.75;$1771.06)	$154,000	$144,000	$127	$1,771

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
3-Month Discontinuation Rate Up to 2 years - AEs Oveporexton (0.008;0.012)	$155,000	$146,000	0.008	0.012

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

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

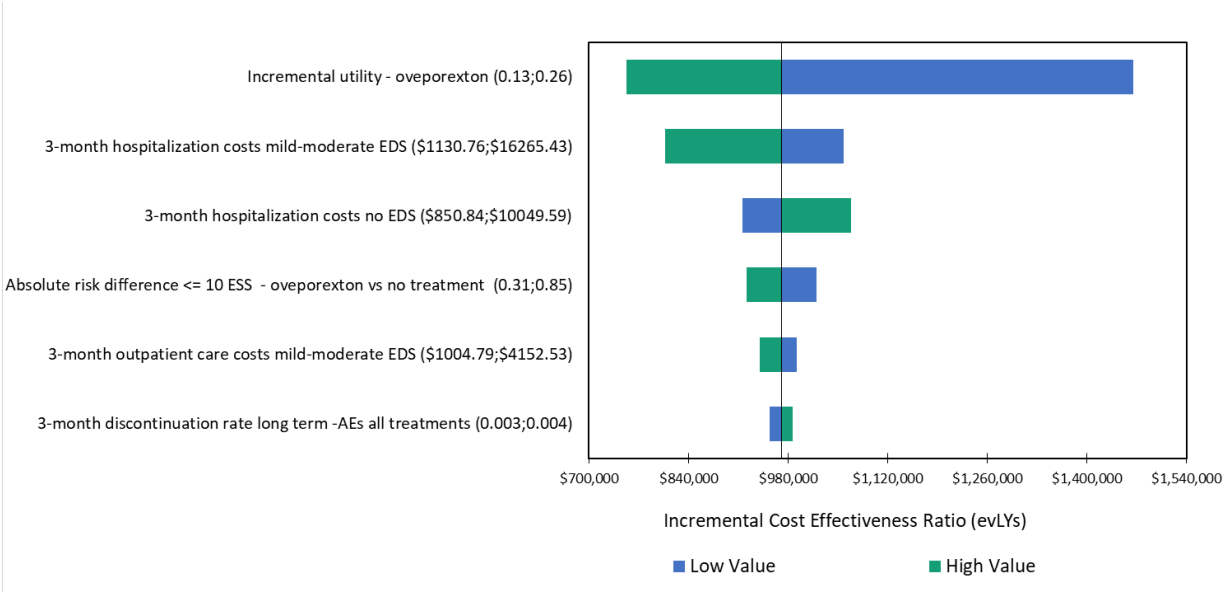
	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
3-Month Hospitalization Costs - Mild-Moderate EDS ($1130.76;$16265.43)	$103,000	-$38,000	$1,131	$16,265
3-Month Hospitalization Costs - No EDS ($850.84;$10049.59)	$23,000	$108,000	$851	$10,050
3-Month Discontinuation Rate Up to 2 years - LOE Modafinil + Venlafaxine (0.028;0.043)	$30,000	$75,000	0.028	0.043
Incremental Utility - Oveporexton (0.13;0.26)	$85,000	$40,000	0.13	0.26
Absolute Risk Difference ≤10 ESS - Oveporexton vs. No Treatment (0.31;0.85)	$55,000	$87,000	0.31	0.85

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
3-Month Discontinuation Rate Up to 2 Years - AEs Pitolisant (0.021;0.031)	$38,000	$68,000	0.021	0.031
3-Month Outpatient Care Costs - Mild-Moderate EDS ($1004.79;$4152.53)	$65,000	$36,000	$1,005	$4,153
Absolute Risk Difference ≤10 ESS - Pitolisant vs. No Treatment (0.02;0.4)	$59,000	$30,000	0.02	0.4
3-Month Discontinuation Rate for First Cycle - LOE Pitolisant (0.073;0.11)	$45,000	$62,000	0.073	0.11

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



AEs: adverse events, 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 (0.13;0.26)	$1,500,000	$752,000	$0	$0
3-Month Hospitalization Costs - Mild-Moderate EDS ($1130.76;$16265.43)	$1,100,000	$807,000	$1,131	$16,265
3-Month Hospitalization Costs - No EDS ($850.84;$10049.59)	$915,000	$1,100,000	$851	$10,050
Absolute Risk Difference ≤10 ESS - Oveporexton vs. No Treatment (0.31;0.85)	$1,000,000	$922,000	0.31	0.85
3-Month Outpatient Care Costs - Mild-Moderate EDS ($1004.79;$4152.53)	$992,000	$940,000	$1,005	$4,153
3-Month Discontinuation Rate Long Term - AEs All Treatments (0.003;0.004)	$954,000	$986,000	0.003	0.004

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.

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

	Oveporexton Mean	Modafinil + Venlafaxine Mean	Incremental
Costs*	$4,091,000	$1,751,000	$2,340,000
QALYs	20.28 (16.18, 23.45)	17.35 (13.28, 20.21)	2.93 (2.90, 3.23)
evLYs	20.28 (16.18, 23.45)	17.35 (13.28, 20.21)	2.93 (2.90, 3.23)
Incremental CE Ratio*			$799,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year
* Based on placeholder price for oveporexton of $175,000 annually

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

	Oveporexton Mean	Sodium Oxybate Mean	Incremental
Costs*	$4,103,000	$3,644,000	$459,000
QALYs	20.27 (16.65, 23.56)	17.30 (13.91, 20.28)	2.98 (2.74, 3.29)
evLYs	20.27 (16.65, 23.56)	17.30 (13.91, 20.28)	2.98 (2.74, 3.29)
Incremental CE Ratio*			$154,000

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year
* Based on placeholder price for oveporexton of $175,000 annually

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

	Oveporexton Mean	Pitolisant Mean	Incremental
Costs*	$4,100,000	$3,932,000	$168,000
QALYs	20.24 (16.30, 23.43)	17.22 (13.41, 20.19)	3.03 (2.89, 3.24)
evLYs	20.24 (16.30, 23.43)	17.22 (13.41, 20.19)	3.03 (2.89, 3.24)
Incremental CE Ratio*			$56,000

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

* Based on placeholder price for oveporexton of $175,000 annually

Table E4.6. Results of Probabilistic Sensitivity Analysis for Oveporexton versus No Pharmacological treatment

	Oveporexton Mean	No Pharmacological Treatment Mean	Incremental
Costs*	$4,097,000	$867,000	$3,230,000
QALYs	20.16 (15.91, 23.60)	16.81 (12.81, 19.85)	3.35 (3.10, 3.76)
evLYs	20.16 (15.91, 23.60)	16.81 (12.81, 19.85)	3.35 (3.10, 3.76)
Incremental CE Ratio*			$964,000

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

* Based on placeholder price for oveporexton of $175,000 annually

E5. Scenario Analyses

Scenario Analysis 1 – Modified Societal Perspective

Our modified societal perspective analysis incorporated productivity cost estimates detailed in Table E2.9. 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 from patients with narcolepsy in Table E2.8.

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).[95]

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 E5.4. 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 E5.3; 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% CI: -11.5; -8.4)	0.152
Modafinil + Venlafaxine	-3.25 (95% CI: -4.35; -2.25)	0.084
Sodium Oxybate	-2.28 (95% CI: -3.54; -1.24)	0.084
Pitolisant	-2.82 (95% CI: -4.19, -1.43)	0.084

CI: confidence 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[95]
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)	

CI: Confidence Interval, EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, mg: milligram SD: Standard Deviation

Scenario Analysis 4 – 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 treatments such as stimulants and sodium oxybate due to lack of data. evLYs were calculated in respect to modafinil + venlafaxine.

Scenario Analysis 5 – Inclusion of Cataplexy Attacks & Discontinuation to No Treatment

Due to differences in study populations, study protocols and reported measurements, cataplexy attacks weren't comparable across all treatments. However, data from oveporexton trials allow us to evaluate oveporexton's impact on cataplexy compared to no pharmacological treatment. In this scenario, weekly cataplexy rates were included to evaluate total cataplexy attacks over the lifetime as a secondary outcome. Weekly rates are detailed in Table E2.4. All patients on oveporexton who discontinued were moved to no treatment, and not the weighted basket. All patients who started on no pharmacological treatment stayed on no treatment while alive.

Table E5.3. Scenario Analysis Results – Total Outcomes

Scenario Analysis 1: Modified Societal Perspective						
Treatment	**Initial Treatment Acquisition Cost***	**Subsequent Treatment Acquisition Cost**	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Oveporexton	$2,800,000	$616,000	$4,206,000	20.22	20.22	24.09
Modafinil + Venlafaxine	$6,800	$1,011,000	$1,915,000	17.32	17.32	24.09
Sodium Oxybate	$2,043,000	$864,000	$3,779,000	17.27	17.27	24.09
Pitolisant	$2,038,000	$1,117,000	$4,069,000	17.22	17.22	24.09
No Pharmacological Treatment	$0	$0	$1,034,000	16.91	16.91	24.09
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs						
Treatment	**Initial Treatment Acquisition Cost***	**Subsequent Treatment Acquisition Cost**	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Oveporexton	$2,800,000	$616,000	$3,514,000	20.22	20.22	24.09
Modafinil + Venlafaxine	$6,800	$1,011,000	$1,203,000	17.32	17.32	24.09
Sodium Oxybate	$2,043,000	$864,000	$3,071,000	17.27	17.27	24.09
Pitolisant	$2,038,000	$1,117,000	$3,354,000	17.22	17.22	24.09

Treatment	Initial Treatment Acquisition Cost*	Subsequent Treatment Acquisition Cost	Total Cost*	QALYs	evLYs	LYs
No Pharmacological Treatment	$0	$0	$297,000	16.91	16.91	24.09
Scenario Analysis 3: ESS Based Utilities						
Treatment	**Initial Treatment Acquisition Cost***	**Subsequent Treatment Acquisition Cost**	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Oveporexton	$2,800,000	$616,000	$4,075,000	20.02	20.02	24.09
Modafinil + Venlafaxine	$6,800	$1,011,000	$1,765,000	18.93	18.93	24.09
Sodium Oxybate	$2,043,000	$864,000	$3,633,000	18.93	18.93	24.09
Pitolisant	$2,038,000	$1,117,000	$3,916,000	18.93	18.93	24.09
No Pharmacological Treatment	$0	$0	$859,000	16.91	16.91	24.09
Scenario Analysis 4: Removal of Elevated Mortality						
Treatment	**Initial Treatment Acquisition Cost***	**Subsequent Treatment Acquisition Cost**	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Oveporexton	$2,892,000	$640,000	$4,212,000	20.91	20.93	24.93
Modafinil + Venlafaxine	$6,900	$1,038,000	$1,806,000	17.73	17.73	24.67
Sodium Oxybate	$2,092,000	$891,000	$3,724,000	17.73	17.74	24.74
Pitolisant	$2,074,000	$1,146,000	$3,994,000	17.60	17.60	24.63
No Pharmacological Treatment	$0	$0	$863,000	17.03	17.03	24.27

Scenario Analysis 5: Inclusion of Cataplexy Attacks & Discontinuation to No Treatment

Treatment	Initial Treatment Acquisition Cost*	Subsequent Treatment Acquisition Cost	Total Cost*	Cataplexy Attacks†	QALYs	evLYs	LYs
Oveporexton	$2,800,000	$616,000	$4,075,000	8613	20.22	20.22	24.09
No Pharmacological Treatment	$0	$0	$859,000	36870	16.91	16.91	24.09

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

*Based on placeholder price for oveporexton of $175,000 annually

†Cataplexy attacks are undiscounted

Table E5.4. Scenario Analysis Results – Incremental Outcomes

Scenario Analysis 1: Modified Societal Perspective				
Treatment	**Comparator**	**Cost per QALY Gained***	**Cost per evLY Gained***	**Cost per Life Year Gained***
Oveporexton	Modafinil + Venlafaxine	$790,000	$790,000	No difference in life years
	Sodium Oxybate	$145,000	$145,000	No difference in life years
	Pitolisant	$46,000	$46,000	No difference in life years
	No Pharmacological Treatment	$957,000	$957,000	No difference in life years
Scenario Analysis 2: Exclusion of Unrelated Health Care Costs				
Treatment	**Comparator**	**Cost per QALY Gained***	**Cost per evLY Gained***	**Cost per Life Year Gained***
Oveporexton	Modafinil + Venlafaxine	$797,000	$797,000	No difference in life years
	Sodium Oxybate	$150,000	$150,000	No difference in life years
	Pitolisant	$53,000	$53,000	No difference in life years
	No Pharmacological Treatment	$970,000	$970,000	No difference in life years
Scenario Analysis 4: Removal of Elevated Mortality				
Treatment	**Comparator**	**Cost per QALY Gained***	**Cost per evLY Gained***	**Cost per Life Year Gained***
Oveporexton	Modafinil + Venlafaxine	$758,000	$754,000	$9,300,000
	Sodium Oxybate	$153,000	$153,000	$2,500,000
	Pitolisant	$66,000	$66,000	$730,000
	No Pharmacological Treatment	$864,000	$861,000	$5,100,000
Scenario Analysis 5: Inclusion of Cataplexy Attacks & Discontinuation to No Treatment				
Treatment	**Comparator**	**Cost per QALY Gained***	**Cost per evLY Gained***	**Cost per Life Year Gained***
Oveporexton	No Pharmacological Treatment	$970,000	$970,000	No difference in life years

ESS: Epworth Sleepiness Scale, 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 $175,000 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.[54] 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 8 weeks compared to 3 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 24.09 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 3 or greater, and utilities were derived using an NHWS mapping algorithm applied to ESS scores from obstructive sleep apnea and narcolepsy patients.[53] This utility approach is comparable to the approached 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.[55] 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 3 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.[57] 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.[56] 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).[1,73] 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.