Better Health, Brighter Future

Takeda Presents Orexin Data from Landmark Oveporexton (TAK-861) Phase 3 Program in Narcolepsy Type 1 at World Sleep 2025

SINGAPORE, OSAKA, Japan and CAMBRIDGE, Massachusetts, September 8, 2025 – Takeda (TSE:4502/NYSE:TAK) will present data from two global Phase 3 double-blind, placebo-controlled studies of oveporexton (TAK-861), a potential first-in-class investigational oral orexin receptor 2 (OX2R)-selective agonist in narcolepsy type 1 (NT1), during multiple oral presentations at the World Sleep 2025 Congress in Singapore beginning at 3:15 p.m. SGT today. Please refer to the attached press release and presentation for details.

The topline results of these studies were disclosed on July 14, 2025 in, "Takeda Announces Positive Results from Two Pivotal Phase 3 Studies of Oveporexton (TAK-861) in Narcolepsy Type 1".

Results from these studies have no significant impact on the full year consolidated forecast for the fiscal year ending March 31, 2026.

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Better Health, Brighter Future

Takeda Presents Orexin Data from Landmark Oveporexton (TAK-861) Phase 3 Program in Narcolepsy Type 1 at World Sleep 2025

– *Takeda is the Leader in Orexin Science and is on Track to Submit Global Regulatory Applications Starting in Fiscal Year 2025*

– *Four Orexin Oral Presentations from Phase 3 Pivotal Studies Highlight Statistically Significant and Clinically Meaningful Improvement in Narcolepsy Type 1 Symptoms Demonstrating the Potential for a New Era of Care*

– *Oveporexton was Generally Well-Tolerated with Safety Profile Consistent with Previous Clinical Studies*

SINGAPORE, OSAKA, Japan and CAMBRIDGE, Massachusetts, September 8, 2025 – Takeda (TSE:4502/NYSE:TAK) will present data from two global Phase 3 double-blind, placebo-controlled studies of oveporexton (TAK-861)[1], a potential first-in-class investigational oral orexin receptor 2 (OX2R)-selective agonist in narcolepsy type 1 (NT1), during multiple oral presentations at the World Sleep 2025 Congress in Singapore beginning at 3:15 p.m. SGT today.

Both the FirstLight (TAK-861-3001) and RadiantLight (TAK-861-3002) studies met all primary and secondary endpoints demonstrating statistically significant improvement across a broad range of NT1 symptoms compared to placebo with p-values of <0.001 across all doses (twice-daily 1mg/twice-daily 2mg) at week 12. Oveporexton was generally well-tolerated with a safety profile consistent across clinical studies to date. No serious treatment-related adverse events were reported. The most common adverse events were insomnia, urinary urgency and frequency.

NT1 is a chronic, rare neurological disease caused by the loss of orexin neurons in the brain that results in a range of debilitating symptoms, which can severely impact every aspect of life. Currently, the standard available therapies only partially address some of the symptoms people face. As an orexin agonist, oveporexton is designed to fully address a broad range of NT1 symptoms by targeting the underlying orexin deficiency.

“Our research has shown that the loss of orexin is the cause of narcolepsy type 1, which results in symptoms like excessive daytime sleepiness and cataplexy,” said Dr. Emmanuel Mignot, M.D., Ph.D., principal investigator for the FirstLight Phase 3 study and one of the presenting authors. “Takeda’s groundbreaking efforts targeting the orexin receptor 2 in clinical studies led to positive Phase 3 results for oveporexton, bringing us a major step closer to having the first orexin therapy that addresses the underlying cause of narcolepsy type 1—with the potential of transforming the current treatment paradigm.”

Oveporexton was discovered in our Takeda labs. The Phase 3 oveporexton program is one of the largest, most comprehensive development programs for NT1. The studies investigated 14 primary and secondary endpoints over a total of 12 weeks in 273 patients across 19 countries. More than 95 percent of the participants who completed the studies enrolled in the ongoing long-term extension (LTE) study.

The oral presentations at World Sleep include data from objective and patient-reported measures of wakefulness, cataplexy, symptom severity and quality of life, including[2,3,4,5]:

- **Wakefulness**: Oveporexton improved excessive daytime sleepiness demonstrating statistically significant improvement from baseline in mean sleep latency on the Maintenance of Wakefulness Test (MWT) and in Epworth Sleepiness Scale (ESS) scores at week 12 across doses compared to placebo. The majority of participants treated with the 2/2mg dose achieved wakefulness within normative range (≥20 min) on the MWT, and close to 85 percent of participants achieved ESS scores comparable to healthy individuals (≤10).

- **Cataplexy**: Oveporexton demonstrated significant reduction in weekly cataplexy rate over 12 weeks across doses compared to placebo (median of percent change from baseline more than 80%). Median cataplexy free days compared to placebo improved from 0 days at baseline to 4-5 days per week at week 12. Cataplexy is a defining symptom for NT1 and is the sudden loss of muscle tone triggered by strong emotions.

- **Symptom Severity**: Oveporexton showed statistically significant changes from baseline in the narcolepsy severity scale (NSS-CT) total score compared to placebo with more than 70 percent of participants reporting the lowest severity level (mild; score 0-14) across doses. Oveporexton also resulted in statistically significant improvements in overall narcolepsy symptoms as assessed by the self-rated Patient Global Impression of Change (PGI-C) scale with nearly all treated participants (97%) reporting improvements.

- **Quality of Life**: Oveporexton resulted in statistically significant improvements in quality of life reaching scores in the normative range as assessed by the Short Form-36-item (SF-36) survey. These outcomes were supported by significant improvements on exploratory endpoints including the EuroQol 5-Dimension 5-Level (EQ-5D-5L).

- **Safety Profile**: Across both studies, oveporexton was generally well-tolerated. No treatment-related serious adverse events were observed. Consistent with our experience from previous clinical studies, the most common adverse events were insomnia, urinary urgency and frequency. Most adverse events were mild to moderate.

“We are leveraging our leadership in orexin science and development with the aim to bring oveporexton to patients expeditiously in partnership with health authorities,” said Sarah Sheikh, M.Sc., B.M., B.Ch., MRCP, Head, Neuroscience Therapeutic Area Unit and Global Development at Takeda. “We are excited to share these transformative results at World Sleep, which demonstrate the potential for a new era of care defined by multiple treatment measures that matter to patients.”

Takeda will share other presentations during the World Sleep Congress in oral and poster sessions, including the impact of stigma on people with NT1, evaluations of sleep algorithms and orexin biomarkers for more accurate NT1 diagnosis and additional analyses from the oveporexton Phase 2b study, including patient satisfaction with treatment survey and impact on cognition, microsleeps and napping.

Results from the Phase 3 studies have no significant impact on the full year consolidated forecast for the fiscal year ending March 31, 2026.

Takeda Investor Conference Call and Webcast Details

Takeda will host an investor call to discuss the Phase 3 data and market opportunity for oveporexton today, September 8, at 7:30-8:45 p.m. SGT/7:30-8:45 a.m. EDT (8:30-9:45 p.m. JST). Presentation slides and a virtual meeting registration link are now available here. An on-demand replay of the webcast will be made available on Takeda’s website after the conclusion of the event.

About Oveporexton (TAK-861)

Oveporexton (TAK-861) is an investigational orexin receptor 2 (OX2R)-selective agonist, which selectively stimulates the OX2R to restore signaling and address the underlying orexin deficiency that causes narcolepsy type 1 (NT1). By activating OX2Rs, oveporexton is designed to promote wakefulness and reduce abnormal rapid eye movement (REM)-sleep like phenomena, including cataplexy, to address the broad spectrum of daytime and nighttime symptoms.

About the FirstLight and RadiantLight Phase 3 Orexin Studies

FirstLight (TAK-861-3001; NCT06470828) and RadiantLight (TAK-861-3002; NCT06505031) are global, multicenter, placebo-controlled studies to evaluate the efficacy, safety and tolerability of oveporexton compared to placebo in patients with narcolepsy type 1 (NT1) over 12 weeks. The studies were conducted in 19 countries with enrollment completed within six months. The FirstLight study enrolled 168 participants randomized to one of three dosing arms (twice-daily 2mg, 1mg and placebo). The RadiantLight study enrolled 105 participants randomized to two dosing arms (twice-daily 2mg and placebo). The primary endpoint in both studies was improvement in excessive daytime sleepiness (EDS) as measured by the Maintenance of Wakefulness Test (MWT), a standard measure of wakefulness. Key secondary endpoints included improvement in EDS as measured by the Epworth Sleepiness Scale (ESS) and in the Weekly Cataplexy Rate (WCR), a measure evaluating cataplexy. The studies also evaluated the effect of oveporexton on participants' ability to maintain attention, participants' overall quality of life, the spectrum of narcolepsy symptoms and daily life functions, as well as the safety and tolerability of oveporexton.

About Takeda's Orexin Franchise

Takeda is the leader in orexin science with a franchise of tailored orexin assets in preclinical and clinical stages with optimized profiles for various orexin disorders. Orexin is a key regulator of sleep and wake patterns and contributes to other essential functions including attention, mood, metabolism and respiration. Oveporexton (TAK-861) is the lead investigational orexin receptor 2 (OX2R) agonist asset in Takeda's orexin franchise and received Breakthrough Therapy designation for the treatment of excessive daytime sleepiness in narcolepsy type 1 (NT1) from the U.S. Food and Drug Administration and the Center for Drug Evaluation of China's National Medical Products Administration. The company is also investigating other orexin agonists in populations with orexin levels in the normal range, including TAK-360, an oral OX2R agonist initially being investigated for the treatment of narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH) in Phase 2 studies, and other potential indications where orexin signaling is implicated. Additional preclinical assets are also in development including TAK-495, which is expected to enter the clinic in fiscal year 2025.

About Takeda

Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and deliver life-transforming treatments in our core therapeutic and business areas, including gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience and vaccines. Together with our partners, we aim to improve the patient experience and advance a new frontier of treatment options through our dynamic and diverse pipeline. As a leading values-based, R&D-driven biopharmaceutical company headquartered in Japan, we are guided by our commitment to patients, our people and the planet. Our employees in approximately 80 countries and regions are driven by our purpose and are grounded in the values that have defined us for more than two centuries. For more information, visit www.takeda.com.

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References

1. The topline results of these studies were disclosed on July 14, 2025 in, "Takeda Announces Positive Results from Two Pivotal Phase 3 Studies of Oveporexton (TAK-861) in Narcolepsy Type 1".
2. Mignot E, Arnulf I, Plazzi G, et al. Efficacy and safety of Oveporexton (TAK-861), an oral orexin receptor 2 agonist for the treatment of narcolepsy type 1: results from a phase 3 randomized study in Europe, Japan, and North America. Presented at: World Sleep Congress 2025; 2025 Sep 8; Singapore.
3. Dauvilliers Y, Antczak J, Buntinx E, et al. Efficacy and safety of Oveporexton (TAK-861) for the treatment of narcolepsy type 1: results from a phase 3 randomized study in Asia, Australia, and Europe. Presented at: World Sleep Congress 2025; 2025 Sep 8; Singapore.
4. Sivam S, Hsiao S, Du Y, et al. Effect of the Oral Orexin Receptor 2 Agonist Oveporexton (TAK-861) on Quality of Life in Individuals with NT1 over 21 weeks. Presented at: World Sleep Congress 2025; 2025 Sep 8; Singapore.
5. Barateau L, Arnulf I, Dauvilliers, Y, et al. Effect of Oral Orexin Receptor 2 Agonist Oveporexton (TAK-861) on the Severity of Symptoms in Individuals With Narcolepsy Type 1: Results From Two Phase 3 Studies. Presented at: World Sleep Congress 2025; 2025 Sep 8; Singapore.

Takeda's Leading Orexin Franchise

Oveporexton Phase 3 Data & Commercial Readiness

World Sleep Congress 2025

September 8th, 2025

Better Health, Brighter Future

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Pioneering Orexin science and catalyzing a potential new era of care for patients with narcolepsy type 1 (NT1) with oveporexton

1

Orexin deficiency is the root cause of NT1

2

Oveporexton is designed to treat the root cause of NT1 and has the potential to be a transformative Orexin therapy

3

Ph3 results demonstrated oveporexton's potential to achieve outcomes that matter most to patients

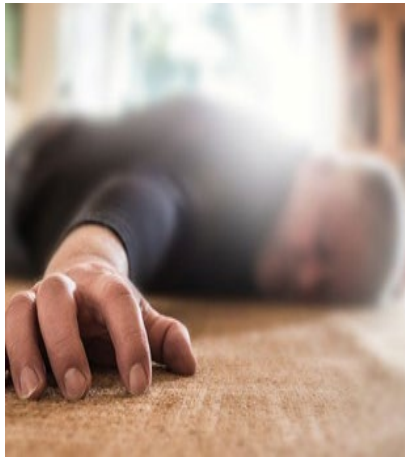
Oveporexton U.S. and global filings on track to start in FY25; global $2-3B+ peak revenue potential

Please refer to the Important Notice at the start of this presentation for more information about peak revenue estimates.

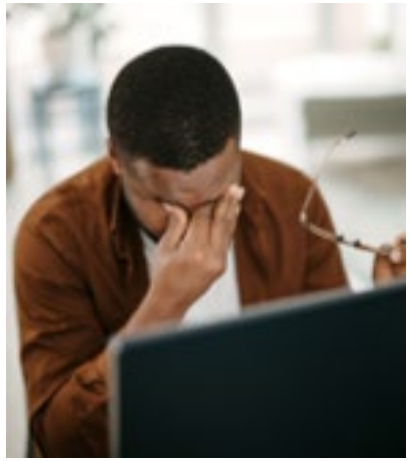
NT1 patients face debilitating daytime and nighttime symptoms often impacting daily function

Daytime Symptoms

Excessive Daytime Sleepiness (EDS)

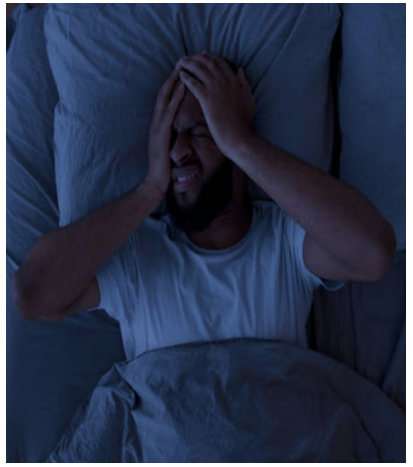


Cataplexy



Cognitive Symptoms

Nighttime Symptoms



Disrupted Nighttime Sleep, Disturbing Dreams[1]

Hallucinations, Sleep Paralysis

These symptoms may have significant impact on daily functions

Reduced **Work Productivity**	Reduced **School Performance**	Challenged **Social Interactions**	Reduced **Personal Responsibilities**	Limited **Recreational Activities**

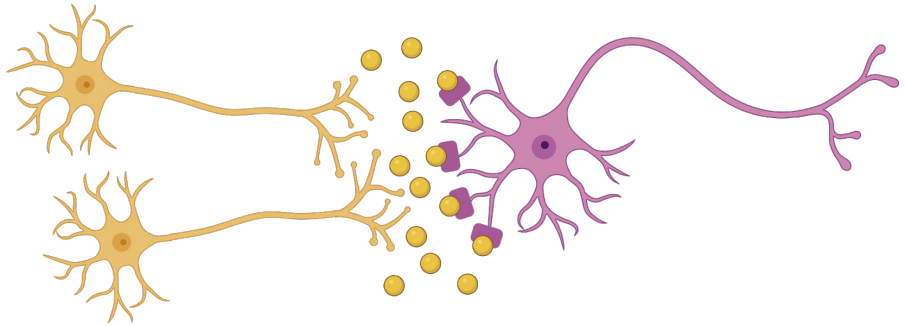
1 Sateia MJ. Chest 2014;146:1387–94

NT1 pathophysiology is caused by the loss of orexin neurons

Downstream signaling

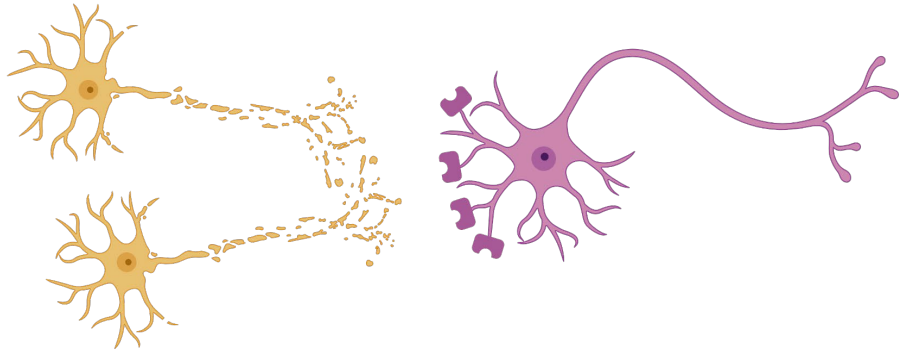
Healthy Individual:

Healthy orexin neurons with normal postsynaptic downstream orexin neurotransmitter activity



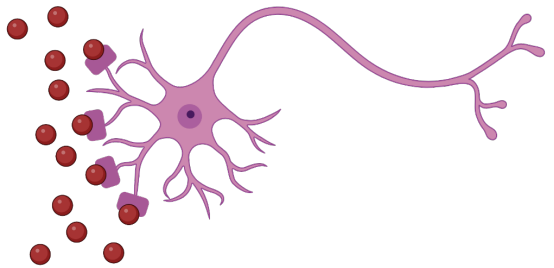
Patient with NT1:

Reduced availability of orexin as orexin neurons are lost, reducing downstream neurotransmitter activity



NT1 patient treated with oveporexton:

Orexin 2 receptor (OX2R) agonist may **restore downstream neurotransmitter activity** lost when endogenous orexin levels decline



Mahoney CE, et al. *Nat Rev Neurosci.* 2019;20(2):83-93; Chastain EM, et al. *Biochim Biophys Acta.* 2011;1812:265–274; Nishino S. *Sleep Med.* 2007;8(4):373-399; Saper CB, et al. *Trends Neurosci.* 2001;24(12):726-731; Yoshida Y, et al. *Eur J Neurosci.* 2001;14(7):1075-1081; Dauvilliers, Y., N Engl J Med, 2023; 389, 309-321

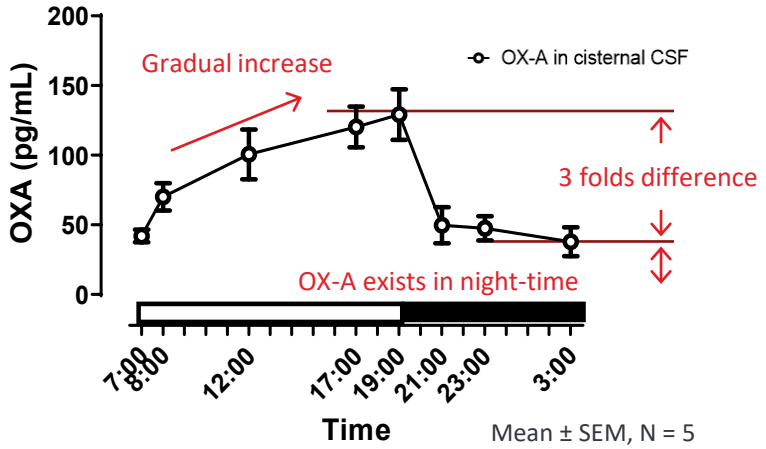
Orexin receptor 2 Orexin Oveporexton

Optimized dosing regimen critical to deliver potentially transformative efficacy while minimizing adverse events

Oveporexton BID profile mimics natural diurnal orexin tone

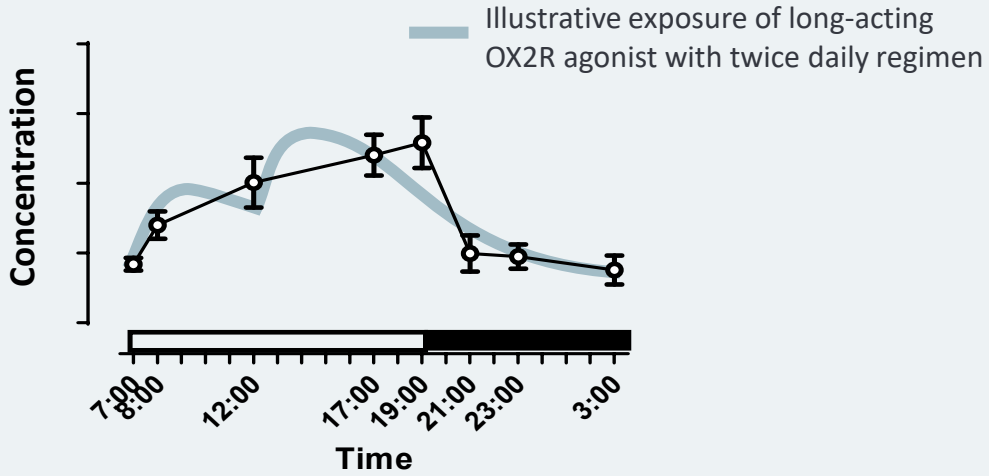
Diurnal fluctuation of orexin levels in monkey CSF

Takeda's novel method enabling accurate measurement of OX-A[1]



- OX-A gradually increases in day-time but still present during nighttime
- Reliable model to predict human PK based on Takeda OX2R experience

Long-acting orexin 2 receptor (OX2R) agonist



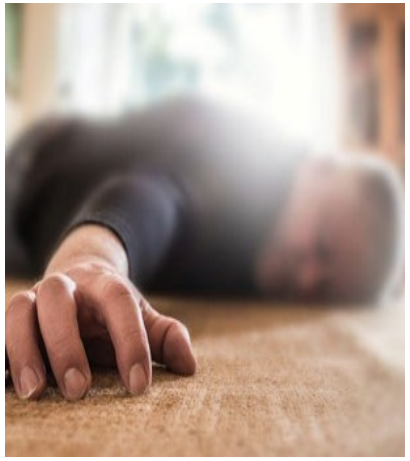
- Long-acting OX2R agonist with BID dosing mimics diurnal orexin fluctuation
- Long half-life maintains sufficient exposure during the day
- Exposure levels are reduced at night, mimicking the natural orexin tone

1. Narita et al., ACS Chem Neurosci, 2023

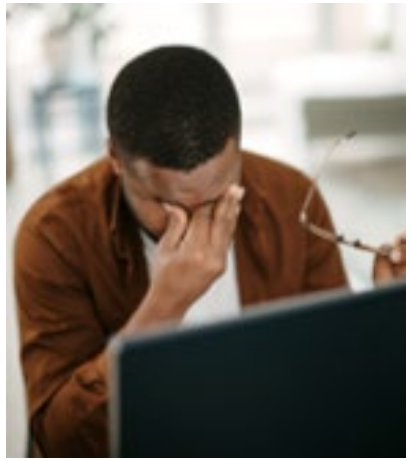
Comprehensive approach to evaluate broad spectrum of NT1 symptoms with established and novel endpoints

Daytime Symptoms

Excessive Daytime Sleepiness (EDS)



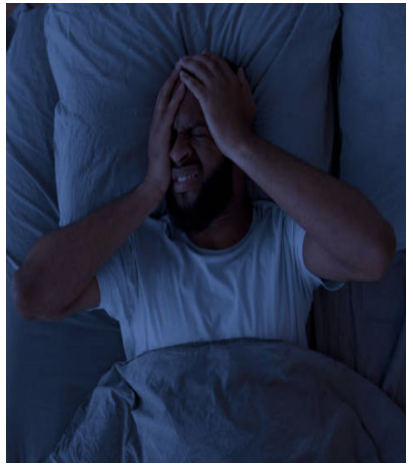
Cataplexy



Cognitive Symptoms

MWT, ESS, KSS | **WCR** | **PVT and other tests**

Nighttime Symptoms



Disrupted Nighttime Sleep, Disturbing Dreams

Hallucinations, Sleep Paralysis

Sleep Diary, PSG

Overall Narcolepsy Symptoms and Daily Function (e.g. **NSS-CT, CGI-C, PGI-C, FINI**)

General Quality of Life and Treatment Satisfaction (e.g. **SF-36, EQ-5D-5L**)

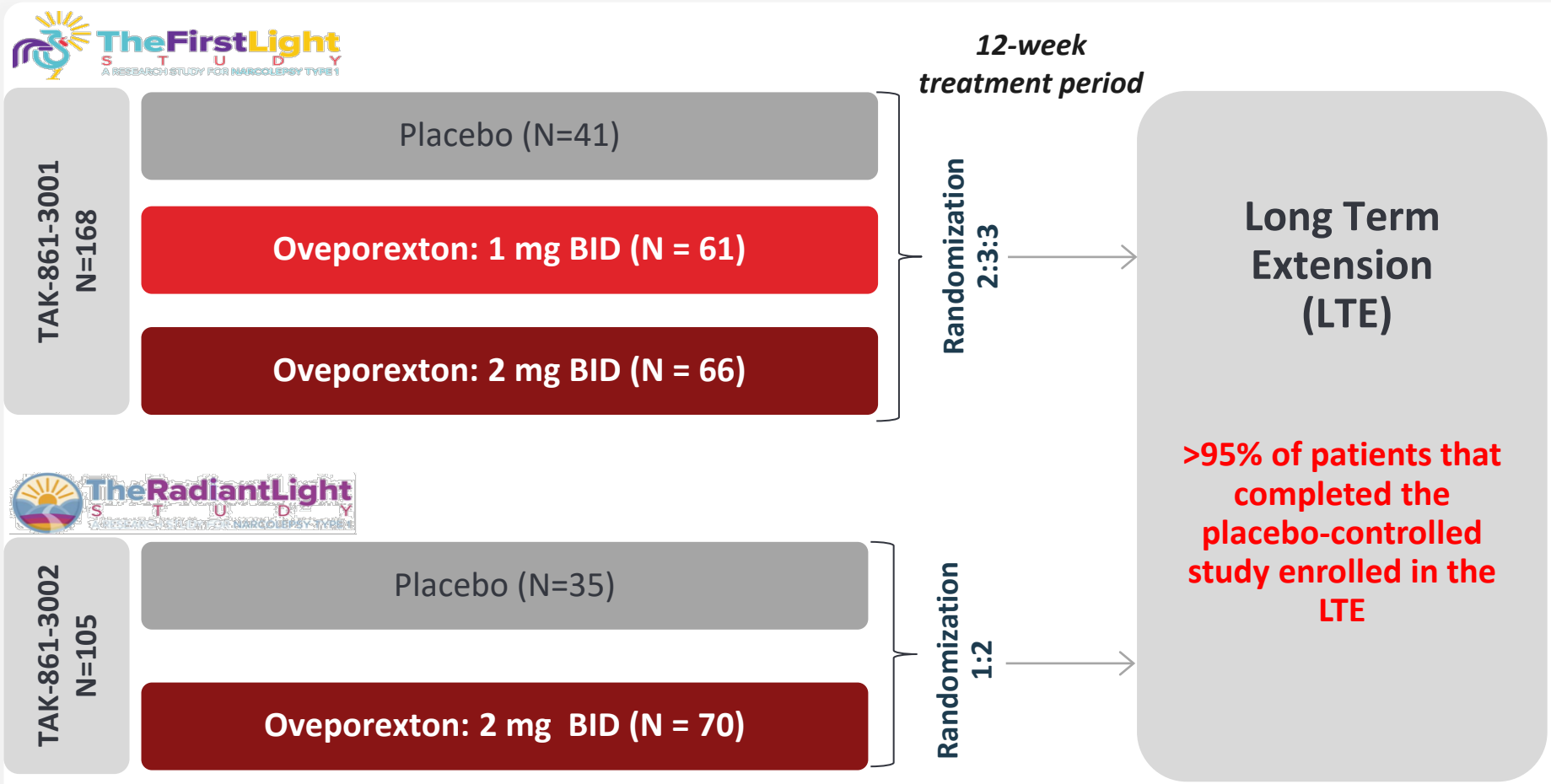
CGI-C: Clinical Global Impression of Change; **EQ-5D-5L:** EuroQol-5 Dimensions 5-levels; **ESS:** Epworth Sleepiness Scale; **FINI:** Functional Impacts of Narcolepsy Instrument; **KSS:** Karolinska Sleepiness Scale; **MWT:** Maintenance of Wakefulness Test; **NSS-CT:** Narcolepsy severity scale; **PGI-C**: Patient Clinical Global Impression of Change; **PSG:** polysomnography; **PVT:** Psychomotor Vigilance Task; **SF-36**: Short Form-36 Survey; **WCR:** Weekly cataplexy rate

Oveporexton

Phase 3 Results

Better Health, Brighter Future

Global placebo controlled randomized Oveporexton Ph3 NT1 studies conducted across 19 countries enrolling 273 subjects



Baseline characteristics balanced across both studies/doses

Primary Endpoint @ 12wks:

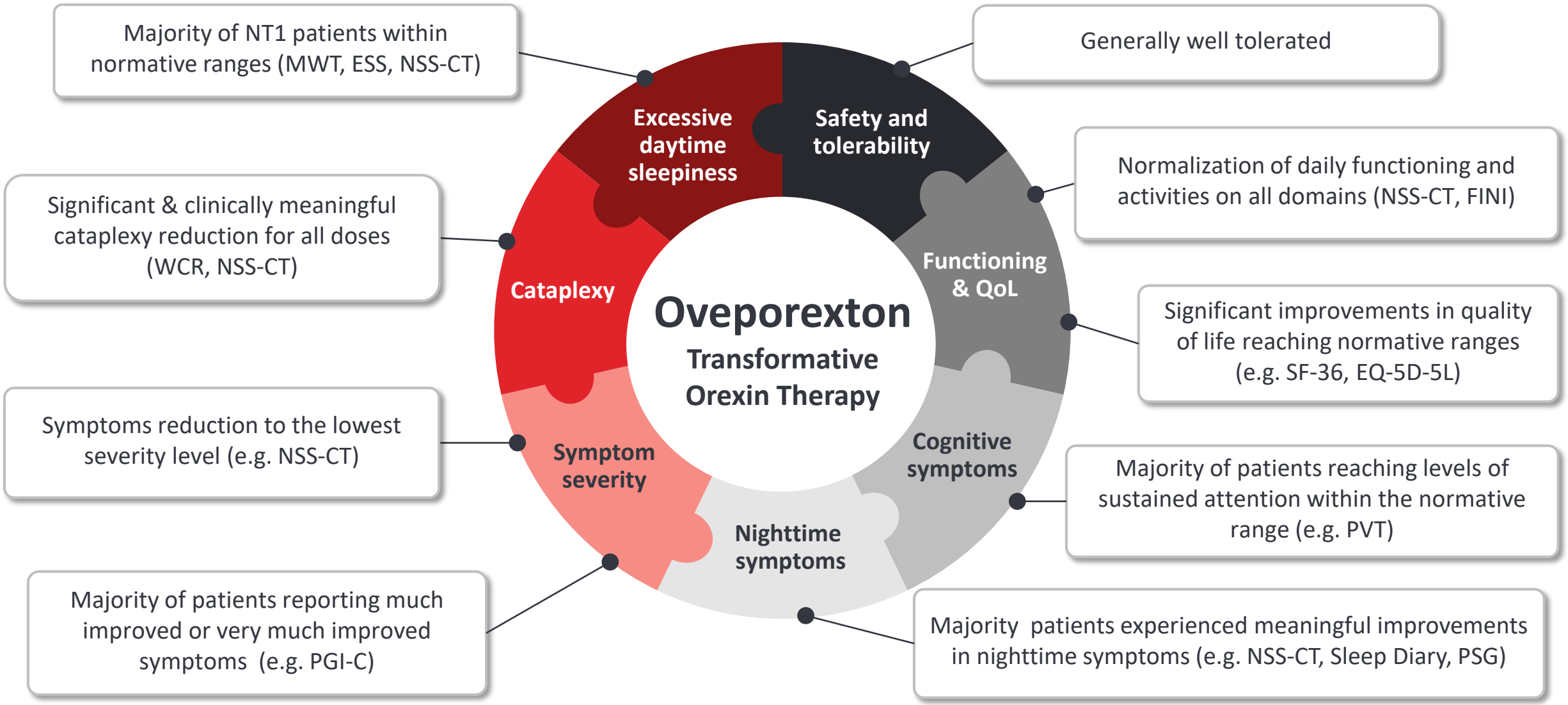
- MWT

Secondary Endpoints @ 12wks including:

- ESS
- WCR
- NSS-CT
- PVT
- Safety/Tolerability

Exploratory Endpoints

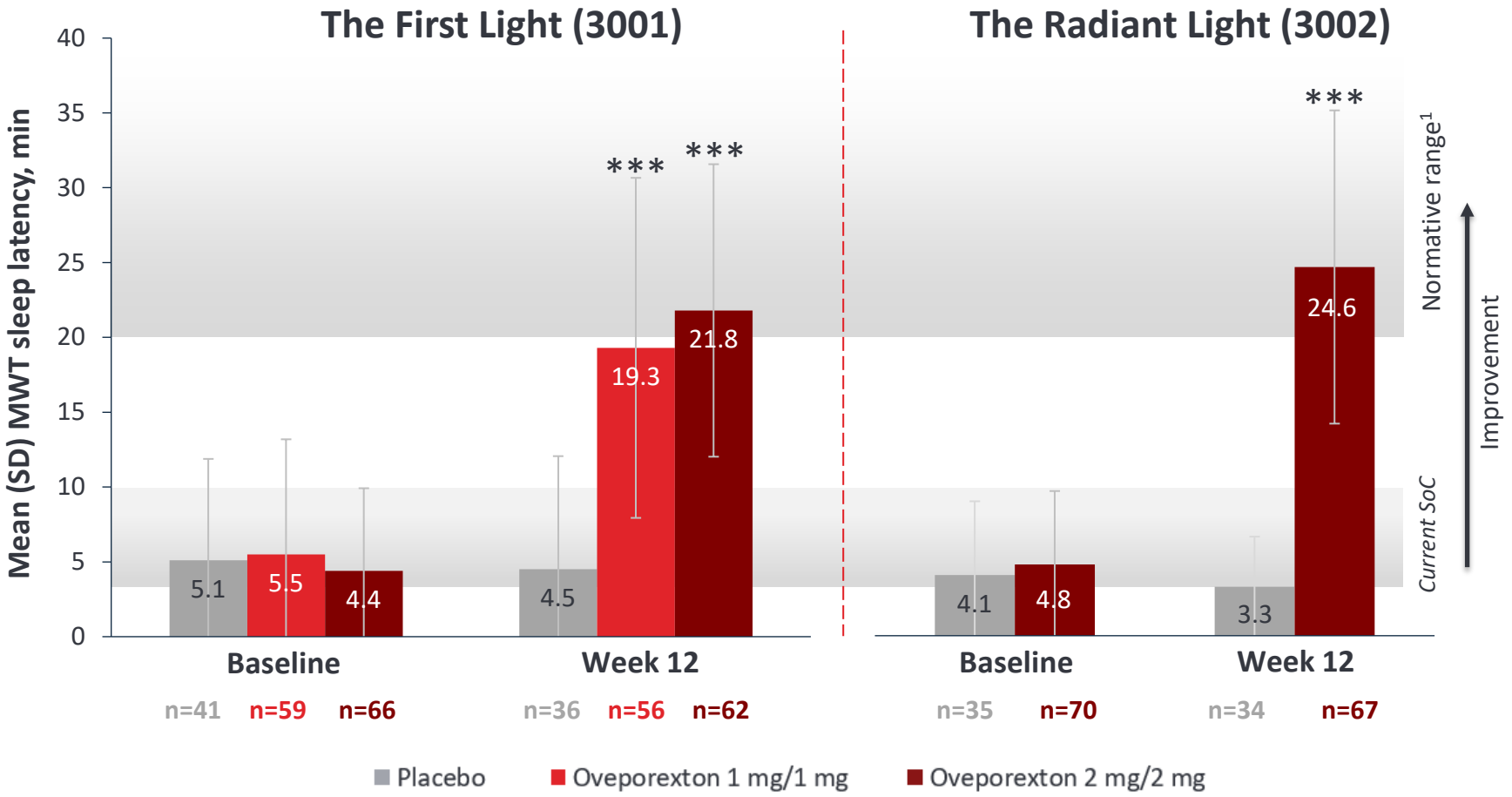
Oveporexton could establish a new standard of care in NT1 addressing the broad spectrum of symptoms



EQ-5D-5L: EuroQol-5 Dimensions 5-levels; **ESS:** Epworth Sleepiness Scale; **FINI:** Functional Impacts of Narcolepsy Instrument; **MWT:** Maintenance of Wakefulness Test; **NSS-CT:** Narcolepsy severity scale; **PGI-C**: Patient Clinical Global Impression of Change; **PSG:** polysomnography; **PVT:** Psychomotor Vigilance Task; **SF-36**: Short Form-36 Survey; **WCR:** Weekly cataplexy rate;

Oveporexton significantly improved sleep latency on MWT at 12 weeks with majority of patients within normative range

The Maintenance of Wakefulness Test (MWT): daytime polysomnographic procedure which quantifies wake tendency by measuring ability to remain awake during soporific circumstances (sleepiness condition such as dark quiet room)



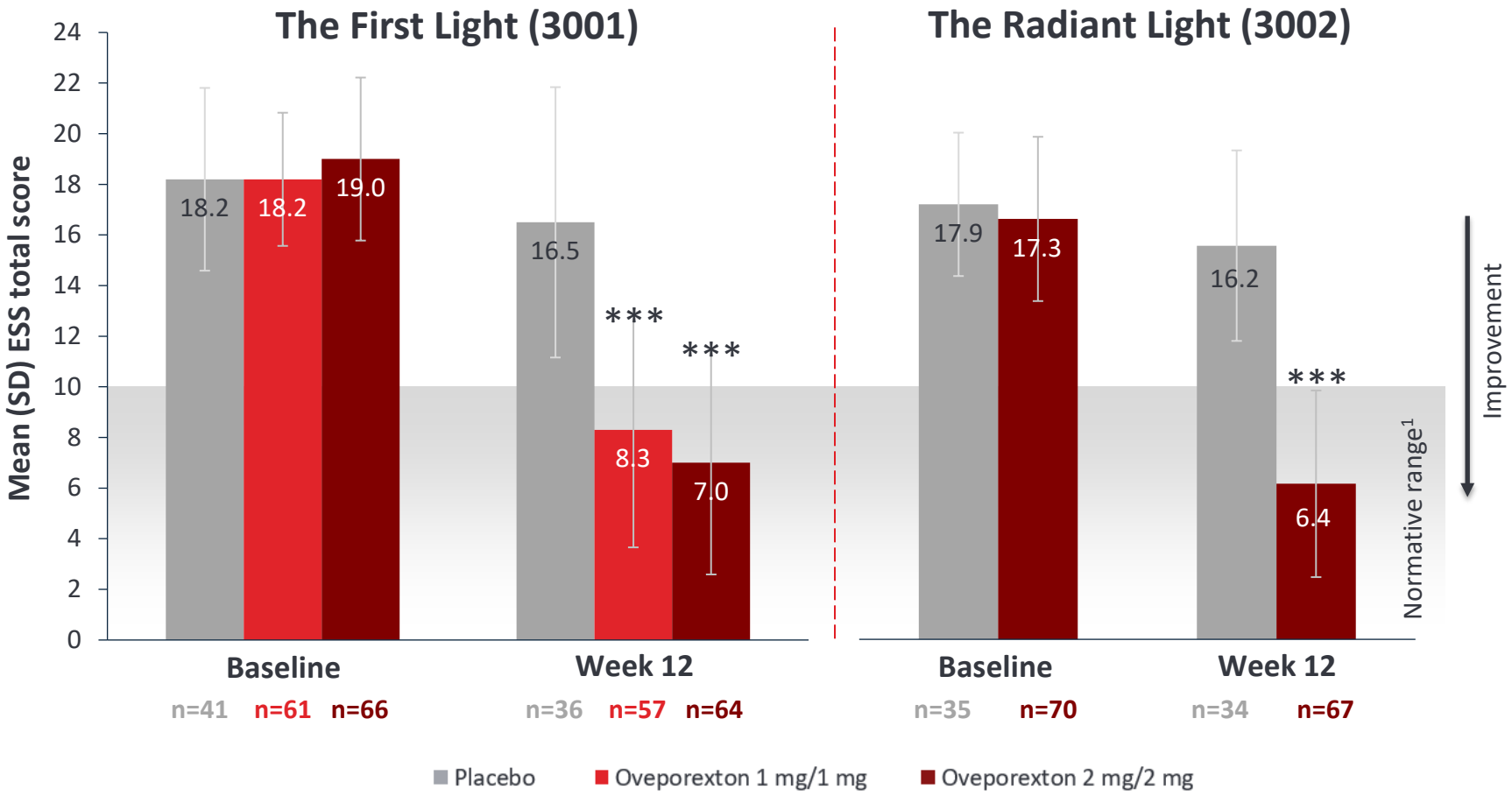
Excessive Daytime Sleepiness (MWT)

- **Statistically significant** and **clinically meaningful** improvement in objective wakefulness (MWT)
- Oveporexton **normalized** (≥20 mins) sleep latency on MWT in majority of patients (63% of Ph3 patients treated with 2 mg/2 mg)
- **Consistent** results between Ph2b and two Ph3 studies
- Efficacy **maintained** over time based on ongoing LTE data from Ph2b

The analysis used a linear mixed effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity. *** indicates significance of p<0.001 for LS mean difference from placebo in change from BL at week 12. BL, baseline; CI, confidence interval; LS, least squares; MWT, Maintenance wakefulness test; SD, standard deviation; SE, standard error; SoC: Standard of Care. **1.** Doghramji K, et al. *Electroencephalogr Clin Neurophysiol* 1997; 103: 554-62.

Oveporexton significantly improved subjective sleepiness at 12 weeks with majority of patients within normative range

The Epworth Sleepiness Scale (ESS): short self-assessment to identify how likely to fall asleep during daytime, measured by eight questions. Total score range 0-24 (each question 0-3). Scores ≤10 reflect normal levels of daytime sleepiness, and scores over 10 reflect excessive daytime sleepiness



Excessive Daytime Sleepiness (ESS)

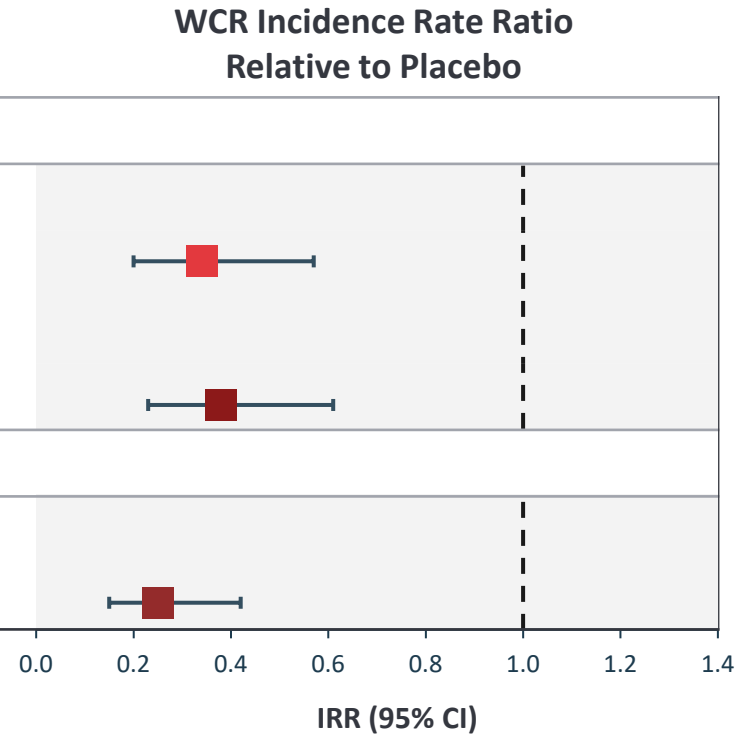
- Oveporexton demonstrated **statistically significant** and **clinically meaningful** improvement in subjective wakefulness (ESS)
- Close to 85% of patients **achieved** ESS scores comparable to healthy individuals (≤10) with oveporexton 2 mg/2 mg
- **Consistent** between Ph2b and Ph3 studies, and other endpoints (e.g. KSS)
- Efficacy **maintained** over time based on ongoing LTE data from Ph2b

The analysis used a linear mixed effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity. *** indicates significance of p<0.001 for LS mean difference from placebo in change from BL at week 12. BL, baseline; CI, confidence interval; LS, least square; ESS, Epworth Sleepiness scale; SD, standard deviation; SE, standard error; KSS, Karolinska Sleepiness scale. **1.** Johns MW. *Sleep* 1991; 14: 540-5.

Oveporexton significantly reduced weekly cataplexy rate over 12 weeks

Cataplexy: sudden loss of muscle tone and strength, often caused by an emotional stimulus; defining symptom of NT1
Incidence Rate Ratio (IRR): incidence rate for the treatment arms over the placebo incidence rate (lower IRR indicates a greater improvement from placebo)

	IRR	95% CI	p-value*
The First Light (3001)			
Oveporexton 1 mg/1 mg			
Week 12	0.34	0.20, 0.57	<0.001
Oveporexton 2 mg/2 mg			
Week 12	0.38	0.23, 0.61	<0.001
The Radiant Light (3002)			
Oveporexton 2 mg/2 mg			
Week 12	0.25	0.15, 0.42	<0.001



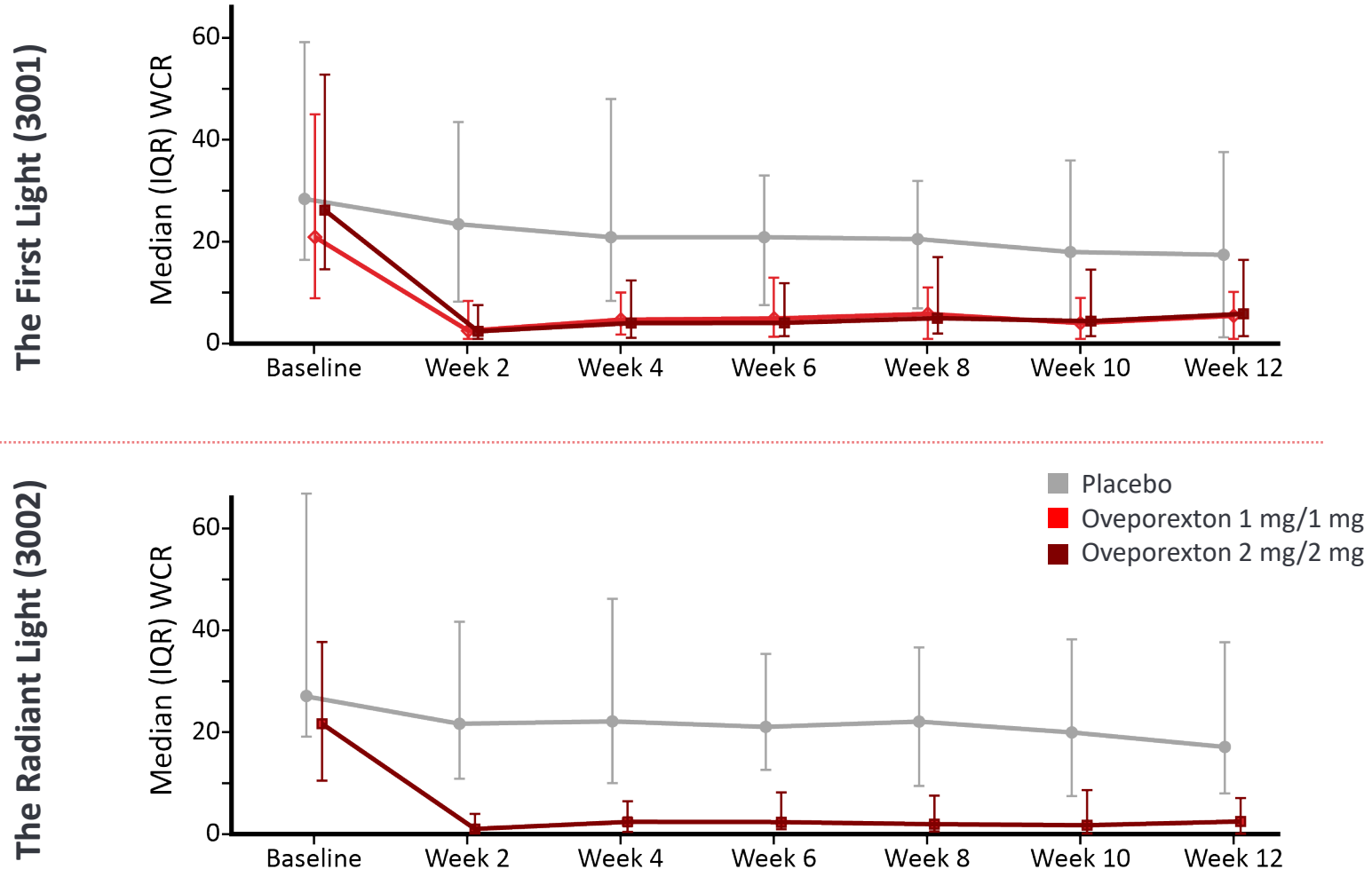
Weekly Cataplexy Rate (WCR)

- Oveporexton demonstrated **statistically significant (p<0.001) and clinically meaningful reduction** in cataplexy events compared to placebo
- Median cataplexy free days/week increased from **0 days at baseline to 4-5 days at week 12 with oveporexton** vs no increase with placebo

*The analysis used a generalized estimating equations model (negative binomial) with placebo-based multiple imputation.
P-values have been adjusted for multiplicity.
The incidence rate ratio was calculated by dividing the incidence rate of the oveporexton group with the incidence of the placebo group.
CI, confidence interval; WCR, weekly cataplexy rate.

Oveporexton demonstrated rapid reduction in cataplexy, sustained over 12 weeks

Weekly Cataplexy Rate (WCR): number of cataplexy events per week



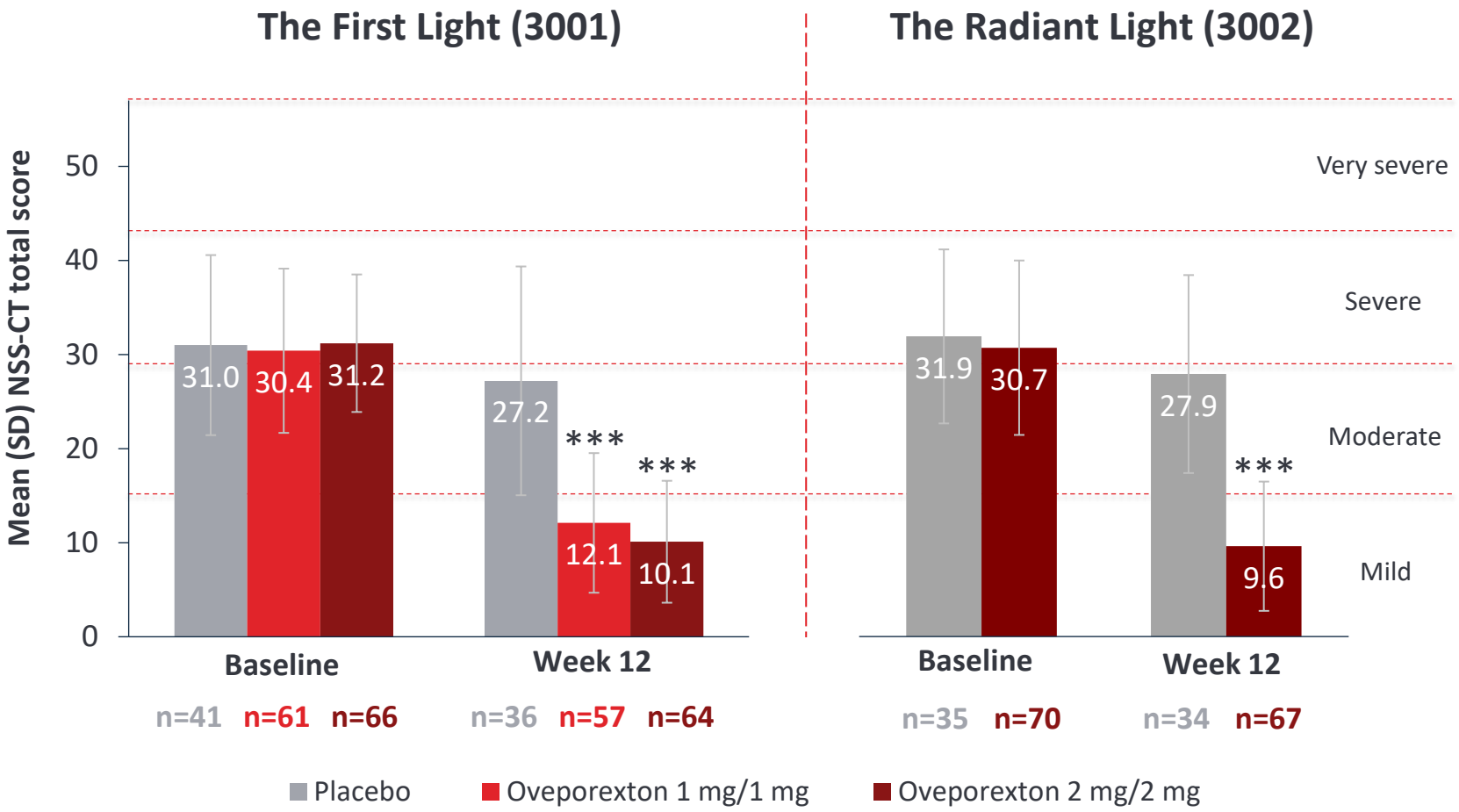
Weekly Cataplexy Rate (WCR)

- **Reduction in median WCR from baseline sustained** over the entire duration of the study
  - 79% 1 mg/1 mg (The First Light)
  - 83% 2 mg/2 mg (The First Light)
  - 89% 2 mg/2 mg (The Radiant Light)
- Efficacy **maintained** over time based on ongoing LTE data from Ph2b

IQR, interquartile range; WCR, weekly cataplexy rate.

Oveporexton improved symptoms across NT1 spectrum and reduced the overall symptom severity

Narcolepsy Severity Scale for Clinical Trials (NSS-CT): validated, self-administered, 15-item scale evaluating severity, frequency and impact of 5 narcolepsy symptoms (sleepiness, cataplexy, sleep paralysis, hallucinations and disrupted nocturnal sleep)



Overall Disease Severity

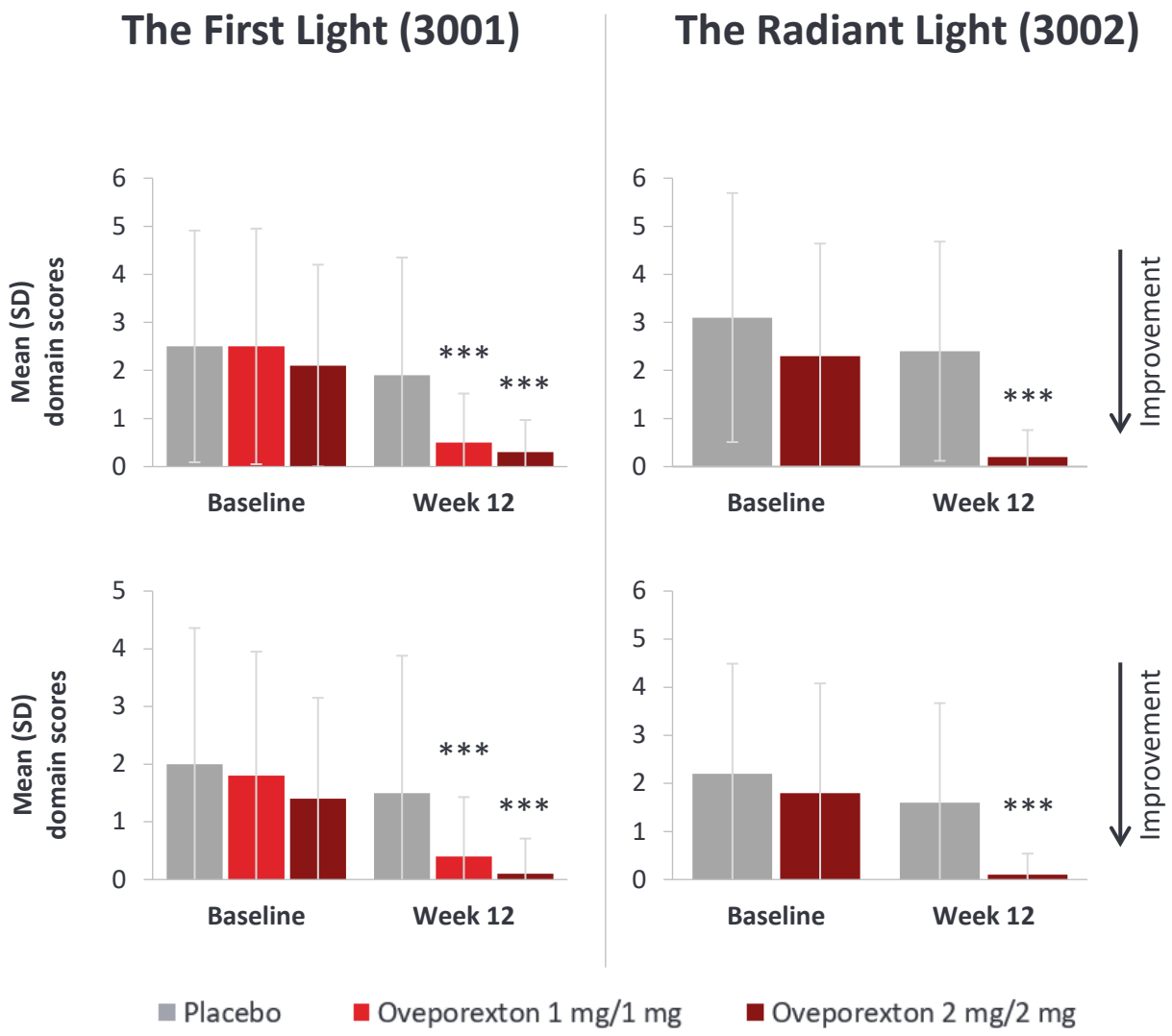
- Oveporexton demonstrated **statistically significant (p<0.001) and clinically meaningful reduction** in overall disease severity compared to placebo
- Across both studies, **70-80%** of patients treated with oveporexton had **mild symptoms** at week 12

The analysis used a linear mixed effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.
*** indicates significance of p<0.001 for LS mean difference from placebo in change from Baseline at week 12

Oveporexton improved nighttime symptoms at week 12

Hallucinations
How frequently do you have hallucinations when falling asleep or waking up? (score 0-6)

Sleep paralysis
How frequently do you experience sleep paralysis when falling asleep or waking up? (score 0-6)



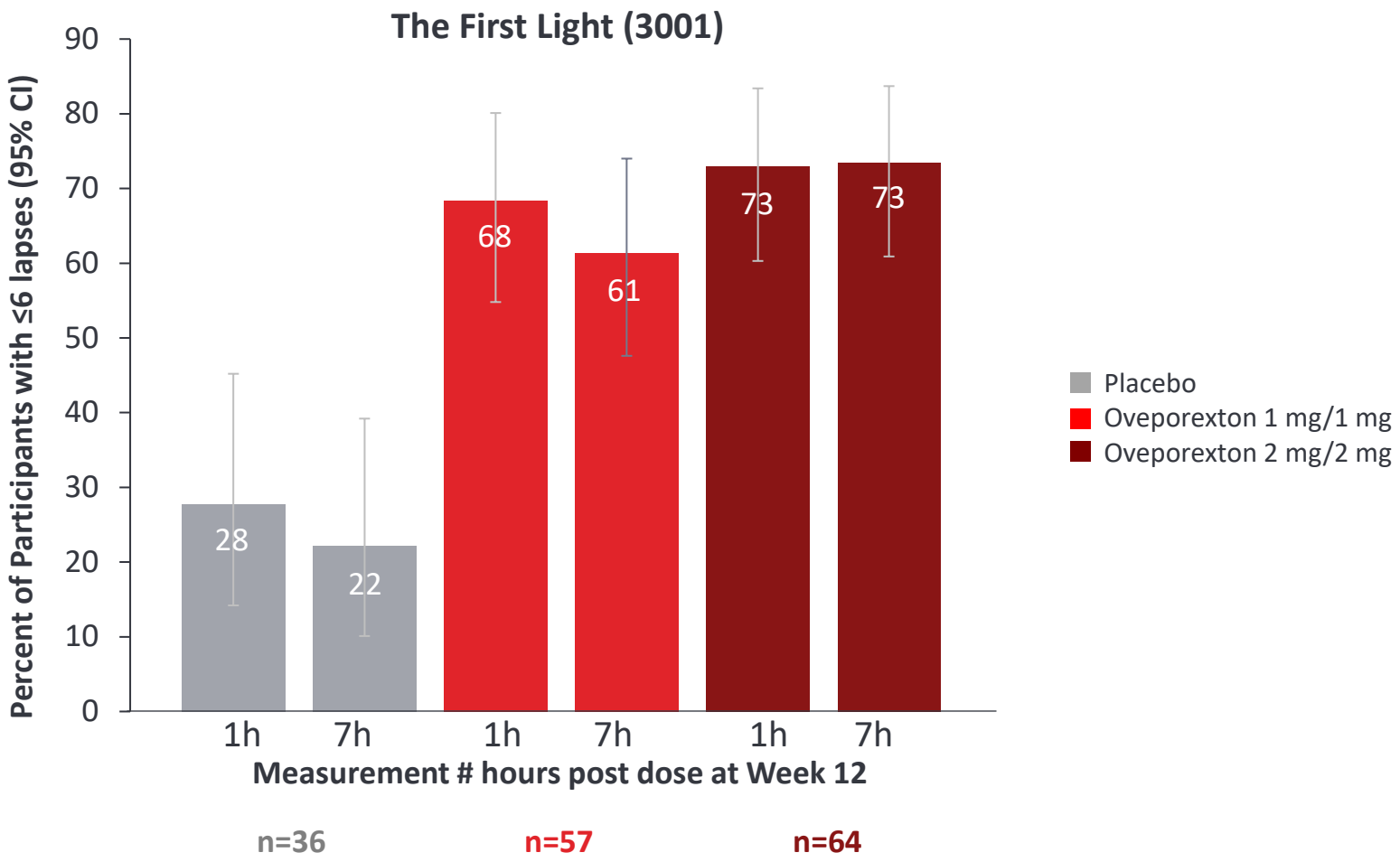
Nighttime symptoms (NSS-CT)

- **~85% of patients** treated with oveporexton with no **hallucinations or sleep paralysis** at week 12
- ~67% of patients showing **meaningful improvement on disturbed nighttime sleep (DNS)**
- Improvements in nighttime symptoms further supported by additional objective (e.g., PSG) and subjective (e.g., sleep diary) exploratory endpoints

LS mean difference from placebo, p-value: *Nominal p<0.05; **Nominal p<0.01; ***Nominal p<0.001. NSS-CT, Narcolepsy Severity Scale for clinical trials; SD, standard deviation; PSG: polysomnography

Oveporexton significantly improved sustained attention throughout the day with ~70% patients within normative range

Psychomotor Vigilance Test (PVT): simple 10 min reaction performance task to measure sustained attention (test counts # of lapses in attention).
Normative levels: PVT lapses ≤ 6



Cognitive Symptoms (PVT)

- **Majority of patients within normative** range for both doses and both studies
- **Significant improvements** also on **other cognitive domains** based on additional exploratory cognitive tests
- **Efficacy maintained** throughout the day (1 and 7 h post dose)

Data on file (oveporexton). TAK-861-3001 and TAK-861-3002 PVT Data. August 2025. VV-MEDMAT-125867

Oveporexton significantly improved overall functioning and quality of life

Oveporexton treatment resulted in group mean EQ-5D-5L index scores reaching **normative values**

SF-36 mental and physical component summary improved with oveporexton bringing majority of patients to normative range

Meaningful improvements across all domains of the Functional Impacts of Narcolepsy Instrument (FINI) vs placebo.

More than 80% of patients reporting no problems on 'Usual Activities' on EQ-5D-5L (compared to 30% of placebo patients)

Oveporexton resulted in significantly higher global treatment satisfaction at 12 weeks vs placebo

Oveporexton improved both physician- (CGI) and patient-reported (PGI-C) measures of overall treatment experience and NT1 disease severity, **with nearly all patients (97%) reported improvements.**

CGI-C: Clinical Global Impression of Change; Associate Learning Test; **EQ-5D-5L:** EuroQol-5 Dimensions 5-levels; **FINI:** Functional Impacts of Narcolepsy Instrument; **PGI-C**: Patient Clinical Global Impression of Change; **SF-36**: Short Form-36 Survey

Oveporexton was generally well tolerated

	The First Light (3001)			The Radiant Light (3002)	
	Placebo (n=41)	1 mg/1 mg (n=60)	2 mg/2 mg (n=66)	Placebo (n=35)	2 mg/2 mg (n=70)
Any TEAE, n (%)	22 (53.7)	52 (86.7)	59 (89.4)	15 (42.9)	60 (85.7)
Mild	14 (34.1)	26 (43.3)	34 (51.5)	9 (25.7)	38 (54.3)
Moderate	7 (17.1)	24 (40.0)	23 (34.8)	5 (14.3)	20 (28.6)
Severe	1 (2.4)	2 (3.3)	2 (3.0)	1 (2.9)	2 (2.9)
Serious TEAE, n (%)	0	1 (1.7)	1 (1.5)	0	0
TEAEs leading to study drug discontinuation, n (%)	1 (2.4)	3 (5.0)	0	0	2 (2.9)
Most frequent TEAEs, n (%)					
Urinary frequency	3 (7.3)	32 (53.3)	36 (54.5)	1 (2.9)	43 (61.4)
Insomnia	0	32 (53.3)	38 (57.6)	1 (2.9)	40 (57.1)
Urinary urgency	1 (2.4)	9 (15.0)	12 (18.2)	0	10 (14.3)
Nasopharyngitis	6 (14.6)	6 (10.0)	10 (15.2)	0	0
Headache	5 (12.2)	4 (6.7)	10 (15.2)	2 (5.7)	3 (4.3)
Salivary hypersecretion	0	5 (8.3)	4 (6.1)	0	5 (7.1)

Adverse Events

- **No** treatment-related **serious TEAEs**
- Most common TEAEs: insomnia and urinary frequency and urgency
- **Majority of TEAEs transient** and started within first few days of treatment
  - ~70% patients who experienced insomnia events resolved within first 2 weeks of treatment
- **No** evidence of **hepatotoxicity**

TEAEs, treatment emergent adverse events.

Oveporexton has the potential to establish a new era of care with transformative efficacy

Oveporexton demonstrated transformative efficacy profile at 12 weeks with BID dosing

- Significant and clinically meaningful improvements across all NT1 symptoms
  - Majority of NT1 patients within normative ranges for MWT and ESS
  - Weekly cataplexy rate reduction (80-90%)
  - Significant improvement in cognition and nighttime symptoms
  - Significant improvement on multiple quality of life scales

Oveporexton was generally well-tolerated

- Most common TEAEs observed were insomnia and urinary events
- Most AEs were mild to moderate, started within first few days of treatment and resolved during the study
- >95% of patients completing the study enrolled into the long-term extension study

Oveporexton is on track to become the first-in-class treatment for NT1

Takeda is pioneering the field of orexin therapeutics with a potentially transformative franchise

Oveporexton: NT1

- **Global filings on track to start FY25**
- **Breakthrough** designation received in USA and China
- **Potential first-in-class potential treatment for NT1**

TAK-360: Fast following in NT2 & IH

- **Novel chemistry and profile** for orexin non-deficient indications
- Fast track designation received
- **NT2 and IH currently in Ph2**

Tailored orexin assets for additional indications

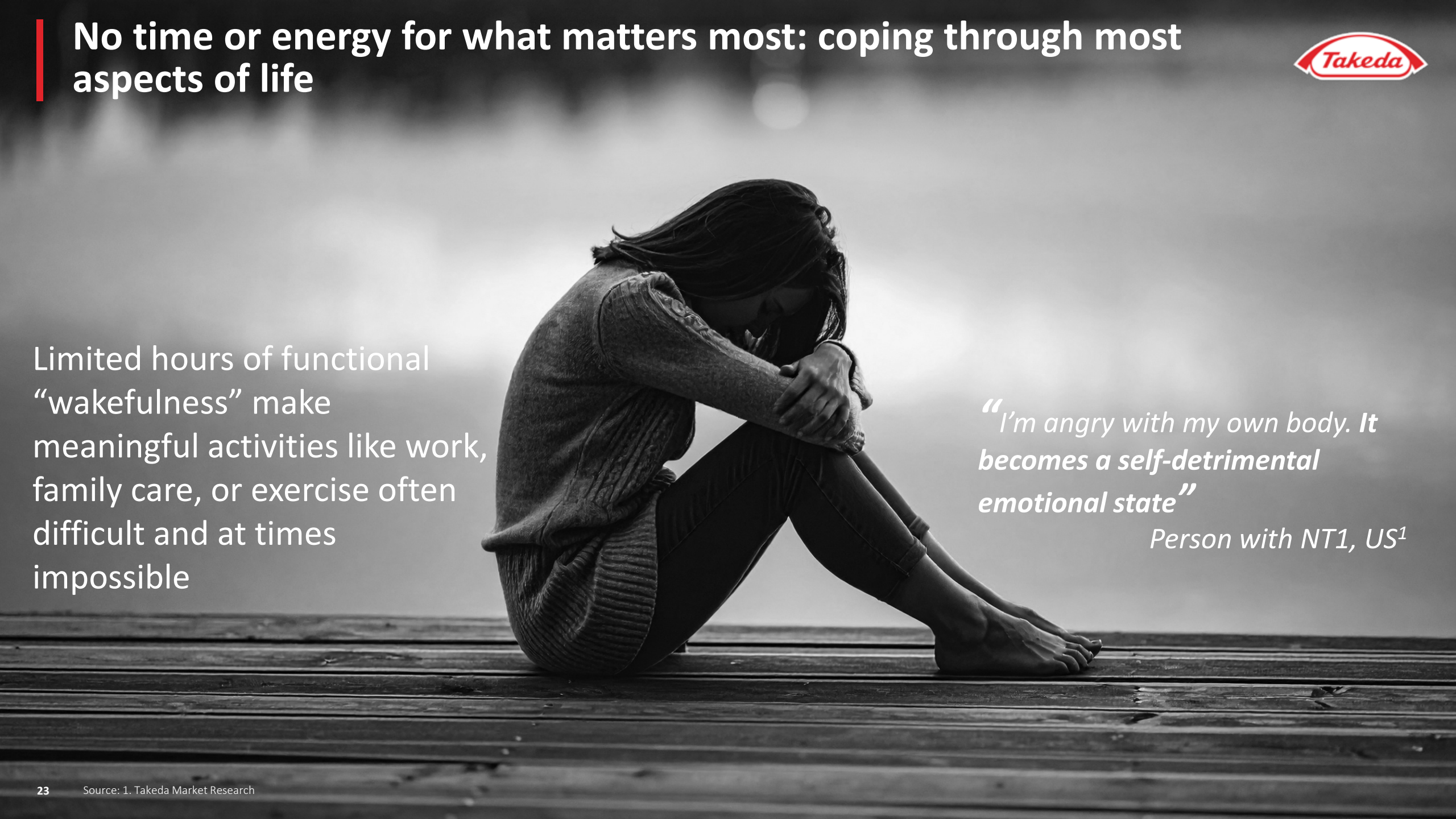
- **Tailored orexin assets** in preclinical/clinical stage (i.e. TAK-495)
- **Optimized profiles for additional indications**: sleep-wake[1], respiration[2], mood, metabolism, and beyond
- **Orexin biomarkers** to **optimize patient outcomes**

1. Dauvilliers, Y., N Engl J Med, 2023; 2. Suzuki M et al., British Journal of Anaesthesia, 2024; IARS Conference, Denver, 2023; HV: Healthy Volunteer

Oveporexton

Market Opportunity & Commercialization

No time or energy for what matters most: coping through most aspects of life



Limited hours of functional "wakefulness" make meaningful activities like work, family care, or exercise often difficult and at times impossible

"I'm angry with my own body. ***It becomes a self-detrimental emotional state"***

Person with NT1, US[1]

Source: 1. Takeda Market Research

Long, exhausting NT1 patient journey is fraught with roadblocks hindering accurate & timely diagnosis, often followed by lifetime of treatment trade-offs

A PATIENT'S JOURNEY TO DIAGNOSIS CAN TAKE DECADES

Symptom Onset

In the US, ***patients can spend ~10-15 years*** *cycling through physicians & misdiagnoses before accurate NT1 diagnosis*[1]

Isolated, Confused, Ashamed[1]

Testing & Diagnosis

~40% of patients *who reach a sleep specialist in the US are still misdiagnosed*[2]

Scared, Frustrated, Discouraged, Relieved[1]

Treatment & Adjustment

>50% polypharmacy cycling in the US:
despite treatment, NT1 is not well controlled[1]

Hopeful, Uncertain, Disillusioned[1]

1. TAK-861-5001: *Burden of Illness Study among Patients with Central Disorders of Hypersomnolence in Europe, US, and Canada*
2. Source: Takeda Market Research

Patients rely on symptomatic treatments, which often lead to persistent breakthrough or residual symptoms and suboptimal disease management

Current standard of care does not target Orexin deficiency, the underlying cause of NT1

75% of U.S. diagnosed patients are treated

75% of U.S. diagnosed patients are treated, but both branded and generic options address limited symptoms like EDS and cataplexy

- EDS: generic stimulants, branded wake promoting agents
- Cataplexy: generic antidepressants, branded oxybates

>50% of treated patients are on polypharmacy

High rates of treatment switching and/or discontinuation

- >50% polypharmacy[1]
- Complex comorbidities and treatment cycling
- Coping mechanisms & lifestyle adjustments often employed

>80% of patients report residual symptoms

Despite existing treatments, key unmet needs remain

- >80% of patients have reported residual symptoms despite treatment[2]
- Managing a range of side effects and potentially inconvenient dosing regimen
- Coverage restrictions and/or prohibitive cost[1]

Sources: 1. Takeda Market Research 2.Burden of Illness Study Among Patients with Central Disorders of Hypersomnolence, Y. Dauvilliers et al, EAN, 2024

Despite treatment, many patients continue to experience symptoms and need to cope with the continued impact of NT1 on many aspects of their lives

Half as likely to have children[1,2]

82% feel restricted in jobs they can pursue[3]

3.5x more likely to be clinically depressed[4]

Sources: 1. Peter-Derex et al. medRxiv. 2024; 2. Ingravallo et al. Sleep Med. 2012; 13(10):1293; 3. Narcolepsy UK Charter. 2023; 4. Li et al. Neuropsychol Rev. 2021; 31(1):89

Pioneering a potential paradigm shift with a development program designed to demonstrate the transformative efficacy of an Orexin therapy

Current SoC

MWT	ESS	WCR
Maintenance of Wakefulness Test	*Epworth Sleepiness Scale*	*Weekly Cataplexy Rate*

oveporexton

- ✓ **MWT** *Maintenance of Wakefulness Test*
- ✓ **PVT** *Psychomotor Vigilance Test*
- ✓ **PGI-C** *Patient Global Impression of Change*
- ✓ **FINI** *Functional Impacts of Narcolepsy Instrument*
- ✓ **ESS** *Epworth Sleepiness Scale*
- ✓ **SF-36** *Short Form-36 Survey*
- ✓ **WCR** *Weekly Cataplexy Rate*
- ✓ **NSS-CT** *Narcolepsy Severity Scale for Clinical Trials*

FINI Domain Scores:

- ✓ *Everyday Activities*
- ✓ *Cognitive Functioning*
- ✓ *Everyday Responsibilities*
- ✓ *Social Activities*
- ✓ *Cataplexy*
- ✓ *Tiredness*

✓ = *Statistically significant in Ph 3 as primary or secondary endpoints*

Oveporexton is poised to redefine treatment outcomes that matter most to patients

> ***Being able to laugh and be sad freely***, *I feel like I've become a* ***normal person*** *and* ***gained confidence***.

> *You* ***recover the life you want****....You also make up for lost time, you start doing* ***the things you couldn't do for years****....*

Quotes from oveporexton phase 2 study exit interviews

OVEPOREXTON Aspiration:

A New Era Of Care

- Designed to treat the root cause of NT1, **OREXIN** deficiency
- Potential to be a transformative **OREXIN** therapy
- Transformative efficacy demonstrated across a broad spectrum of NT1 symptoms

Takeda is leveraging its neuroscience and rare expertise to advance oveporexton towards the market*, preparing for a seamless patient and HCP experience

ASPIRING TO A NEW ERA OF CARE FOR NT1 PATIENTS:

EDUCATION & AWARENESS OF NT1 TRUE BURDEN AND ROLE OF OREXIN

Knowledge & empowerment

- Largest real-world studies on burden
- Pioneering data on broader impacts
- Education on Orexin deficiency

ENABLING ACCESS TO TREATMENT

Redefine treatment outcomes

- First cost of illness & disease severity model
- First disease-specific PRO measure
- Real-world monitoring of outcomes

ADVANCING & ACCELERATING DIAGNOSIS

Exploring innovative patient journey solutions

- Orexin biomarkers
- Wearable & home test solutions
- AI algorithms of high accuracy

Takeda Leadership & Global Commercial Footprint

* Subject to regulatory review, feedback, and approval

PRO: Patient Reported Outcome

Successful launch of oveporexton* will unlock the potential of a new era of care in NT1, starting in the US

~95-120k
Prevalent U.S. NT1 patients[1]

Uncovering the true burden of narcolepsy

10-20%
Diagnosis Rate Optimization
Today's Diagnosis Rate: ~50%

Improving rate, speed and accuracy of NT1 diagnosis utilizing digital tools

5-10% +
Treatment Rate Increase
Today's Treatment Rate: ~75%

Redefine treatment outcomes with new MOA that addresses root cause of NT1

30-50% +
Preference Share

A new level of efficacy by addressing Orexin deficiency

Oveporexton's NT1 global peak revenue potential : $2-3B+

Source: 1. Silber MH, et al. Sleep. 2002;25(2):197-202. Scheer D, et al. Sleep. 2019 Jul 8;42(7):zsz091. Abioye, et al Sleep Medicine Volume 100, Supplement 1, December 2022, Page S154.
Takeda claims analysis; Takeda physician research; company filings. AT: Advanced therapies
Please refer to the Important Notice at the start of this presentation for more information about peak revenue estimates.
*Subject to regulatory review, feedback, and approval

Takeda is the leader in Orexin biology, aiming to transform patient outcomes

Oveporexton:

$2-3B+

NT1 PEAK REVENUE POTENTIAL

TAK-360: Accelerated Development

Tailored to address unique unmet needs in NT2 & IH

Tailored Orexin Assets For Additional Indications

- Sleep-Wake
- Respiratory conditions
- Metabolic disorders
- Mood
- And beyond

Strong foundation of Takeda capabilities maximizing global launches and advancing patient care ecosystems; powered by our leadership in Orexin science & development

Pioneering Orexin science and catalyzing a potential new era of care for patients with narcolepsy type 1 (NT1) with oveporexton

1

Orexin deficiency is the root cause of NT1

2

Oveporexton is designed to treat the root cause of NT1 and has the potential to be a transformative Orexin therapy

3

Ph3 results demonstrated oveporexton's potential to achieve outcomes that matter most to patients

Oveporexton U.S. and global filings on track to start in FY25; global $2-3B+ peak revenue potential

Please refer to the Important Notice at the start of this presentation for more information about peak revenue estimates.

Q&A Session

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Glossary of Abbreviations

Regional Abbreviations:
CN: China; EU: Europe; JP: Japan; U.S.: United States of America

AE	adverse event
AI	artifcial inetlligence
ASN	American Society of Nephrology
BID	bis in die, twice a day
BL	baseline
BTD	breakthrough therapy designation
CGI-C	Clinical Global Impression of Change
CI	confidence interval
CSF	cerebrospinal fluid
CY	calender year
EDS	excessive daytime sleepiness
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 Dimensions 5-levels
ESRS	European Sleep Research Society
ESS	Epworth Sleepiness Scale
FDA	U.S. Food & Drug Administration
FIH	first in human
FINI	Functional Impacts of Narcolepsy Instrument
FSI	first subject in
FY	fiscal year
HCP	healthcare professional
IH	idiopathic hypersomnia
IND	investigational new drug
IQR	Interquartile Range
IRR	Incidence Rate Ratio
JPY	Japanese Yen
KSS	Karolinska Sleepiness Scale
LFT	liver function test
LS	least square
LTE	long-term extension
MOA	mechanism of action
MWT	maintenance of wakefulness test
NDA	new drug application
NEJM	New England Journal of Medicine
NMPA	(China's) National Medical Products Administration
nPSG	nocturnal polysomnography
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1 or 2	narcolepsy type 1 or 2
OX2R	orexin receptor 2
OX-A	orexin A
PGI-C	Patient Clinical Global Impression of Change
Ph1, Ph2, Ph3	phase 1, 2 ,3
PK	pharmacokinetics
PMDA	Japan's Pharmaceuticals and Medical Devices Agency
POC	proof of concept
PRIME	Priority medicines scheme by EMA
PRO	patient reported outcomes
PSG	polysomnography
PVT	Psychomotor Vigilance Task
QOL	quality of life
R&D	Research and Development
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form-36 Survey
SOC	standard of care
TEAE	treatment emergent adverse event
Tx	therapy
USD	US dollar
WCR	weekly cataplexy rate
wk(s)	week(s)
WW	worldwide

Medical Presentation
as presented at World Sleep 2025

Singapore 2025
WORLD SLEEP
September 5-10

Emmanuel Mignot, MD, PhD, USA

The First Light: Efficacy and safety of a multi-dose study of oveporexton (TAK-861), an oral orexin receptor 2 agonist, for the treatment of narcolepsy type 1

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Disclosures

Disclosures

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- Mitsutaka Taniguchi received funds for seminars and travel to conferences from Daiichi-Sankyo, Eisai, Shionogi, Taisho, Takeda, and Teijin.
- Yves Dauvilliers received funds for seminars, board engagements, and travel to conferences from Avadel, Bioprojet, Idorsia, Jazz Pharmaceuticals, Orexia, and Takeda.
- Harisha Kadali, Yeting Du, Samuel Hsiao, Tina Olsson, Sarah Sheikh, Christian von Hehn, and Mark Etherton are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceuticals Company Limited.

Acknowledgments

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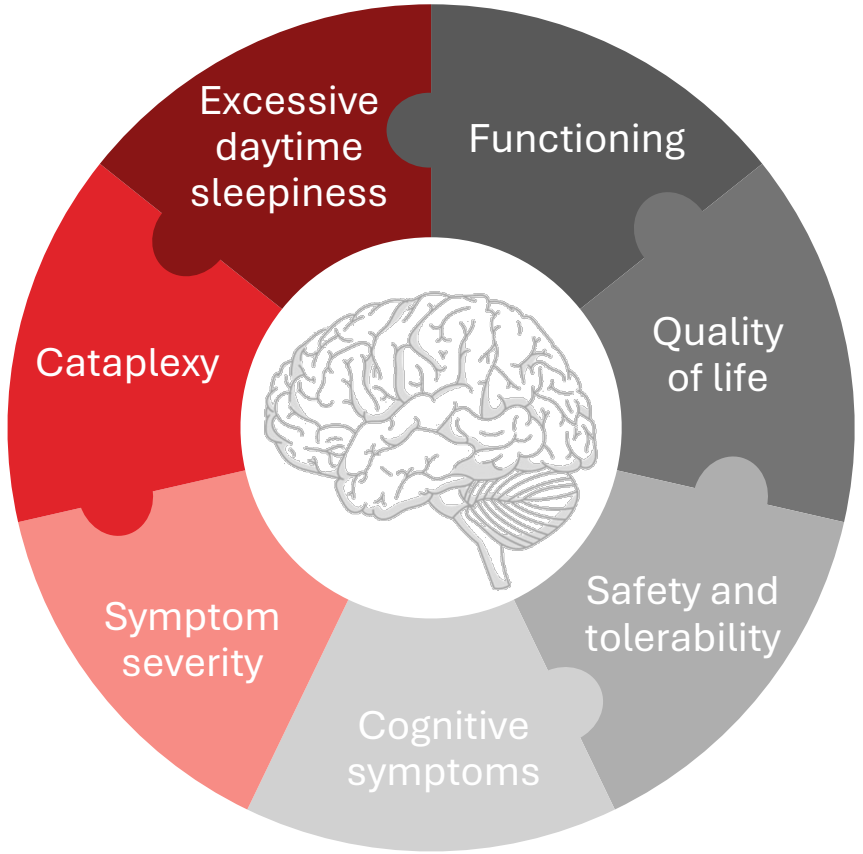
- Under the direction of the authors, Lindsay Napier, PhD, CMPP, and Megan Cafro, PhD, employees of Envision Catalyst, an Envision Medical Communications agency, a part of Envision Pharma Group, provided writing assistance for this presentation. Editorial assistance in formatting, proofreading, and copy editing was also provided by Envision Catalyst. Takeda Development Center Americas, Inc., provided funding to Envision Catalyst for support in writing and editing this presentation.

Background

Narcolepsy type 1 (NT1) is a chronic, rare, neurologic disorder of hypersomnolence characterized by a range of debilitating symptoms.[1-3]

NT1 is caused by loss of the orexin-producing neurons in the brain, which regulate wakefulness, sleep, and attention through activation of orexin receptors.[1-3]

Oveporexton (TAK-861) is a next-generation, highly potent oral orexin receptor 2 (OX2R)-selective agonist that activates the OX2R to restore signaling addressing the underlying orexin deficiency in NT1.[4-6]



OX2R, orexin receptor 2.

1. Scammell TE. *N Engl J Med* 2015;373:2654-62. **2.** Sateia M, American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd Ed. Darien, IL: AASM; 2014. **3.** American Psychiatric Association. Sleep–wake disorders; narcolepsy. In: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: APA; 2013:372-82. **4.** Mitsukawa K, et al. *Sleep Med* 2024;115(suppl 1):12. **5.** Kimura H, et al. *Sleep Med* 2024;115(suppl1):16. **6.** Naylor M, et al. *Sleep Med* 2024;115(suppl 1):225.

Oveporexton development

Balanced efficacy and on-target/off-target tolerability and safety[1]

Early-phase clinical trials showed significant and meaningful improvements across the spectrum of NT1 symptoms.[2]

Here, we report the first data from **The First Light phase 3 study** designed to confirm the efficacy and safety of oveporexton in participants with NT1.

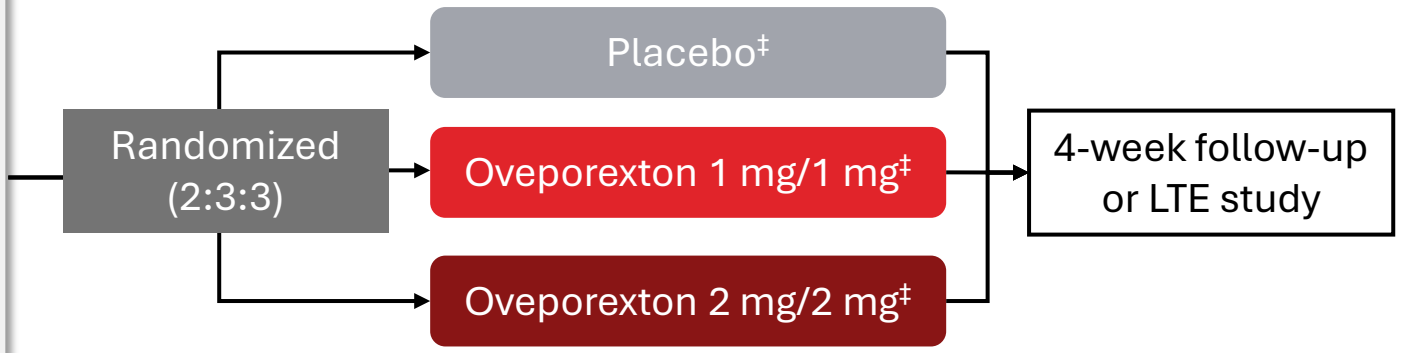
NT1, narcolepsy type 1.

1. Mitsukawa K, et al. *Sci Rep* 2024;14:20838. **2.** Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

The First Light study design

- Randomized, double-blind, placebo-controlled, phase 3 study of twice-daily doses of oral oveporexton, an orexin receptor 2 agonist, conducted across Europe, Japan, and North America.

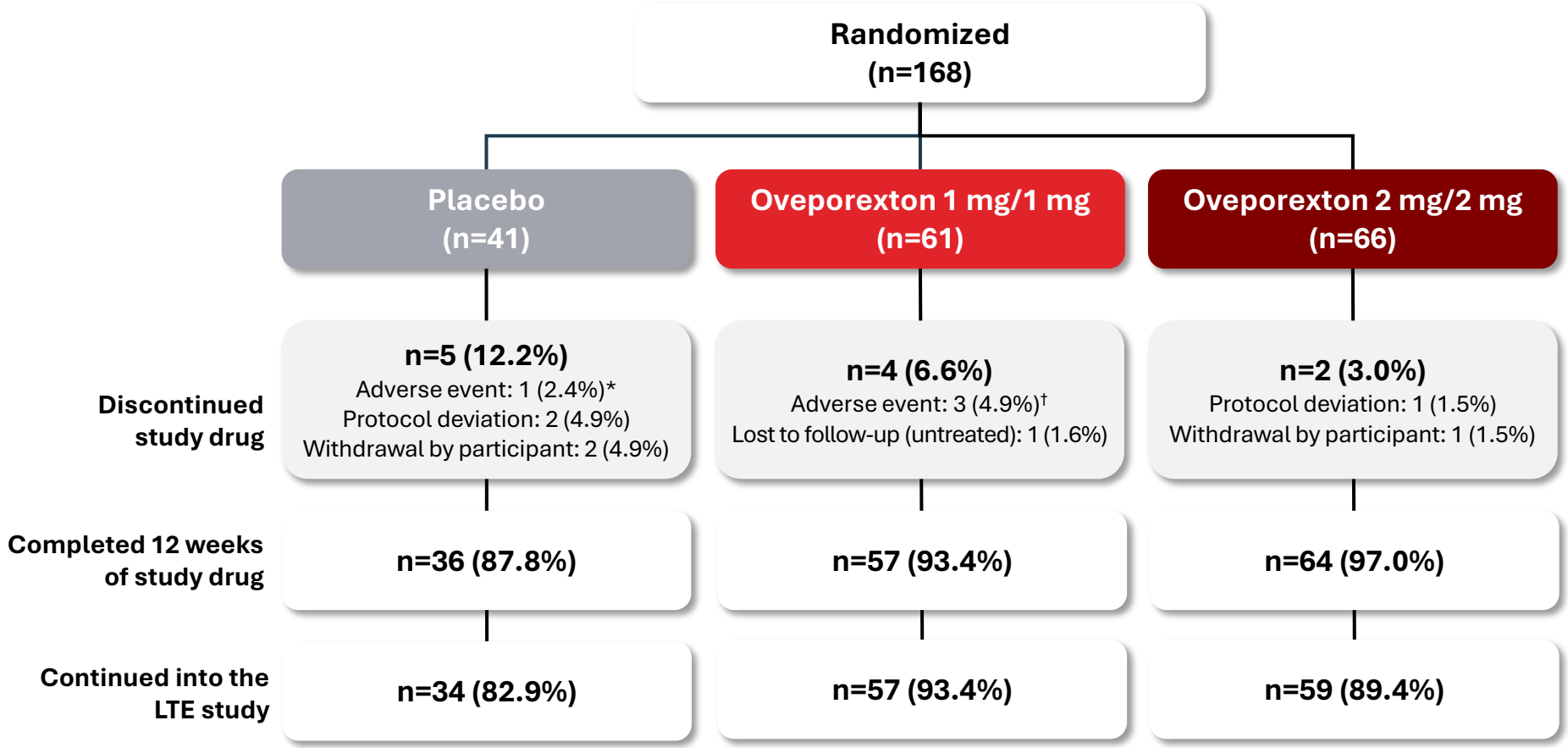
Inclusion criteria†:
- Participants aged 16–70 years
- ICSD-3/ICSD-3 TR diagnosis of NT1 supported by PSG/MSLT or orexin CSF ≤110 pg/mL
- ESS score ≥11
- ≥4 partial/complete episodes of cataplexy per week
- Positive for the HLA genotype HLA-DQB1*06:02 (in the absence of orexin CSF testing)



Endpoints		
Primary	MWT	Change from baseline to week 12 in mean sleep latency from the 4 MWT sessions
Secondary	ESS WCR TEAEs	Change from baseline to week 12 in ESS total score WCR at week 12 Incidence of adverse events

CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; ICSD-3, International Classification of Sleep Disorders, Third Edition; ICSD-3 TR, International Classification of Sleep Disorders, Third Edition, Text Revision; LTE, long-term extension; MSLT, multiple sleep latency test; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; PSG, polysomnography; TEAE, treatment-emergent adverse event; WCR, weekly cataplexy rate. †US-based sites primarily used PSG/MSLT and HLA status for eligibility requirements. ‡Doses were given at least 3 h apart.

Participant disposition



- 168 participants randomized.
- 157 completed 12 weeks
- 150/157 (>95%) of those who completed the study continued into the long-term extension study.

LTE, long-term extension.
*Liver function test increase (not related to study drug). †1 urinary frequency, 1 urinary incontinence, 1 liver function test increase (not related to study drug).

Participant characteristics at baseline

	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=61)	Oveporexton 2 mg/2 mg (n=66)
Mean (SD) age, years	30.9 (12.7)	33.5 (11.8)	29.7 (9.6)
Female, n (%)	24 (58.5)	28 (45.9)	46 (69.7)
Race, n (%)			
Asian	6 (14.6)	10 (16.4)	10 (15.2)
Black/African American	4 (9.8)	3 (4.9)	0
White	15 (36.6)	17 (27.9)	27 (40.9)
Other/unknown	16 (39.0)	31 (50.8)	29 (43.9)
Mean (SD) ESS total score	18.2 (3.6)	18.2 (2.6)	19.0 (3.2)
Mean (SD) MWT sleep latency, min	5.1 (6.8)	5.5 (7.7)	4.4 (5.5)
Median (IQR) WCR	28.5 (16.5–59.5)	21.0 (9.0–45.0)	26.3 (14.5–52.8)
Mean (SD) NSS-CT total score	31.0 (9.6)	30.4 (8.7)	31.2 (7.3)
On prior medication for narcolepsy requiring washout, n (%)*	33 (80.5)	50 (83.3)	51 (77.3)

Demographics and disease characteristics were generally balanced across groups at baseline.

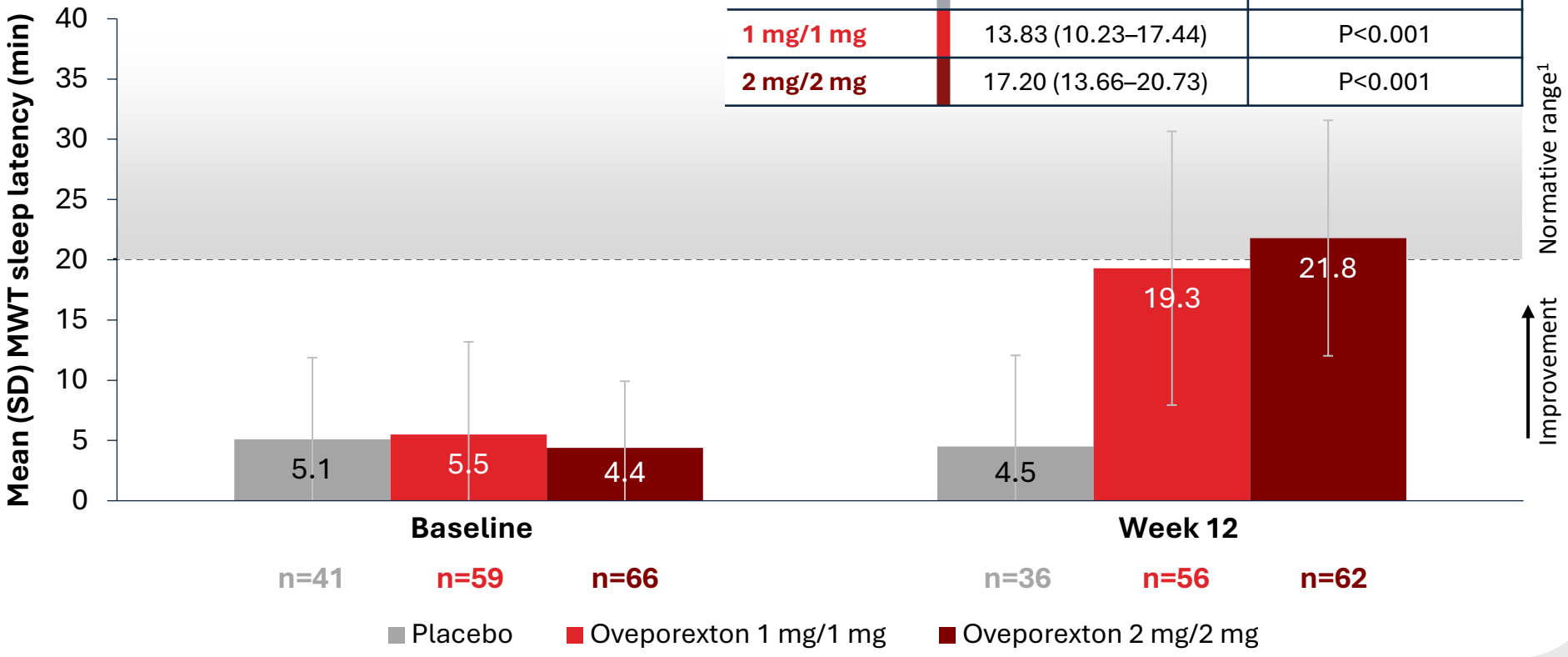
ESS, Epworth Sleepiness Scale; IQR, interquartile range; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; WCR, weekly cataplexy rate.
*Based on EDC data.

Oveporexton significantly improved mean sleep latency at 12 weeks compared with placebo, with majority of participants within the normative range

Maintenance of Wakefulness Test (MWT)

LS mean difference from placebo in change from baseline at week 12 (primary endpoint)

Oveporexton	LS mean (95% CI)	Adjusted P-value*
1 mg/1 mg	13.83 (10.23–17.44)	P<0.001
2 mg/2 mg	17.20 (13.66–20.73)	P<0.001



Proportion of participants achieving mean sleep latency ≥20 min at week 12:

Placebo: **2 (6%)**

1 mg/1 mg: **27 (48%)**

2 mg/2 mg: **35 (56%)**

LS, least squares.
*The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.

1. Doghramji K, et al. *Electroencephalogr Clin Neurophysiol* 1997;103:554-62.

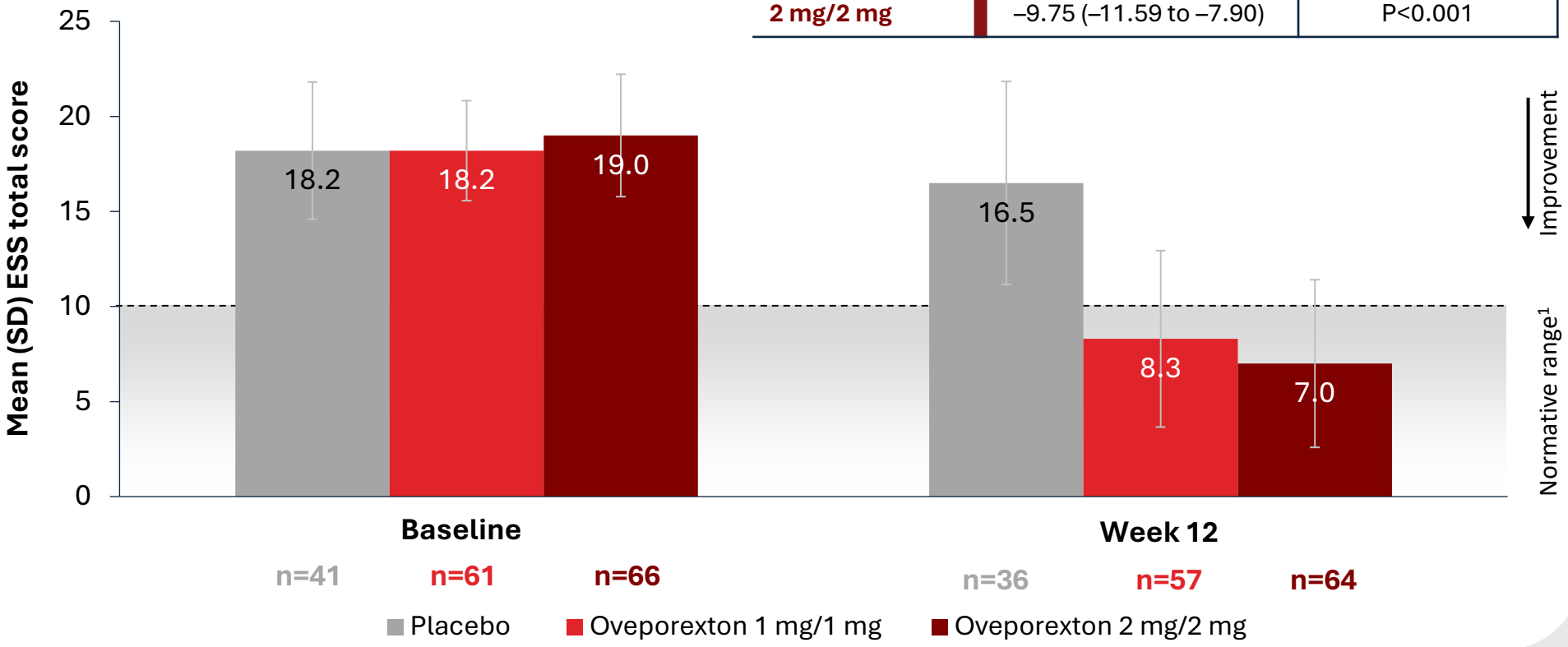
Oveporexton significantly improved subjective sleepiness at 12 weeks compared with placebo, with majority of participants within the normative range

September 5-10 2025 WORLD SLEEP Singapore

Epworth Sleepiness Scale (ESS)

LS mean difference from placebo in change from baseline at week 12

Oveporexton	LS mean (95% CI)	Adjusted P-value*
1 mg/1 mg	–8.00 (–9.87 to –6.13)	P<0.001
2 mg/2 mg	–9.75 (–11.59 to –7.90)	P<0.001



Proportion of participants achieving ESS total score ≤10 at week 12:

Placebo: **6 (17%)**

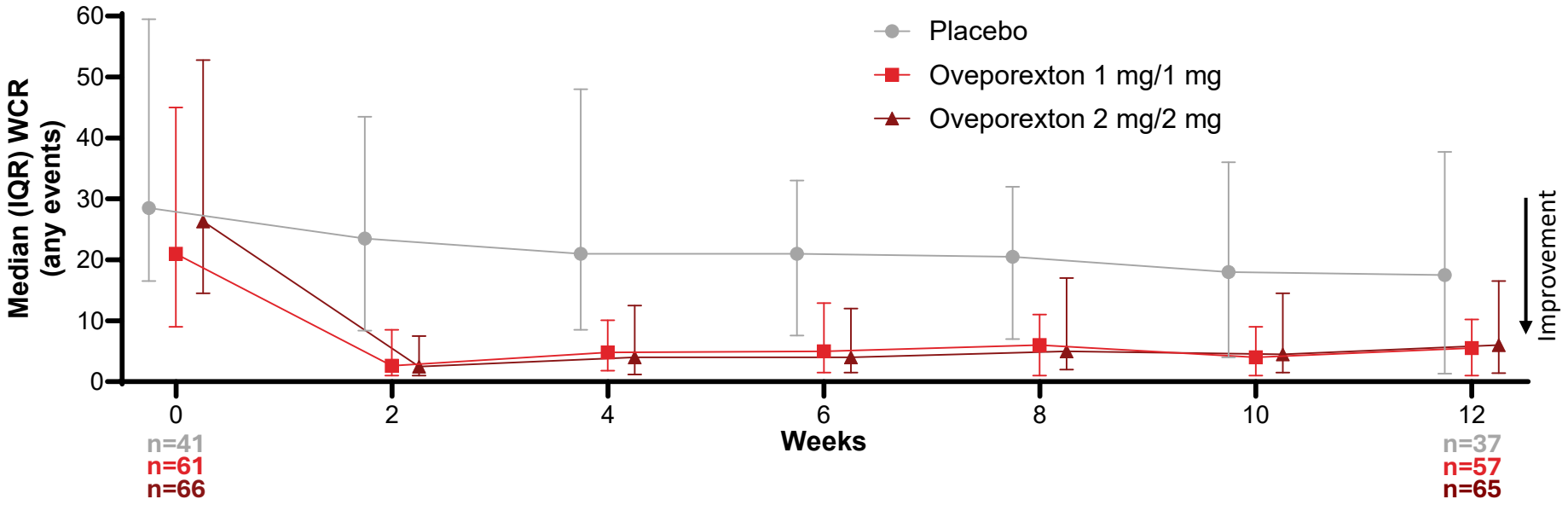
1 mg/1 mg: **38 (67%)**

2 mg/2 mg: **53 (83%)**

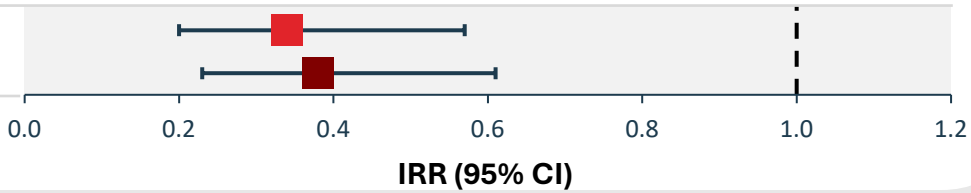
LS, least squares.
*The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.
1. Johns MW. *Sleep* 1991;14:540-5.

Oveporexton significantly reduced WCR over 12 weeks versus placebo and increased the number of cataplexy-free days for both doses

Weekly Cataplexy Rate (WCR)



	IRR	(95% CI)	Adjusted P-value*
Oveporexton			
1 mg/1 mg	0.34	(0.20–0.57)	<0.001
2 mg/2 mg	0.38	(0.23–0.61)	<0.001



- Median cataplexy-free days/week increased from **0 days at baseline (all arms) to ~4 days at week 12 with oveporexton doses** versus 0.5 days with placebo.
- Median percentage reductions in WCR from baseline were **82.6% and 79.0% with oveporexton** 1 mg and 2 mg doses, respectively, at week 12.

IQR, interquartile range; IRR, incidence rate ratio. *The analysis used a generalized estimating equations model (negative binomial) with placebo-based multiple imputation. P-values have been adjusted for multiplicity. The IRR is the incidence rate of the oveporexton group divided by the incidence rate of the placebo group.

Oveporexton was generally safe and well tolerated

Safety population

Participants with:	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=60)	Oveporexton 2 mg/2 mg (n=66)
Any TEAE, n (%)	22 (53.7)	52 (86.7)	59 (89.4)
Mild	14 (34.1)	26 (43.3)	34 (51.5)
Moderate	7 (17.1)	24 (40.0)	23 (34.8)
Severe*	1 (2.4)	2 (3.3)	2 (3.0)
Serious TEAE, n (%)†	0	1 (1.7)	1 (1.5)
TEAEs related to study drug, n (%)	9 (22.0)	46 (76.7)	53 (80.3)
TEAEs leading to study drug discontinuation, n (%)‡	1 (2.4)	3 (5.0)	0
Most frequent TEAEs, n (%)			
Urinary frequency	3 (7.3)	32 (53.3)	36 (54.5)
Insomnia	0	32 (53.3)	38 (57.6)
Urinary urgency	1 (2.4)	9 (15.0)	12 (18.2)
Nasopharyngitis	6 (14.6)	6 (10.0)	10 (15.2)
Headache	5 (12.2)	4 (6.7)	10 (15.2)
Salivary hypersecretion	0	5 (8.3)	4 (6.1)

- Most TEAEs were mild to moderate in severity and on-target events.
- No treatment-related serious TEAEs.
- The most common TEAEs of special interest were insomnia and urinary events.
  - Most were mild to moderate in severity and started within first days of treatment.
  - Did not require medical intervention.
- No safety concerns relating to any laboratory parameters and vital signs, and no evidence of hepatotoxicity.
- >95% of participants completing the study continued into the long-term extension study.

LFT, liver function test; TEAE, treatment-emergent adverse event. *Placebo: LFT increase; 1 mg/1 mg: ureterolithiasis, insomnia; 2 mg/2 mg: urinary frequency, insomnia, erythema. †1 mg/1 mg: ureterolithiasis (not related); 2 mg/2 mg: chest pain (not related). ‡Placebo: LFT increase; 1 mg/1 mg: urinary frequency, urinary incontinence, LFT increase (not related).

Conclusions

- This is the first report of phase 3 clinical data with an orexin receptor 2 agonist in people with NT1.
- In **The First Light phase 3 study**, twice-daily 1 mg and 2 mg doses of oral oveporexton resulted in statistically significant and clinically meaningful improvements versus placebo over 12 weeks.
  - Majority of participants receiving oveporexton reached normative levels of objective (MWT) wakefulness and subjective (ESS) sleepiness.
  - ~80% median reduction in weekly cataplexy rate for both doses.
- Oveporexton was generally safe and well tolerated.
  - Most TEAEs were mild to moderate in severity and self-limiting and were primarily on-target effects.
  - No safety concerns in relation to adverse events, vital signs, laboratory, or ECG data.
- Consistent with results from phase 2 study in participants with NT1 over 8 weeks.[1]

Results from The First Light phase 3 study confirm that oveporexton, an oral orexin receptor agonist, provides meaningful improvement with the potential of transformational benefit to people with NT1.

ECG, electrocardiogram; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; OX2R, orexin receptor 2; TEAE, treatment-emergent adverse event.

1. Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

Questions

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Yves Dauvilliers, MD, PhD, France

The Radiant Light: Efficacy and safety of oveporexton (TAK-861), an oral orexin receptor 2 agonist, for the treatment of narcolepsy type 1

Contributors

Yves Dauvilliers,[1,2,3] Jakub Antczak,[4] Erik Buntinx,[5] Rafael del Rio Villegas,[6,7] Seung-Chul Hong,[8] Sheila Sivam,[9] Shuqin Zhan,[10] Elena Koundourakis,[11] Rachel Neuwirth,[11] Tina Olsson,[11] Sarah Sheikh,[11] Philipp von Rosenstiel,[11] Baiyun Yao,[11] Alice Cai,[11,*] Giuseppe Plazzi[12,13,*]

1 Sleep-Wake Disorders Center, Department of Neurology, Gui-de-Chauliac Hospital, CHU, Montpellier, France; **2** Institute of Neurosciences of Montpellier, INSERM, University of Montpellier, France; **3** National Reference Network for Narcolepsy, Montpellier, France; **4** Department of Neurology, Jagiellonian University Medical College, Kraków, Poland; **5** ANIMA Research, Alken, Belgium; **6** Neurophysiology and Sleep Disorders Unit, Vithas Hospitals, Madrid, Spain; **7** Universidad CEU San Pablo, CEU Universities, Madrid, Spain; **8** Department of Psychiatry, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea; **9** Woolcock Institute of Medical Research and Royal Prince Alfred Hospital, Sydney, NSW, Australia; **10** Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; **11** Takeda Development Center Americas, Inc., Cambridge, MA, USA; **12** Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio-Emilia, Modena, Italy; **13** IRCCS, Istituto delle Scienze Neurologiche, Bologna, Italy

*Co-senior authors

Disclosures

Disclosures

- Yves Dauvilliers received funds for seminars, board engagements, and travel to conferences from Avadel, Bioprojet, Idorsia, Jazz Pharmaceuticals, Orexia, and Takeda.
- Jakub Antczak has no disclosures to declare.
- Erik Buntinx received consultancy fees from Alkermes, Eli Lilly, and Johnson & Johnson and is a major shareholder of ANeuroTech.
- Rafael del Rio Villegas received consultancy fees from Alkermes, Bioprojet, and Takeda, and travel funds from Bioprojet, Jazz Pharmaceuticals, and Takeda.
- Seung-Chul Hong was a principal investigator for Takeda.
- Sheila Sivam has received funding to attend clinical trial related investigator meetings or speaker fees from Avadel, Somnomed, Takeda, Teva, and Vertex Pharmaceuticals.
- Shuqin Zhan received consultancy fees from Takeda and travel funds from Eisai.
- Giuseppe Plazzi received consultancy fees from Bioprojet, Jazz Pharmaceuticals, Orexia, and Takeda.
- Elena Koundourakis, Rachel Neuwirth, Tina Olsson, Sarah Sheikh, Philipp von Rosenstiel, Baiyun Yao, and Alice Cai are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceuticals Company Limited.

Acknowledgments

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Oveporexton development

Balanced efficacy and on-target/off-target tolerability and safety[1]

Early-phase clinical trials showed significant and meaningful improvements across the spectrum of NT1 symptoms.[2]

Here, we report the first data from **The Radiant Light phase 3 study** designed to confirm the efficacy and safety of oveporexton in participants with NT1.

NT1, narcolepsy type 1.

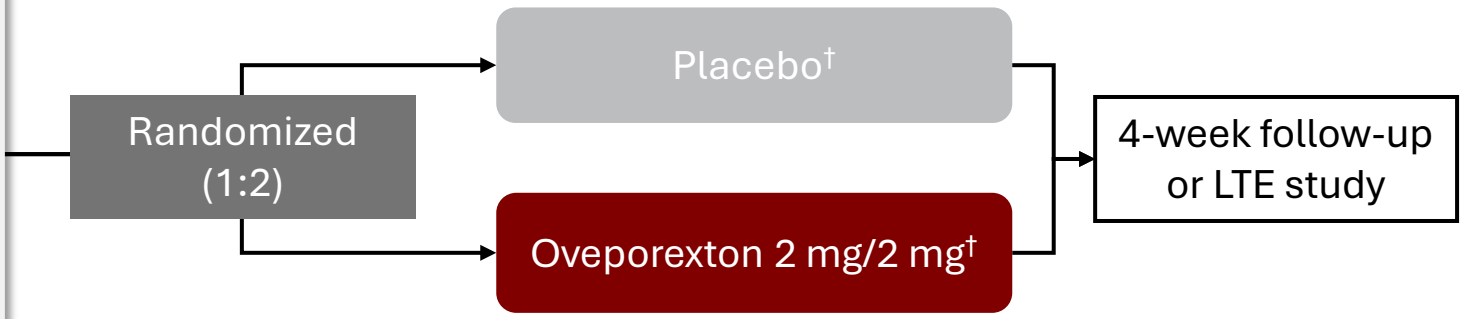
1. Mitsukawa K, et al. *Sci Rep* 2024;14:20838. **2.** Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

The Radiant Light study design

- Randomized, double-blind, placebo-controlled, phase 3 study of 2 mg twice-daily oral oveporexton, an orexin receptor 2 agonist, conducted across Asia, Australia, and Europe.

Inclusion criteria:

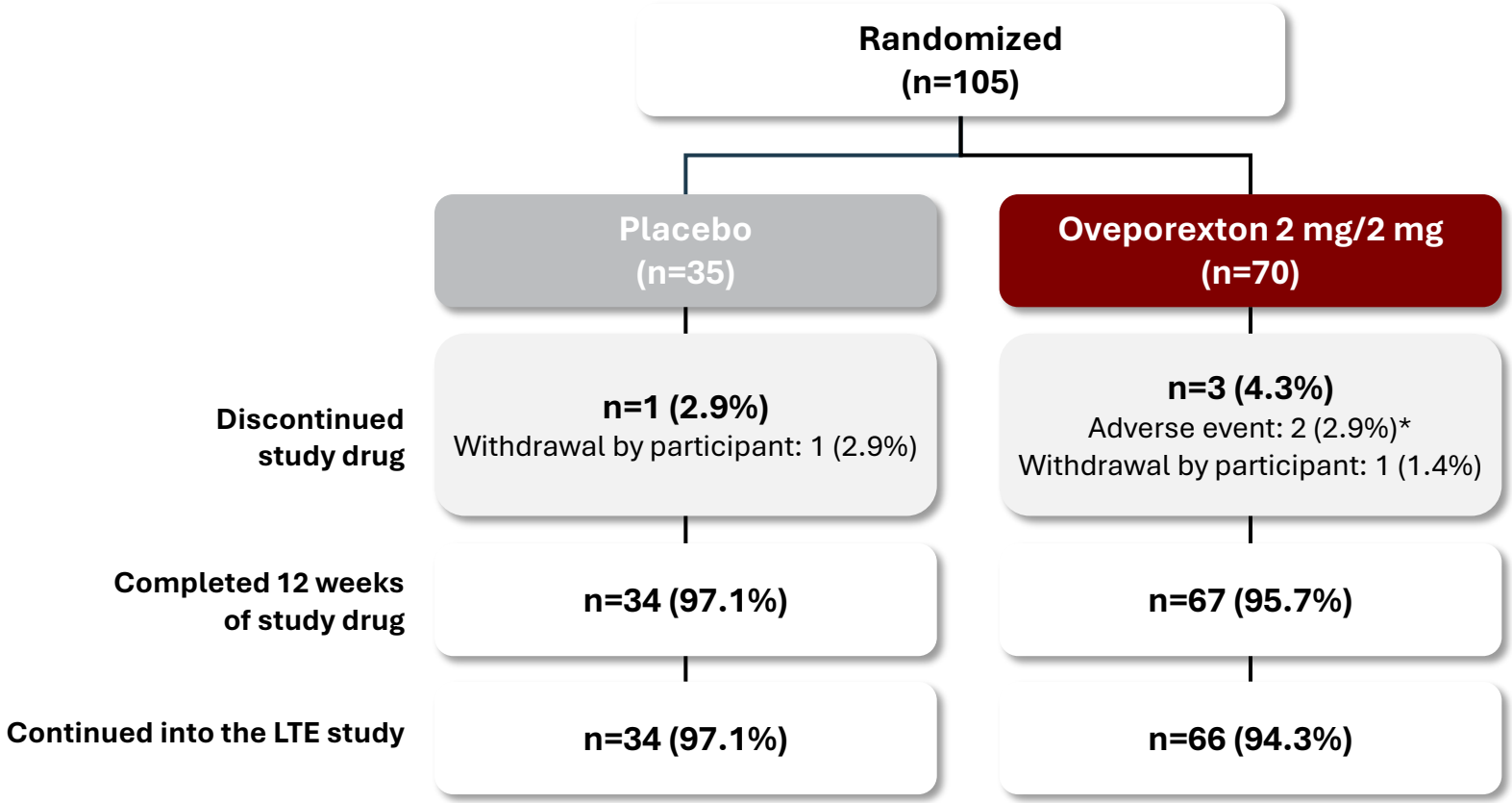
- Participants aged 16–70 years
- ICSD-3/ICSD-3 TR diagnosis of NT1 supported by PSG/MSLT or orexin CSF ≤110 pg/mL
- ESS score ≥11
- ≥4 partial/complete episodes of cataplexy per week
- Positive for the HLA genotype HLA-DQB1*06:02 (in the absence of orexin CSF testing)



Endpoints		
Primary	MWT	Change from baseline to week 12 in mean sleep latency from the 4 MWT sessions
Secondary	ESS	Change from baseline to week 12 in ESS total score
	WCR	WCR at week 12
	TEAEs	Incidence of adverse events

CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; ICSD-3, International Classification of Sleep Disorders, Third Edition; ICSD-3 TR, International Classification of Sleep Disorders, Third Edition, Text Revision; LTE, long-term extension; MSLT, multiple sleep latency test; MWT, Maintenance of Wakefulness Test; PSG, polysomnography; TEAE, treatment-emergent adverse event; WCR, weekly cataplexy rate. †Doses were given at least 3 h apart.

Participant disposition



- 105 participants were randomized.
- 101 completed 12 weeks
- 100/101 (99%) of those who completed the study drug continued into the long-term extension study.

LTE, long-term extension
*2 cases reported as rhabdomyolysis, both due to intense exercise associated with asymptomatic transaminase increase.

Participant characteristics at baseline

	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Mean (SD) age, years	34.0 (13.1)	29.1 (9.6)
Female, n (%)	13 (37.1)	37 (52.9)
Race, n (%)		
Asian	7 (20.0)	14 (20.0)
Black/African American	0	0
White	19 (54.3)	28 (40.0)
Unknown	9 (25.7)	28 (40.0)
Mean (SD) ESS total score	17.9 (3.0)	17.3 (3.4)
Mean (SD) MWT sleep latency, min	4.1 (4.9)	4.8 (4.9)
Median (IQR) WCR	27.0 (19.0–66.5)	21.8 (10.5–37.5)
Mean (SD) NSS-CT total score	31.9 (9.3)	30.7 (9.3)
On prior narcolepsy medication for narcolepsy requiring washout, n (%)*	26 (74.3)	59 (84.3)

Demographics and disease characteristics were generally balanced across groups at baseline.

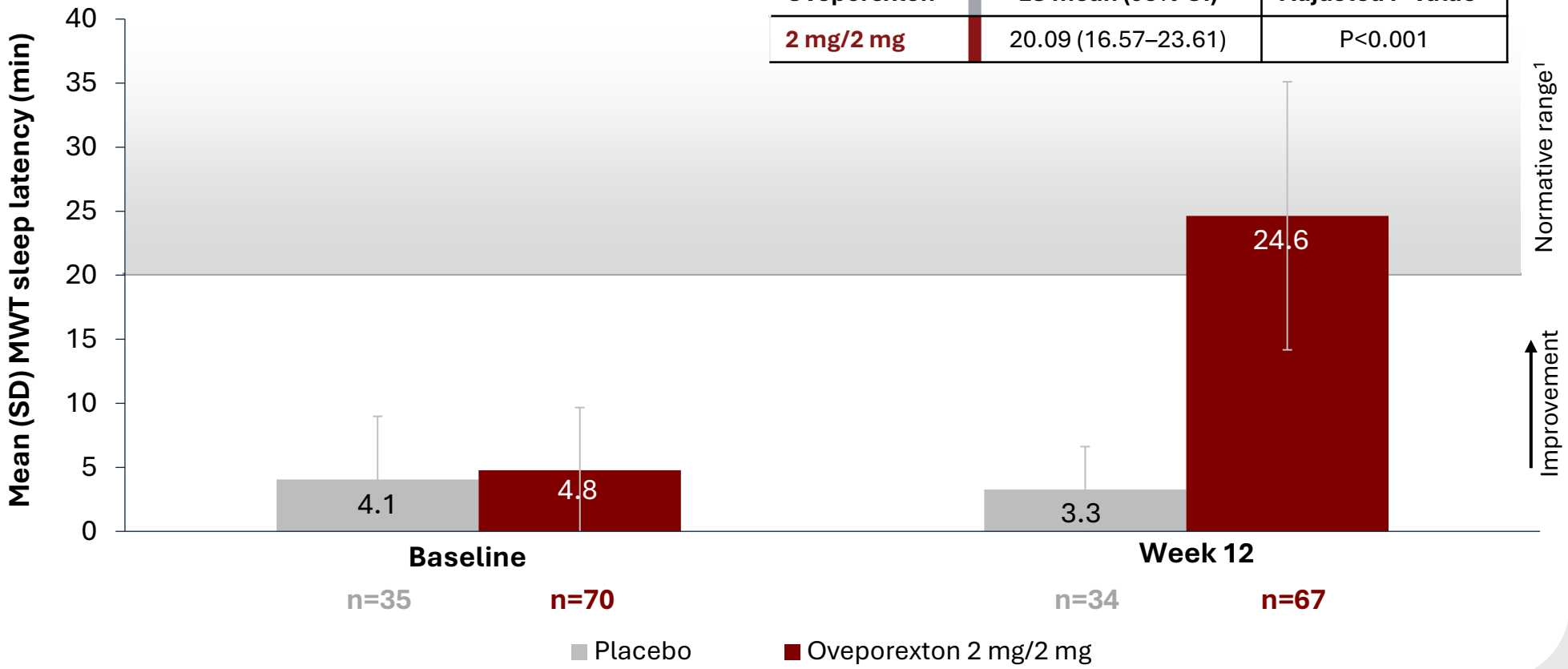
ESS, Epworth Sleepiness Scale; IQR, interquartile range; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; WCR, weekly cataplexy rate.
*Based on EDC data.

Oveporexton significantly improved mean sleep latency at 12 weeks compared with placebo, with majority of participants within the normative range

Maintenance of Wakefulness Test (MWT)

LS mean difference from placebo in change from baseline at week 12 (primary endpoint)

Oveporexton	LS mean (95% CI)	Adjusted P-value*
2 mg/2 mg	20.09 (16.57–23.61)	P<0.001



Proportion of participants achieving mean sleep latency ≥20 min at week 12:

Placebo: 0

2 mg/2 mg: 46 (69%)

LS, least squares. *The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.

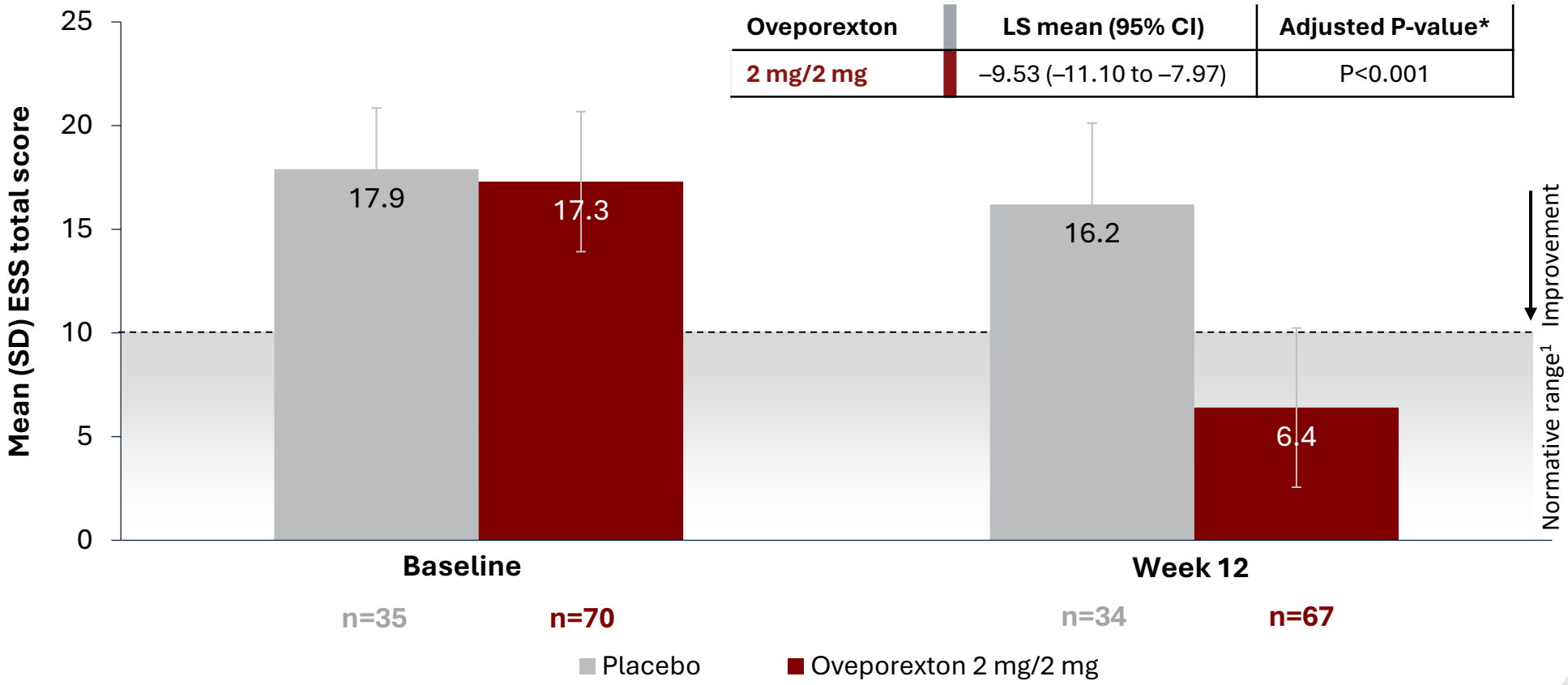
1. Doghramji K, et al. *Electroencephalogr Clin Neurophysiol* 1997;103:554-62.

Oveporexton significantly improved subjective sleepiness at 12 weeks compared with placebo, with majority of participants within the normative range

Epworth Sleepiness Scale (ESS)

LS mean difference from placebo in change from baseline at week 12

Oveporexton	LS mean (95% CI)	Adjusted P-value*
2 mg/2 mg	–9.53 (–11.10 to –7.97)	P<0.001



Proportion of participants achieving ESS total score ≤10 at week 12:

Placebo: **4 (12%)**

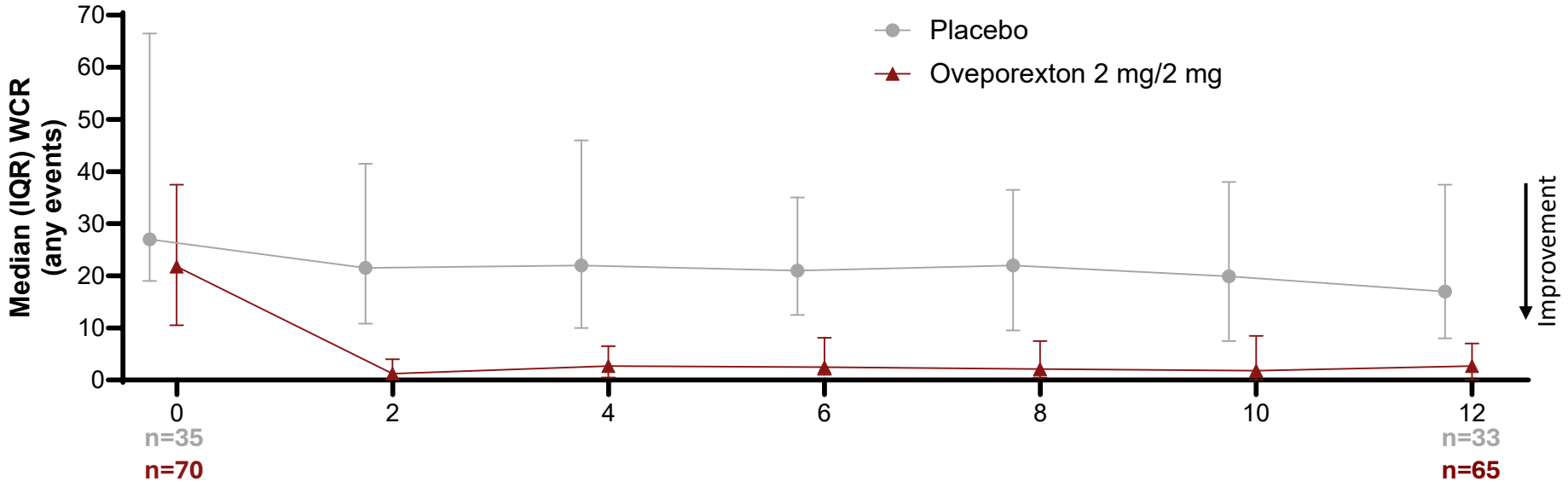
2 mg/2 mg: 56 (84%)

LS, least squares. *The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.

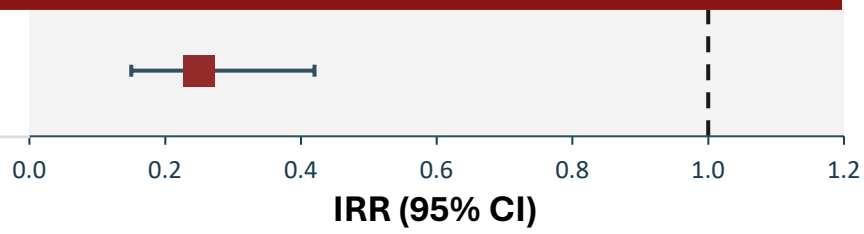
1. Johns MW. *Sleep* 1991;14:540-5.

Oveporexton significantly reduced WCR over 12 weeks versus placebo and increased the number of cataplexy-free days

Weekly Cataplexy Rate (WCR)



	IRR	(95% CI)	Adjusted P-value*	WCR IRR relative to placebo at week 12
Oveporexton 2 mg/2 mg	0.25	(0.15–0.42)	<0.001	



- Median cataplexy-free days/week increased from **0 days at baseline to 5 days at week 12 with oveporexton** versus no increase with placebo.
- Median percentage reduction in WCR from baseline was **88.8% with oveporexton** 2 mg doses at week 12.

IQR, interquartile range; IRR, incidence rate ratio. *The analysis used a generalized estimating equations model (negative binomial) with placebo-based multiple imputation. P-values have been adjusted for multiplicity. The IRR is the incidence rate of the oveporexton group divided by the incidence rate of the placebo group.

Oveporexton was generally safe and well tolerated

Participants with:	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Any TEAE, n (%)	15 (42.9)	60 (85.7)
Mild	9 (25.7)	38 (54.3)
Moderate	5 (14.3)	20 (28.6)
Severe*	1 (2.9)	2 (2.9)
Serious TEAE, n (%)	0	0
TEAEs related to study drug, n (%)	3 (8.6)	56 (80.0)
TEAEs leading to study drug discontinuation, n (%)†	0	2 (2.9)
Most frequent TEAEs, n (%)		
Urinary frequency	1 (2.9)	43 (61.4)
Insomnia	1 (2.9)	40 (57.1)
Urinary urgency	0	10 (14.3)
Headache	2 (5.7)	3 (4.3)
Salivary hypersecretion	0	5 (7.1)

- Most TEAEs were mild to moderate in severity and on-target events.
- No treatment-related serious TEAEs.
- The most common TEAEs of special interest were insomnia and urinary events.
  - Most were mild to moderate in severity, started within first days of treatment, and were transient in nature.
  - Did not require medical intervention.
- No blood pressure–related TEAEs,‡ no safety concerns relating to any laboratory parameters, and no evidence of hepatotoxicity.
- 99% of participants completing the study drug continued into the long-term extension study.

TEAE, treatment-emergent adverse event. *Placebo: tooth infection (unrelated); 2 mg/2 mg: urinary frequency (related), insomnia (related). †2 mg/2 mg: 2 reports of rhabdomyolysis due to intensive exercise, both asymptomatic, discontinued per protocol. ‡1 case of transient palpitations with 2 mg/2 mg oveporexton.

Conclusions

- The first results from **The Radiant Light phase 3 study** in Asia, Australia, and Europe are consistent with those from **The First Light study** in Europe, Japan, and North America[1] and with the 8-week phase 2 TAK-861-2001 study in participants with NT1.[2]
- Oveporexton 2 mg/2 mg demonstrated statistically significant and clinically meaningful improvements versus placebo.
  - The majority of participants receiving oveporexton reached normative levels of objective (MWT) wakefulness and subjective (ESS) sleepiness.
  - ~90% median reduction in weekly cataplexy rate.
- Observed TEAEs were similar between the 2 studies.
  - Most TEAEs were mild to moderate in severity and self-limiting and were primarily on-target effects.
  - No safety concerns in relation to adverse events, vital signs, laboratory, or ECG data.

Results from The Radiant Light phase 3 study confirm that oveporexton, an oral orexin receptor 2 agonist, provides meaningful improvement with the potential of transformational benefit to people with NT1.

ECG, electrocardiogram; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; TEAE, treatment-emergent adverse event.

1. Mignot E, et al. WSC oral presentation O-09. **2.** Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

Questions

Lucie Barateau, MD, PhD, France

Effect of oral orexin receptor 2 agonist oveporexton (TAK-861) on the severity of symptoms in individuals with narcolepsy type 1: Results from two phase 3 studies

Contributors

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Disclosures

Disclosures

- Lucie Barateau received funds for travel to conferences from Bioprojet and Idorsia and for board engagement from Bioprojet, Idorsia, Jazz Pharmaceuticals, and Takeda.
- Isabelle Arnulf has no disclosures to declare.
- Yves Dauvilliers received funds for seminars, board engagements, and travel to conferences from Avadel, Bioprojet, Idorsia, Jazz Pharmaceuticals, Orexia, and Takeda.
- Claudio Liguori received funds for research from Bioprojet, Idorsia, and Jazz Pharmaceuticals, and is a consultant for Idorsia.
- Fabio Pizza participated in an advisory board for Takeda and received support for congress participation and funding from Bioprojet.
- Oliver Sum-Ping has received speaking honoraria from Takeda and research funding from Avadel.
- Ellie Stukalin, Tina Olsson, and Philipp von Rosenstiel are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceutical Company Limited.

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- This work was funded by Takeda Development Center Americas, Inc.
- Under the direction of the authors, Lindsay Napier, PhD, CMPP, and Becky Ayles, PhD, employees of Envision Catalyst, an Envision Medical Communications agency, a part of Envision Pharma Group, provided writing assistance for this presentation. Editorial assistance in formatting, proofreading, copy editing, and fact-checking was also provided by Envision Catalyst. Takeda Development Center Americas, Inc., provided funding to Envision Catalyst for support in writing and editing this presentation.

Background

- In **The First Light** (Europe, Japan, and North America) and **The Radiant Light** (Asia, Australia, and Europe) **phase 3 studies,** twice-daily oral doses of 1 mg and 2 mg oveporexton, an orexin receptor 2 agonist, given at least 3 h apart demonstrated statistically significant and clinically meaningful improvements on measures of wakefulness (MWT), sleepiness (ESS), and cataplexy frequency over 12 weeks versus placebo.

In this analysis of data from **The First Light and The Radiant Light phase 3 studies,** we evaluated the effect of oveporexton on NT1 symptom severity using the Narcolepsy Severity Scale for Clinical Trials (NSS-CT) and the Patient Global Impression (PGI) scales.

ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test.

Narcolepsy Severity Scale for Clinical Trials (NSS-CT)

- The **NSS-CT** is a validated, self-administered, 15-item scale evaluating severity, frequency, and impact of **the spectrum of narcolepsy symptoms**, with domains for **sleepiness, cataplexy, sleep paralysis, hallucinations, and disrupted nocturnal sleep.**[1,2]

	Scoring	Items, n
Symptom severity	6-point Likert scale (0–5)	6
Symptoms consequences on daily life	4-point Likert scale (0–3)	9
Total score = 0–57		

4 severity levels:	Score
Very severe	43–57
Severe	29–42
Moderate	15–28
Mild	0–14

- In adults, an 8-point difference between treated and untreated patients is considered clinically meaningful.[1,2]
- A pediatric version is also available.

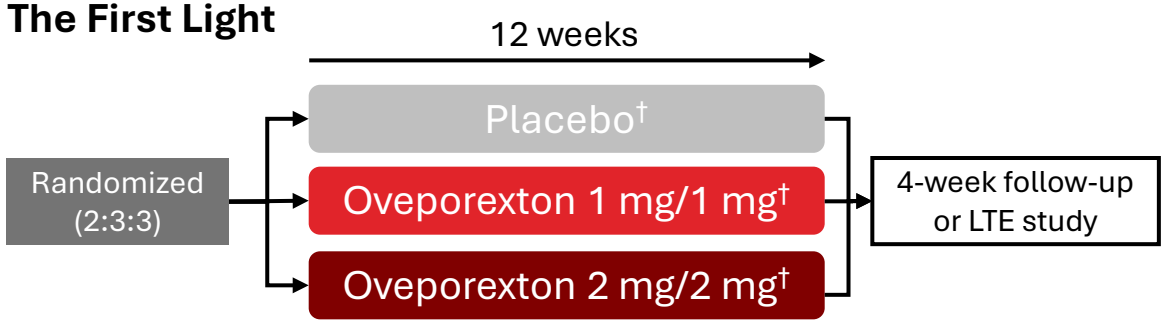
The NSS-CT is distributed worldwide by Mapi Research Trust, https://eprovide.mapi-trust.org/instruments/narcolepsy-severity-scale-for-clinical-trials

1. Dauvilliers Y, et al. *Sleep* 2020;43:1-11. **2**. Dauvilliers Y, et al. *Neurology* 2017;88:1358-65.

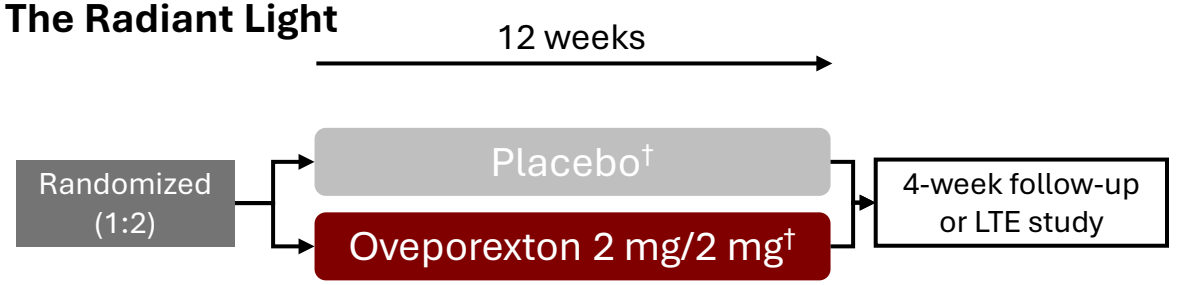
The First Light & The Radiant Light study designs

- 2 randomized, double-blind, placebo-controlled, phase 3 studies of twice-daily oral oveporexton, an orexin receptor 2 agonist, conducted across Asia, Australia, Europe, and North America.

The First Light



The Radiant Light



Inclusion criteria:

- Aged 16–70 years
- ICSD-3/ICSD-3 TR diagnosis of NT1 supported by PSG/MSLT or orexin CSF ≤110 pg/mL
- ESS score ≥11
- ≥4 partial/complete episodes of cataplexy per week
- Positive for the HLA genotype HLA-DQB1*06:02 (in the absence of orexin testing)

Selected endpoints		
Secondary	NSS-CT	Change from baseline to week 12
	PGI-C	Proportion of subjects reporting "much" or "very much" improved at week 12
Exploratory	PGI-S	Proportion of subjects reporting at least 1 levels of improvement at week 12

CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; ICSD-3, International Classification of Sleep Disorders, Third Edition; ICSD-3 TR, International Classification of Sleep Disorders, Third Edition, Text Revision; LTE, long-term extension; MSLT, multiple sleep latency test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; NT1, narcolepsy type 1; PGI-S/C, Patient Global Impression of Symptom Severity/Change; PSG, polysomnography. †Doses were given at least 3 h apart.

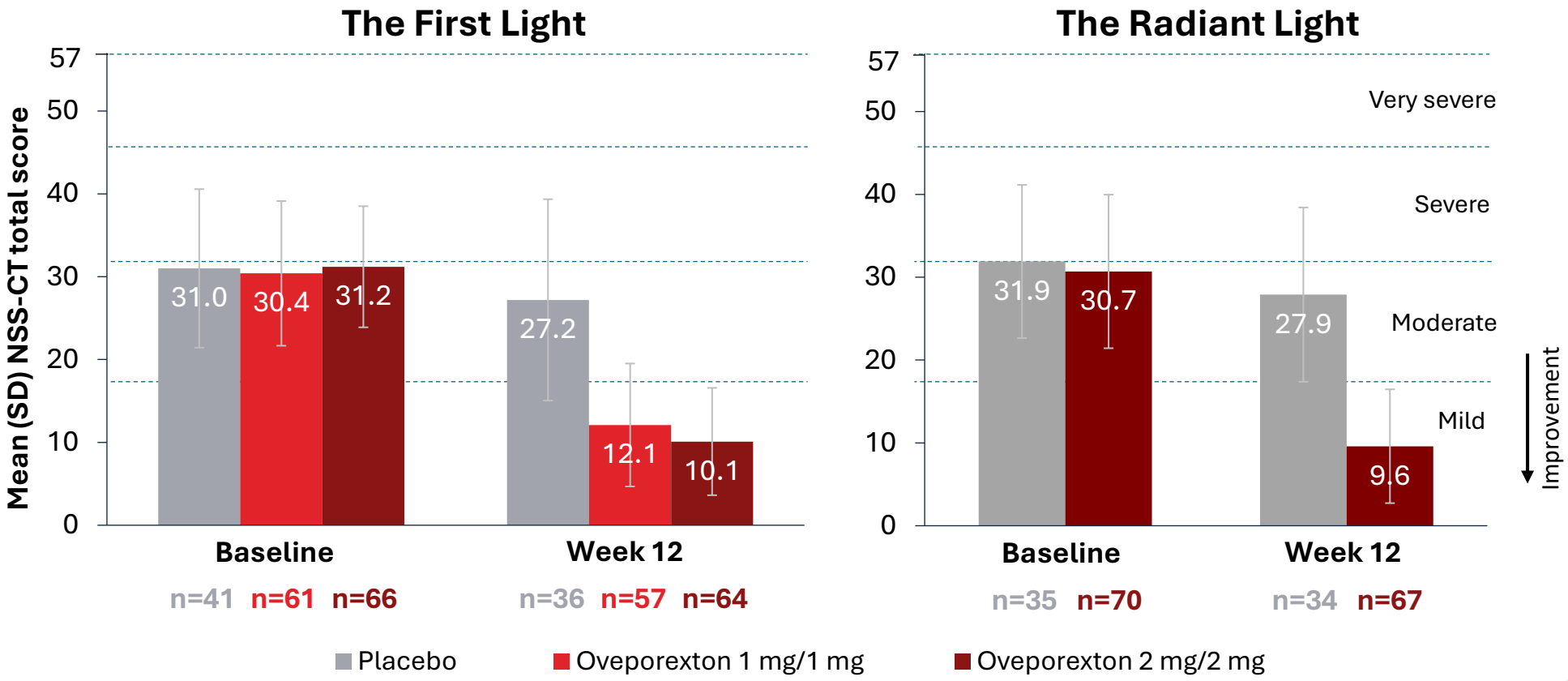
Disease characteristics were generally similar across groups at baseline

	The First Light			The Radiant Light	
	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=61)	Oveporexton 2 mg/2 mg (n=66)	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Mean (SD) age, years	30.9 (12.7)	33.5 (11.8)	29.7 (9.6)	34.0 (13.1)	29.1 (9.6)
Female, n (%)	24 (58.5)	28 (45.9)	46 (69.7)	13 (37.1)	37 (52.9)
Mean (SD) ESS total score	18.2 (3.6)	18.2 (2.6)	19.0 (3.2)	17.9 (3.0)	17.3 (3.4)
Mean (SD) MWT sleep latency, min	5.1 (6.8)	5.5 (7.7)	4.4 (5.5)	4.1 (4.9)	4.8 (4.9)
Median (IQR) WCR	28.5 (16.5–59.5)	21.0 (9.0–45.0)	26.3 (14.5–52.8)	27.0 (19.0–66.5)	21.8 (10.5–37.5)
Mean (SD) NSS-CT total score	31.0 (9.6)	30.4 (8.7)	31.2 (7.3)	31.9 (9.3)	30.7 (9.3)
PGI-S "severe" or "very severe", n (%)	26 (63.4)	37 (60.7)	47 (71.2)	22 (62.9)	47 (67.1)

ESS, Epworth Sleepiness Scale; IQR, interquartile range; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PGI-S, Patient Global Impression-Severity; WCR, weekly cataplexy rate.

Oveporexton resulted in statistically significant and clinically meaningful changes in NSS-CT total score versus placebo

Narcolepsy Severity Scale for Clinical Trials (NSS-CT)



LS mean (95% CI) change from baseline versus placebo at week 12:

TAK-861-3001

1 mg/1 mg: –14.4 (–17.8 to –10.9)

2 mg/2 mg: –16.9 (–20.2 to –13.5)

TAK-861-3002

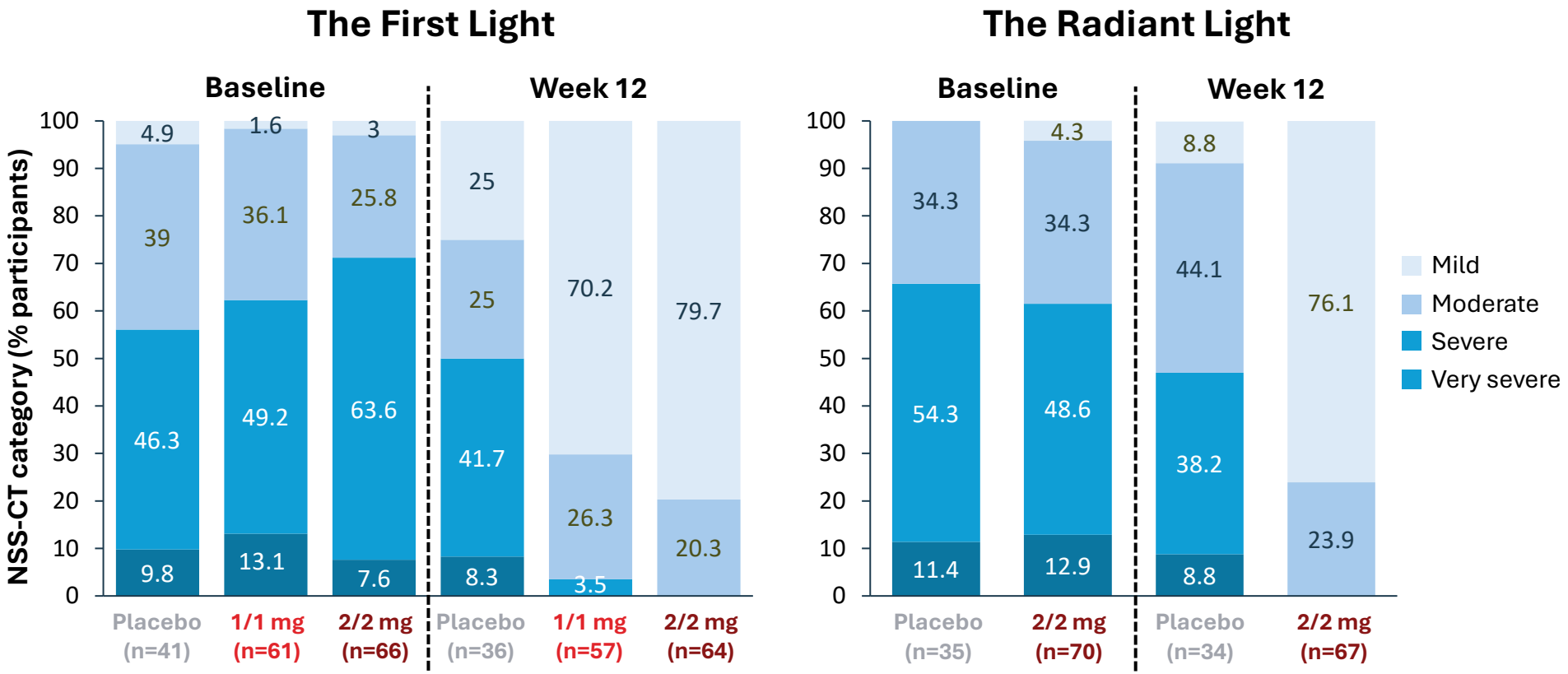
2 mg/2 mg: –18.1 (–21.3 to –15.0)

All P<0.001

LS, least squares.
The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation for missing data.

Most participants achieved mild or moderate symptom severity over 12 weeks of oveporexton

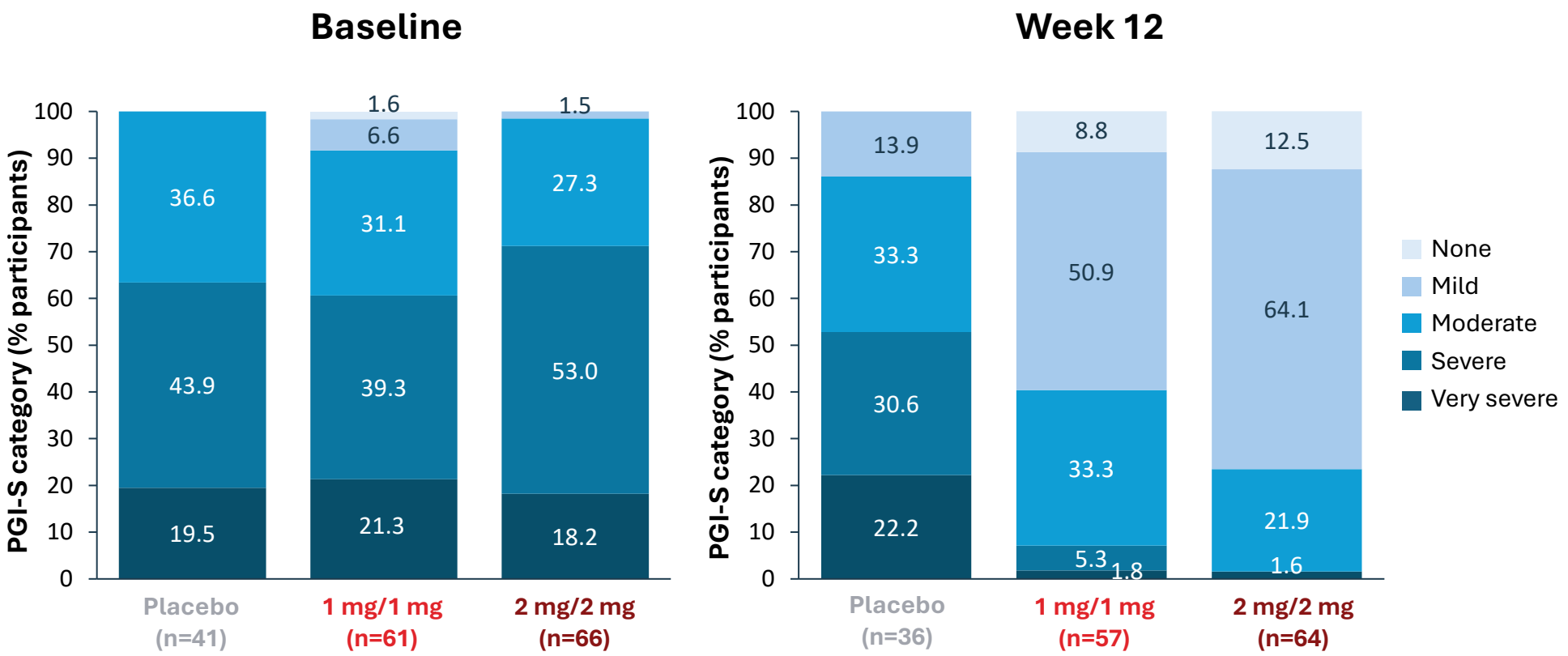
Narcolepsy Severity Scale for Clinical Trials (NSS-CT)



Across both studies, >70% of participants treated with oveporexton had mild symptoms at week 12 versus <25% with placebo.

The First Light: Most oveporexton-treated participants reported no or mild symptoms at week 12 versus placebo

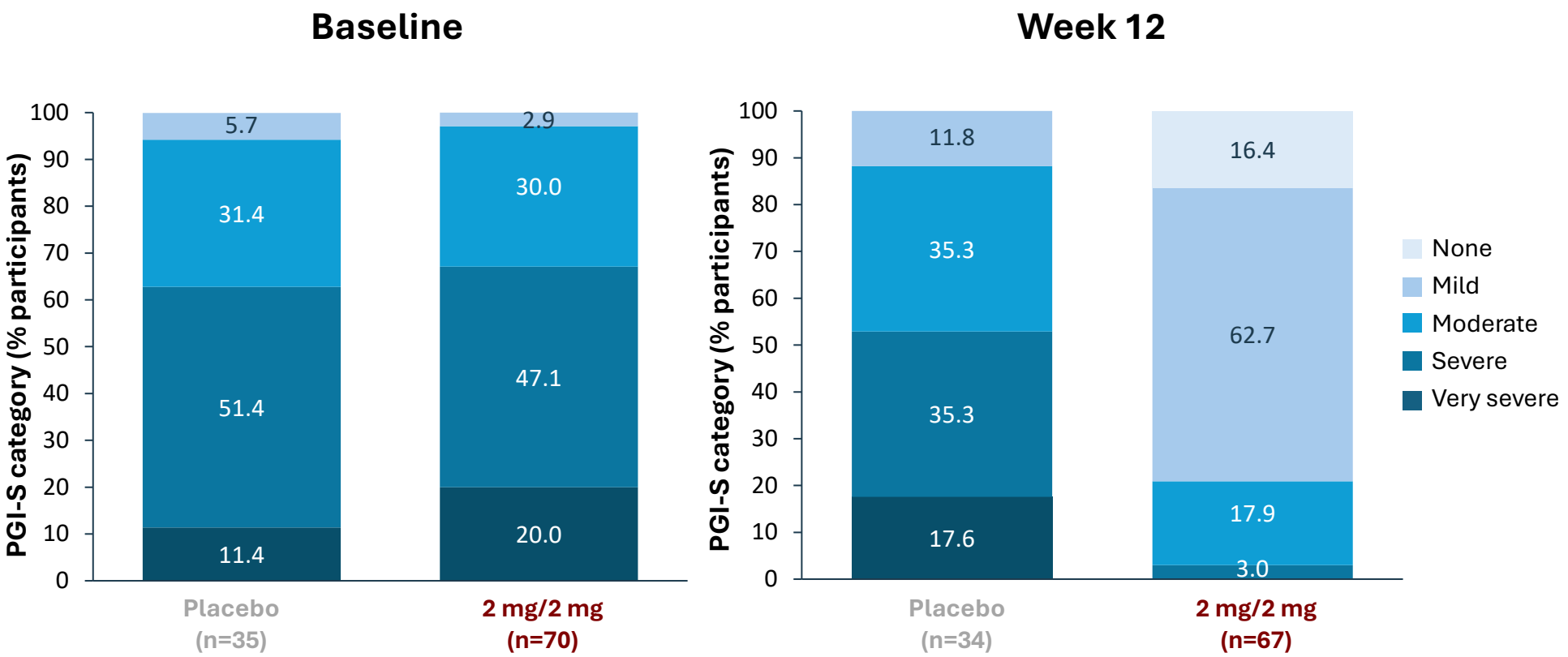
Patient Global Impression of Symptom Severity (PGI-S)



69% of participants treated with oveporexton overall had no or mild symptom severity at week 12 versus 14% with placebo (nominal P-value <0.001 for both doses).

The Radiant Light: Most oveporexton-treated participants reported no or mild symptoms at week 12 versus placebo

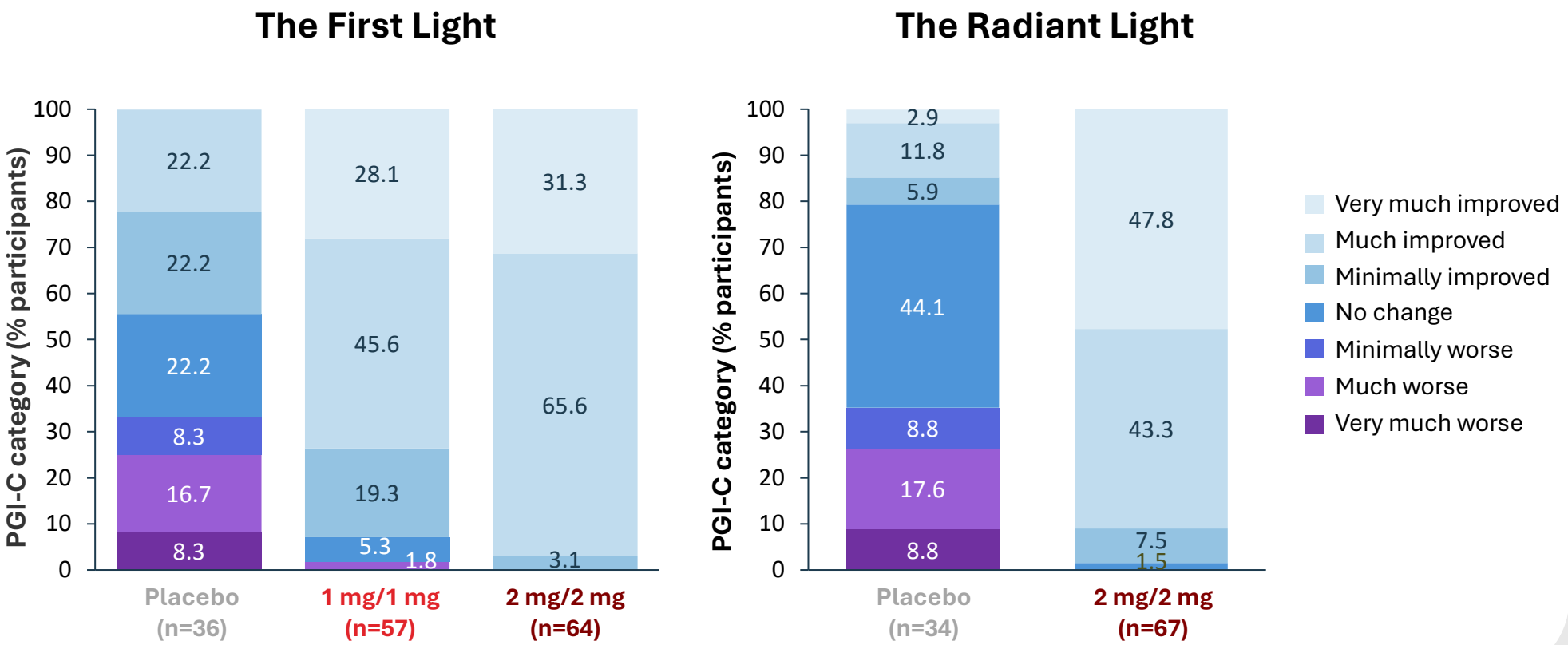
Patient Global Impression of Symptom Severity (PGI-S)



79% of participants treated with oveporexton had no or mild symptom severity at week 12 versus 12% with placebo (nominal P-value <0.001).

Oveporexton resulted in statistically significant improvements in PGI-C at week 12 versus placebo*

Patient Global Impression of Change (PGI-C)



Across both studies, 74–97% of participants treated with oveporexton had much improved or very much improved symptoms at week 12 versus 12-22% with placebo.

*Statistically significant improvements (proportion very much improved or much improved); secondary endpoint.

Oveporexton was generally safe and well tolerated

	The First Light			The Radiant Light	
	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=60)	Oveporexton 2 mg/2 mg (n=66)	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Any TEAE, n (%)	22 (53.7)	52 (86.7)	59 (89.4)	15 (42.9)	60 (85.7)
Mild	14 (34.1)	26 (43.3)	34 (51.5)	9 (25.7)	38 (54.3)
Moderate	7 (17.1)	24 (40.0)	23 (34.8)	5 (14.3)	20 (28.6)
Severe	1 (2.4)	2 (3.3)	2 (3.0)	1 (2.9)	2 (2.9)
Serious TEAE, n (%)	0	1 (1.7)	1 (1.5)	0	0
TEAEs related to study drug, n (%)	9 (22.0)	46 (76.7)	53 (80.3)	3 (8.6)	56 (80.0)
TEAEs leading to study drug discontinuation, n (%)	1 (2.4)	3 (5.0)	0	0	2 (2.9)
Most frequent TEAEs, n (%)					
Urinary frequency	3 (7.3)	32 (53.3)	36 (54.5)	1 (2.9)	43 (61.4)
Insomnia	0	32 (53.3)	38 (57.6)	1 (2.9)	40 (57.1)
Urinary urgency	1 (2.4)	9 (15.0)	12 (18.2)	0	10 (14.3)
Nasopharyngitis	6 (14.6)	6 (10.0)	10 (15.2)	0	0
Headache	5 (12.2)	4 (6.7)	10 (15.2)	2 (5.7)	3 (4.3)
Salivary hypersecretion	0	5 (8.3)	4 (6.1)	0	5 (7.1)

TEAE, treatment-emergent adverse event.

Conclusions

- In **The First Light and The Radiant Light phase 3 studies**, twice-daily 1 mg and 2 mg doses of oral oveporexton significantly improved disease severity as assessed with the NSS-CT, PGI-S, and PGI-C scales versus placebo in participants with NT1 over 12 weeks.
- Oveporexton was generally safe and well tolerated.
- These results are consistent with those from the phase 2 TAK-861-2001 study in participants with NT1 over 8 weeks.[1]

Phase 3 studies confirmed that treatment with oveporexton, an oral orexin receptor 2 agonist, shows improvements across the full NT1 spectrum of symptoms.

NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Symptom Severity.

1. Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

Questions

Singapore 2025
WORLD SLEEP
September 5-10

Sheila Sivam, MD, PhD, Australia

Effect of the oral orexin receptor 2 agonist oveporexton (TAK-861) on quality of life in individuals with NT1 over 12 weeks

Contributors

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Disclosures

Disclosures

- Sheila Sivam has received funding to attend clinical trial related investigator meetings or speaker fees from Avadel, Somnomed, Takeda, Teva, and Vertex Pharmaceuticals.
- Samuel Hsiao, Yeting Du, Heather Romero, and Tina Olsson are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceutical Company Limited.

Acknowledgments

- This work was funded by Takeda Development Center Americas, Inc.
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Background

- In **The First Light** (Europe, Japan, and North America) and **The Radiant Light** (Asia, Australia, and Europe) **phase 3 studies,** twice-daily oral doses of 1 mg and 2 mg oveporexton, an orexin receptor 2 agonist, given at least 3 h apart demonstrated statistically significant and clinically meaningful improvements on measures of wakefulness (MWT), sleepiness (ESS), and cataplexy frequency over 12 weeks versus placebo.
- In **The First Light** and **The Radiant Light phase 3 studies,** oral oveporexton significantly improved disease severity, as assessed with the NSS-CT and PGI-C scales, versus placebo in participants with NT1 over 12 weeks.

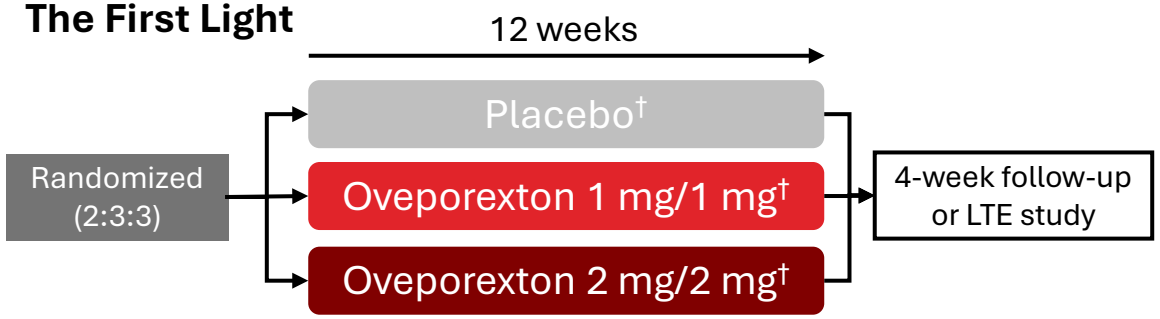
We evaluated the effect of oveporexton (TAK-861) on measures of health-related quality of life (HRQoL) in participants with NT1 from **The First Light and The Radiant Light phase 3 studies**.

ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PGI-C, Patient Global Impression of Change.

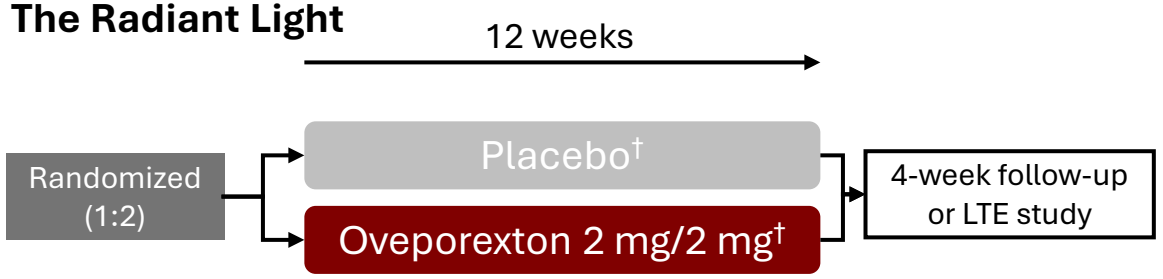
The First Light & The Radiant Light study designs

- 2 randomized, double-blind, placebo-controlled, phase 3 studies of twice-daily oral oveporexton, an orexin receptor 2 agonist, conducted across Asia, Australia, Europe, and North America.

The First Light



The Radiant Light



Inclusion criteria:

- Adults aged 16–70 years
- ICSD-3/ICSD-3 TR diagnosis of NT1 supported by PSG/MSLT or orexin CSF ≤110 pg/mL
- ESS score ≥11
- ≥4 partial/complete episodes of cataplexy per week
- Positive for the HLA genotype HLA-DQB1*06:02 (in the absence of orexin CSF testing)

Selected endpoints		
Secondary	SF-36 MCS/PCS	Change from baseline to week 12
Exploratory	SF-36 domains EQ-5D-5L Index EQ-5D-5L VAS	Change from baseline to week 12

CSF, cerebrospinal fluid; EQ-5D-5L VAS, EuroQol 5-Dimension-5 Level visual analog scale; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; ICSD-3, International Classification of Sleep Disorders, Third Edition; ICSD-3 TR, International Classification of Sleep Disorders, Third Edition, Text Revision; LTE, long-term extension; MSLT, Multiple Sleep Latency Test; PSG, polysomnography; SF-36 MCS/PCS, 36-Item Short Form Mental Component Summary/Physical Component Summary. †Doses were given at least 3 h apart.

Short Form-36 Survey (SF-36)

- SF-36 is a patient-reported assessment of quality of life and overall health status.[1]

- 36 items: 35 items constitute the domain scores, and 1 general health item.
- Norm-based scoring of each domain is based on the US general population: standardized with mean = 50, SD = 10.
- Domain scores range from 0 to 100; higher scores indicate better health.
- 3-point difference between treatment groups is considered clinically meaningful.[2]

Health domain scales	*Items, n*	*Physical Component Summary**	*Mental Component Summary**
Physical Functioning (PF)	10		
Role-Physical (RP)	4		
Bodily Pain (BP)	2		
General Health (GH)	5		
Vitality (VT)	4		
Social Functioning (SF)	2		
Role-Emotional (RE)	3		
Mental Health (MH)	5		

*Some domains contribute questions to both the Physical and Mental Component Summaries.

1. Maruish ME. User's manual for the SF-36v2 Health Survey (3rd ed). Lincoln, RI: QualityMetric Incorporated; 2011. **2.** Maski K, et al. *J Clin Sleep Med* 2021;17:1895-945.

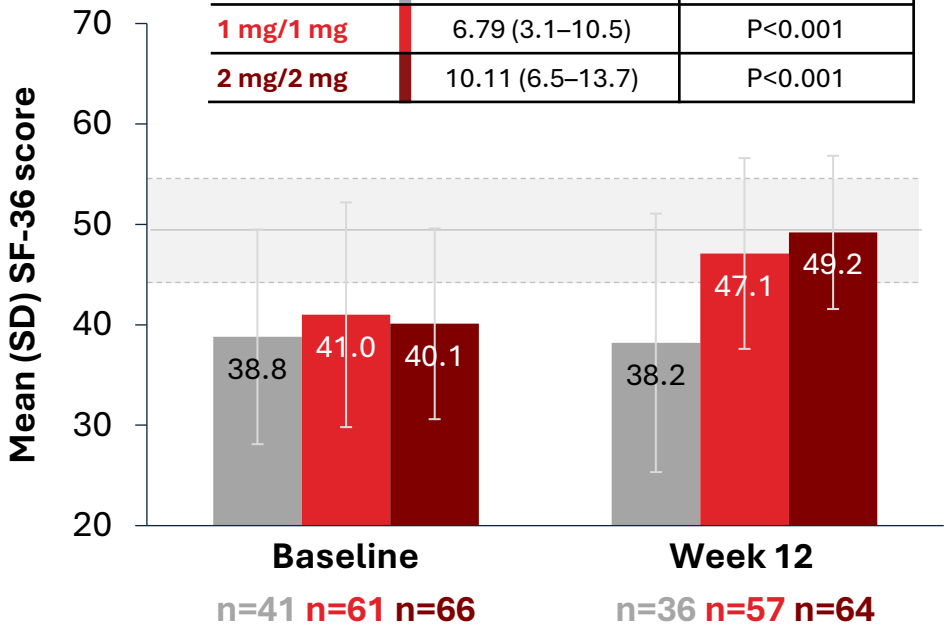
Oveporexton significantly improved patient-reported QoL on the SF-36 Mental Component Summary over 12 weeks

Short Form-36 Survey (SF-36)

The First Light

LS mean difference from placebo in change from baseline at week 12

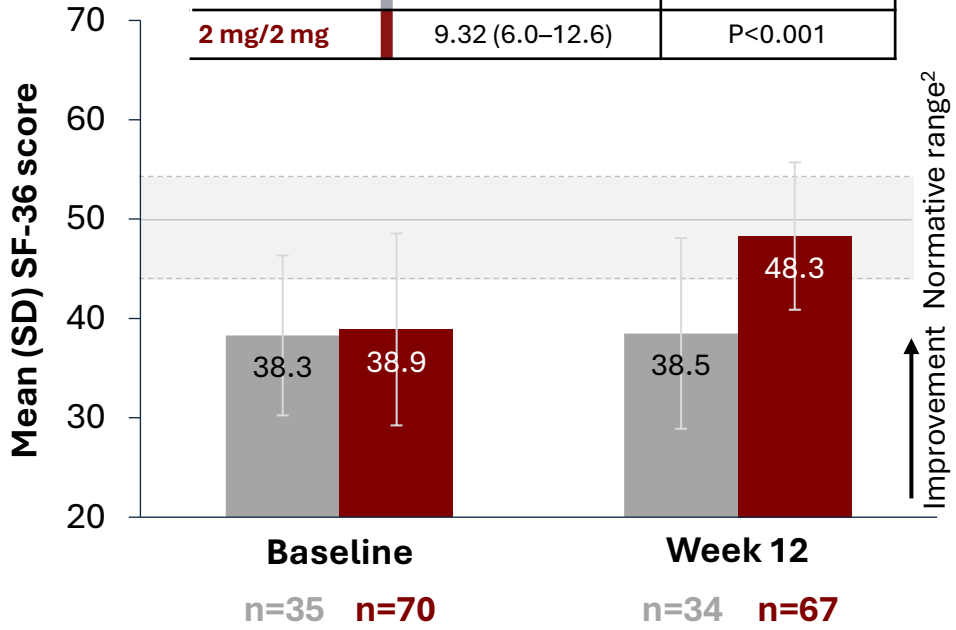
Oveporexton	LS mean (95% CI)	P-value
1 mg/1 mg	6.79 (3.1–10.5)	P<0.001
2 mg/2 mg	10.11 (6.5–13.7)	P<0.001



The Radiant Light

LS mean difference from placebo in change from baseline at week 12

Oveporexton	LS mean (95% CI)	P-value
2 mg/2 mg	9.32 (6.0–12.6)	P<0.001



Placebo Oveporexton 1 mg/1 mg Oveporexton 2 mg/2 mg

Improvements on the SF-36 MCS exceeded the minimum clinically relevant difference of 3 points.[1]

LS, least squares; MCS, Mental Component Summary; QoL, quality of life. The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.

1. Maski K, et al. *J Clin Sleep Med* 2021;17:1895-945. **2.** Maruish ME. User's manual for the SF-36v2 Health Survey (3rd ed). Lincoln, RI: QualityMetric Incorporated; 2011.

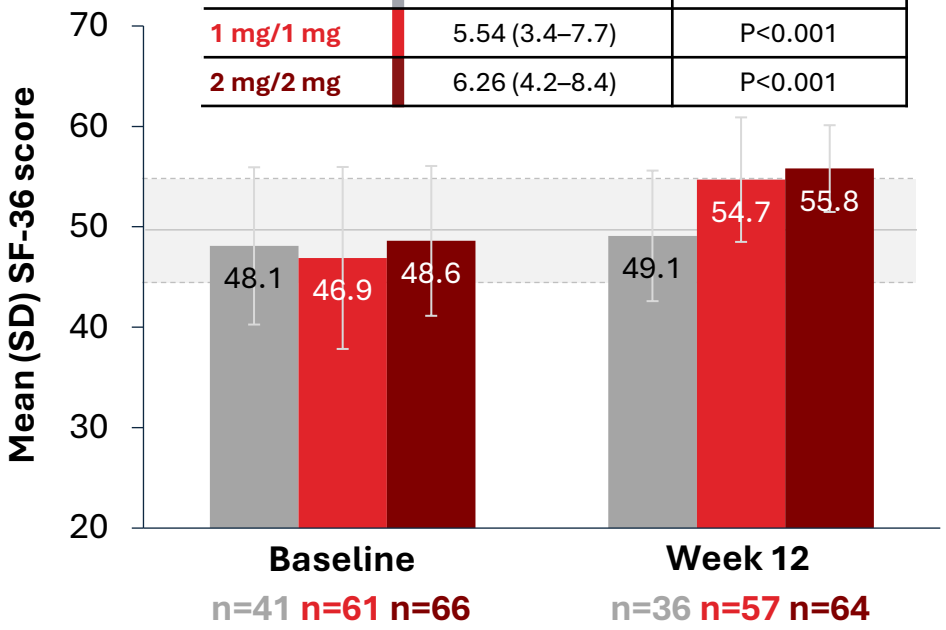
Oveporexton significantly improved patient-reported QoL on the SF-36 Physical Component Summary over 12 weeks

Short Form-36 Survey (SF-36)

The First Light

LS mean difference from placebo in change from baseline at week 12

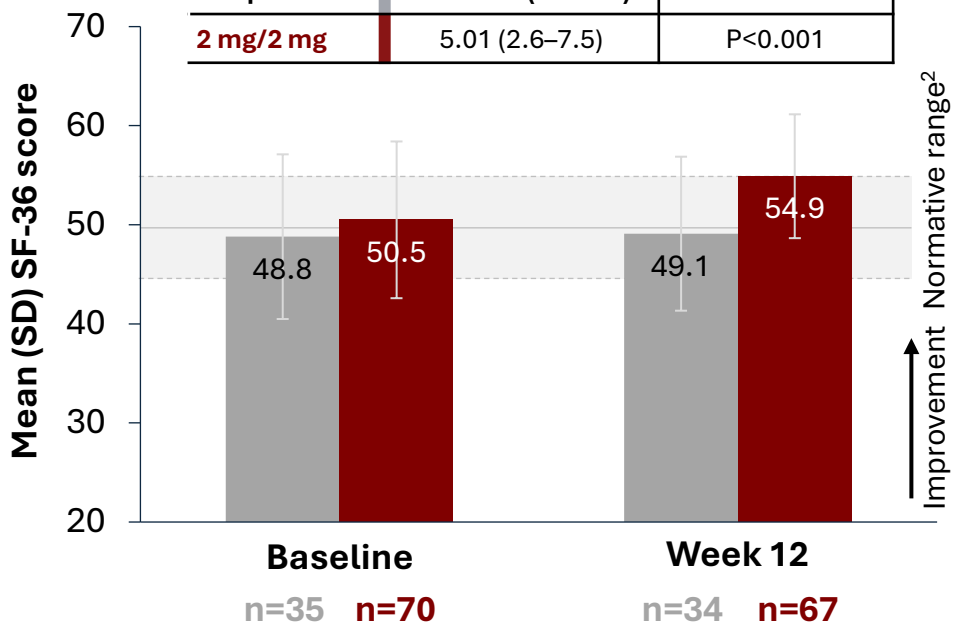
Oveporexton	LS mean (95% CI)	P-value
1 mg/1 mg	5.54 (3.4–7.7)	P<0.001
2 mg/2 mg	6.26 (4.2–8.4)	P<0.001



The Radiant Light

LS mean difference from placebo in change from baseline at week 12

Oveporexton	LS mean (95% CI)	P-value
2 mg/2 mg	5.01 (2.6–7.5)	P<0.001



Placebo Oveporexton 1 mg/1 mg Oveporexton 2 mg/2 mg

Improvements on the SF-36 PCS exceeded the minimum clinically relevant difference of 3 points.[1]

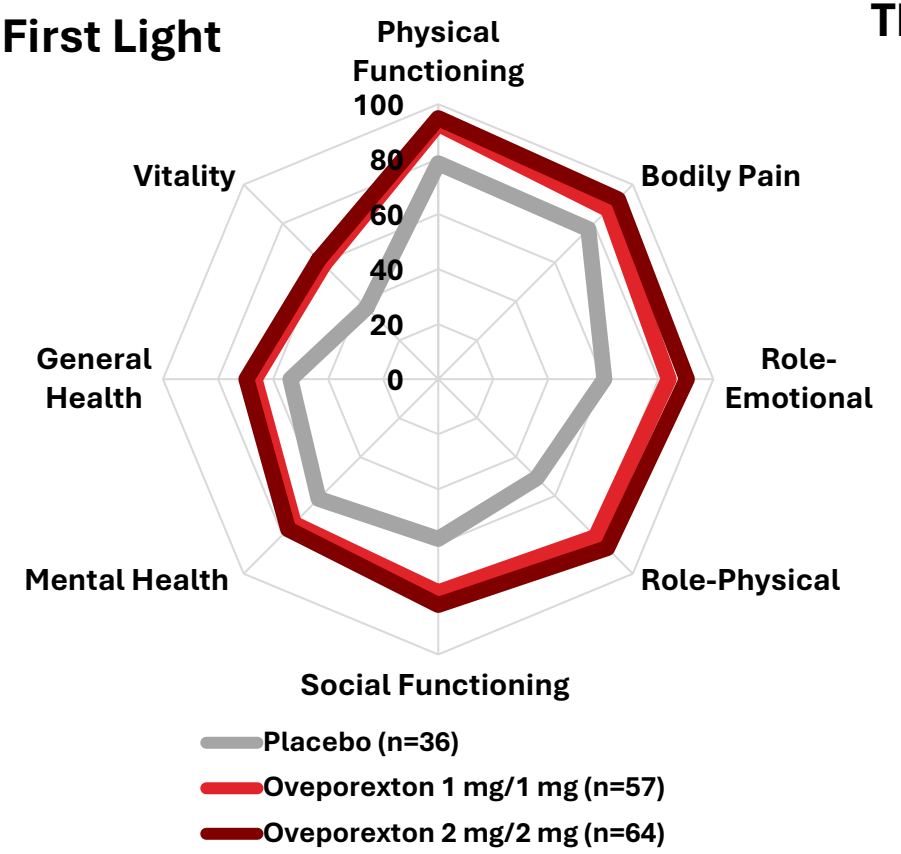
LS, least squares; PCS, Physical Component Summary; QoL, quality of life. The analysis used a linear mixed-effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity.

1. Maski K, et al. *J Clin Sleep Med* 2021;17:1895-945. **2.** Maruish ME. User's manual for the SF-36v2 Health Survey (3rd ed). Lincoln, RI: QualityMetric Incorporated; 2011.

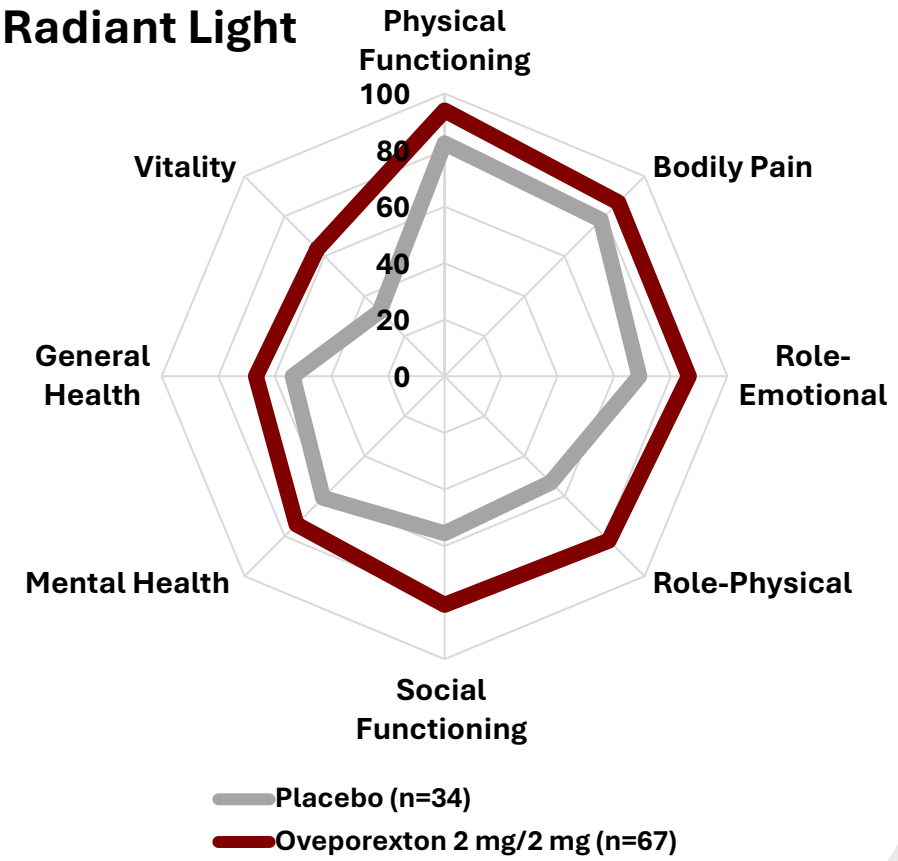
Oveporexton improved SF-36 domain scores over multiple domains at 12 weeks versus placebo in both studies

Short Form-36 Survey (SF-36)

The First Light



The Radiant Light



Changes from baseline to week 12 for nearly all SF-36 domain scores were nominally significant with oveporexton versus placebo (exploratory endpoint).

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

- EQ-5D-5L is a patient-reported assessment of quality of life and overall health status.

- 5 dimensions are rated on 5-point Likert scale, from “No problems” to “Unable/extreme.”
- 1-item VAS scored from 0 (worst health) to 100 (best health).
- A preference-based index score can be generated from the 5 dimensions, yielding a score from 0 (death) to 1.0 (perfect health).
- Mean (SD) normative scores (US population): Index score, 0.85 (0.21); VAS, 80.4 (15.6).[1]

	EQ-5D scores	*Items, n*	*5 severity levels (dimension scores)**
Dimension scores	**Usual Activities**	1	**No problems**
	Self-care	1	**Slight problems**
	Pain/Discomfort	1	**Moderate problems**
	Mobility	1	**Severe problems**
	Anxiety/Depression	1	**Unable/extreme**
VAS	**Self-rated Health**	1	

VAS, visual analog scale. *Categories for Anxiety/Depression domain: not anxious or depressed; slightly anxious or depressed; moderately anxious or depressed; severely anxious or depressed; extremely anxious or depressed. Categories for Pain/Discomfort domain: no pain/discomfort; slight pain/discomfort; moderate pain/discomfort; severe pain/discomfort; extreme pain/discomfort.

1. Jiang R, et al. *Qual Life Res* 2021;30:803-16.

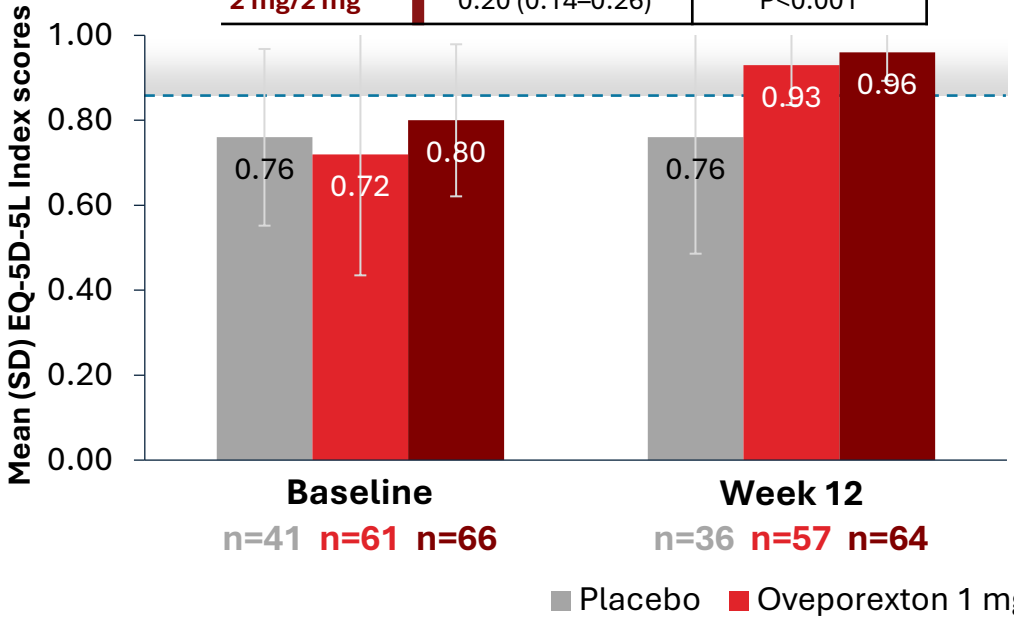
Oveporexton significantly improved patients' EQ-5D-5L Index scores at 12 weeks versus placebo

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The First Light

LS mean difference from placebo in change from BL at week 12

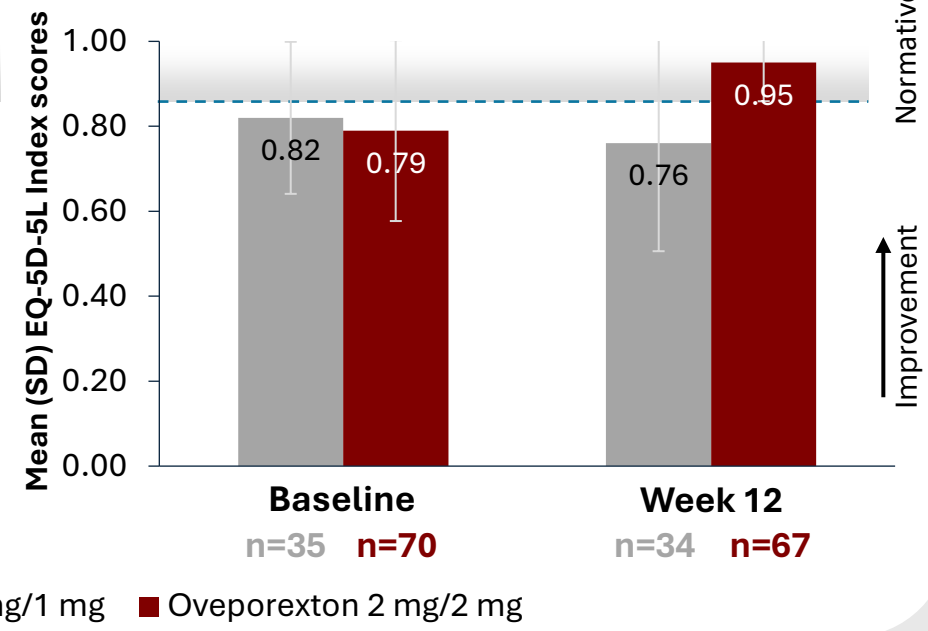
Oveporexton	LS mean (95% CI)	P-value
1 mg/1 mg	0.18 (0.11–0.24)	P<0.001
2 mg/2 mg	0.20 (0.14–0.26)	P<0.001



The Radiant Light

LS mean difference from placebo in change from BL at week 12

Oveporexton	LS mean (95% CI)	P-value
2 mg/2 mg	0.20 (0.13–0.26)	P<0.001



Placebo Oveporexton 1 mg/1 mg Oveporexton 2 mg/2 mg

LS mean difference from placebo in change from baseline to week 12 in **EQ-5D-5L** Index score with oveporexton doses were nominally significant (all **P<0.001**).

Oveporexton treatment resulted in group mean EQ-5D-5L Index scores reaching normative values.

BL, baseline; LS, least squares. The analysis used a linear mixed-effects model for repeated measures with no imputation for missing data. P-values are nominal (not adjusted for multiplicity).

1. Jiang R, et al. *Qual Life Res* 2021;30:803-16.

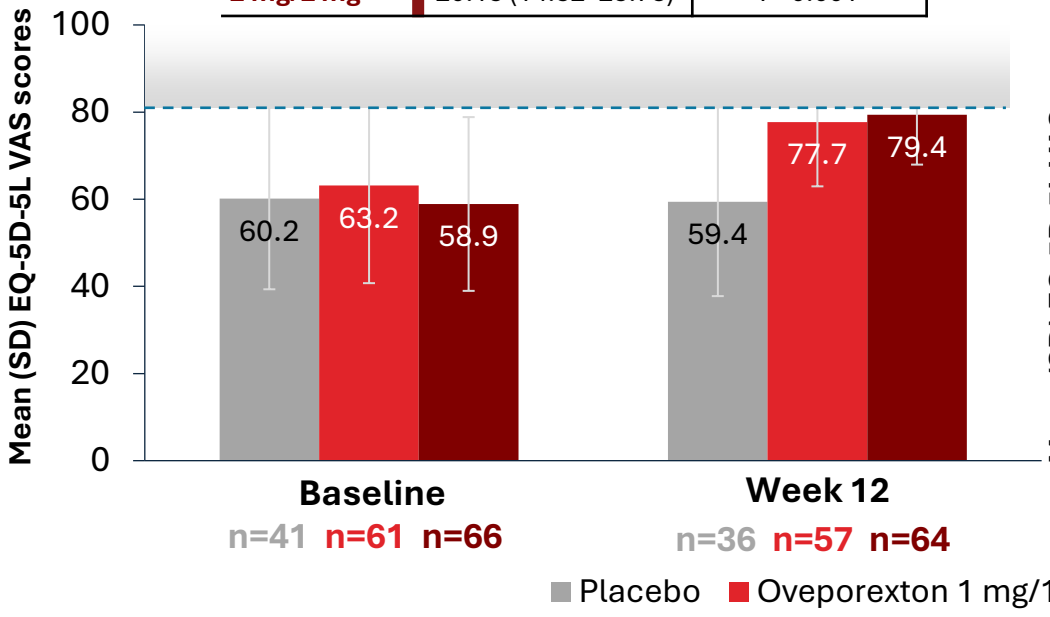
Oveporexton significantly improved patients' self-rated EQ-5D-5L VAS scores at 12 weeks versus placebo

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The First Light

LS mean difference from placebo in change from BL at week 12

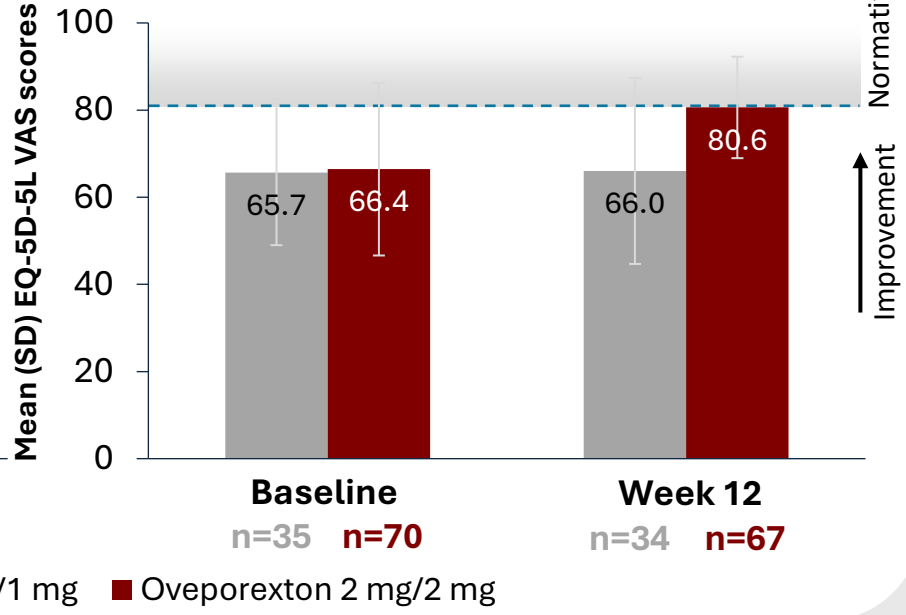
Oveporexton	LS mean (95% CI)	P-value
1 mg/1 mg	16.28 (10.48–22.08)	P<0.001
2 mg/2 mg	20.15 (14.52–25.78)	P<0.001



The Radiant Light

LS mean difference from placebo in change from BL at week 12

Oveporexton	LS mean (95% CI)	P-value
2 mg/2 mg	14.65 (8.93–20.38)	P<0.001



Placebo ■ Oveporexton 1 mg/1 mg ■ Oveporexton 2 mg/2 mg

LS mean difference from placebo in change from baseline to week 12 in **EQ-5D-5L VAS** score with oveporexton doses were nominally significant (all **P<0.001**).

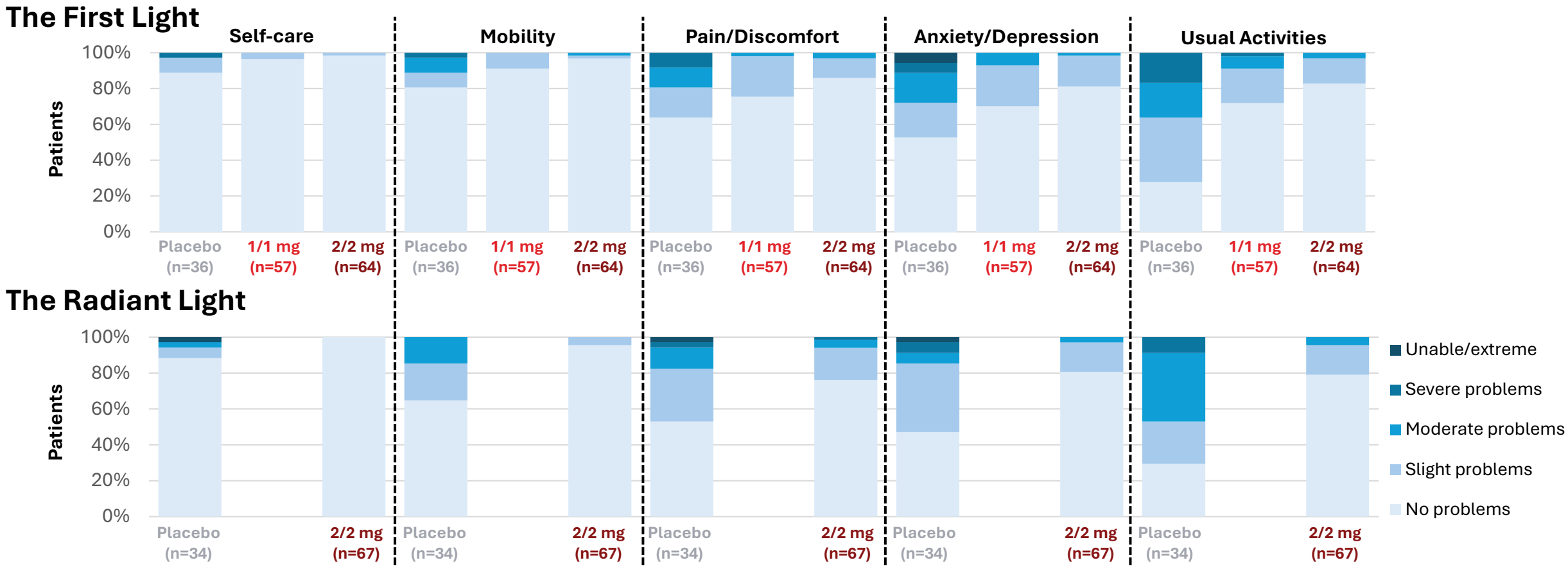
Oveporexton treatment resulted in group mean EQ-5D-5L VAS scores approaching or achieving normative values.

BL, baseline; LS, least squares; VAS, visual analog scale. The analysis used a linear mixed-effects model for repeated measures with no imputation for missing data. P-values are nominal (not adjusted for multiplicity).

1. Jiang R, et al. *Qual Life Res* 2021;30:803-16.

Oveporexton improved patients' self-rated EQ-5D-5L domain scores at 12 weeks versus placebo

EuroQol-5 Dimension-5 Level (EQ-5D-5L)



EQ-5D-5L, EuroQol-5 Dimension-5 Level.
Categories for Anxiety/Depression domain: not anxious or depressed; slightly anxious or depressed; moderately anxious or depressed; severely anxious or depressed; extremely anxious or depressed.
Categories for Pain/Discomfort domain: no pain/discomfort; slight pain/discomfort; moderate pain/discomfort; severe pain/discomfort; extreme pain/discomfort.

Oveporexton was generally safe and well tolerated

	The First Light			The Radiant Light	
	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=60)	Oveporexton 2 mg/2 mg (n=66)	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Any TEAE, n (%)	22 (53.7)	52 (86.7)	59 (89.4)	15 (42.9)	60 (85.7)
Mild	14 (34.1)	26 (43.3)	34 (51.5)	9 (25.7)	38 (54.3)
Moderate	7 (17.1)	24 (40.0)	23 (34.8)	5 (14.3)	20 (28.6)
Severe	1 (2.4)	2 (3.3)	2 (3.0)	1 (2.9)	2 (2.9)
Serious TEAE, n (%)	0	1 (1.7)	1 (1.5)	0	0
TEAEs related to study drug, n (%)	9 (22.0)	46 (76.7)	53 (80.3)	3 (8.6)	56 (80.0)
TEAEs leading to study drug discontinuation, n (%)	1 (2.4)	3 (5.0)	0	0	2 (2.9)
Most frequent TEAEs, n (%)					
Urinary frequency	3 (7.3)	32 (53.3)	36 (54.5)	1 (2.9)	43 (61.4)
Insomnia	0	32 (53.3)	38 (57.6)	1 (2.9)	40 (57.1)
Urinary urgency	1 (2.4)	9 (15.0)	12 (18.2)	0	10 (14.3)
Nasopharyngitis	6 (14.6)	6 (10.0)	10 (15.2)	0	2 (2.9)
Headache	5 (12.2)	4 (6.7)	10 (15.2)	2 (5.7)	3 (4.3)
Salivary hypersecretion	0	5 (8.3)	4 (6.1)	0	5 (7.1)

TEAE, treatment-emergent adverse event.

Conclusions

- In **The First Light and The Radiant Light phase 3 studies,** twice-daily 1 mg and 2 mg doses of oral oveporexton showed significant improvements in HRQoL over 12 weeks versus placebo in participants with NT1.
- Oveporexton was generally safe and well tolerated.
- These results are consistent with those from the phase 2 TAK-861-2001 study in participants with NT1 over 8 weeks.[1]

These findings supplement primary and secondary results from the phase 3 trials and indicate that oveporexton, an oral orexin receptor 2 agonist, has the potential of transformational benefit to people with NT1.

EDS, excessive daytime sleepiness; HRQoL, health-related quality of life; NT1, narcolepsy type 1.

1. Dauvilliers Y, et al. *N Engl J Med* 2025;392:1905-16.

Questions