CHEST

Long-Term Efficacy and Safety of Pitolisant for Residual Sleepiness Due to OSA

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BACKGROUND: In people with OSA, excessive daytime sleepiness is a prominent symptom and can persist despite adherence to CPAP, the first-line therapy for OSA. Pitolisant was effective in reducing daytime sleepiness in two 12-week randomized controlled trials (RCTs), one in patients adherent to CPAP (BF2.649 in Patients With OSA and Treated by CPAP But Still Complaining of EDS [HAROSA 1]) and the other in patients refusing or not tolerating CPAP (BF2.649 in Patients With OSA, Still Complaining of EDS and Refusing to be Treated by CPAP [HAROSA 2]).

RESEARCH QUESTION: Does the efficacy and safety of pitolisant persist when these patients take it long-term?

STUDY DESIGN AND METHODS: All adults included in the HAROSA 1 and HAROSA 2 RCTs (both pitolisant and placebo arms) were offered pitolisant (up to 20 mg/d) after completion of the short-term double-anonymized phase (ie, from week 13) in an open-label cohort study. The primary efficacy outcome was the change in Epworth Sleepiness Scale score between baseline and week 52. Safety outcomes were treatment-emergent adverse event(s) (TEAE[s]), serious TEAEs, and special interest TEAEs.

RESULTS: Out of 512 adults included in the two RCTs, 376 completed the 1-year follow-up. The pooled mean difference in Epworth Sleepiness Scale score from baseline to 1 year for the intention-to-treat sample was −8.0 (95% CI, −8.3 to −7.5). The overall proportions of TEAEs, serious TEAEs, and TEAEs of special interest were 35.1%, 2.0%, and 11.1%, respectively, without any significant difference between patients in the initial pitolisant and placebo arms. No cardiovascular safety issues were reported.

INTERPRETATION: Pitolisant is effective in reducing daytime sleepiness over 1 year in adults with OSA, with or without CPAP treatment. Taken for 1 year, it has a good safety profile (including cardiovascular).

TRIAL REGISTRATION: ClinicalTrials.gov; Nos.: NCT01071876 and NCT01072968; URL: www.clinicaltrials.gov

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KEY WORDS: Epworth Sleepiness Scale score; excessive daytime sleepiness; insomnia; long-term pitolisant; OSA; safety

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ABBREVIATIONS: HAROSA 1 = BF2.649 in Patients With OSA and Treated by CPAP But Still Complaining of EDS; HAROSA 2 = BF2.649 in Patients With OSA, Still Complaining of EDS and Refusing to be Treated by CPAP; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; HAROSA = Histamine Antagonist Receptor in Obstructive Sleep Apnea; LSEQ = Leeds Sleep Evaluation Questionnaire; OsLer = Oxford Sleep Resistance Test; RCT = randomized controlled trial; rEDS = residual excessive daytime sleepiness; TEAE = treatment-emergent adverse event; TEAESI = treatment-emergent adverse event of special interest; TESAE = serious treatment-emergent adverse event

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Take-home Points

Study Question: Pitolisant was effective in reducing daytime sleepiness caused by OSA in two 12-week randomized controlled trials, but does the efficacy and safety of pitolisant persist when these patients take it long term?

Results: The efficacy of pitolisant persisted during continuation to 1 year and reduced daytime sleepiness in patients initially on placebo, in both cases with a good safety profile, including no emergent cardiovascular issues.

Interpretation: One-year treatment with pitolisant is effective and safe in reducing residual daytime sleepiness in patients with OSA, with or without CPAP.

Worldwide, > 1 billion people suffer from OSA.[1,2] Beyond its cardiometabolic consequences, excessive daytime sleepiness (EDS) is the most prominent symptom, reported by up to 50% of patients with OSA. EDS is associated with impaired everyday functioning, including loss of productivity at work, degraded quality of life, and diminution in fitness to drive, leading to a higher risk of traffic accidents.[3,4]

CPAP is the first-line primary treatment for symptomatic moderate to severe OSA.[5] CPAP has a substantial effect in eradicating apneas and hypopneas during sleep, suppressing the associated hypoxic burden and normalizing sleep quality and architecture. In the vast majority of patients with OSA, CPAP reduces daytime sleepiness and improves their quality of life with a dose-response relationship between the extent of recovery and duration of CPAP nightly usage.[6] Despite appropriate management of CPAP therapy, residual EDS (rEDS) continues to be reported as disabling in a subgroup of 6% to 15% of patients with OSA being treated with CPAP.[7-9]

Pitolisant is a selective histamine H3 receptor antagonist and inverse agonist with strong wake promoting effects. The efficacy and safety of pitolisant have been demonstrated in EDS associated with narcolepsy.[10,11] Among wake-promoting agents that have been studied for treatment of rEDS in OSA, efficacy and safety of pitolisant were also demonstrated in two pivotal 12-week randomized controlled trials (RCTs), the first in patients with moderate OSA and rEDS adherent to CPAP (BF2.649 in Patients With OSA and Treated by CPAP But Still Complaining of EDS [HAROSA 1]) and the second in those refusing or not tolerating CPAP (BF2.649 in Patients With OSA, Still Complaining of EDS and Refusing to be Treated by CPAP [HAROSA 2]).[12,13] rEDS is a chronic condition that often requires the long-term use of stimulants on top of primary OSA therapy[9]; however, demonstration of their sustained efficacy and long-term safety is necessary. In short-term RCTs in OSA,[12,13] the safety profile of pitolisant appeared favorable, in particular regarding cardiovascular outcomes. Long-term safety has been confirmed in narcolepsy[14] but remains to be studied in OSA over longer exposure to the compound, particularly in a multimorbid OSA population.

This long-term open-label study of pitolisant for up to 1 year, which included participants from the two previous short-term (12-week) placebo-controlled, double-anonymized, randomized trials, evaluated the maintenance of efficacy and safety of pitolisant in adults with OSA and rEDS at inclusion.

Study Design and Methods

Design and Data

HAROSA 1[13] and HAROSA 2[12] were prospective, multicenter, European, randomized, double-anonymized trials of pitolisant (maximum dosage 20 mg) vs placebo, in patients with moderate to severe OSA and EDS (Epworth Sleepiness Scale [ESS] score ≥ 12), adherent to CPAP (HAROSA 1) or refusing or not tolerating CPAP (HAROSA 2). The intervention was pitolisant taken fasted once daily, with individual titration starting from 5 mg/d for 1 week, then 10 mg/d and 20 mg/d based on efficacy and tolerability.

Both studies started with a 12-week double-anonymized period[12,13]: visit 1 screening visit (day 14), visit 2 inclusion baseline visit (day 0), visit 3 end

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of up-titration (week 2), follow-up intermediate visits 4 (week 3) and 5 (week 7), end-point visit 6 (week 12), and then one single-anonymized washout period of 1 week with placebo (week 13). From week 13, patients optionally entered the open-label phase. The patients initially treated with pitolisant (group 1) continued their treatment after the end of the RCT (week 13), whereas patients initially treated with placebo (group 2) were treated with pitolisant starting at week 13. At the end of the RCTs, a 2-week titration procedure was conducted in both groups with the following visits: visit 7 (week 14), visit 8 (week 16), visit 9 (week 28), visit 10 (week 40), visit 11 (week 52; start of a washout period without treatment), and visit 12 at the end of the trial (week 53).

The following variables were measured at baseline: age, sex, BMI, daily work duration, medical history including comorbidities, and time since OSA diagnosis. Whether to include a patient with a history of cardiovascular disease was left to the discretion of the investigator. The patient's QTc interval was checked on the ECG trace. The following end points were collected at each visit: ESS score, EQ-5D score, Leeds Sleep Evaluation Questionnaire (LSEQ) score, Trail Making Test with subscores A and B, Clinical Global Impression of Improvement score, Patient's Global Opinion of the Effect score, and Pichot Fatigue Scale score. The Oxford Sleep Resistance Test (OsLer) was performed at baseline, week 12, and week 52. OsLers were done over 40 min, at 9 AM, 11 AM, and 1 PM (with a 2-h interval between each test).

Safety was measured by the number of patients having experienced one or more treatment-emergent adverse events (TEAEs) of at least moderate intensity, serious TEAEs (TESAEs), and TEAEs of special interest (TEAESIs) (anxiety, depression, drug misuse, drug dependence, fertility disorders, gastric disorders caused by hyperactivity, insomnia, proconvulsive potential, QT-interval prolongation, rebound effect, and/or weight increase). Repeated measurements of BP and heart rate were collected at each clinical visit.

Ethics

HAROSA 1 and HAROSA 2 were conducted in, respectively, 35 and 28 sleep centers in 10 European countries between August 12, 2011, and May 7, 2015. The parent RCTs were registered in the ClinicalTrials.gov registry (HAROSA 1: NCT01071876 and HAROSA 2: NCT01072968). The RCTs had been approved by the appropriate institutional review board or ethics committee of each study center (names of committees and approval dates are listed in e-supplementary materials). The RCTs were performed in respect of the Declaration of Helsinki. The possibility of continuation or switch to pitolisant at the end of short-term (12-week) follow-up together with 1-year follow-up had been included in the study protocols and in the written informed consent given by all included patients.

Statistical Methods

All randomized patients of the HAROSA 1 and HAROSA 2 studies were analyzed (intention-to-treat sample). The primary end point was the change in ESS score from baseline of the RCTs to the 1-year follow-up visit. The inferential model appropriate for this double-anonymized trial followed by an open-label cohort study was a longitudinal multistudy mixed repeated measurement model[15] assuming random patient factor, fixed time, fixed treatment group, treatment factor changing over time, fixed study and sex factors, age as a fixed covariate, and group $\times$ time interaction. We considered an interaction to be statistically significant when the P value of the interaction term was $< .05$, and when the test of the change in the residual sum of squares when comparing the model with and without interaction was significant at the $\alpha = .05$ level. For sensitivity purposes, we investigated the homogeneity of the treatment effect across centers and the homogeneity of the treatment effect across possible subgroups of patients defined by age, sex, country, and social status. Although the placebo was not studied after week 12, the effect of pitolisant at 1 year compared with placebo was estimated using a nonlinear longitudinal regression model, assuming a Mitscherlich asymptotic law[16] with random treatment and the slope of treatment dependency. The rationale for the use of this model is given in e-Material 3.

Our analysis is based on full missing data imputation. We used a multiple imputation procedure that was predetermined to adjust for any variable that might influence the dropout: age, sex, end of trial status, and time. If the reason for ending participation in the study was lack of satisfaction with treatment, the imputation of the data was the worst-case imputation, meaning that the treatment was considered as having failed the patient. This analysis was prespecified in our statistical analysis plan (ie, before we started this analysis). The nonmissing at random jump to reference option assumed that after dropout, the participant's

conditional outcomes deteriorate similarly to those of placebo. Secondary end points and pitolisant safety compared with placebo were analyzed according to the main aforementioned model for the primary end point. Statistical tests were performed with a two-sided 5% level of significance.

Results

Study Population and Study Flow

By pooling the HAROSA 1 and HAROSA 2 parent pivotal studies (244 and 268 randomized patients, respectively), a total of 512 patients with OSA were included. Within each study, the sociodemographic and baseline clinical profiles were comparable between the two groups (Table 1). At inclusion in the RCTs, approximately one-half of the patients had a history of cardiovascular disease for which they were still being treated. This was predominately hypertension (e-Table 1). The study flowchart is shown in Figure 1, with 376 participants (73.4%) completing the 1-year study. e-Table 2 provides a comparison of demographic and clinical parameters between patients who remained until the end (normal end) and those who dropped out. This comparison is provided for both studies separately and for the whole population of the two studies. As shown in e-Table 2, we did not find any marked differences between the two subsets of patients. We also studied the change in weight and BMI of the patients over time. From a mean weight of 98.8 kg at baseline, the final weight slightly decreased by −1.06 kg (95% CI, −1.88 to −0.26) without significant difference between the two groups (−0.02 kg; 95% CI, −3.06 to 3.1; $P = .988$).

Efficacy Analysis

The results of the mixed longitudinal model of mean ESS score changes over time (Table 2) are shown in Figure 2. The mean baseline ESS score of those initially treated with placebo was 15.2 (95% CI, 14.4 to 16.0), without a significant difference between the studies ($P = .538$), and likewise for age ($P = .06$), sex ($P = .09$), or group ($P = .726$). For the control subjects (group 2) treated with placebo until week 12, a significant change in ESS score ($\cong -3$) was observed until week 12. Further to pitolisant administration, a decrease of −7.2 in week 16 compared with baseline plateaued at $\cong -8$ until week 52, followed by a small change to −7.7 after treatment interruption from week 52. For group 1 (pitolisant treated since baseline), a mean change of −6.4 was

TABLE 1] Study Participants

Characteristic	HAROSA 1 (n = 244)				HAROSA 2 (n = 268)				Total (N = 512)			
	Placebo (n = 61)		Pitolisant (n = 183)		Placebo (n = 67)		Pitolisant (n = 201)		Placebo (n = 128)		Pitolisant (n = 384)	
Age, y	51.0	± 10.6	53.8	± 10.5	52.1	± 11.0	51.9	± 10.6	51.6	± 10.8	52.8	± 10.6
BMI, kg/m^2	32.2	± 4.3	32.7	± 5.2	32.9	± 4.3	32.8	± 4.6	32.5	± 4.3	32.7	± 4.9
Time since OSA diagnosis, y	4.1	± 4.8	3.7	± 3.7	1.0	± 1.9	1.0	± 2.1	2.4	± 3.9	2.3	± 3.2
Female	13.1	(8)	18.6	(34)	23.9	(16)	24.9	(50)	18.8	(24)	21.9	(84)
History of cardiovascular disease	44.3	(27)	60.7	(111)	52.2	(35)	54.7	(110)	48.4	(62)	57.6	(221)

Values are mean ± SD or % (No.). HAROSA = Histamine Antagonist Receptor in Obstructive Sleep Apnea.

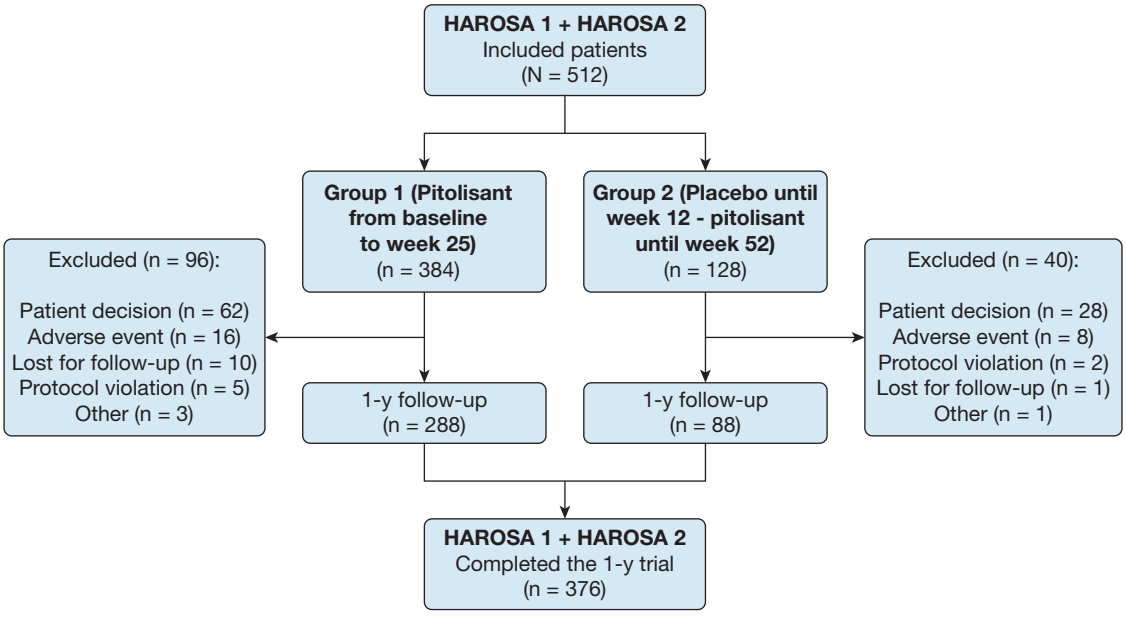

Figure 1 – *HAROSA 1 was with patients adherent to CPAP; HAROSA 2 was with patients refusing or not tolerating CPAP. HAROSA = Histamine Antagonist Receptor in Obstructive Sleep Apnea.*

found at week 12 (with a significant difference compared with group 2 of −3.3 [95% CI, −4.1 to −2.5; $P < .001$]), followed by a slight decrease reaching −7.8 at 1 year (without significant difference compared with group 2 of 0.7 [95% CI, −0.2 to 1.7; $P = .105$]). The pooled mean difference in ESS score from baseline to 1 year for the whole intention-to-treat sample was −8.0 (95% CI, −8.3 to −7.5).

Secondary end points are summarized in Table 3. All the end points are characterized by a significant improvement from baseline until the end of 1-year follow-up. More precisely, a significant difference was found in mean OsLer results in group 1 treated by pitolisant compared with group 2 (placebo) at week 12, with a significant change from baseline for the entire sample (both groups) at week 52 (Fig 3, Table 3).

TABLE 2] Mixed Longitudinal Model of Changes in ESS Over Time

	Group 2 (n = 128)			Group 1 (n = 384)		
	(Placebo Treated Until Week 12)			(Pitolisant Treated From Baseline)		
Study Visit	Change[a]	95% CI	Change[b]	Diff 1-2[c]	95% CI	*P* Value
Baseline ESS: mean, 15.2 (95% CI, 14.4-16.0)[d]						
Week 2	−3.1	−3.8 to −2.4	−3.6	*−0.5*	−1.3 to 0.3	.234
Week 3	−3.3	−4.0 to −2.6	−4.9	**−1.6**	−2.4 to −0.8	< .001
Week 7	−3.0	−3.7 to −2.3	−5.9	−2.9	−3.7 to −2.1	< .001
Week 12	**−3.1**	**−3.8 to −2.4**	**−6.4**	**−3.3**	**−4.1 to −2.5**	**< .001**
Week 16	−7.2	−8.0 to −6.5	−6.9	0.3	−0.6 to 1.1	.572
Week 28	−8.0	−8.8 to −7.2	−7.7	0.3	−0.6 to 1.2	.507
Week 45	−8.2	−9.0 to −7.4	−7.9	0.3	−0.6 to 1.2	.492
Week 52	**−8.5**	**−9.3 to −7.7**	**−7.8**	**0.7**	**−0.2 to 1.7**	**.105**
Week 53	−7.7	−8.5 to −6.9	−7.1	0.6	−0.3 to 1.5	.209

Trajectory in time of the two groups from baseline. Results of the longitudinal analysis (estimated marginal means from mixed model assessing treatment effect and treatment-time interaction). The rows in bold are key timepoints in the study: Week 12 end of double-anonymized period; week 52 end of open-label long-term pitolisant. Diff = difference; ESS = Epworth Sleepiness Scale.

[a]For each visit from week 2, mean change and 95% CI from baseline for group 2 (placebo treated until week 12).

[b]For each visit from week 2, mean change from baseline for group 1 (pitolisant treated from baseline).

[c]For each postbaseline visit, difference between group 1 and group 2, 95% CI and *P* value.

[d]Overall mean is the mean estimated ESS score at baseline for a reference group defined as 50-year-old male patients with placebo until week 12.

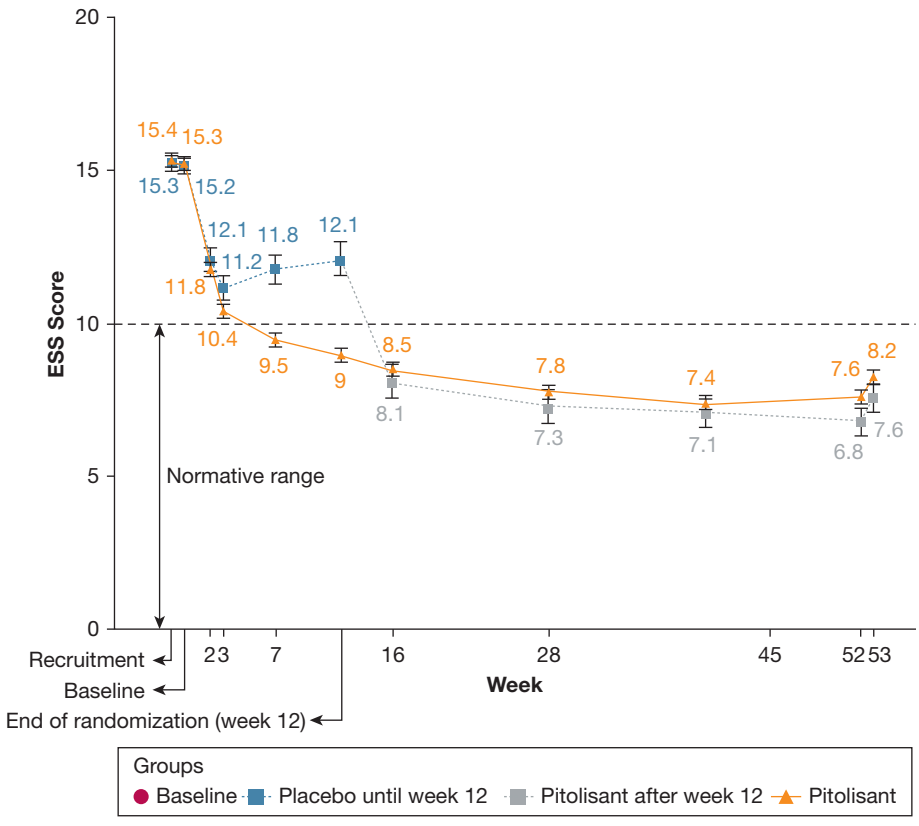

Figure 2 – *Mean changes over time in ESS score. ESS = Epworth Sleepiness Scale.*

EQ-5D, LSEQ getting to sleep, LSEQ total, Clinical Global Impression of Improvement, Patient's Global Opinion of the Effect, and Pichot Fatigue scale scores were significantly improved at week 12 in group 1 compared with group 2, whereas no differences were observed for the other end points (LSEQ quality of sleep, LSEQ alertness and behavior following wakefulness, LSEQ ease of awakening from sleep, and Trail Making Test part A and part B scores). Significant changes from baseline for the entire sample (both groups) were observed for all secondary end points at week 52. At 1 year, for all end points, the mean change from baseline was not significantly different between groups 1 and 2.

Sensitivity Analyses

The potential effect of center on treatment effect tested by an additional random treatment effect across centers analysis was found to be nonsignificant (SD across centers, 1.9; 0-3.9). The homogeneity of the treatment effect size across possible subgroups of patients was tested by adding age, sex, country, and BMI as main factors and for interactions with treatment. No significant interaction effect or effect of these variables was found.

Finally, the long-term effect of pitolisant was modeled against placebo by conducting a nonlinear regression based on the Mitscherlich asymptotic regression law. The goodness of fit of the model was confirmed by a coefficient of determination $R^2 = 0.81$ (0.77-0.85). After this model, the estimated effect of pitolisant (20 mg/d) compared with placebo at 1 year was a reduction in ESS score of −4.44 (95% CI, −4.84 to −4.04; $P < .001$) (Fig 4). See e-material 3 for the presentation and discussion of this approach

Safety

Cardiovascular Safety: The longitudinal analysis of systolic BP (Fig 5) provided evidence of an increasingly significant effect of age (0.12 [95% CI, 0.4 to 0.19]; $P = .003$), a reduced effect in women (−3.7 [95% CI, −5.6 to −1.7]; $P < .001$), no time effect (analysis of variance, $P = .233$), and no effect of the treatment at any time (analysis of variance, interaction time × treatment, $P = .694$). Similar results were found for diastolic BP (Fig 5) and heart rate (Fig 5). A slight increase in QTc of 5.9 ± 1.94 milliseconds (95% CI, 2.1, 9.7) (baseline: 375.5 ± 35.2

TABLE 3] Summary Table for All Secondary End Points

End Point	Baseline[a]		Week 12[b]		Week 52[c]		Diff Week 12[d]		Diff Week 52[e]		Change[f]	
OsLer	20.7	± 22.5	7.6	± 2.6	8.2	± 3.1	5.7	± 3.0[g]	2.7	± 3.5	11.9	± 1.4[g]
EQ-5D	69.6	± 17.0	2.6	± 1.4	5.2	± 1.6	3.9	± 1.7[g]	3.7	± 1.9	8.2	± 0.9[g]
LSEQ-GTS	42.5	± 18.2	1.2	± 2.4	3.2	± 2.6	7.1	± 2.8[g]	4.6	± 3.2	7.5	± 1.2[g]
LSEQ-QOL	42.3	± 19.8	14.1	± 2.6	19.7	± 2.8	1.3	± 3.0	−1.4	± 3.3	17.9	± 1.3[g]
LSE-AFS	45.2	± 21.6	13.3	± 3.0	17.1	± 3.4	3.5	± 3.5	2.7	± 3.8	18.8	± 1.5[g]
LSEQ-BFW	41.9	± 19.3	14.2	± 2.9	21.8	± 3.6	6.5	± 3.4[g]	4.0	± 3.9	24.1	± 1.2[g]
LSEQ total	43.0	± 12.5	10.6	± 1.7	15.0	± 1.8	4.8	± 1.9[g]	2.9	± 2.1	17.1	± 0.9[g]
Trail Making Test part A	50.2	± 21.7	−6.7	± 1.2	−9.3	± 1.2	−0.8	± 1.4	0.3	± 1.4	−9.3	± 0.8[g]
Trail Making Test part B	107.0	± 48.8	−5.5	± 3.3	−21.5	± 3.5	−1.9	± 3.8	−2.6	± 3.9	−23.9	± 2.1[g]
CGI	3.6	± 0.9	−0.4	± 0.1	−1.3	± 0.1	−0.6	± 0.1[g]	0.0	± 0.1	−1.4	± 0.1[g]
PGO	4.0	± 0.0	−1.1	± 0.1	−1.9	± 0.1	−0.6	± 0.1[g]	0.0	± 0.1	−2.0	± 0.1[g]
Pichot Fatigue Scale	12.6	± 6.8	−1.8	± 0.5	−3.8	± 0.6	−1.9	± 0.6[g]	−1.4	± 0.6	−4.9	± 0.3[g]

Both CGI and Pichot Fatigue scales vary in range from 0 to 5, with a decrease indicating perceived improvement. CGI = Clinical Global Impression of Improvement; Diff = difference; LSEQ-AFS = Leeds Sleep Evaluation Questionnaire ease of awakening from sleep; LSEQ-BFW = Leeds Sleep Evaluation Questionnaire alertness and behavior following wakefulness; LSEQ-GTS = Leeds Sleep Evaluation Questionnaire getting to sleep; LSEQ-QOL = Leeds Sleep Evaluation Questionnaire quality of sleep; OsLer = Oxford Sleep Resistance Test; PGO = Patient's Global Opinion of the Effect.

[a]Baseline values ± SD for the overall sample.

[b]Mean changes from baseline ± SE of control group 2 (placebo treated during the double-anonymized phase) at week 12.

[c]Mean changes from baseline ± SE of control group 2 (placebo treated during the double-anonymized phase) at week 52.

[d]Mean difference ± SE between both groups at week 12.

[e]Mean difference ± SE between both groups at week 52.

[f]Mean change from baseline ± SE for the whole sample (both groups).

[g]Significant difference at $P < .05$.

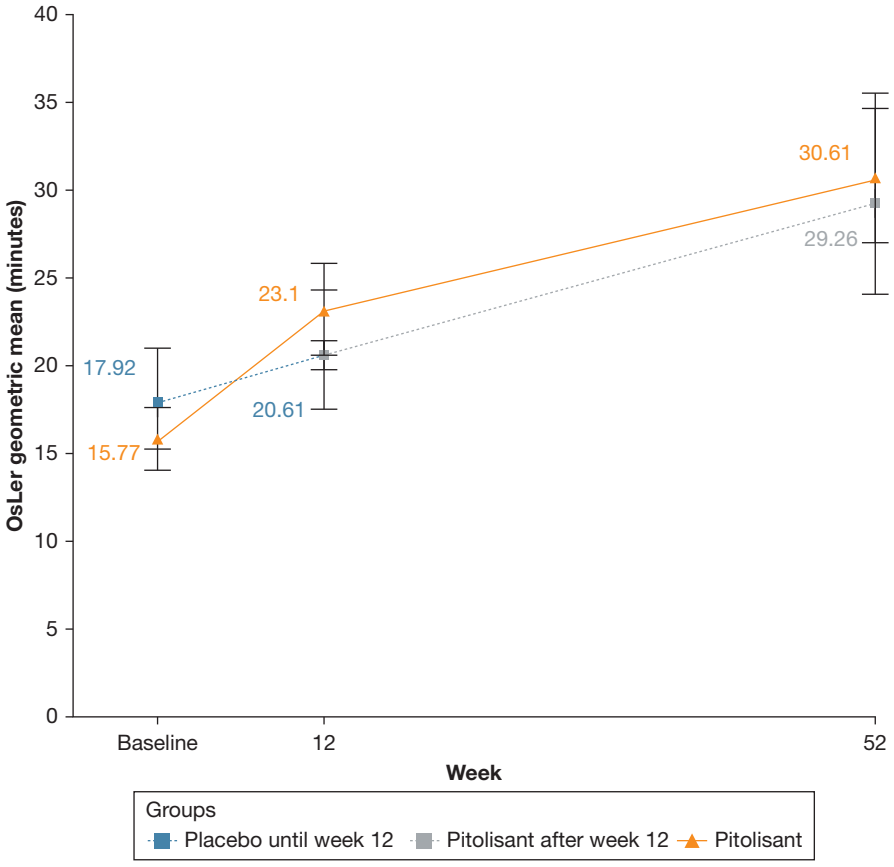

Figure 3 – *OsLer: mean changes over time in mean sleep latencies (mixed longitudinal model). OsLer = Oxford Sleep Resistance Test.*

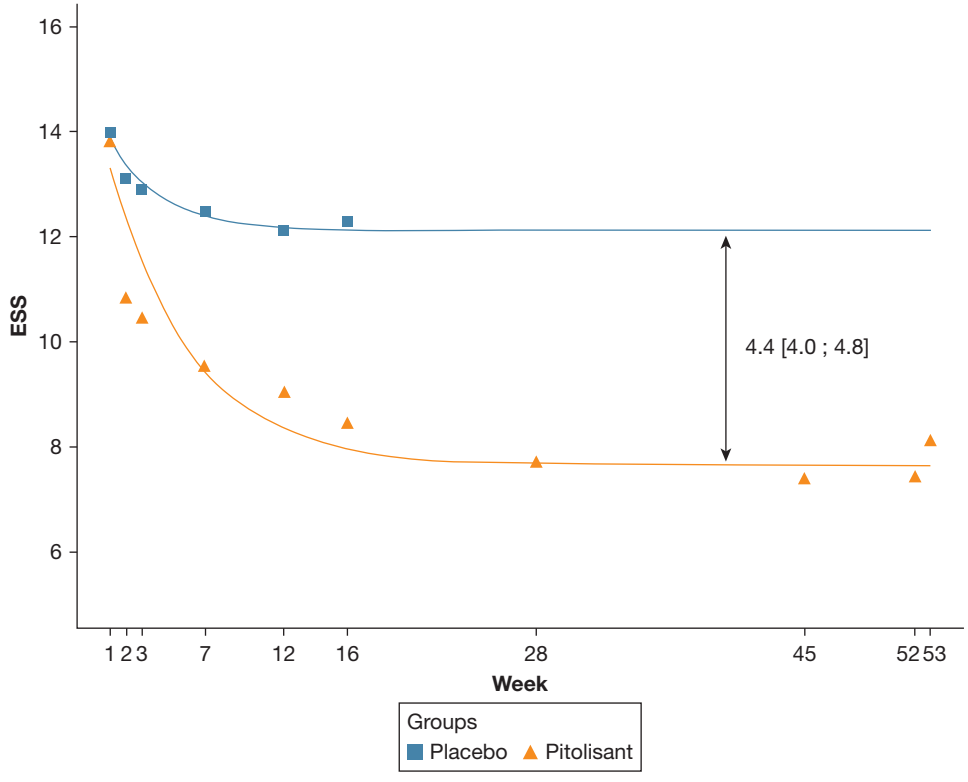

Figure 4 – *Determination of the long-term effect using the Mitscherlich model. ESS = Epworth Sleepiness Scale.*

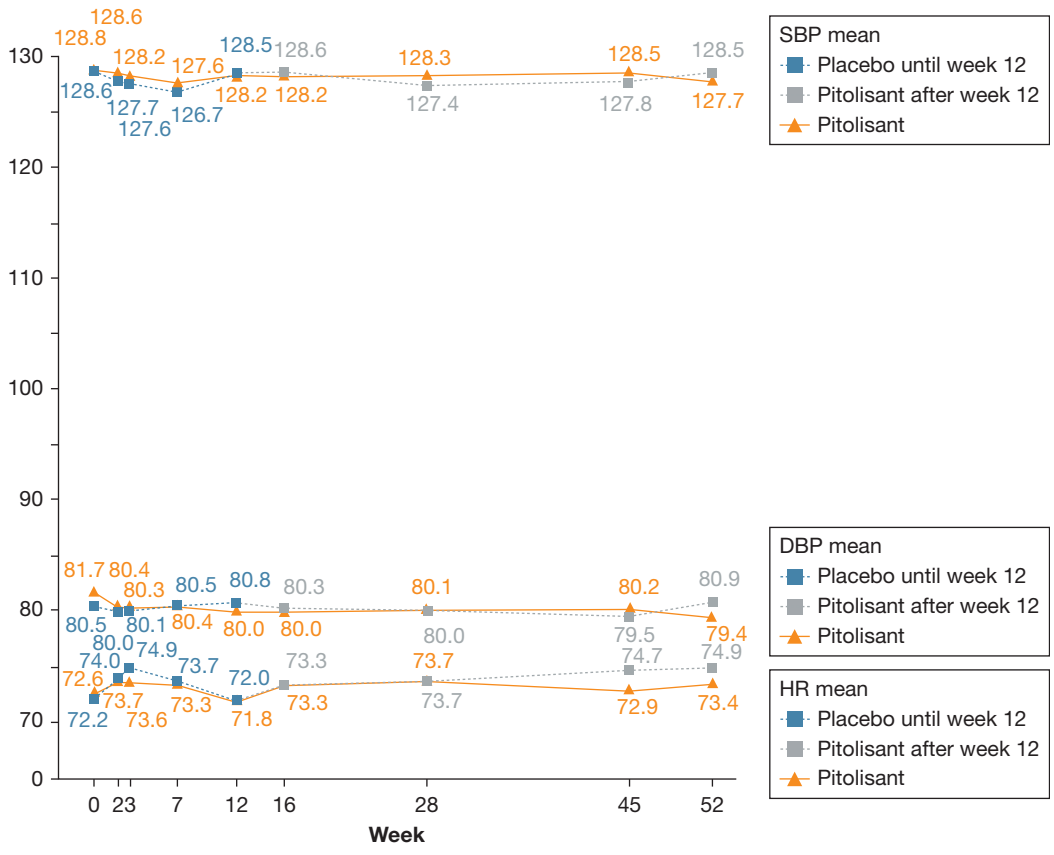

Figure 5 – *BP changes over time (mixed longitudinal model). DBP = diastolic BP; HR = heart rate; SBP = systolic BP.*

milliseconds vs month 12: 381.4 ± 30.7 milliseconds) occurred in HAROSA 1 at month 12 only (e-Table 3), with no changes reported in the HAROSA 2 study at any of the evaluation points.

Only one case of incident moderate hypertension occurred in a patient treated by CPAP during the 1-year follow-up, considered possibly treatment-related by the investigator (see narratives in e-Material 2). No changes were found between baseline and month 12 regarding weight and BMI in either HAROSA 1 or HAROSA 2 studies.

Safety was evaluated as the proportion of patients having experienced at least one occurrence of the three aggregated end points TEAE, TESAE, and TEAESI during the whole follow-up (Table 4).

Serious Adverse Events: Overall, in the open-label period, a total of 11 out of 435 patients (2.5%) experienced 12 TESAEs. Among them, 10 events were reported in nine patients (with CPAP) in group 1 (nine of 332, 2.7%) and two events in two patients (one with CPAP, one without CPAP) in group 2 (two of 103, 1.9%) (e-Material 1).

TABLE 4] Patients With TEAE, TESAE, and TEAESI in the Open Label Study

	HAROSA 1 (Open Label)		HAROSA 2 (Open Label)		Total	
Events	Placebo[a] (n = 48)	Pitolisant[b] 20 mg/d (n = 151)	Placebo[a] (n = 55)	Pitolisant[b] 20 mg/d (n = 181)	Placebo[a] (n = 103)	Pitolisant[b] 20 mg/d (n = 332)
TEAE	(23) 47.9	(83) 55.0	(18) 32.7	(52) 28.7	(41) 39.8	(135) 40.7
TESAE	(1) 2.1	(9) 6.0	(1) 1.8	(0) 0.0	(2) 1.9	(9) 2.7
TEAESI	(10) 20.8	(17) 11.3	(5) 9.1	(15) 8.3	(15) 14.6	(32) 9.6

Values are (No. of patients) and percent. HAROSA = Histamine Antagonist Receptor in Obstructive Sleep Apnea; TEAE = treatment-emergent adverse event; TEAESI = TEAE of special interest; TESAE = serious treatment-emergent adverse event.
[a]Group 2: placebo treated until week 12.
[b]Group 1: pitolisant treated from baseline.

Death: One death was reported during open-label follow-up (a patient without CPAP in group 1 [ie, pitolisant in double-anonymized phase]). It was considered unlikely to be related to the study treatment (see narrative in the e-Material 2).

Adverse Events of Special Interest: During the open-label phase after the HAROSA 1 study (with CPAP), 29 TEAESIs were reported in 27 patients (13.6%): 19 events in 17 patients (11.3%) in group 1 and 10 events in 10 patients (20.8%) in group 2 (e-Table 4). The most frequently reported TEAESI was insomnia, with 11 patients (7.3%) in group 1 and four patients (8.3%) in group 2. None was considered severe, but treatment-related for nine patients in group 1 and not treatment-related for two patients. In three of the four patients in group 2, insomnia was considered treatment-related. The other TEAESIs reported during the open-label phase are shown in e-Table 4.

In group 1 (pitolisant in the double-anonymized phase), three TEAESIs were considered severe: anxiety and depressed mood, both considered as likely treatment-related, and depression considered as unlikely treatment-related. In group 2, the only severe TEAESI was upper abdominal pain, which was considered possibly treatment-related.

In the open-label phase after the HAROSA 2 study (no CPAP), 21 TEAESIs were reported in 20 patients (8.5%): 16 events in 15 patients (8.3%) in group 1 and five events in five patients (9.1%) in group 2 (e-Table 5). The most frequently reported TEAESI was insomnia, which was observed for seven patients (3.9%) in group 1 and four patients (7.3%) in group 2. Other TEAESIs reported during the double-blind phase are shown in e-Table 5. For all but one patient, the TEAESIs were of mild or moderate severity. One patient in group 1 experienced a severe TEAESI (insomnia) during the open-label phase. For all patients for whom insomnia was reported, the relationship was considered either possible or likely.

Discussion

This study demonstrated that the efficacy of pitolisant for treating residual sleepiness in OSA is maintained for up to 1 year of treatment. In the subgroup of 376 patients (73.4%) completing the study, the primary ESS baseline overall mean value was 15.2 ± 3, with a clinically meaningful reduction at week 52 (end of open-label period) of −8.1 ± 0.4. Comparable 1-year ESS mean values were found for patients who had initially been started on placebo or immediately started on pitolisant (6.8 ± 4.5 and 7.6 ± 4.4, respectively). Our modeling of ESS trajectories demonstrated that the sharpest ESS decrease was observed soon after the initiation of effective treatment (2-4 weeks) and seems to reach a plateau after 6 or 7 weeks with a maintenance of long-term efficacy. This study also confirms for the first time the long-term safety and tolerability profile of pitolisant in multimorbid OSA, in particular for cardiovascular comorbidities.

The observed sustained reduction at 1 year in daytime sleepiness is meaningful and by far above the minimal clinically important difference in the ESS, consistently estimated at between −2 and −3 points[17,18] in patients with OSA. The ESS, which quantifies the complaint of EDS, is the tool most frequently used in RCTs to assess the effect of wake-promoting treatments for residual EDS in OSA. The placebo effect is significant especially in subjective measures and has been reported in a recent systematic review and meta-analysis as slightly higher than the minimal clinically important difference.[19] The placebo effect in our study was in the range of values reported by the systematic review,[19] and our results are strengthened by the significant improvements in objective measurements of alertness via the OsLer (included in the study).

The two pivotal, parent, randomized, short-term studies with pitolisant were conducted in two distinct OSA populations[12,13]: patients adherent to CPAP[13] and patients nonadherent and refusing CPAP.[12] We found no heterogeneity in the long-term efficacy of pitolisant in these two situations, with similar final values for ESS at 1 year.

Residual sleepiness is associated with a constellation of multidimensional symptoms (eg, fatigue, depression), altering quality of life and the patient's overall perception of good health.[7,20] In the current study, significant and sustained improvements were also demonstrated for a vigilance test (OsLer) and for functional status (fatigue, quality of life, and the physician's global assessment scales).

In sensitivity analyses, we demonstrated a homogeneous effect of the treatment irrespective of the baseline characteristics (age, sex, BMI, and country). These data enhance the generalizability of our results in a real-world setting and complete the homogeneous response between participants who were adherent and nonadherent to primary OSA therapy.

This remains even though follow-up management pathways of patients treated with CPAP do vary between countries, but also because residual sleepiness and the perception of sleepiness are influenced by sex, age, and cultural or environmental contexts. In data from the European Sleep Apnea Database,[21] EDS appeared heterogeneous among different European countries both at baseline and under CPAP treatment, suggesting that it is influenced by cultural and lifestyle factors. Participants in our study were from several different European countries, and it is reassuring for the generalization of the findings that no significant difference was found across centers in the sensitivity analyses.

To our knowledge, this is the first study providing results regarding the long-term safety profile of pitolisant in a population with OSA. Overall, the safety profile was good during the 1-year follow-up, with infrequent mild to moderate side effects, confirming the long-term safety profile of pitolisant already obtained in patients with narcolepsy.[14] OSA is a multimorbid disease, and particular attention should be paid to cardiovascular risk in individuals with cardiac arrhythmias and uncontrolled hypertension. This cardiovascular risk together with an insufficient risk/benefit ratio led to the suspension of reimbursement of modafinil in Europe for this indication.[22] Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is an alternative wake stimulant reducing sleepiness by another mechanistic pathway to that of pitolisant. Like pitolisant, the efficacy of solriamfetol has also been reported as equivalent regardless of adherence or not to primary OSA therapy.[23,24] However, the 300-mg dose of solriamfetol increases BP, and both European and US health agencies have limited the maximum daily dose to 150 mg.[20] In our long-term open-label study, at 1 year, no significant changes in BP or heart rate were reported with pitolisant. Only a small QTc increase of 6 milliseconds, considered nonclinically relevant, was found in HAROSA 1 at month 12. Nevertheless, the concurrent use of pitolisant with drugs that may prolong the QT interval should be avoided. Although 376 patients completed the study with 1 year of follow-up, the study was not powered to assess impact on long-term cardiovascular outcomes. Such an effect is unlikely because of the compound's mechanism of action. However, data on long-term hard outcomes are lacking, and future collaborative studies between sleep specialists and cardiologists are required.

Study limitations include the difference in patient selection in the pivotal parent studies; however, the two trials had the same design, duration, and end points. Almost all the patients used a final dose of 20 mg of pitolisant. Potential bias of design conditions (double-anonymized/open label and delayed start of the control group) had no effect on the observed efficacy, therefore confirming the pooled estimate of the mean ESS reduction of -8.1 ± 0.4 after 1 year of treatment. Another limitation of the study was related to the participants who dropped out during the 1-year treatment period, with a potential selection bias in favor of good responders with good tolerance. Our imputation of missing data for dropouts considered all the reasons for dropout, including patients stopping for lack of efficacy, or for a drug-related adverse effect. Despite the existence of dropouts at 1 year, this analysis can be considered as conducted on a full intent-to-treat basis, and therefore included all the 512 patients starting at baseline. We did not plan a double-anonymized randomized withdrawal phase during the open-label study, which prevents us from formally demonstrating long-term maintenance of the efficacy of pitolisant. Finally, BP and heart rate were not assessed using 24-h ambulatory BP monitoring.

Interpretation

Our data support the long-term maintenance of efficacy of pitolisant in the treatment of rEDS in individuals with OSA. The good safety profile was consistent with the prior short-term RCTs of pitolisant and long-term follow-up in narcolepsy. In particular, no safety issues concerning cardiovascular parameters emerged with long-term administration of pitolisant for up to 1 year.

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