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Original Article

Efficacy of pitolisant in patients with high burden of narcolepsy symptoms: pooled analysis of short-term, placebo-controlled studies

Craig W. Davis [a, *], Ulf Kallweit [b], Jean-Charles Schwartz [c], Lois E. Krahn [d], Ben Vaughn [e], Michael J. Thorpy [f]

[a] Harmony Biosciences, LLC, Plymouth Meeting, PA, USA
[b] Universität Witten/Herdecke, Witten, Germany
[c] Bioprojet Pharma, Paris, France
[d] Mayo Clinic Hospital, Phoenix, AZ, USA
[e] Rho, Durham, NC, USA
[f] Albert Einstein College of Medicine, Bronx, NY, USA

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ABSTRACT

Study objective: To evaluate the efficacy of pitolisant, a histamine 3 (H_3)-receptor antagonist/inverse agonist, in adult patients with high burden of narcolepsy symptoms.
Methods: Data were pooled from two randomized, placebo-controlled, 7- or 8-week studies of pitolisant (titrated to a potential maximum dose of 35.6 mg/day) in adults with narcolepsy. Analyses included three independent patient subgroups: Epworth Sleepiness Scale (ESS) baseline score ≥16, Maintenance of Wakefulness Test (MWT) sleep latency ≤8 min, and ≥15 cataplexy attacks per week.
Results: The analysis populations included 118 patients for ESS (pitolisant, n = 60; placebo, n = 58), 105 for MWT (pitolisant, n = 59; placebo, n = 46), and 31 for cataplexy (pitolisant, n = 20; placebo, n = 11). On the ESS, least-squares mean change from baseline was significantly greater for pitolisant (−6.1) compared with placebo (−2.3; $P < 0.001$). Significantly more pitolisant-treated patients were classified as treatment responders: ESS score reduction ≥3, 69.0% in the pitolisant group versus 35.1% in the placebo group ($P = 0.001$); final ESS score ≤10, 36.2% versus 10.5%, respectively ($P = 0.005$). On the MWT, mean sleep latency increased from 3.5 min to 10.4 min with pitolisant and from 3.4 min to 6.8 min with placebo ($P = 0.017$). Least-squares mean change in the weekly rate of cataplexy was significantly greater for pitolisant (−14.5; baseline, 23.9; final, 9.4) compared with placebo (−0.1; baseline, 23.1; final, 23.0; $P = 0.004$). Headache was the most common adverse event with pitolisant.
Conclusions: Pitolisant, at once-daily doses up to 35.6 mg, was efficacious for reducing excessive daytime sleepiness and cataplexy in patients with severe narcolepsy symptom burden.

1. Introduction

Narcolepsy is a chronic, debilitating neurological disorder characterized by sleep-wake state instability [1–3]. The symptoms of narcolepsy include excessive daytime sleepiness (EDS, which is present in all patients), cataplexy, and other manifestations of rapid eye movement (REM) sleep dysregulation (eg, sleep paralysis, hypnagogic hallucinations) that intrude into wakefulness, which are present to a variable degree in some patients [1,4]. Narcolepsy imposes a substantial burden on patients, especially those with severe symptoms [5]. School performance is compromised in students with narcolepsy and, in adults, unemployment rates are higher and incomes are lower relative to matched controls [6–8]. In employed patients, work productivity is reduced and rates of absenteeism are increased [9]. In addition, narcolepsy is associated with decreased quality of life and disruptions in social functioning and daily activities [5,9–11].

Abbreviations: BMI, body mass index; CGI-C, Clinical Global Impression of Change; ECG, electrocardiogram; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; H_3, histamine; ICSD-2, *International Classification of Sleep Disorders,* second edition; MWT, Maintenance of Wakefulness Test; PGO, Patient Global Opinion; REM, rapid eye movement; SEM, standard error of the mean; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; WRC, weekly rate of cataplexy.

* Corresponding author. Harmony Biosciences, LLC, 630 W. Germantown Pike, Suite 215, Plymouth Meeting, PA 19462, USA.
E-mail address: cdavis@harmonybiosciences.com (C.W. Davis).

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Narcolepsy type 1 (narcolepsy with cataplexy) is caused by an immune-mediated, selective loss of hypothalamic neurons that produce hypocretin-1 and hypocretin-2 (also known as orexin-A and orexin-B), neuropeptides that are essential for regulating wakefulness and sleep [1,2,12–14]. The pathophysiology of narcolepsy type 2 (narcolepsy without cataplexy) remains largely unknown [13,15], although an immune-related etiology has been suggested in some cases [12].

Recent research suggests that histamine, a wake-promoting neurotransmitter, may play an important role in narcolepsy [16]. Histamine neurons originate in the tuberomammillary nucleus of the hypothalamus and project to multiple brain regions involved in the regulation of sleep and wakefulness [2,17]. Preclinical research shows that histamine is important for normal sleep-wake behavior [16] and may serve complementary and synergistic roles to hypocretin [18]. Histaminergic activation of cortical and subcortical neurons, including other wake-promoting neurons (eg, norepinephrine neurons in the locus coeruleus, acetylcholine neurons in the pons and forebrain, and serotonin neurons in the dorsal raphe nucleus), serves to promote and maintain wakefulness [17,19,20]. In addition, histamine appears to suppress both non-REM and REM sleep by inhibiting neurons in sleep-promoting brain regions (eg, ventrolateral preoptic area, pons) [2,14,16,17]. The effects of histamine on wakefulness and sleep are mediated via stimulation of postsynaptic H_1 receptors (the soporific effects of H_1-receptor antagonists crossing the blood–brain barrier are widely known); presynaptic H_3 autoreceptors, which modulate histamine synthesis and release; and presynaptic H_3 heteroreceptors on other neurons [19,20].

Pitolisant, a selective H_3-receptor antagonist/inverse agonist, is a first-in-class molecule with a novel mechanism of action in the treatment of narcolepsy [21–23]. Pitolisant binds competitively to presynaptic H_3 autoreceptors, which increases the synthesis and release of histamine in the brain [19,21]. Binding of histamine at postsynaptic H_1 receptors increases histamine signaling and activates wake-promoting brain regions [20]. Presynaptic H_3 receptors located on nonhistaminergic neurons modulate the release of other neurotransmitters, including those that promote wakefulness (eg, acetylcholine, dopamine, norepinephrine, serotonin) and reduce symptoms of REM sleep dysregulation such as cataplexy (eg, norepinephrine, serotonin) [24,25]. Thus, pitolisant may exert effects on narcolepsy symptoms directly via histaminergic activity and indirectly via effects on other neurotransmitter systems.

The efficacy of pitolisant for the reduction of EDS and cataplexy in patients with narcolepsy was demonstrated in two randomized, double-blind, placebo-controlled studies in which pitolisant was individually titrated to a potential maximum dose of 35.6 mg/day [26,27]. The aim of this analysis was to evaluate the efficacy of pitolisant, administered up to the highest recommended dose (35.6 mg/day), in patients with a high burden of narcolepsy symptoms.

2. Methods

Two placebo-controlled studies of pitolisant included the highest recommended dose (35.6 mg/day) in patients with narcolepsy. Patient-level data from these studies (HARMONY CTP [ClinicalTrials.gov: NCT01800045], HARMONY 1 [NCT01067222]) were pooled in the current analyses. Each study was a phase 3, short-term (7- or 8-week) clinical trial that examined the efficacy and safety of pitolisant in the treatment of patients with narcolepsy. Primary results of these studies have been reported elsewhere [26,27].

Study conduct was consistent with the Good Clinical Practice guidelines of the International Council for Harmonisation and the ethical principles of the Declaration of Helsinki. Each study protocol was approved by an institutional review board or independent ethics committee, and all patients provided written informed consent before study enrollment.

2.1. Patients

Inclusion/exclusion criteria varied somewhat between the two studies. Key inclusion criteria were as follows: adults aged 18 or older with a diagnosis of narcolepsy with cataplexy (HARMONY CTP), or narcolepsy with or without cataplexy (HARMONY 1), according to *International Classification of Sleep Disorders* (ICSD-2) criteria. All patients were experiencing EDS, as evidenced by an Epworth Sleepiness Scale (ESS) score of at least 12 (HARMONY CTP) or 14 (HARMONY 1). The presence of cataplexy (at least three attacks per week at baseline) was required in HARMONY CTP but was not required in HARMONY 1. Patients were excluded from study participation if they had another condition that causes EDS (eg, sleep-related breathing disorder with apnea index $\geq$10/hour or apnea/hypopnea index $\geq$15/hour, periodic limb movement disorder with arousal index $\geq$10/hour, shift work, circadian rhythm disorder), current or recent (within 1 year) substance abuse or dependence, significant cardiovascular abnormality, severe hepatic or renal impairment, psychiatric or neurological disorders, or other active clinically significant illness.

2.2. Study procedures

Patients taking other medications for EDS (eg, methylphenidate, amphetamines, modafinil) were to discontinue treatment prior to study baseline. Other anticataplectic medications (eg, sodium oxybate, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) were permitted, provided the dose had been stable for 1 month prior to screening and was not altered during the study. Tricyclic antidepressants were not allowed, due to their antagonist activity at H_1 receptors.

Study medication was individually titrated based on efficacy and tolerability. Pitolisant was initiated at a dose of 4.45 mg/day (HARMONY CTP) or 8.9 mg/day (HARMONY 1) and titrated, during a 3-week flexible-dose period, to a potential maximum of 35.6 mg/day[1]. The individualized pitolisant dose (8.9, 17.8, or 35.6 mg/day) then remained stable for the subsequent 4 weeks (HARMONY CTP) or 5 weeks (HARMONY 1) of study treatment.

Efficacy was evaluated using the ESS [28], Maintenance of Wakefulness Test (MWT) [29], frequency of cataplexy attacks, Clinical Global Impression of Change (CGI-C) [30] for EDS and for cataplexy, and Patient Global Opinion (PGO) for the effect of treatment on EDS. The ESS is a commonly used 8-item self-report questionnaire that assesses daytime sleepiness. The total score ranges from 0 to 24; a score >10 is indicative of EDS, and a score of $\geq$16 denotes severe EDS [28]. The MWT was administered in four 40-min sessions at 2-hour intervals in accordance with validated procedures [29,31]. The CGI-C is a 7-point clinician-rated scale with scores ranging from 1 (very much improved) to 7 (very much worse) [30], and the PGO is a 6-point patient-rated scale with scores ranging from 1 (marked effect; complete or near remission of EDS) to 6 (much worse; substantial increase in EDS). The ESS and CGI-C scales were administered at baseline (prior to the first dose of

[1] Pitolisant doses reported in some previous publications have included the hydrochloride salt (5 mg, 10 mg, 20 mg, 40 mg). The doses presented here reflect the pitolisant base, consistent with US Food and Drug Administration guidance (4.45 mg, 8.9 mg, 17.8 mg, 35.6 mg). In Europe, doses reflect the pitolisant base but are rounded to one fewer decimal place (4.5 mg, 9 mg, 18 mg, 36 mg).

study medication) and at all postbaseline study visits, the MWT was administered at baseline and end of treatment, and the PGO was administered at selected postbaseline visits. Treatment response on the ESS was defined in two ways: a score reduction of ≥3 from baseline and a final score of ≤10. Improvements were defined on the CGI-C by responses of "very much" or "much" improved and on the PGO by responses of "marked effect; complete or near remission of EDS" or "moderate effect; partial remission of EDS." The weekly rate of cataplexy (WRC) attacks was calculated using information recorded in patient diaries.

2.3. Patients included in this analysis

Patient-level data from the two studies were pooled for those who received pitolisant or placebo. The analyzed populations were three independent patient subgroups identified as having a high burden of narcolepsy symptoms based on the following criteria: baseline score of ≥16 on the ESS, baseline sleep latency of ≤8 min on the MWT, and baseline frequency of cataplexy attacks ≥15 per week.

2.4. Statistical analysis

Change from baseline to the end of treatment was evaluated for pitolisant compared with placebo in each patient subgroup. Changes in ESS score and MWT sleep latency were also evaluated in patients with a high burden of EDS based on both subjective (baseline score of ≥16 on the ESS) and objective (baseline sleep latency of ≤8 min on the MWT) measures. The final value was the last assessment for the ESS and the MWT, and the stable dosing period (4 or 5 weeks) for the WRC. For the ESS score and WRC, analyses of change from baseline for pitolisant versus placebo were performed using analysis of covariance, with treatment as a fixed effect, study site as a random effect, and baseline score as a covariate. For sleep latency on the MWT, data were not normally distributed, and a nonparametric approach (Hodges-Lehman-Sen methodology and Wilcoxon rank sum test) was used to compare pitolisant to placebo. Differences in the response rates between pitolisant and placebo on the ESS, CGI-C, and PGO were analyzed using Fisher's exact test. For the ESS, MWT, and WRC, the last observation was carried forward for patients who did not complete the study.

3. Results

3.1. Baseline demographics and clinical characteristics

The analysis populations included 118 patients for the ESS subgroup (pitolisant, n = 60; placebo, n = 58), 105 patients for the MWT subgroup (pitolisant, n = 59; placebo, n = 46), and 31 patients for the cataplexy subgroup (pitolisant, n = 20; placebo, n = 11). Baseline demographic and clinical characteristics were similar for patients who were treated with pitolisant and those who received placebo (Table 1). Mean values at baseline for ESS score (19.0 in the pitolisant group and 19.4 in the placebo group), MWT sleep latency (3.5 and 3.4 min, respectively), and WRC (21.8 and 20.9, respectively) are indicative of severe EDS and cataplexy.

Pitolisant was titrated to the maximum recommended dose of 35.6 mg/day in 65.0% of patients in the ESS analysis, 64.4% in the MWT analysis, and 40.0% in the WRC analysis. Compared with pitolisant-treated patients, the use of concomitant anticataplectic medications was generally more common in patients who were receiving placebo (Table 2).

3.2. Excessive daytime sleepiness

The least-squares mean change in ESS score from baseline to end of treatment was significantly greater for pitolisant (−6.1) compared with placebo (−2.3) in patients with a high EDS burden based on ESS score ($P < 0.001$; Fig. 1). In this patient population, two definitions of treatment response were evaluated. Response defined as an ESS score reduction of ≥3 was observed in 69.0% of patients treated with pitolisant versus 35.1% with placebo ($P = 0.001$; Fig. 2); response defined as final ESS score ≤10 was observed in 36.2% and 10.5% of patients, respectively ($P = 0.005$). Among pitolisant-treated patients, responders (ESS final score ≤10) were similar to nonresponders (ESS final score >10) in demographic characteristics (age, sex, body mass index [BMI]) and clinical characteristics (age at diagnosis, time since diagnosis; $P > 0.05$ for all comparisons). In patients with high EDS burden based on MWT, mean sleep latency

Table 1
Demographics and clinical characteristics.

Characteristic	High burden ESS*		High burden MWT*		High burden WRC*	
	Pitolisant (n = 60)	Placebo (n = 58)	Pitolisant (n = 59)	Placebo (n = 46)	Pitolisant (n = 20)	Placebo (n = 11)
Age, y, mean	35.6	39.7	35.2	39.4	32.9	38.8
Female sex, n (%)	25 (41.7)	32 (55.2)	27 (45.8)	22 (47.8)	7 (35.0)	6 (54.5)
Body mass index, kg/m^2, mean	28.1	29.0	27.5	28.5	27.9	30.4
Age at diagnosis, y, mean	27.6	27.9	27.4	30.5	28.5	31.2
Time since diagnosis, y, mean	7.6	11.3	7.4	8.5	4.3	7.0
Baseline score, mean						
ESS score	19.0	19.4	17.8	18.4	16.5	18.4
Sleep latency on MWT, min	7.5	9.3	3.5	3.4	6.9	6.2
WRC	11.7	9.6	11.2	10.2	23.9	23.1
Prior narcolepsy medications, n (%)†						
≥1 prior medication	23 (38.3)	20 (34.5)	20 (33.9)	22 (47.8)	6 (30.0)	6 (54.5)
Stimulants	4 (6.7)	5 (8.6)	5 (8.5)	7 (15.2)	3 (15.0)	1 (9.1)
Modafinil	4 (6.7)	7 (12.1)	3 (5.1)	8 (17.4)	1 (5.0)	0
SSRIs	5 (8.3)	4 (6.9)	2 (3.4)	3 (6.5)	1 (5.0)	0
SNRIs	4 (6.7)	5 (8.6)	3 (5.1)	4 (8.7)	1 (5.0)	2 (18.2)
TCAs	9 (15.0)	5 (8.6)	6 (10.2)	6 (13.0)	1 (5.0)	2 (18.2)
Other antidepressants	1 (1.7)	5 (8.6)	1 (1.7)	4 (8.7)	0	2 (18.2)
Sodium oxybate	2 (3.3)	2 (3.4)	2 (3.4)	2 (4.3)	0	1 (9.1)

*The high burden ESS analysis included 52 patients from HARMONY 1 and 66 patients from HARMONY CTP; the high burden MWT analysis included 30 patients from HARMONY 1 and 75 patients from HARMONY CTP; and the high burden WRC analysis included 5 patients from HARMONY 1 and 26 patients from HARMONY CTP. †Within 3 months before study enrollment. ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; WRC = weekly rate of cataplexy.

Table 2
Concomitant anticataplectic medications.

Medication, n (%)	High burden ESS		High burden MWT		High burden WRC	
	Pitolisant (n = 60)	Placebo (n = 58)	Pitolisant (n = 59)	Placebo (n = 46)	Pitolisant (n = 20)	Placebo (n = 11)
≥1 concomitant medication	10 (16.7)	13 (22.4)	6 (10.2)	10 (21.7)	2 (10.0)	4 (36.4)
SSRIs						
Fluoxetine	3 (5.0)	2 (3.4)	1 (1.7)	2 (4.3)	1 (5.0)	0
Citalopram	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Escitalopram	0	1 (1.7)	0	1 (2.2)	0	0
Paroxetine	1 (1.7)	0	0	0	0	0
SNRIs						
Venlafaxine	4 (6.7)	5 (8.6)	3 (5.1)	4 (8.7)	1 (5.0)	2 (18.2)
Other antidepressants						
Reboxetine	0	2 (3.4)	0	1 (2.2)	0	1 (9.1)
Sodium oxybate	1 (1.7)	2 (3.4)	1 (1.7)	2 (4.3)	0	1 (9.1)

ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; WRC = weekly rate of cataplexy.

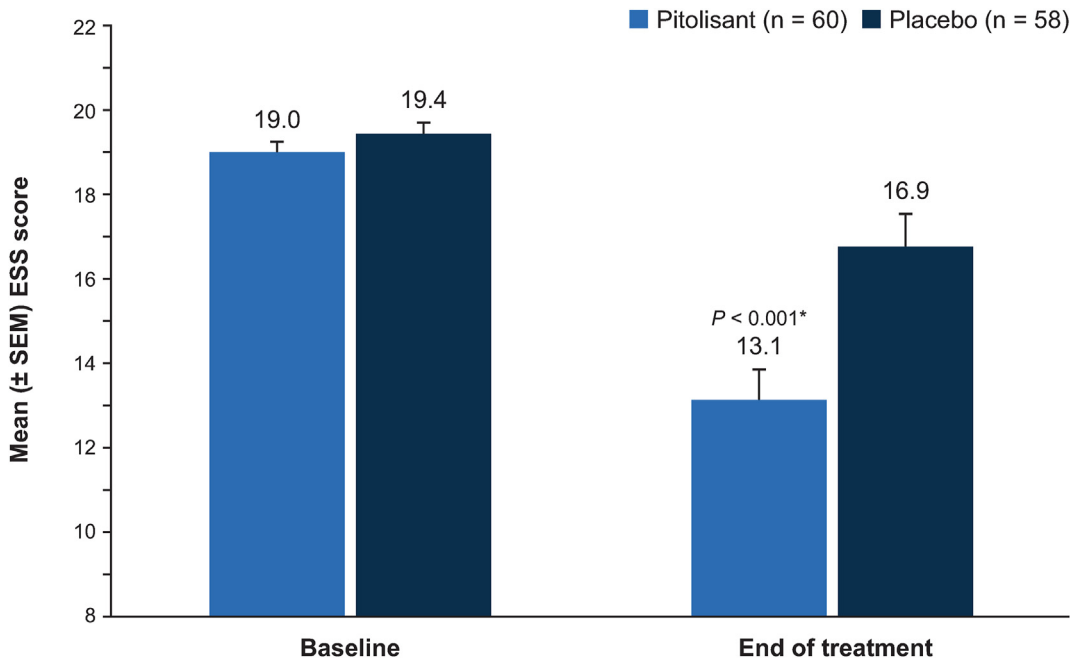

Fig. 1. ESS scores in patients with high EDS burden, based on ESS score at baseline. *Analysis of least-squares mean difference for pitolisant versus placebo. EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; SEM = standard error of the mean.

increased from 3.5 min (median, 3.5) at baseline to 10.4 min (median, 5.0) at end of treatment in the pitolisant group, and from 3.4 min (median, 2.9) to 6.8 min (median, 3.4) in the placebo group (Fig. 3). Mean change in MWT sleep latency from baseline to end of treatment was 6.9 min (median, 2.5) for pitolisant and 3.4 min (median, 0.4) for placebo ($P = 0.017$).

On the CGI-C for EDS, the proportion of patients considered to be very much improved or much improved was significantly greater in the pitolisant group compared with the placebo group (Fig. 4) in both high EDS burden subgroups. Similarly, on the PGO, significantly more patients reported a marked or moderate effect of treatment on EDS for pitolisant compared with placebo: 59.6% versus 32.7% ($P = 0.023$) in patients with high burden of EDS based on ESS score, and 57.4% versus 30.2% ($P = 0.027$) for high burden of EDS based on MWT.

In patients who experienced a high EDS burden based on both ESS score and MWT sleep latency (pitolisant, n = 43; placebo, n = 34), least-squares mean change in ESS score was significantly greater ($P = 0.003$) for pitolisant (baseline, 19.2; endpoint, 13.8; Δ −5.7) relative to placebo (baseline, 19.8; endpoint, 17.4; Δ −2.0). In this population, mean sleep latency on the MWT increased from 3.3 min (median, 3.0) at baseline to 8.7 min (median, 3.8) at end of treatment in the pitolisant group, and from 3.1 min (median, 2.8) to 3.5 min (median, 2.4) in the placebo group. Mean change from baseline was 5.4 min (median, 1.5) for pitolisant and 0.4 min (median, 0.0) for placebo ($P = 0.011$).

3.3. Cataplexy

In patients with a high burden of cataplexy, least-squares mean change in the WRC was significantly greater for pitolisant (−14.5) compared with placebo (−0.1; $P = 0.004$; Fig. 5). On average, the frequency of cataplexy attacks was reduced by 60.6% in the pitolisant group and <1% in the placebo group. On the CGI-C for cataplexy, a substantially greater proportion of pitolisant-treated patients was considered very much or much improved compared with patients receiving placebo (Fig. 4).

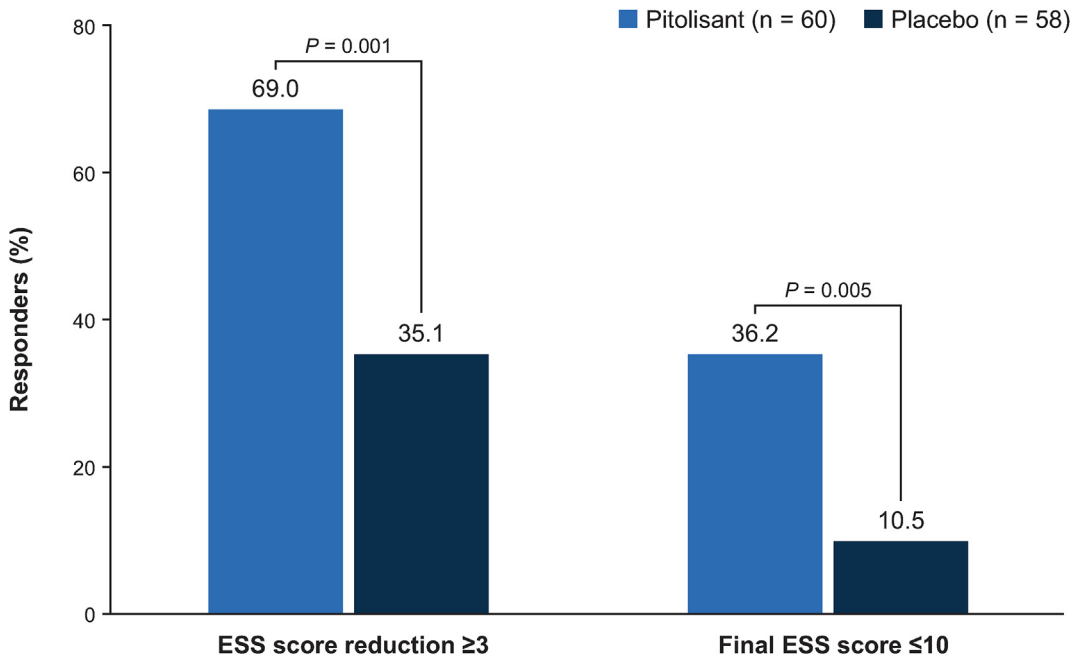

Fig. 2. ESS treatment responders among patients with high EDS burden, based on ESS score at baseline. EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale.

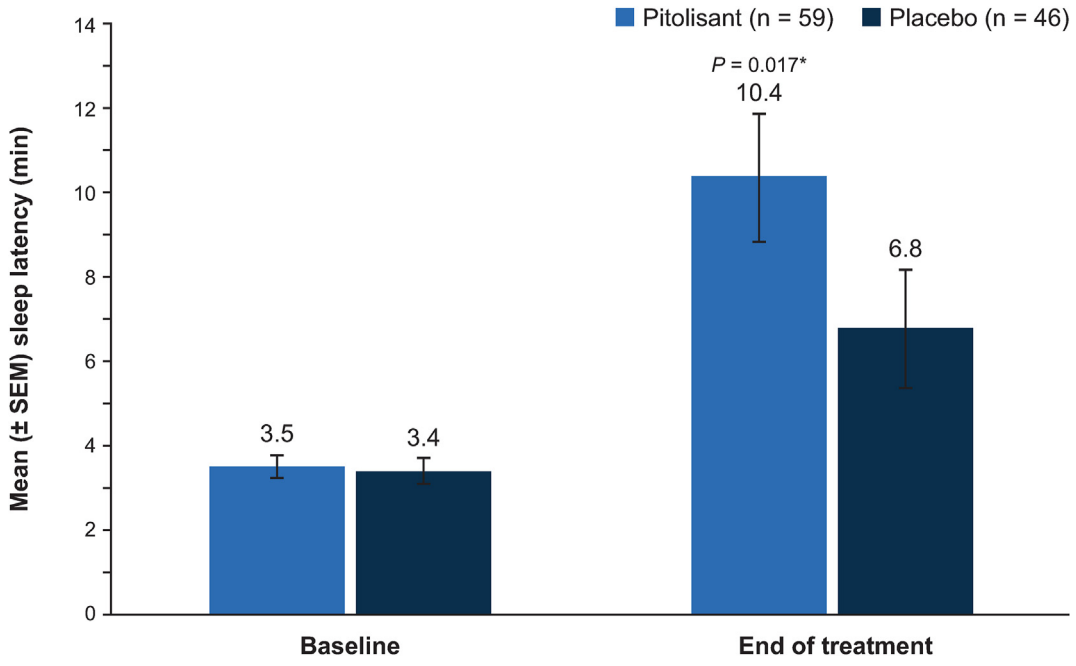

Fig. 3. Sleep latency on the MWT in patients with high EDS burden, based on MWT sleep latency at baseline. *P value from Wilcoxon rank sum test for pitolisant versus placebo. EDS = excessive daytime sleepiness; MWT = Maintenance of Wakefulness Test; SEM = standard error of the mean.

3.4. Safety

Detailed safety and tolerability findings for each study included in this analysis have been previously published [26,27]. The adverse event profiles for the patient populations in this analysis were consistent with the known safety profile for pitolisant; headache, nausea, and anxiety were the most common adverse events in pitolisant-treated patients (Table 3).

4. Discussion

This post hoc analysis of pooled patient-level data from two short-term studies supports the use of pitolisant to treat patients who have a high burden of narcolepsy symptoms. In this analysis, pitolisant, titrated to a potential maximum dose of 35.6 mg/day, was superior to placebo for the reduction of both EDS, as assessed using subjective (ESS, CGI-C) and objective (MWT) measures, and

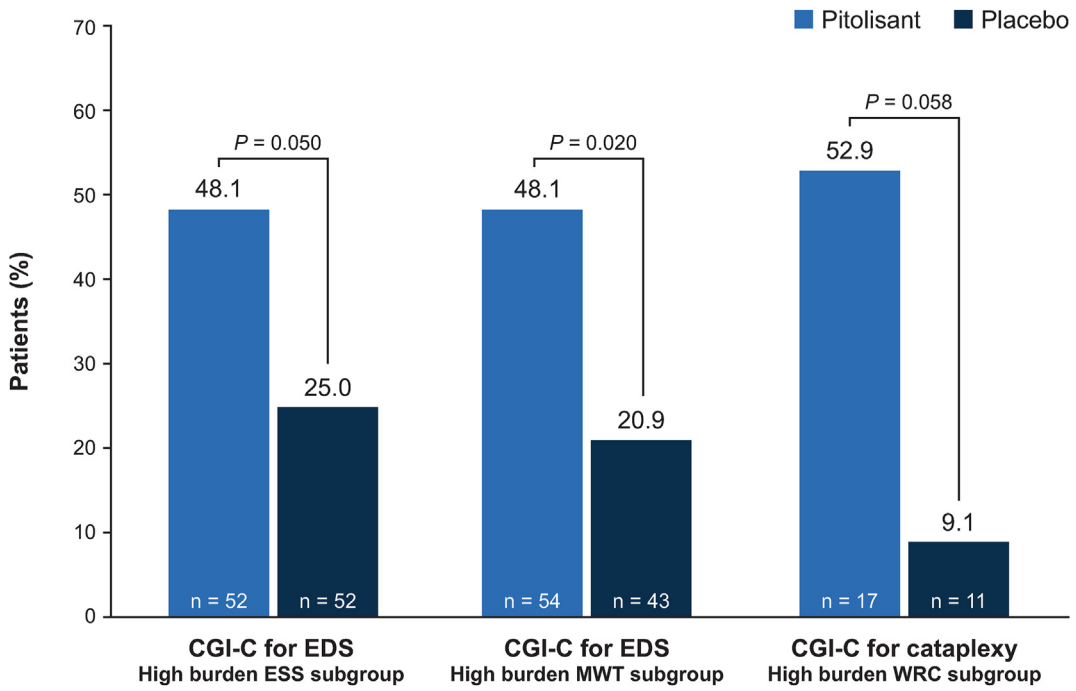

Fig. 4. CGI-C for EDS and cataplexy. Patients considered very much or much improved on the CGI-C. CGI-C = Clinical Global Impression of Change; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; WRC = weekly rate of cataplexy.

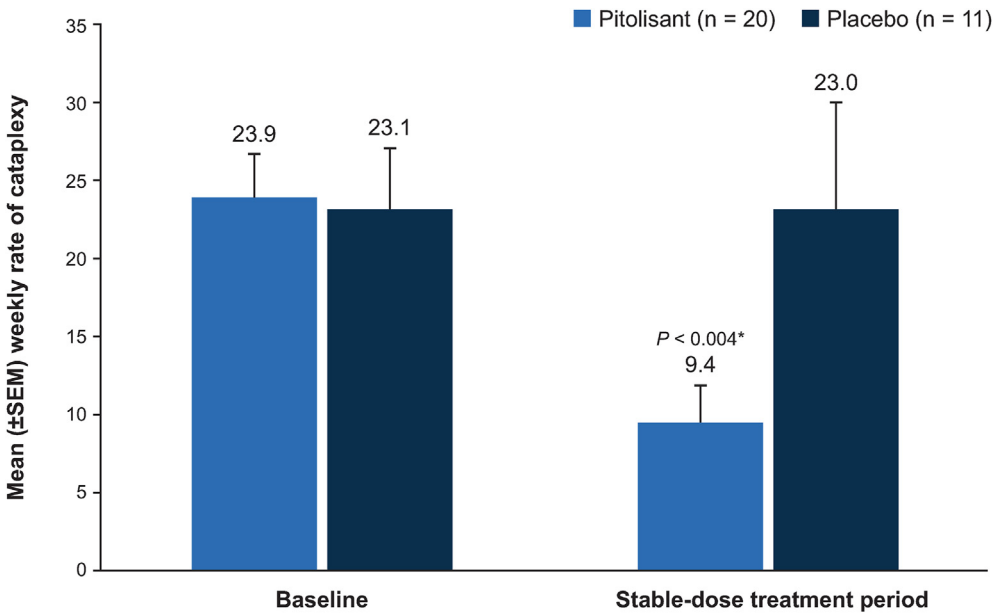

Fig. 5. WRC in patients with high burden of cataplexy based on WRC at baseline. *Analysis of least-squares mean difference for pitolisant versus placebo. SEM = standard error of the mean; WRC = weekly rate of cataplexy.

cataplexy. Pitolisant is approved by the European Medicines Agency for the treatment of narcolepsy with or without cataplexy in adults [32] and by the US Food and Drug Administration for the treatment of EDS and cataplexy in adult patients with narcolepsy [33]. The maximum recommended dose of pitolisant is the same in Europe (36 mg/day) and the United States (35.6 mg/day). In the studies included in this analysis, pitolisant was individually titrated based on therapeutic response. It is interesting to note, however, that a substantial number of patients did not receive the maximum dose, despite the high symptom burden of EDS and/or cataplexy. In general, the treatment effect appears to be somewhat larger for pitolisant 35.6 mg/day compared with 17.8 mg/day [33].

Available demographic information (age, sex, BMI) and clinical characteristics (age at diagnosis, time since diagnosis) were evaluated as predictors of treatment response, as measured using the ESS. However, none of these variables distinguished pitolisant responders from nonresponders. Furthermore, the efficacy of pitolisant in the treatment of cataplexy was not accounted for by the use of concomitant anticataplectic medications, which was more common in the placebo group than the pitolisant group. In addition,

Table 3
Adverse events (incidence ≥2% in pitolisant-treated patients in any subgroup).

Adverse event, n (%)	High burden ESS		High burden MWT		High burden WRC	
	Pitolisant (n = 60)	Placebo (n = 58)	Pitolisant (n = 59)	Placebo (n = 46)	Pitolisant (n = 20)	Placebo (n = 11)
≥1 adverse event	23 (38.3)	28 (48.3)	23 (39.0)	17 (37.0)	10 (50.0)	3 (27.3)
Headache	12 (20.0)	8 (13.8)	9 (15.3)	5 (10.9)	2 (10.0)	0
Nausea	3 (5.0)	2 (3.4)	2 (3.4)	1 (2.2)	1 (5.0)	0
Anxiety	2 (3.3)	0	3 (5.1)	0	2 (10.0)	0
Insomnia	2 (3.3)	0	2 (3.4)	0	0	0
Fatigue	2 (3.3)	0	2 (3.4)	0	1 (5.0)	1 (9.1)
Heart rate increased	2 (3.3)	0	2 (3.4)	0	1 (5.0)	0
Irritability	1 (1.7)	0	3 (5.1)	0	2 (10.0)	0
Apathy	1 (1.7)	0	1 (1.7)	0	1 (5.0)	1 (9.1)
Asthenia	1 (1.7)	1 (1.7)	1 (1.7)	0	1 (5.0)	0
Dyssomnia	1 (1.7)	1 (1.7)	1 (1.7)	0	1 (5.0)	0
ECG T-wave inversion	0	0	0	0	1 (5.0)	0
Hallucination	0	0	1 (1.7)	0	1 (5.0)	0
Palpitations	0	0	1 (1.7)	0	1 (5.0)	0
Sleep disorder	0	1 (1.7)	1 (1.7)	0	1 (5.0)	0
Somnolence	1 (1.7)	3 (5.2)	1 (1.7)	0	1 (5.0)	1 (9.1)

ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; WRC = weekly rate of cataplexy.

stimulants and wake-promoting agents were prohibited in the HARMONY CTP and HARMONY 1 clinical trials.

Clinician and patient ratings of treatment outcomes further support the effectiveness of pitolisant in narcolepsy patients with high symptom burden. Ratings on the CGI-C and PGO were significantly better for pitolisant compared with placebo. Investigators rated EDS and cataplexy as “much” or “very much” improved in approximately 50% of pitolisant-treated patients compared with 10%–25% of patients in the placebo group. Similarly, the majority of patients in the pitolisant group (approximately twice the rate in the placebo group) reported a moderate or marked effect of treatment on EDS.

The safety profile of pitolisant in patients with a high burden of narcolepsy symptoms was similar to that observed in the overall population. In this analysis, headache, nausea, and anxiety were the most common adverse events in pitolisant-treated patients. In the overall clinical development program for narcolepsy, the most common adverse events with pitolisant in short-term, placebo-controlled studies were headache, insomnia, and nausea [33].

An H_3-receptor antagonist/inverse agonist, pitolisant increases histaminergic transmission in the brain and modulates the release of other neurotransmitters [19,21,24,25]. This pharmacologic profile may be linked to improvement in multiple symptoms of narcolepsy, including EDS and cataplexy. Unlike some of the other commonly used treatments for narcolepsy, pitolisant does not increase dopamine release in the nucleus accumbens (a brain region associated with rewarding drug effects) [34] and has demonstrated minimal potential for abuse [35]. Based on the results from preclinical abuse liability studies and a clinical human abuse potential study, pitolisant was approved without being scheduled as a controlled substance.

For this analysis, threshold scores on measures of EDS and cataplexy were selected to ensure that the analysis population consisted of patients with severe narcolepsy symptoms. On the ESS, scores of ≥16 are considered indicative of severe EDS [28]. For the MWT, a threshold score has not been clearly established. However, an analysis of 530 unmedicated patients with narcolepsy found that mean sleep latency on the MWT was ≤5 min in 50% of patients and ≤9 min in 75%; by contrast, fewer than 5% of individuals without sleep/alertness complaints had mean sleep latency <8 min on the MWT [31,36]. Therefore, a mean sleep latency of 8 min on the MWT was deemed a reasonable threshold for identifying patients with a high burden of EDS. For the WRC, 15 attacks per week, an average of more than two attacks per day, was selected in HARMONY CTP as an indicator of a high rate of cataplexy [27]. Applying the selected threshold values to the HARMONY CTP and HARMONY 1 patient populations identified 71.1% and 63.3% of patients as having high EDS burden, based on ESS and MWT scores, respectively, and 18.7% as having high cataplexy burden at baseline.

Limitations of this analysis include its post hoc nature, the short-term (7- to 8-week) duration of the studies, and the relatively small sample size in the cataplexy subgroup. Despite the small number of patients with high burden of cataplexy, this analysis demonstrated a clear treatment effect for pitolisant in patients with frequent attacks. Although an ESS score ≥16 is widely accepted as an indicator of severe EDS, the threshold values used in this analysis for sleep latency on the MWT and frequency of cataplexy attacks have not been validated as indicators of symptom severity. In addition, the PGO is a nonstandardized rating scale for patients' impressions of treatment outcome. As the majority of patients in these studies were diagnosed with narcolepsy type 1, a comparison of EDS responder status between narcolepsy type 1 and narcolepsy type 2 was not possible.

5. Conclusion

In this analysis of patients with severe burden of narcolepsy symptoms, pitolisant was efficacious for reducing both EDS and cataplexy and was well tolerated. Given its benefit–risk profile, clinicians should consider the use of pitolisant in the treatment of patients with narcolepsy, including those with more severe symptoms and high disease burden.

CRediT authorship contribution statement

Craig W. Davis: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing-Review and Editing, Visualization.

Ulf Kallweit: Formal Analysis (interpretation), Writing-Review and Editing, Visualization.

Jean-Charles Schwartz: Conceptualization, Methodology, Formal Analysis (interpretation), Writing-Review and Editing, Visualization.

Lois E. Krahn: Formal Analysis (interpretation), Writing-Review and Editing, Visualization.

Ben Vaughn: Formal Analysis, Data Curation, Writing-Review and Editing, Visualization.

Michael J. Thorpy: Formal Analysis (interpretation), Writing-Review and Editing, Visualization.

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Conflict of interest

CWD is an employee of Harmony Biosciences. UK reports receiving research grants from Bioprojet Pharma, the European Narcolepsy Network, Jazz Pharmaceuticals, UCB Pharma, and Universität Witten/Herdecke (internal research grant); and serving as a consultant or advisory board member for AOP Orphan Pharmaceuticals, Bioprojet Pharma, Harmony Biosciences, Jazz Pharmaceuticals, Takeda Pharmaceutical Co., Ltd., and UCB Pharma. JCS is a cofounder of Bioprojet Pharma. LEK reports receiving research support from Harmony Biosciences, Jazz Pharmaceuticals, and Takeda Pharmaceutical Co., Ltd; and serving on advisory boards for Harmony Biosciences and Takeda. BV is an employee of Rho. MJT reports serving as a consultant or advisory board member for Axsome, Balance Therapeutics, Eisai Pharmaceuticals, Flamel/Avadel, Harmony Biosciences, LLC, Jazz Pharmaceuticals, Suven Life Sciences Ltd., and Takeda Pharmaceutical Co., Ltd.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.02.037.

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