ORIGINAL ARTICLE

Oveporexton, an Oral Orexin Receptor 2–Selective Agonist, in Narcolepsy Type 1

Yves Dauvilliers, M.D.,[1,2] Giuseppe Plazzi, M.D.,[3,4] Emmanuel Mignot, M.D.,[5] Gert Jan Lammers, M.D.,[6,7] Rafael del Río Villegas, M.D., Ph.D.,[8,9] Ramin Khatami, M.D.,[10,11] Mitsutaka Taniguchi, M.D.,[12] Anson Abraham, Ph.D.,[13] Yaming Hang, Ph.D.,[13] Harisha Kadali, M.D.,[13] Marta Lamberton, B.S.Engr.,[13] Sarah Sheikh, B.M., B.Ch.,[13] Ellie Stukalin, Ph.D.,[13] Rachel Neuwirth, M.S.,[13] Todd J. Swick, M.D.,[13] Shinichiro Tanaka, Ph.D.,[13] Christian von Hehn, M.D., Ph.D.,[13] Philipp von Rosenstiel, M.D.,[13] Hao Wang, Ph.D.,[13] Alice Cai, M.D.,[13] Melissa Naylor, M.D., Ph.D.,[13] and Tina Olsson, Ph.D.[13]

ABSTRACT

BACKGROUND

Narcolepsy type 1 is a disorder of hypersomnolence caused by a loss of orexin neurons, which results in low orexin levels in the brain.

METHODS

In this phase 2, randomized, placebo-controlled trial, participants with narcolepsy type 1 received once- or twice-daily oveporexton (TAK-861), an oral orexin receptor 2–selective agonist, or placebo. The primary end point was the mean change from baseline to week 8 in average sleep latency (the time it takes to fall asleep) on the Maintenance of Wakefulness Test (MWT) (range, 0 to 40 minutes; normal, ≥20). Secondary end points included the change from baseline to week 8 in the Epworth Sleepiness Scale (ESS) total score (range, 0 to 24; normal, ≤10), the weekly cataplexy rate at week 8, and the occurrence of adverse events.

RESULTS

A total of 90 participants received oveporexton (0.5 mg twice daily, 23 participants; 2 mg twice daily, 21 participants; 2 mg followed by 5 mg daily, 23 participants; and 7 mg once daily, 23 participants), and 22 received placebo. The mean changes from baseline to week 8 in average sleep latency on the MWT were 12.5, 23.5, 25.4, 15.0, and –1.2 minutes, respectively (adjusted $P \leq 0.001$ for all comparisons vs. placebo). The mean changes in the ESS total score at week 8 were –8.9, –13.8, –12.8, –11.3, and –2.5, respectively (adjusted $P \leq 0.004$ for all comparisons vs. placebo). The weekly incidence of cataplexy at week 8 was 4.24, 3.14, 2.48, 5.89, and 8.76, respectively (adjusted $P < 0.05$ for 2 mg twice daily and 2 mg followed by 5 mg daily vs. placebo). The most common adverse events associated with oveporexton were insomnia (in 48% of the participants; most cases resolved within 1 week), urinary urgency (in 33%), and urinary frequency (in 32%), without any hepatotoxic effects.

CONCLUSIONS

In this phase 2 trial involving participants with narcolepsy type 1, oveporexton significantly improved measures of wakefulness, sleepiness, and cataplexy over a period of 8 weeks. (Funded by Takeda Development Center Americas; TAK-861-2001 ClinicalTrials.gov number, NCT05687903.)

Author affiliations are listed at the end of the article. Dr. Olsson can be contacted at tina.olsson@takeda.com or at Takeda Development Center Americas, 500 Kendall St., Cambridge, MA 02142.

A list of the investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Dauvilliers and Plazzi contributed equally to this article.

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Narcolepsy type 1 is a disorder of hypersomnolence defined by excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, hypnagogic or hypnopompic hallucinations, sleep paralysis, and markedly reduced quality of life.[1-3] The disorder is characterized by loss of hypothalamic orexin-producing neurons, with low to absent orexin levels in cerebrospinal fluid.[1,4,5] Orexins act through two G-protein–coupled receptors, orexin receptor 1 and orexin receptor 2 (OX2R), with overlapping but distinct distributions within the brain.[6,7] Although both receptors have roles in a range of physiological responses,[8-10] OX2R has functions in wakefulness, rapid-eye-movement (REM) sleep, and prevention of cataplexy in animal models of narcolepsy.[10,11]

Available treatments do not target pathways underlying the pathophysiological features of narcolepsy type 1 but instead aim to increase daytime wakefulness and reduce cataplexy. Preclinical and clinical evidence with an intravenous OX2R agonist, danavorexton (TAK-925),[12,13] and an oral OX2R agonist, TAK-994,[14] support the potential for OX2R-selective agonists as treatments for narcolepsy. In participants with narcolepsy type 1, danavorexton promoted wakefulness,[15] and TAK-994 improved measures of wakefulness and cataplexy as compared with placebo over a period of 8 weeks.[14] However, TAK-994 was associated with hepatotoxic effects in three cases (all with a dose of 90 mg or 180 mg twice daily), effects that were thought to be unrelated to OX2R stimulation.[14]

Oveporexton (TAK-861) is a highly selective oral OX2R agonist that crosses the blood–brain barrier and has been shown to improve wakefulness in preclinical models[16,17] and in sleep-deprived healthy adults.[18] We tested the efficacy and safety of oveporexton for the treatment of narcolepsy type 1 in a phase 2, double-blind, randomized, placebo-controlled trial.

Materials and Methods

Trial Design and Oversight

The TAK-861-2001 trial was approved by regulatory authorities in each country and the institutional review board or ethics committee at each site and was performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation E6 guidelines for Good Clinical Practice. All the participants provided written informed consent. The sponsor, Takeda Development Center Americas, in collaboration with the authors, designed the trial and gathered, analyzed, and interpreted the data. The first author and next-to-last author wrote the first draft of the manuscript with professional medical writing assistance funded by the sponsor. The sponsor also provided funding for editorial assistance. All the authors provided critical review, contributed to subsequent drafts, and approved submission of the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). All the authors signed a confidentiality disclosure agreement with the sponsor.

Trial Design

TAK-861-2001 was a phase 2, double-blind, randomized, placebo-controlled trial involving persons with narcolepsy type 1 that was conducted in North America (United States), Europe, Asia (Japan), and Australia (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Participants were randomly assigned with the use of interactive response technology in a 1:1:1:1:1 ratio to receive once- or twice-daily oral oveporexton or matching placebo, administered 3 hours apart (at 8 a.m. and 11 a.m.), for 8 weeks: 0.5 mg twice daily, 2 mg twice daily, 2 mg followed by 5 mg daily, 7 mg followed by placebo daily, or placebo twice daily. Randomization was stratified according to geographic region (United States, Europe, or Asia–Pacific). The randomization schedule was generated by a third-party interactive response technology vendor with a block size of 5.

Participants

The trial included adults 18 to 70 years of age with a diagnosis of narcolepsy type 1 that was made in accordance with the criteria of the International Classification of Sleep Disorders, Third Edition,[2] and confirmed by nocturnal polysomnography and a Multiple Sleep Latency Test performed within the previous 10 years. Participants also had a baseline Epworth Sleepiness Scale (ESS) total score of more than 12 (range, 0 to 24, with higher scores indicating greater daytime sleepiness; normal, ≤10), at least

four episodes of partial or complete cataplexy per week during screening (2-week average), and either a cerebrospinal fluid orexin-A or hypocretin-1 concentration of less than 110 pg per milliliter (where tested) or a positive test for HLA genotype HLA-DQB1*06:02, to ensure a high likelihood of orexin deficiency in the presence of cataplexy.[19] Participants agreed to discontinue restricted medications and drugs used to treat narcolepsy type 1, if applicable. Participants with medically significant liver disease were excluded. Additional inclusion and exclusion criteria are provided in the Supplementary Methods section of the Supplementary Appendix.

END POINTS

The primary end point was the mean change from baseline to week 8 in average sleep latency on the 40-minute Maintenance of Wakefulness Test (MWT), a measure in minutes of a person's ability to stay awake under soporific conditions.[20] Healthy persons stay awake for 20 minutes or more,[21] as compared with less than 10 minutes for persons with narcolepsy type 1.[22] At baseline, week 4, and week 8, sleep latencies were measured in four MWT sessions at 2, 4, 6, and 8 hours after the 8 a.m. dose (after the 8 a.m. at baseline). The MWT was performed at trial sites; all site personnel received standardized MWT training from a third-party vendor (Clinilabs), which received the MWT data and performed scoring in a blinded manner.

Secondary efficacy end points were the change from baseline to week 8 in the ESS total score and the weekly cataplexy rate at week 8. The ESS total score was assessed at screening, baseline, and weeks 2, 4, and 8. The weekly cataplexy rate was assessed through completion of an electronic participant-reported outcome diary. The number of cataplexy episodes was averaged over a period of 2 weeks before the first dose and every 2 weeks thereafter. To assess the effect across narcolepsy symptoms, changes in scores on the Narcolepsy Severity Scale for Clinical Trials (NSS-CT)[23] were evaluated at baseline and weeks 4 and 8 as an exploratory end point. The NSS-CT is a self-administered, 15-item scale that assesses the severity, frequency, and effect of five key narcolepsy symptoms: excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed nighttime sleep (range, 0 to 57, with higher scores indicating greater severity) (see the Supplementary Methods). Nocturnal polysomnography preceding each MWT and electronic-diary data were used to assess sleep symptoms. The 36-Item Short Form Survey (SF-36) was used to assess quality of life.[24] Additional exploratory end points are listed in the Supplementary Methods.

The occurrence of adverse events with an onset on or after the first dose of oveporexton or placebo was assessed as a secondary end point. Additional safety end points included laboratory values, vital signs, blood pressure and heart rate (including 24-hour ambulatory blood-pressure monitoring at baseline and week 6), and Columbia Suicide Severity Rating Scale (C-SSRS) score. Specifications for liver-function tests are provided in the Supplementary Methods.

STATISTICAL ANALYSIS

We estimated that a sample size of 16 participants per trial group would provide adequate power to detect a 14-minute difference in the mean change from baseline in average sleep latency on the MWT (with >90% power), an 8-point difference in the mean change from baseline in the ESS total score (with 88% power), and a 0.50 incidence rate ratio for the weekly cataplexy rate (with 86% power) between each oveporexton dose group and the placebo group. Calculations assumed standard deviations of 11 minutes (MWT) and 7 points (ESS total score) and were based on a two-sample t-test. For the weekly cataplexy rate, calculations were based on a test of the incidence rate ratio that assumed Poisson counts. All calculations were based on a 5% two-sided significance level. To allow for a 20% dropout rate, we planned to enroll 20 participants per group.

Efficacy and safety analyses were conducted in participants who had undergone randomization and received at least one dose of oveporexton or placebo. The primary analyses for MWT, ESS, and NSS-CT used linear mixed-effects models for repeated measures. The primary analysis for the weekly cataplexy rate used a negative binomial generalized estimating equation model with a logarithm link function to estimate incidence rate ratios between active treatment and placebo. In both cases, the following fixed effects were included: baseline age, previous use of narcolepsy medication (yes or no), baseline value of the respective end point, visit, dose group,

Table 1. Demographic, Clinical, and Biologic Characteristics of the Participants.*

Characteristic	Placebo (N=22)	Oveporexton, 0.5 mg Twice Daily (N=23)	Oveporexton, 2 mg Twice Daily (N=21)	Oveporexton, 2 mg and 5 mg Daily (N=23)	Oveporexton, 7 mg Once Daily (N=23)	Total (N=112)
Age — yr						
Mean	37.5±11.9	32.7±11.1	31.7±11.3	34.7±11.5	33.3±11.9	34.0±11.5
Median (range)	38.0 (19–58)	33.0 (18–59)	32.0 (18–53)	35.0 (18–58)	32.0 (18–57)	34.0 (18–59)
Sex — no. (%)						
Male	8 (36)	12 (52)	12 (57)	9 (39)	13 (57)	54 (48)
Female	14 (64)	11 (48)	9 (43)	14 (61)	10 (43)	58 (52)
Race — no. (%)†						
Asian	1 (5)	2 (9)	0	3 (13)	2 (9)	8 (7)
Black	2 (9)	1 (4)	2 (10)	0	1 (4)	6 (5)
White	19 (86)	19 (83)	19 (90)	19 (83)	20 (87)	96 (86)
Multiple	0	1 (4)	0	1 (4)	0	2 (2)
Average sleep latency on MWT — min‡						
Mean	6.1±8.8	5.6±7.9	3.9±6.0	4.2±3.6	3.6±4.9	4.7±6.5
Median (range)	2.0 (0.5–32.0)	2.3 (0.5–29.0)	1.8 (0.3–26.4)	2.8 (0.1–14.6)	2.5 (0.1–19.6)	2.5 (0.1–32.0)
ESS total score§						
Mean	18.6±2.7	18.3±3.4	19.0±3.1	18.6±3.0	18.0±3.0	18.5±3.0
Median (range)	19.0 (12.0–23.0)	19.0 (11.0–24.0)	19.0 (14.0–24.0)	19.0 (14.0–23.0)	18.0 (12.0–24.0)	19.0 (11.0–24.0)
Weekly cataplexy rate — no. of episodes						
Mean	23.1±25.7	18.6±16.9	21.0±30.0	15.7±13.5	31.1±29.1	21.9±24.0
Median (range)	13.3 (5.0–100.9)	11.0 (2.7–71.0)	11.3 (1.2–130.5)	9.5 (4.0–53.5)	20.0 (7.0–107.5)	12.0 (1.2–130.5)
NSS-CT total score¶						
Mean	32.5±9.3	30.2±9.8	28.8±9.5	28.7±8.3	33.5±6.9	30.7±8.9
Median (range)	30.0 (18–50)	32.0 (14–52)	26.0 (14–53)	27.0 (12–48)	33.0 (22–48)	30.0 (12–53)

Liver-function tests at baseline						
ALT — U/liter	23.6±12.7	19.5±10.0	22.4±12.2	20.0±9.3	21.8±11.5	21.4±11.1
AST — U/liter	21.2±7.4	19.0±6.6	19.9±8.3	19.1±6.9	17.3±4.8	19.3±6.9
Bilirubin — μmol/liter	7.2±7.6	7.3±5.1	8.5±6.9	6.8±4.3	6.1±2.8	7.1±5.4
GGT — U/liter	21.7±17.6	19.1±14.6	19.4±10.1	30.4±33.5	16.9±7.7	21.5±19.4

* Plus–minus values are means ±SD. In all groups, doses were administered at 8 a.m. and 11 a.m. each day for 8 weeks (in the once-daily oveporexton group, participants received 7 mg of oveporexton at 8 a.m. and placebo at 11 a.m). ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and GGT γ-glutamyltransferase.
† Race was reported by the participant.
‡ Values on the Maintenance of Wakefulness Test (MWT) range from 0 to 40 minutes (normal ability to stay awake, ≥20).[21]
§ Total scores on the Epworth Sleepiness Scale (ESS) range from 0 to 24, with higher scores indicating greater daytime sleepiness (normal, ≤10).[26]
¶ Total scores on the Narcolepsy Severity Scale for Clinical Trials (NSS-CT) range from 0 to 57, with higher scores indicating greater severity of narcolepsy symptoms.[23,27]

and dose-group-by-visit interaction. To adjust for multiplicity and provide strong control of the familywise error rate, the graphical approach of Bretz et al.[25] was used in testing the primary and secondary efficacy end points (see the Supplementary Methods). Adjusted P values are presented for analyses of sleep latency on the MWT, ESS total score, and weekly cataplexy rate. Unadjusted confidence intervals are presented for additional analyses and should not be used to infer definitive treatment effects.

Analyses were performed with the use of SAS software, version 9.4. No imputation for missing data was performed (see the Supplementary Methods).

RESULTS

PARTICIPANT CHARACTERISTICS

Participants underwent randomization between February 8, 2023, and October 18, 2023. Of 161 participants screened, 112 underwent randomization and received at least one dose of oveporexton (0.5 mg twice daily, 23 participants; 2 mg twice daily, 21 participants; 2 mg followed by 5 mg daily, 23 participants; and 7 mg once daily, 23 participants) or placebo (22 participants). A total of 109 participants (97%) completed the trial, and 3 (3%) discontinued prematurely, all owing to protocol deviations (Fig. S2). Participants had a mean age of 34 years, and 52% were women. Baseline characteristics were similar across trial groups, except for a higher weekly cataplexy rate in the 7-mg group (Table 1),[26,27] and were generally representative of the broader population of persons affected by narcolepsy type 1 (Table S1).

EFFICACY

A total of 104 participants had evaluable data for the primary end point at 8 weeks (5 participants did not have the required three of four MWT sessions at baseline [1 participant] or week 8 [4 participants]). Average sleep latency on the MWT changed from 3.6 to 5.6 minutes at baseline across oveporexton doses to 16.5 to 30.7 minutes at week 8 in a dose-dependent manner, as compared with a change from 6.1 minutes at baseline to 4.7 minutes at week 8 with placebo (Fig. 1A). Least-squares mean differences in the mean change from baseline to week 8 as compared with placebo were 13.7 to 26.6 minutes

across oveporexton doses (adjusted P≤0.001 for all comparisons) (Table 2 and Fig. S3). After 8 weeks, 37 to 81% of participants in the oveporexton groups had an average sleep latency on the MWT of 20 minutes or more (the duration in healthy persons[21]), as compared with 5% of the participants in the placebo group (Table 2).

Dose-dependent decreases in mean ESS total scores were observed with oveporexton, decreasing from 18.0 to 19.0 at baseline to 4.8 to 8.9 at week 8, as compared with a change from 18.6 at baseline to 16.0 at week 8 with placebo (Fig. 1B). Least-squares mean differences in the change from baseline to week 8 in ESS total scores as compared with placebo were −6.4 to −11.3 (adjusted P<0.005 for all comparisons) (Table 2). Of participants receiving oveporexton, 67 to 95% had an ESS total score of 10 or lower at week 8, as compared with 19% of the participants in the placebo group (Table 2).

The mean weekly cataplexy rate decreased in a dose-dependent manner from 15.7 to 31.1 episodes at baseline to 2.1 to 10.1 episodes at week 8 with oveporexton, as compared with 23.1 episodes at baseline to 9.0 episodes at week 8 with placebo (Fig. 1C). After 8 weeks, incidence rate ratios (oveporexton vs. placebo) decreased with increasing twice-daily oveporexton doses, reaching significance in the groups taking 2 mg twice daily and 2 mg followed by 5 mg daily (Table 2).

Mean NSS-CT total scores improved from 28.7 to 33.5 at baseline to 8.1 to 14.5 at week 8 with oveporexton, as compared with a change from 32.5 at baseline to 26.8 at week 8 with placebo (Fig. 1D). Least-squares mean differences in the change from baseline to week 8 as compared with placebo were −13.7 to −17.6 with oveporexton doses, exceeding the clinically meaningful threshold of 8 points between untreated and treated patients[23] (Table 2). At week 8, a total of 65 to 91% of the participants reported mild disease (scores of 0 to 14) on the NSS-CT with oveporexton, as compared with 10% with placebo. NSS-CT domain scores indicated marked improvements across most domains (excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis) (Table S2).

Improvements in sleep latency on the MWT, ESS total score, weekly cataplexy rate, and NSS-CT total score appeared at the earliest assessed time points. These improvements were maintained to week 8 (Fig. 1).

Nocturnal polysomnography and electronic-diary findings were supportive of improved sleep characteristics and symptoms. Nocturnal polysomnography data showed that treatment with oveporexton led to a mean increase in REM latency of 32 minutes, without increasing nocturnal wakefulness. Total time in stage N3 sleep, time awake after sleep onset, and sleep-onset latency were not changed with oveporexton at any dose as compared with placebo (Table S3). Reductions in participant-reported disturbing dreams, sleep paralysis, and hypnagogic hallucinations were reported (Fig. S4).

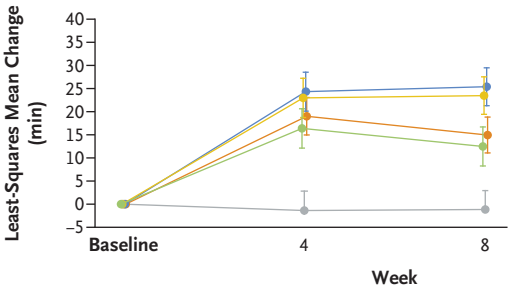
Clinically meaningful improvements in quality of life were observed with all oveporexton doses as compared with placebo at weeks 4 and 8 for the SF-36 mental component summary score. A clinically meaningful improvement was also observed at week 8 for the SF-36 physical component summary score (Fig. S5).

SAFETY

A total of 77 of 112 participants (69%) had at least one adverse event: 70 of 90 (78%) with oveporexton and 7 of 22 (32%) with placebo (Table 3). The most common adverse events with oveporexton were insomnia (48%), increased urinary urgency (33%), and increased urinary frequency (32%). Most cases of insomnia resolved within 1 week, as corroborated by sleep-diary responses relating to problems falling asleep (Fig. S6). Most adverse events with oveporexton were mild to moderate as judged by investigators; 7 participants had at least one severe adverse event (Table 3). One serious adverse event, ankle fracture, was considered by the investigator to be unrelated to oveporexton or placebo. No participants discontinued the trial because of an adverse event (Table 3). No participants reported suicidal behavior or ideation on the C-SSRS. Ambulatory blood-pressure monitoring revealed no marked changes in 24-hour mean blood pressure or heart rate; the least-squares mean change from baseline in blood pressure was less than 2 mm Hg at week 6 for all oveporexton doses (Fig. S7).

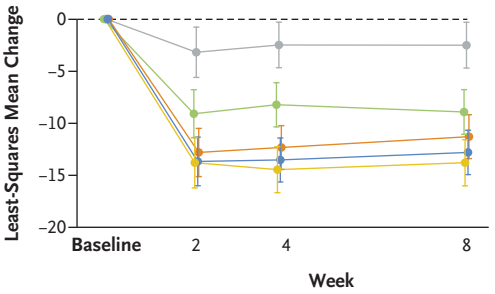
No hepatotoxic effects attributable to oveporexton were reported, and no clinically significant trends were noted in urinalysis variables. A total of 8 participants (5 of 90 [6%] with oveporexton

A Change from Baseline in Average Sleep Latency on MWT



No. of Participants			
Placebo	22	22	21
Oveporexton, 0.5 mg twice daily	23	21	19
Oveporexton, 2 mg twice daily	21	21	21
Oveporexton, 2 mg and 5 mg daily	22	21	20
Oveporexton, 7 mg once daily	23	23	23

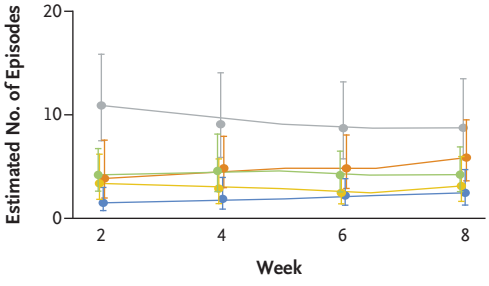
B Change from Baseline in ESS Total Score



No. of Participants				
Placebo	22	21	22	21
Oveporexton, 0.5 mg twice daily	23	23	22	21
Oveporexton, 2 mg twice daily	21	21	21	21
Oveporexton, 2 mg and 5 mg daily	23	22	23	22
Oveporexton, 7 mg once daily	23	23	23	23

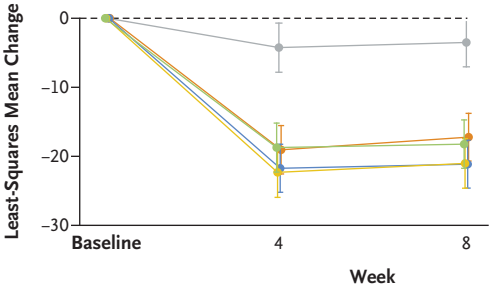
C Weekly Cataplexy Rate

	Placebo	Oveporexton			
		0.5 mg twice daily	2 mg twice daily	2 and 5 mg daily	7 mg once daily
Mean Rate at Baseline	23.1	18.6	21.0	15.7	31.1



No. of Participants				
Placebo	22	22	22	20
Oveporexton, 0.5 mg twice daily	23	23	21	21
Oveporexton, 2 mg twice daily	21	21	21	21
Oveporexton, 2 mg and 5 mg daily	23	23	23	22
Oveporexton, 7 mg once daily	23	23	23	23

D Change from Baseline in NSS-CT Total Score



No. of Participants			
Placebo	22	22	21
Oveporexton, 0.5 mg twice daily	23	22	22
Oveporexton, 2 mg twice daily	21	21	21
Oveporexton, 2 mg and 5 mg daily	23	23	22
Oveporexton, 7 mg once daily	23	23	23

Figure 1. Summary of Efficacy End Points from Baseline to Week 8.

Shown are the change from baseline in average sleep latency on the Maintenance of Wakefulness Test (MWT) (Panel A), the change from baseline in the Epworth Sleepiness Scale (ESS) total score (Panel B), the weekly cataplexy rate (Panel C), and the change from baseline in the Narcolepsy Severity Scale for Clinical Trials (NSS-CT) total score (Panel D). Values on the MWT range from 0 to 40 minutes (normal ability to stay awake, ≥20). ESS total scores range from 0 to 24, with higher scores indicating greater daytime sleepiness (normal, ≤10). NSS-CT total scores range from 0 to 57, with higher scores indicating greater severity of narcolepsy symptoms. In all groups, doses were administered at 8 a.m. and 11 a.m. each day for 8 weeks (in the once-daily oveporexton group, participants received 7 mg of oveporexton at 8 a.m. and placebo at 11 a.m). I bars indicate 95% confidence intervals.

Table 2. Efficacy End Points.*

End Point	Placebo (N=22)	Oveporexton, 0.5 mg Twice Daily (N=23)	Oveporexton, 2 mg Twice Daily (N=21)	Oveporexton, 2 mg and 5 mg Daily (N=23)	Oveporexton, 7 mg Once Daily (N=23)
Average sleep latency on MWT†					
No. of participants evaluated	21	19	21	20	23
Mean at wk 8 — min	4.7±8.9	16.5±11.4	27.6±9.5	30.7±9.3	19.5±9.7
Least-squares mean change from baseline to wk 8 (95% CI)	−1.2 (−5.3 to 2.9)	12.5 (8.3 to 16.7)	23.5 (19.5 to 27.6)	25.4 (21.3 to 29.5)	15.0 (11.1 to 18.8)
Least-squares mean difference from placebo (95% CI)	—	13.7 (7.7 to 19.6)	24.7 (18.9 to 30.5)	26.6 (20.8 to 32.4)	16.1 (10.5 to 21.8)
Adjusted P value	—	0.001	<0.001	<0.001	<0.001
Sleep latency of ≥20 min at wk 8 — no./total no. (%)	1/21 (5)	7/19 (37)	17/21 (81)	17/21 (81)	14/23 (61)
ESS total score‡					
No. of participants evaluated	21	21	21	22	23
Mean at wk 8	16.0±5.8	8.9±5.4	4.8±3.0	5.2±4.4	7.0±5.4
Least-squares mean change from baseline to wk 8 (95% CI)	−2.5 (−4.7 to −0.3)	−8.9 (−11.1 to −6.8)	−13.8 (−16.0 to −11.6)	−12.8 (−14.9 to −10.7)	−11.3 (−13.4 to −9.2)
Least-squares mean difference from placebo (95% CI)	—	−6.4 (−9.5 to −3.3)	−11.3 (−14.4 to −8.2)	−10.3 (−13.3 to −7.3)	−8.8 (−11.8 to −5.8)
Adjusted P value	—	0.004	<0.001	<0.001	<0.001
Total score of ≤10 at wk 8 — no. (%)	4 (19)	14 (67)	20 (95)	18 (82)	17 (74)
Weekly cataplexy rate					
No. of participants evaluated	20	21	21	22	23
Mean no. of episodes at wk 8	9.0±9.9	3.3±3.9	3.2±4.3	2.1±3.3	10.1±15.6
Mean change from baseline to wk 8§	−10.3±21.7	−14.5±15.4	−17.9±28.4	−13.9±14.5	−21.0±23.1
Incidence rate (95% CI)¶	8.76 (5.68 to 13.51)	4.24 (2.60 to 6.92)	3.14 (1.65 to 5.98)	2.48 (1.30 to 4.73)	5.89 (3.64 to 9.53)
Incidence rate ratio vs. placebo (95% CI)¶	—	0.48 (0.25 to 0.93)	0.36 (0.16 to 0.79)	0.28 (0.13 to 0.60)	0.67 (0.35 to 1.29)
Adjusted P value	—	0.25	0.03	0.003	0.25

NSS-CT total score					
No. of participants evaluated	21	22	21	22	23
Mean at wk 8	26.8±11.0	11.9±6.6	8.8±7.7	8.1±6.0	14.5±10.5
Mean change from baseline to wk 8	−4.9±8.1	−17.6±8.4	−20.0±10.6	−20.7±9.6	−19.0±11.6
Least-squares mean change from baseline to wk 8 (95% CI)	−3.5 (−7.0 to 0.0)	−18.2 (−21.7 to −14.7)	−21.0 (−24.6 to −17.4)	−21.1 (−24.6 to −17.7)	−17.2 (−20.7 to −13.8)
Least-squares mean difference from placebo (95% CI)	—	−14.7 (−19.7 to −9.7)	−17.5 (−22.6 to −12.5)	−17.6 (−22.6 to −12.7)	−13.7 (−18.7 to −8.8)
Total score of 0 to 14: mild disease — no. (%)	2 (10)	18 (82)	18 (86)	20 (91)	15 (65)

* Plus–minus values are means ±SD. CI denotes confidence interval.
† A normal value is defined as 20 minutes or more.[21]
‡ A normal value is defined as 0 to 10.[26]
§ Values were averaged for 2 weeks before the time point.
¶ Estimation of incidence rate and incidence rate ratio, and inference, are based on negative binomial generalized estimating equations.

and 3 of 22 [14%] with placebo) met prespecified criteria for markedly abnormal values on liver-function tests; however, the abnormal values were self-limited, not related to oveporexton or placebo, and were attributable to other factors by investigators (Table S6).

DISCUSSION

This phase 2 trial showed significant improvements in objective measures of wakefulness and marked improvements in participant-reported measures of daytime sleepiness with oveporexton doses between baseline and week 8 as compared with placebo. Decreases in cataplexy frequency were observed with all doses, reaching significance with 2 mg twice daily and 2 mg followed by 5 mg daily as compared with placebo at week 8. Average sleep latency on the MWT reached values seen in healthy controls by week 4, and the effect was maintained at week 8. Improvements on the MWT met previously defined thresholds for clinical relevance based on expert opinion.[28]

Although the trial was not designed to compare the efficacy of oveporexton with that of other narcolepsy medications, dose-dependent improvements of nearly 14 to 27 minutes in average sleep latency on the MWT with oveporexton were markedly greater than mean improvements of 2 to 12 minutes observed with currently available narcolepsy medications.[29-33] Similarly, improvements in ESS total scores were more pronounced than those observed with currently available narcolepsy medications,[29-32] with 79% of participants who received oveporexton (95% who received 2 mg twice daily) having scores at or below the normative threshold of 10 points[26] at week 8. These findings are supported by improvements in disease severity (NSS-CT) and quality of life (SF-36) and are consistent with efficacy results with the oral OX2R-selective agonist TAK-994 over a period of 8 weeks[14] and with exposure to the intravenous OX2R-selective agonist danavorexton.[13]

Adverse events were more frequent with oveporexton than with placebo, and the frequency increased with greater oveporexton exposure. Most adverse events were mild to moderate in intensity and resolved during continued treatment without medical intervention, and none led to discontinuation from the trial. The most frequently reported adverse events (insomnia and increased urinary

Table 3. Summary of Safety Evaluations.*

Variable	Placebo (N=22)	Oveporexton, 0.5 mg Twice Daily (N=23)	Oveporexton, 2 mg Twice Daily (N=21)	Oveporexton, 2 mg and 5 mg Daily (N=23)	Oveporexton, 7 mg Once Daily (N=23)
Adverse events — no. of participants (%)					
Any	7 (32)	13 (57)	15 (71)	21 (91)	21 (91)
Mild	5 (23)	10 (43)	6 (29)	11 (48)	12 (52)
Moderate	2 (9)	3 (13)	5 (24)	8 (35)	8 (35)
Severe†	0	0	4 (19)	2 (9)	1 (4)
Adverse events related to oveporexton or placebo — no. of participants (%)‡					
Any	3 (14)	12 (52)	14 (67)	20 (87)	20 (87)
Severe§	0	0	3 (14)	1 (4)	1 (4)
Adverse events resulting in discontinuation from trial — no. of participants (%)	0	0	0	0	0
Serious adverse events — no. of participants (%)					
Any	0	0	0	1 (4.3)¶	0
Related to oveporexton or placebo‡	0	0	0	0	0
Most frequent adverse events — no. of participants (%)‖					
Insomnia	1 (5)	5 (22)	10 (48)	13 (57)	15 (65)
Urinary urgency	1 (5)	5 (22)	4 (19)	12 (52)	9 (39)
Urinary frequency	1 (5)	3 (13)	7 (33)	7 (30)	12 (52)
Salivary hypersecretion	1 (5)	2 (9)	2 (10)	6 (26)	2 (9)
Headache	1 (5)	1 (4)	3 (14)	2 (9)	2 (9)
Nasopharyngitis	0	0	2 (10)	2 (9)	2 (9)
Liver-function tests at wk 8					
ALT — U/liter	21.2±14.6	15.3±7.0	20.7±11.8	20.5±10.3	18.7±13.0
AST — U/liter	18.3±4.9	16.8±2.9	19.3±7.1	18.5±5.4	17.0±5.2
Bilirubin — mmol/liter	8.3±7.5	7.9±3.3	8.6±6.0	7.9±3.8	6.3±2.1
GGT — U/liter	20.1±19.6	19.3±19.9	16.7±9.4	28.6±31.7	16.5±8.0

* Plus–minus values are means ±SD. Shown are adverse events with a date of onset on or after the first dose of oveporexton or placebo.
† Severe adverse events were as follows: among participants receiving 2 mg of oveporexton twice daily, one each had cataplexy, insomnia, and coronavirus disease 2019, and one had headache and insomnia; among participants receiving 2 mg followed by 5 mg daily, one had an ankle fracture, and one had headache, cataplexy, insomnia, mood swings, and vomiting; and among participants receiving 7 mg once daily, one had insomnia.
‡ The relatedness of adverse events to oveporexton or placebo was determined by the investigator.
§ Severe adverse events that were considered to be related to oveporexton were as follows: among participants receiving 2 mg twice daily, one had cataplexy, one had insomnia, and one had headache and insomnia; among participants receiving 2 mg followed by 5 mg daily, one had headache, cataplexy, and insomnia; and among participants receiving 7 mg once daily, one had insomnia.
¶ A serious adverse event involving ankle fracture was reported in one participant.
‖ Shown are events that were reported in at least 5% of participants overall.

urgency and frequency) were consistent with those occurring with danavorexton[13] and TAK-994[14] and align with expected on-target effects of the drug class. In contrast, the TAK-994 phase 2 trial had more trial discontinuations due to adverse events than the current trial, and hepatotoxic effects were observed in three participants in the TAK-994 trial but were not observed with oveporexton.[33] There were no new safety risks relative to previous OX2R-selective agonists and no marked changes in blood pressure according to ambulatory blood-pressure monitoring.

Although oveporexton and placebo were indistinguishable, functional unblinding owing to efficacy improvements and the side-effect profile was possible. The use of objective end points (e.g., average sleep latency on the MWT) mitigated this potential effect. To confirm these results, a phase 3 trial has been initiated, and a long-term extension study is ongoing.

In this phase 2 trial involving participants with narcolepsy type 1, total daily oveporexton doses of up to 7 mg resulted in dose-dependent clinically meaningful improvements in objective measures of wakefulness, participant-reported measures of daytime sleepiness, cataplexy frequency, quality of life on the SF-36, and disease severity on the NSS-CT as compared with placebo, without hepatotoxic effects.

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AUTHOR INFORMATION

[1] National Reference Network for Narcolepsy, Sleep and Wake Disorders Center, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France; [2] University of Montpellier, INSERM Institute for Neurosciences Montpellier, Montpellier, France; [3] IRCCS, Istituto delle Scienze Neurologiche, Bologna, Italy; [4] Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [5] Stanford Center for Sleep Sciences and Medicine, Redwood City, CA; [6] Sleep–Wake Center, Stichting Epilepsie Instellingen Nederland, Heemstede, the Netherlands; [7] Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands; [8] Neurophysiology and Sleep Disorders Unit, Vithas Hospitals, Madrid; [9] Departamento de Ciencias Médicas Clínicas, Universidad San Pablo-CEU, CEU Universities, Madrid; [10] Center of Sleep Medicine and Sleep Research, Klinik Barmelweid, Barmelweid, Switzerland; [11] Department of Neurology, University Hospital of Bern, Bern, Switzerland; [12] Sleep Medical Center, Osaka Kaisei Hospital, Osaka, Japan; [13] Takeda Development Center Americas, Cambridge, MA.

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