ORIGINAL ARTICLE

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial

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Abstract

Rationale: Excessive daytime sleepiness is a common disabling symptom in obstructive sleep apnea syndrome.

Objectives: To evaluate the efficacy and safety of pitolisant, a selective histamine H3 receptor antagonist with wake-promoting effects, for the treatment of daytime sleepiness in patients with moderate to severe obstructive sleep apnea refusing continuous positive airway pressure treatment.

Methods: In an international, multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial, pitolisant was individually titrated at up to 20 mg/d over 12 weeks. The primary endpoint was the change in the Epworth Sleepiness Scale score. Key secondary endpoints were maintenance of wakefulness assessed on the basis of the Oxford Sleep Resistance test, safety, Clinical Global Impression of severity, patient's global opinion, EuroQol quality-of-life questionnaire, and Pichot fatigue questionnaire.

Measurements and Main Results: A total of 268 patients with obstructive sleep apnea (75% male; mean age, 52 yr; apnea–hypopnea index, 49/h; baseline sleepiness score, 15.7) were randomized (200 to pitolisant and 68 to placebo) and analyzed on an intention-to-treat basis. The Epworth Sleepiness Scale score was reduced more with pitolisant than with placebo (−2.8; 95% confidence interval, −4.0 to −1.5; $P < 0.001$). Wake maintenance tests were not improved. The Pichot fatigue score was reduced with pitolisant. The overall impact of pitolisant was confirmed by both physicians' and patients' questionnaires. Adverse event incidence, mainly headache, insomnia, nausea, and vertigo, was similar in the pitolisant and placebo groups (29.5% and 25.4%, respectively), with no cardiovascular or other significant safety concerns.

Conclusions: Pitolisant significantly reduced self-reported daytime sleepiness and fatigue and improved patient-reported outcomes and physician disease severity assessment in sleepy patients with obstructive sleep apnea refusing or nonadherent to continuous positive airway pressure.

Clinical trial registered with www.clinicaltrials.gov (NCT01072968) and EU Clinical Trials Register (EudraCT 2009-017251-94).

Keywords: excessive daytime sleepiness; obstructive sleep apnea; continuous positive airway pressure; pitolisant

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A complete list of HAROSA II Study Group members may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: Some patients with obstructive sleep apnea who refuse or do not adhere to continuous positive airway pressure treatment have persistent daytime sleepiness.

What This Study Adds to the Field: In this randomized placebo-controlled trial, pitolisant, a selective histamine H3 receptor antagonist with wake-promoting effects, significantly reduced sleepiness and fatigue and improved both global patient-reported outcomes and the physician's disease severity assessment. Importantly, no detrimental cardiovascular impact was associated with this therapy.

Obstructive sleep apnea (OSA) is a major health concern worldwide that has multiorgan consequences and results in considerable economic, healthcare, and social burdens (1, 2). OSA is often associated with comorbidities such as arterial hypertension, arrhythmia, stroke, coronary heart disease, and metabolic dysfunction. Excessive daytime sleepiness (EDS) and fatigue are among the chief complaints of patients with OSA, and they have disabling consequences: impaired attention and vigilance, cognitive dysfunction, loss of productivity at work, deterioration in quality of life, and increased risk of occupational and motor vehicle accidents (3, 4).

Continuous positive airway pressure (CPAP) is the first-line therapy for symptomatic moderate to severe OSA. When used properly, CPAP normalizes the apnea–hypopnea index (AHI), suppresses nocturnal oxygen desaturations, and decreases sleep fragmentation. As a consequence, there is a general reduction in EDS, and improvements in alertness, cognitive function, and quality of life are seen. CPAP is particularly effective in patients with more pronounced sleepiness and OSA severity (5, 6). However, sleepiness is known to persist in approximately 15% of patients in spite of adequate CPAP therapy, and this residual component may represent a considerable therapeutic drawback (7–9). Wake-promoting agents such as modafinil and armodafinil, as well as, more recently, solriamfetol, in combination with CPAP have been demonstrated to decrease residual sleepiness and improve quality of life in randomized controlled trials (10, 11).

A major issue with CPAP treatment is adherence, with 15% of patients with OSA refusing to try CPAP and 20–30% discontinuing CPAP in the long term (12, 13). Hence, prescribing a wake-promoting agent to selectively treat EDS and not treating the underlying cause is frequently debated, and efficacy data are scarce in this specific context.

Pitolisant is a novel selective histamine H3 receptor antagonist/inverse agonist with strong wake-promoting effects that is well tolerated in patients with narcolepsy (14, 15). This provides a rationale to assess its efficacy and safety in the treatment of EDS in patients with OSA who refuse or do not adhere to CPAP therapy. The objectives of this study were to demonstrate the efficacy and safety of pitolisant administered at 5, 10, or 20 mg once per day versus placebo during 12 weeks for the treatment of EDS in patients with moderate to severe OSA and refusing CPAP therapy.

Methods

Study Design

This phase 3, prospective, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the efficacy and safety of pitolisant over 12 weeks in adult patients with moderate to severe OSA (AHI, $\geq$15 events/h) experiencing EDS (Epworth Sleepiness Scale [ESS] score, $\geq$12), refusing CPAP treatment, and without significant cardiovascular disease. The study was conducted in 28 hospital sleep clinics in 10 European countries between October 6, 2011, and May 7, 2014. The study was approved by the appropriate institutional review board or ethics committee of each study center and was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before participation. The study is registered with www.clinicaltrials.gov (NCT01072968) and the EU Clinical Trials Register (EudraCT 2009-017251-94).

Patients

Patients were adults with OSA diagnosed according to the International Classification of Sleep Disorders 2nd Edition (16) criteria and refusing or not adhering to CPAP therapy. Included patients with OSA were those with an AHI $\geq$15 events per hour assessed during the previous year and a complaint of EDS, defined as an ESS score $\geq$12.

Key noninclusion criteria were as follows:

- History of a medical disorder other than OSA associated with EDS (periodic limb movement arousal index, >10 events/h; 13-item Beck Depression Inventory [BDI-13] score, >16 or item G = 0; Mini Mental State Examination score < 28)
- Body mass index (BMI) >40 kg/m^2 (owing to the risk of obesity hypoventilation syndrome and because morbid obesity might be a significant cause of sleepiness)
- Surgery for OSA, including uvulopalatopharyngoplasty
- Use of a mandibular advancement device
- Nighttime or variable work shifts

Author Contributions: J.V., M.P., J.H., T.S., O.G., R. Tiholov, R. Tamisier, and C.S.-G. participated in data acquisition, data interpretation, and revision of the paper. I.L. and J.-M.L. participated in the conception, design, and organization of the study and revision of the paper. P.L. participated in the conception, design, international coordination, and revision of the paper. Y.D. and J.-L.P. participated in the conception and design of the study and wrote the paper. J.-C.S. participated in the conception and design of the study and revised the paper. All authors shared in the decision to submit the manuscript for publication, and all authors attest to the accuracy and completeness of the data and compliance with the study protocol.

Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others after the publication of this article, as will additional related documents (study protocol, statistical analysis plan, and informed consent form), for academic purposes (e.g., meta-analyses), upon request to the sponsor, Bioprojet (jm.lecomte@bioprojet.com), and with a signed data access agreement.

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- Current or recent history of drug, alcohol, or other substance abuse or dependence
- Presence of an unstable or clinically significant medical condition
- A behavior or psychiatric disorder or medical history that could affect safety or interfere with study assessments
- Use of any treatment that could affect the evaluation of EDS

Cardiovascular disease, including myocardial infarction, hypertension, angina, arterial hypertension or dysrhythmia, electrocardiogram, Bazett's corrected QT interval longer than 450 ms on an ECG, left ventricular hypertrophy, or mitral valve prolapse, was not exclusionary, unless the investigator deemed it unstable or recent.

Randomization Procedure

Randomization was centralized and performed via an electronic web randomization server (Arone Projection; https://www.bioprojet-studies.org/) that automatically assigned a patient number at screening and then automatically assigned a study treatment number when the patient was randomized. The randomization list was established on a balanced 3:1 (three active for one placebo) basis. Pitolisant and placebo were contained within sealed capsules, similar in appearance and taste, and containing a one-fourth, one-half, or one full tablet of pitolisant 20 mg or lactose only (placebo). The patients, their sleep and/or respiratory physicians, and staff were blinded to the treatment allocation.

Intervention

Patients who fulfilled selection criteria were randomized 3:1 to the following treatment groups: pitolisant at 5, 10, or 20 mg once daily or placebo consumed on an empty stomach within 1 hour of waking in the morning. Treatment was initiated at 5 mg by an individual 2-week titration period, escalating the dose on the basis of efficacy and tolerance to the treatment, followed by treatment with the selected dose for a further 10 weeks (Figure 1).

Outcomes

The primary efficacy endpoint was the change from baseline to Week 12 in the ESS score, a reliable patient self-assessment method to measure EDS. The key secondary endpoint was the change from baseline to Week 12 in the Oxford Sleep Resistance (OSLER) test, a test of behavioral maintenance of wakefulness that objectively measures the ability to maintain wakefulness. The OSLER test consisted of three sessions each of 40-minute sleep resistance challenges performed at 9:00 A.M., 11:00 A.M., and 1:00 P.M. The mean sleep latency (mean of the three tests) and the number of errors (three to six consecutive errors indicating microsleep and seven or more errors indicating sleep onset) were calculated (17, 18). Other secondary endpoints were responders according to the ESS (ESS score, $\leqslant 10$ or improvement $\geqslant 3$ points), Pichot fatigue scale, sleep diary (sleepiness and sleep episodes), Trail Making Test parts A and B, Clinical Global Impression (CGI) severity and change scales, patient's global opinion (PGO), Leeds Sleep Evaluation Questionnaire (LSEQ), and EuroQol quality-of-life questionnaire (EQ-5D). Safety was assessed by evaluating adverse events (particularly treatment-emergent adverse events [TEAEs]), clinical laboratory parameters (hematology, biochemistry, and electrolytes), vital signs, physical examination, ECG data, BDI-13 score, amphetamine-like withdrawal symptoms, and the patient's overall evaluation of tolerance.

Statistical Analysis

Sample size calculation. Results of exploratory studies on pitolisant provided an estimate of ESS score residual variability with an SD of 6 points. The minimal clinically important difference was arbitrarily fixed by agreement between the investigators at ESS score –3, corresponding to an effect size of 0.5. Recent independent studies (19, 20) have established the minimal clinically important improvement of the ESS score to lie between -2 and -3. The correlation between final and baseline ESS scores was conservatively estimated as $r = 0.4$. Assuming an analysis of covariance with a 0.95 confidence level as the main confirmatory test, a difference of at least 3 points should be detected with a power of 90% by including at least 60 patients in the placebo group and 180 patients in the pitolisant treatment group.

Description of the different populations analyzed. The intention-to-treat (ITT) population included all randomized patients. The safety population corresponded to all patients who received at least one dose of study medication, regardless of the outcome, and for whom at least one valid postbaseline evaluation (including any adverse event) was available. The per-protocol population included all patients in the ITT population with no major protocol violation regarding inclusion or noninclusion criteria or during the treatment phase and no premature discontinuation in the double-blind phase of the study. The per-protocol population was confirmed by blinded review of the data before database lock.

Demographic data and other baseline characteristics were analyzed for the ITT population. The efficacy analysis of the ITT population was considered as the primary analysis. The safety population was used for safety, concomitant medications, exposure, dosing, and compliance analyses.

The statistical analysis was performed by an independent external statistician. Another third-party statistician independently reviewed the statistical analysis report. Descriptive statistics were used for the quantitative variables, and the frequency distribution was used for the ordinal and nominal variables. Exact 95% confidence intervals (CIs) are given for selected variables.

The final ESS score was compared between the two arms using a linear mixed effects model, considering treatment as a fixed factor, center as a random factor, and ESS score and BMI at baseline as adjustment covariates. It was foreseen that the ESS score might be logarithmically transformed, depending on normality of the residuals. However, it appeared that this was not necessary.

The analysis of safety data was descriptive, except for between-group comparisons of the frequencies of TEAEs by means of logistic regression. Missing data for the primary efficacy variable and for response were allocated using the last observation carried forward (LOCF) method. An additional sensitivity analysis was performed in which missing data were allocated using multiple imputation (*see* additional analysis and Tables E1 and E2 in the online supplement). A sensitivity analysis for the primary efficacy variable was performed using the baseline ESS value carried forward, adjusting for ESS score and BMI at baseline.

The statistical analysis took into account the possibility of imbalance between centers and treatment by considering a

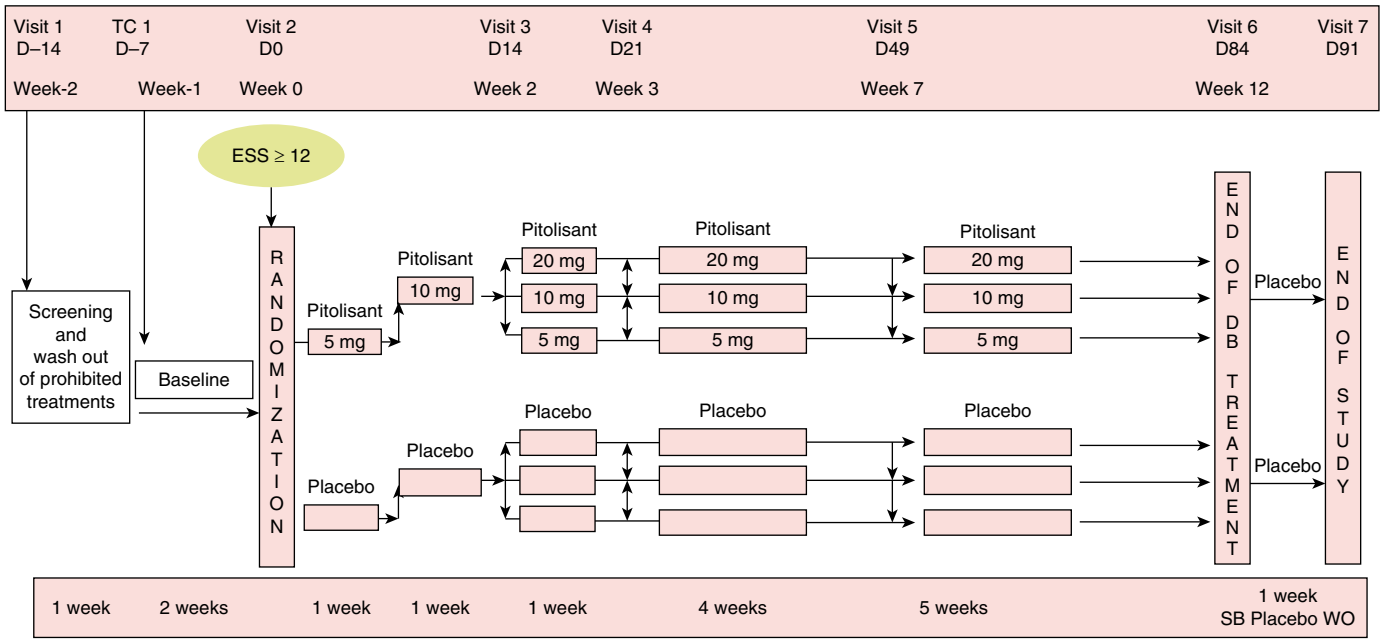

Figure 1. Study design. D = day; DB = double-blind; ESS = Epworth Sleepiness Scale; SB = single blind; TC = telephone call; WO = wash out.

random factor for centers. All statistical tests were two sided at a 5% level of significance.

Results

Patient Flow

Two hundred ninety-eight patients were screened for inclusion (Figure 2). Of these, 268 patients (89.9%) were eligible for entry into the double-blind phase of the study and were randomized to pitolisant ($n = 201$) or placebo ($n = 67$). Among patients in this ITT population, 267 received at least one dose of study medication and had a validated postbaseline assessment, comprising 200 in the pitolisant group and 67 in the placebo group. These patients constituted the safety population. Twelve patients in the ITT population had at least one major protocol deviation (Table E3), and 14 patients discontinued the study prematurely. These 26 patients were excluded from the per-protocol analysis that included 181 in the pitolisant group and 61 in the placebo group.

The ITT population was primarily male (75.4%) and obese, and the mean age was 52.0 years. On average, the time since diagnosis of OSA was 11.9 months; AHI at diagnosis was 49.3 events per hour; nocturnal Sa_{O_2} was 90.1%; and Mini Mental State Examination score was 29.4. No significant differences in demographic or clinical characteristics were found between the treatment groups (Table 1).

Primary Efficacy Endpoint

The primary endpoint, change in ESS score from baseline to end of intervention (LOCF for ESS), was −6.3 in the pitolisant group and −3.6 in the placebo group ($P < 0.001$). For the mean LOCF for the final ESS score, the 95% CI for pitolisant (8.8–10.1) versus placebo (10.7–13.5) did not overlap. The primary analysis showed a significant difference in effect between arms of −2.8 (95% CI, −4.0 to −1.5; $P < 0.001$) (Figure 3 and Table 2). When missing data were allocated using multiple imputation, the multiple imputation analysis confirmed the LOCF analysis (*see* Tables E1 and E2). This was due to the small number of missing values in this study, which was only 3.0% of the final ESS dataset. Predefined sensitivity analyses (baseline observation carried forward) adjusted for BMI and ESS at baseline showed the same significant treatment effects.

Secondary Efficacy Outcomes

Pitolisant normalized the ESS score (ESS, ≤10) in 67.2% of patients in the study arm versus 44.8% in the placebo group. An "ESS response," defined as either an ESS score ≤10 or improvement by 3 or more points, was observed in 80.6% in the pitolisant group and 53.7% in the placebo group ($P < 0.001$) (Table 2).

The baseline mean sleep latencies during OSLER tests were 14.79 ± 10.95 minutes and 15.92 ± 11.04 minutes for the pitolisant and placebo groups, respectively. The percentages of patients exhibiting the maximum of 40 minutes were 5.5% and 6%, whereas those in the 30–40-minute range were 6.5% and 4.5%, in the pitolisant and placebo groups, respectively.

The ratios of increase in mean sleep latency during OSLER tests were 1.65 and 1.39 in the pitolisant and placebo groups, respectively ($P = 0.108$ using a mixed model). The analysis of the mean difference of the logarithms of sleep latencies between pitolisant and placebo showed an estimate of 0.1 (95% CI, −0.0 to 0.3), not reaching significance. The numbers and types of errors did not differ between the treatment groups (Table 3). Similar results were found in the per-protocol analysis.

There were trends in improvement in sleep diary variables in the pitolisant group compared with the placebo group (number and duration of sleep and sleepiness episodes; $P = 0.056$ and $P = 0.066$, respectively). Significance was achieved for these variables in per-protocol analysis (number and duration of sleep and sleepiness episodes; $P = 0.049$ and $P = 0.05$, respectively).

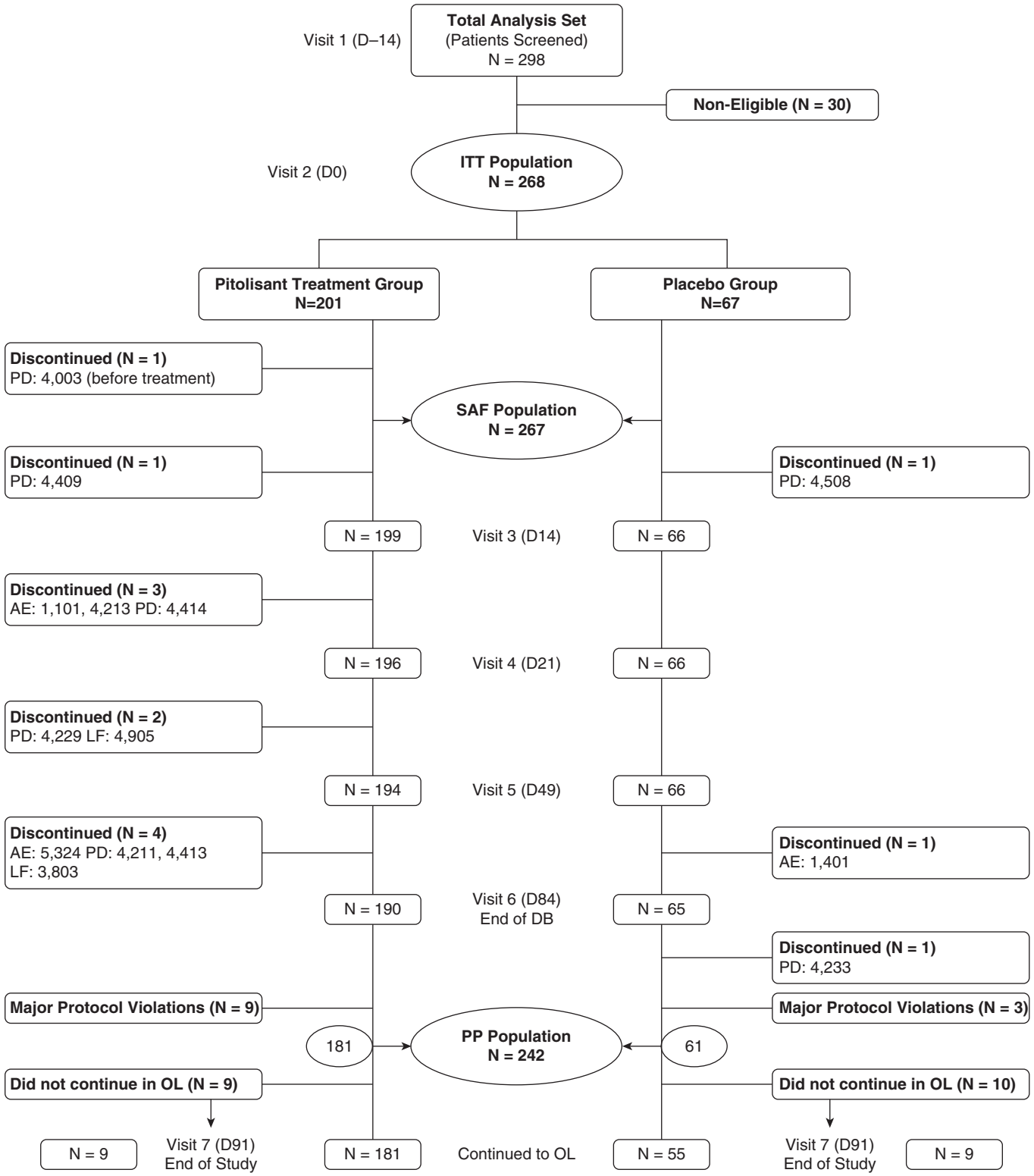

Figure 2. Study flowchart. Causes of noneligibility were as follows: 10 due to patient decision and 20 due to exclusion criteria (6 significant cardiovascular disease or abnormality, 3 Epworth Sleepiness Scale score <12, 2 severe insomnia not associated with obstructive sleep apnea, 2 apnea–hypopnea index <15 events/h, 2 positive serological test [HIV], 1 severe depression [Beck Depression Inventory score >16], 1 substance abuse [opioids], 1 significant periodic limb movement disorder and central sleep apnea, 1 age <18 yr, and 1 adhering to continuous positive airway pressure therapy). AE = adverse event; D = day; DB = double-blind; ITT = intention to treat; LF = lost to follow-up; OL = open label; PD = patient decision; PP = per protocol; SAF = safety.

Table 1. Demography and Characteristics at Baseline

Parameter	Pitolisant (*n* = 201)	Placebo (*n* = 67)	All Patients (*N* = 268)
Age, yr, mean (SD) (range)	51.9 (10.6) (25–75)	52.1 (11.0) (30–76)	52.0 (10.6) (25–76)
Sex, *n* (%)			
M	151 (75.1)	51 (76.1)	202 (75.4)
F	50 (24.9)	16 (23.9)	66 (24.6)
Weight at inclusion, kg, mean (SD)	97.7 (15.7)	99.8 (16.1)	—
BMI, kg/m^2, mean (SD)	32.8 (4.6)	33.0 (4.3)	—
Cardiovascular disease, *n* (%)	110 (54.7)	35 (52.2)	145 (54.1)
AHI at date of diagnosis, events/h, mean (SD)	50.2 (44.3)	46.9 (22.8)	49.3 (40.0)
Nocturnal Sa_{O_2} at date of diagnosis, %, mean (SD)	89.8 (9.1)	90.9 (3.8)	90.1 (8.2)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index.

The EQ-5D visual analogue scale showed average increases of 7.3 mm in the pitolisant group and 1.8 mm in the placebo group ($P = 0.059$). No between-group differences were found regarding the items in the LSEQ, except for behavior after waking with pitolisant ($P = 0.018$). No changes were found for the mean time to perform Trail Making Test part A or B. At the end of the double-blind phase, 84.2% of patients in the pitolisant group had improved their CGI severity and change scale scores (11.1% very much improved, 44.2% much improved, and 28.9% minimally improved) compared with 56.3% in the placebo group (4.7% very much improved, 29.7% much improved, and 21.9% minimally improved) ($P < 0.001$).

Improvement in the PGO was expressed by 86.3% of patients in the pitolisant group (marked effect, 30.0%; moderate effect, 33.7%; minimal effect, 22.6%) compared with 60.9% in the placebo group (marked effect, 21.9%; moderate effect, 18.8%; minimal effect, 20.3%) ($P < 0.001$). The mean Pichot fatigue scale scores decreased from 13.0 ± 6.5 at baseline to 9.2 ± 6.6 at 12 weeks in the pitolisant group and from 11.1 ± 5.9 to 10.5 ± 6.1 in the placebo group, with a significant mean change between groups (−3.6 ± 5.6 vs. −1.0 ± 6.3; $P = 0.005$) (Table 3). During the double-blind phase, the maximum dose prescribed was 20 mg/d for 82.5% of patients in the pitolisant group and for 86.6% of the patients in the placebo group.

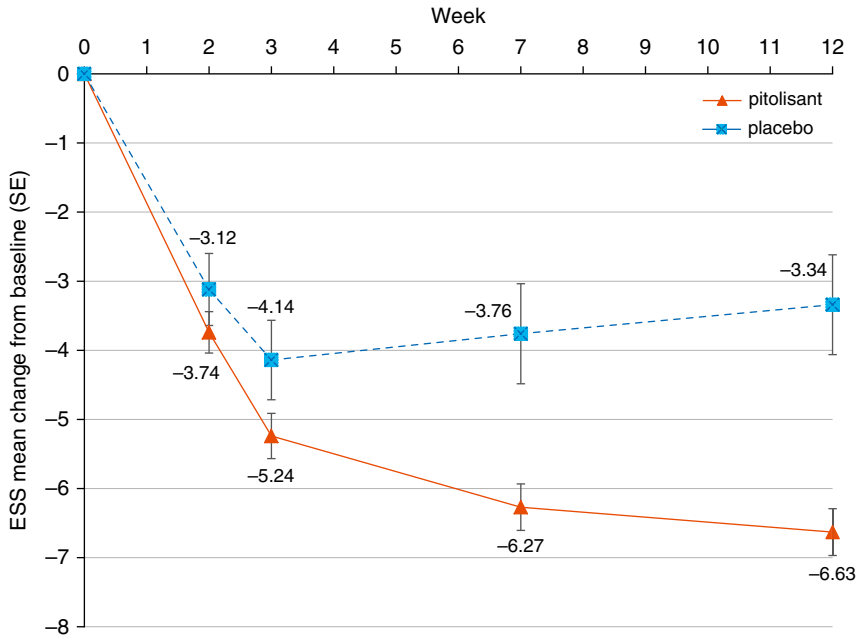

Figure 3. Changes in Epworth Sleepiness Scale (ESS) score during treatment.

Safety

The safety evaluation was based on the incidence of TEAEs. No differences were found for TEAE frequency between the pitolisant (29.5%) and placebo groups (25.4%). The most frequently reported TEAE was headache (8.5% and 11.9% in the pitolisant and placebo groups, respectively). Other frequent TEAEs were insomnia, nausea, and vertigo, reported in 5.5%, 2.5%, and 2.0% with pitolisant, respectively, and in 3.0%, 1.5%, and 2.0% with placebo, respectively (Table 4). Moreover, the frequency of TEAEs that were considered treatment related was similar (24.0% with pitolisant and 19.4% with placebo; $P = 0.377$).

TEAEs leading to study drug withdrawal were reported for three patients (1.5%) in the pitolisant group and two patients (3.0%) in the placebo group. Serious TEAEs were reported for two patients (1.0%; one prolonged QT interval on the ECG and one cardiopulmonary failure leading to death) during pitolisant treatment and considered unlikely to be treatment related and in none of the patients receiving placebo.

The occurrence of amphetamine-like withdrawal syndrome (dysphoria, defined as at least three of the following symptoms: fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, and psychomotor retardation and/or agitation [21]) was assessed in all participants. None of the patients experienced amphetamine-like withdrawal syndrome, and specifically neither hypersomnia nor fatigue rebound, at treatment interruption at the end of the study. All features and symptoms of withdrawal syndrome are reported in Table E4. BDI scores, blood chemistry,

Table 2. Efficacy Results for Primary Endpoint: ESS Score

Parameter	Pitolisant (*n* = 201)	Placebo (*n* = 67)	*P* Value
ESS score at inclusion, mean (SD)	15.7 (3.1)	15.7 (3.6)	—
ESS score at end of treatment, mean (SD)	9.1 (4.7)	12.2 (6.1)	—
Final ESS score, DB-LOCF, mean (SD) (95% CI)	9.4 (4.6) (8.8–10.1)	12.1 (5.8) (10.7–13.5)	<0.001
ESS score change, DB-LOCF – V2	−6.3 (4.5)	−3.6 (5.5)	<0.001
R_1 response (ESS score ⩽10)			
n (%)	135 (67.2)	30 (44.8)	<0.001
95% CI	60.2–73.6	32.6–57.4	
R_2 response (ESS score ⩽10 or ESS score improvement ⩾3)			
n (%)	162 (80.6)	36 (53.7)	<0.001
95% CI	74.4–85.8	41.1–66.0	

Definition of abbreviations: CI = confidence interval; DB-LOCF = database with last observation carried forward; ESS = Epworth Sleepiness Scale; R_1 = first secondary enpoint result; R_2 = second secondary endpoint result; V2 = visit 2.

and hematological or cardiovascular parameters did not change in either group. During treatment, there were no changes from baseline in systolic and diastolic blood pressure or heart rate for both groups (Table 4). Mean values of the ECG variables were comparable in the two treatment groups. However, in the pitolisant treatment group, three patients (1.5%) had at least one postdose corrected QT interval by Fredericia's corrected QT interval (QTcF) longer than 450 ms, and four patients (2.0%) had one QTcF elongation greater than or equal to 60 ms, whereas there was one patient with QTcF longer than 450 ms in the placebo group.

Discussion

Pitolisant reduced self-reported EDS as measured by the ESS score together with an overall improvement in both patient-reported outcomes and physician-assessed severity in adult patients with OSA with daytime sleepiness refusing CPAP treatment. The study population corresponded to patients with OSA refusing or not tolerating CPAP treatment. Personalization of sleep apnea treatment is crucial (22) and is a prerequisite for optimizing adherence, which in turn leads to effectiveness. In the case of CPAP refusal or nonadherence, clinicians should attempt alternative treatments to CPAP (23) before offering solely pharmacologic treatment for sleepiness. Evidence supports the use of mandibular advancement devices in mild to moderate OSAS as providing a health benefit equivalent to CPAP (24). Maxillomandibular osteotomy and upper airway stimulation seem to be as efficient as CPAP in selected young patients with OSA without comorbidities. Finally, lifestyle interventions, including weight loss (25), exercise (26), and/or positional therapy (27) can be considered as able to at least reduce OSA severity.

After the dose escalation period, the mean ESS score was significantly reduced compared with placebo. The estimate of the treatment effect based on the change in ESS score between the beginning and end of the double-blind intervention was −2.8 (95% CI, −4.0 to −1.5). Moreover, the normalization (ESS score ⩽ 10) and responder rates (ESS score ⩽ 10 or improvement ⩾3) were greater in the group treated with pitolisant. The magnitude of the change in ESS score was close to that observed in studies of modafinil, armodafinil, and solriamfetol in patients with OSA (10, 11, 28). However, this should be confirmed by head-to-head comparisons between wake-promoting agents. The magnitude of ESS improvement with pitolisant at Week 12 was substantial and clinically relevant (19, 20), albeit slightly weaker than that reported for patients with narcolepsy treated with pitolisant with doses often reaching 40 mg (14, 15).

ESS is a patient-reported assessment of propensity to fall asleep in different situations of everyday life, whereas the OSLER test is an objective measure of ability to maintain wakefulness in a laboratory environment and the related daytime vigilance. We found no significant between-group changes in the OSLER test. However, the pitolisant group had lower mean sleep latency at baseline (14.79) than the placebo group (15.92), and a considerable proportion of patients exhibited OSLER test mean sleep latencies in the normal range at baseline (12% had mean sleep latency ⩾30 min in the pitolisant group compared with 10% in the placebo group), and this may have limited the potential for improvement because of a ceiling effect.

For several other secondary outcomes (sleep diaries and EQ-5D), results were close to statistical significance, becoming statistically significant in per-protocol analysis. This suggests that the study might have been underpowered for some secondary outcomes. This may also be due to the inclusion criteria of without CPAP treatment and with baseline ESS scores ⩾12. Our population thus differs from the pivotal trials of modafinil, armodafinil, and solriamfetol for treatment of EDS in OSA, in which most of the patients were receiving CPAP therapy and with an ESS score ⩾10. Pitolisant was superior to placebo at the end of the double-blind phase, with major improvements compared with placebo in terms of patient-centered outcomes, including the Pichot fatigue scale and a feeling of restorative sleep upon waking (explored by the LSEQ). A clear improvement was also observed via the physician-scored (CGI of change) and patient-scored (PGO) questionnaires.

Adherence to CPAP is a major issue when treating OSA. It is estimated that 10–15% of patients with OSA initially refuse or quickly abandon CPAP in the first weeks of treatment. The long-term rate of CPAP discontinuation is consistent across studies at between 20% and 40% (13). No clear improvement in mean CPAP adherence has been seen over the last 20 years, despite considerable technical advances, behavioral interventions, and multimodal telemonitoring systems (29, 30). This leaves

Table 3. Efficacy Results for Secondary Outcomes

Parameter	Pitolisant (*n* = 201)	Placebo (*n* = 67)	*P* Value
OSLER test			
OSLER test mean sleep latency at inclusion, min, (SD)	14.79 (10.95)	15.92 (11.04)	—
Number of patients with OSLER test = 40 min at inclusion	11 (5.5%)	4 (6%)	—
Number of patients with OSLER test ⩾30 min and <40 min at inclusion	13 (6.5%)	3 (4.5%)	—
OSLER test mean sleep latency at end of treatment, min	21.95 (13.53)	20.25 (13.42)	—
Ratio of OSLER test V6/OSLER test V2, geometric mean	1.65	1.39	0.120
Mean difference of pitolisant and placebo logarithms of sleep latency at end of DB treatment (95% CI)	0.1 (0.0–0.3)		—
Normal vigilance (number of 3–6 and ⩾7 errors = 0 for each of the three tests)			
At baseline (V2)	2.0% (0.5–5.0%)	3.0% (0.4–10.4%)	—
At the end of DB treatment (V6)	8.5% (4.9–13.5%)	6.3% (1.7–15.2%)	0.487
Pichot fatigue score, mean change (SD)	−3.6 (5.6)	−1.0 (6.3)	0.005
Sleep diary variables			
Mean change in daily number of sleep/sleepiness episodes (SD)	−1.79 (1.97)	−1.30 (1.86)	0.056*
Mean change in daily duration of sleep/sleepiness episodes (SD)	−47.87 (53.39)	−32.24 (48.82)	0.066†
EQ-5D, mean change in VAS score	7.3 ± 16.2	1.8 ± 16.3	0.059
Leeds Sleep Evaluation Questionnaire			
Mean change in modified getting to sleep (SD)	10.21 (24.99)	2.42 (23.51)	0.155
Mean change in quality of sleep (SD)	17.70 (26.08)	13.00 (25.56)	0.108
Mean change in awake after sleep (SD)	19.19 (26.61)	14.00 (25.18)	0.160
Mean change in behavior after awakening (SD)	21.96 (22.26)	13.35 (20.89)	0.018
Mean change in global LSEQ score (SD)	17.26 (14.80)	10.69 (14.80)	0.005
TMT A, mean change in average time (SD)	−8.9 (12.7)	−7.3 (13.7)	0.389
TMT B, mean change in average time (SD)	−22.5 (40.0)	−16.3 (33.8)	0.648
CGI			<0.001
Very much improved	21 (11.1%)	3 (4.7%)	
Much improved	84 (44.2%)	19 (29.7%)	
Minimally improved	55 (28.9%)	14 (21.9%)	
No change	30 (15.8%)	22 (34.4%)	
Minimally worse	0 (0.0%)	6 (9.4%)	
Much worse	0 (0.0%)	0 (0.0%)	
Very much worse	0 (0.0%)	0 (0.0%)	
CGI improvement at end of DB treatment (V6)			
n (%)	160 (84.2%)	36 (56.3%)	
95% CI	78.2–89.1%	43.3–68.6%	
Patient's global opinion			<0.001
Improvement at V6, *n* (%)	164 (86.3%)	39 (60.9%)	
95% CI	80.6–90.9%	47.9–72.9%	

Definition of abbreviations: CGI = Clinical Global Impression; CI = confidence interval; DB = double-blind; EQ-5D = EuroQol five-dimension quality of life scale; LSEQ = Leeds Sleep Evaluation Questionnaire; OSLER = Oxford Sleep Resistance test; TMT = Trail Making Test; V2 = visit 2; V6 = visit 6; VAS = visual analogue scale.

*$P = 0.049$ in the per-protocol population.

†$P = 0.050$ in the per-protocol population.

thousands of patients with symptomatic OSA with untreated daytime sleepiness. An original and unique aspect of our study was the targeted OSA population comprising only patients with EDS refusing CPAP. In the two recent solriamfetol studies (11, 28), the study populations were heterogeneous, with approximately one-third of patients having no OSA primary treatment. In the study by Strollo and colleagues (11), a *post hoc* subanalysis showed that ESS score, maintenance of wakefulness, and CGI change scale score were slightly better in nonadherent patients than in those adhering to CPAP. It remains controversial whether targeting EDS alone without addressing the underlying cause is an acceptable practice, and doing so might lead to misuse. However, from a pragmatic point of view, these patients often remain untreated and have a poor quality of life, loss of productivity, and risk of EDS-related accidents. Another major issue beyond symptom improvement is to ensure that a given wake-promoting agent

Table 4. Safety Parameters

Parameter	Pitolisant (*n* = 200)	Placebo (*n* = 67)	*P* Value
Any TEAE, *n* (%)	59 (29.5)	17 (25.4)	
Any treatment-related TEAE, *n* (%)	48 (24.0)	13 (19.4)	0.377
Any serious TEAE, *n* (%)	2 (1.0)	0 (0.0)	
Any TEAEs leading to study drug withdrawal, *n* (%)	3 (1.5)	2 (3.0)	
Systolic blood pressure (SD)			
At baseline (V2)	128.2 (11.6)	127.2 (7.2)	
Range	97 to 180	110 to 145	
At end of DB treatment (V6)	127.4 (11.4)	128.5 (10.1)	
Range	95 to 185	110 to 160	
Mean change (SD)	−0.7 (11.6)	1.3 (9.3)	0.313
Range	−55 to 30	−20 to 33	
Diastolic blood pressure (SD)			
At baseline (V2)	80.1 (6.6)	80.3 (5.1)	
Range	57 to 112	60 to 91	
At end of DB treatment (V6)	79.8 (6.4)	80.4 (5.2)	
Range	60 to 108	64 to 101	
Mean change (SD)	−0.2 (7.5)	0.2 (5.9)	0.622
Range	−42 to 24	−24 to 33	
Heart rate (SD)			
At baseline (V2)	74.2 (10.2)	72.9 (10.2)	
Range	50 to 104	57 to 101	
At end of DB treatment (V6)	73.5 (9.8)	73.7 (10.8)	
Range	46 to 103	48 to 99	
Mean change (SD)	−0.3 (9.7)	0.3 (8.4)	0.725
Range	−24 to 26	−24 to 10	
BDI* total score			
Mean score at baseline (V2) (SD)	4.7 (3.4)	4.4 (3.6)	
95% CI	4.3 to 5.2	3.5 to 5.2	
Mean score at end of DB treatment (V6) (SD)	3.7 (3.3)	3.5 (3.7)	
95% CI	3.2 to 4.2	2.6 to 4.5	
Mean change between baseline and end of DB treatment	−1.0 (2.7)	−0.9 (3.2)	0.960
95% CI	−1.4 to −0.6	−1.7 to −0.1	

Definition of abbreviations: BDI = Beck Depression Inventory; CI = confidence interval; DB = double-blind; TEAE = treatment-emergent adverse event; V2 = visit 2; V6 = visit 6.
*Thirteen items.

does not precipitate or exacerbate OSA-related cardiovascular comorbidities, as already reported for psychostimulants used in narcolepsy acting via dopamine or norepinephrine release (31, 32). However, in this pitolisant trial, no significant changes were found in terms of blood pressure or heart rate, which provides a reassurance of safety. In contrast, in a recent meta-analysis, modafinil and armodafinil were associated with a mean increase in systolic blood pressure of 3.0 mm Hg (95% CI, 0.8–5.2 mm Hg) and a mean increase in diastolic blood pressure of 1.9 mm Hg (95% CI, 0.5–3.3 mm Hg) in three of seven trials (33). In a recent study using solriamfetol, the highest dose caused increases in systolic and diastolic blood pressure of 2.5 and 1.5 mm Hg, respectively, and heart rate increased by 2–3 beats per minute at doses greater than 75 mg. Again, head-to-head comparisons of the various clinically available wake-promoting agents, with particular focus on cardiovascular outcomes, are needed.

Our results confirm the favorable safety profile of pitolisant already reported in patients with narcolepsy (14, 15). No key changes were found in physical examination parameters or vital signs, depressive symptoms, and ECG or laboratory test results during the study. The changes reported in QTc (QTcF, >450 ms and elongation >60 ms) did not differ significantly between pitolisant and placebo. The pitolisant to placebo subject ratio was 3:1. Hence, there was no difference in the number of subjects with post-treatment QTcF values greater than 450 ms (3 of 201 patients [1.5%] in the pitolisant treatment group and 1 of 67 patients [1.5%] in the placebo group). These results are similar to those observed in the previous clinical cardiovascular safety study (through QT/QTc) with pitolisant (40 and 120 mg acute), including 58 healthy volunteers (males and females), in which 1 (1.7%) of 58 subjects exhibited a postdose QTcF longer than 450 ms, comparable to the incidence reported in the placebo period. Accordingly, results reported with pitolisant in the previous randomized controlled trials in patients with narcolepsy (14, 15) did not show any significant increase in QTc. A recent 1-year open-label trial in patients with narcolepsy confirmed the absence of significant ECG changes, including in the QTc (409 ± 25 ms at baseline and 416 ± 25 ms after 12 mo) (34). In line with reports of pitolisant use in patients with narcolepsy, there were no withdrawal symptoms after abrupt discontinuation of the drug in sleepy patients with OSA (14, 15). The overall tolerance was good, and the incidence rates of global as well as treatment-related TEAEs or TEAEs leading to study withdrawal were similar in both treatment groups, with no major safety concerns raised during the study. The most frequently reported TEAE was headache at a frequency of 8.5% with pitolisant and 11.9% with placebo, followed by insomnia, nausea, and vertigo.

The main limitation of this study was its 12-week duration. Long-term maintenance of efficacy and safety are being evaluated in an extension of the study. For most patients, the maximum dose of 20 mg was administered (82.5% in the pitolisant group and 86.6% in the placebo group); however, this dose may potentially have been too low to achieve maximum efficiency, as suggested by narcolepsy studies in which the maximum dose could be as high as 40 mg/d (14, 15). Moreover, no dose–response assessment was conducted, because dose assignment was not randomized, and dose uptitration is the standard approach in the clinical use of pitolisant. In conclusion, in this 12-week, phase 3 clinical trial, pitolisant reduced self-reported EDS and improved patient-reported outcomes, confirmed by the physician's CGI, in patients with OSA refusing or not adhering to CPAP treatment. ■

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