



Clinical Impact of Pitolisant on Excessive Daytime Sleepiness and Cataplexy in Adults With Narcolepsy: An Analysis of Randomized Placebo-Controlled Trials

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Abstract

Background Pitolisant, a selective histamine 3 receptor antagonist/inverse agonist, is indicated for the treatment of excessive daytime sleepiness or cataplexy in adults with narcolepsy. The efficacy and safety of pitolisant have been demonstrated in randomized placebo-controlled trials. When evaluating the results of randomized placebo-controlled trials, the clinical impact of a treatment can be assessed using effect size metrics that include Cohen's *d* (the standardized mean difference of an effect) and number needed to treat (NNT; number of patients that need to be treated to achieve a specific outcome for one person).

Objective The objective of this study was to evaluate the clinical impact of pitolisant for the reduction in excessive daytime sleepiness or cataplexy in adults with narcolepsy.

Methods This post hoc analysis incorporated data from two 7-week or 8-week randomized placebo-controlled trials (HARMONY 1, HARMONY CTP). Study medication was individually titrated, with a maximum possible pitolisant dose of 35.6 mg/day. Efficacy was assessed using the Epworth Sleepiness Scale (ESS) and weekly rate of cataplexy (HARMONY CTP only). Cohen's *d* was derived from the least-squares mean difference between treatment groups (pitolisant vs placebo), and NNTs were calculated from response rates. Treatment response was defined for excessive daytime sleepiness in two ways: (a) reduction in ESS score ≥ 3 or final ESS score ≤ 10 and (b) final ESS score ≤ 10 . Treatment response was defined for cataplexy as a $\geq 25\%$, $\geq 50\%$, or $\geq 75\%$ reduction in weekly rate of cataplexy.

Results The analysis population included 61 patients in HARMONY 1 (pitolisant, $n = 31$; placebo, $n = 30$) and 105 patients in HARMONY CTP (pitolisant, $n = 54$; placebo, $n = 51$). For pitolisant vs placebo, Cohen's *d* effect size values were 0.61 (HARMONY 1) and 0.86 (HARMONY CTP) based on changes in ESS scores, and 0.86 (HARMONY CTP) based on changes in weekly rate of cataplexy. NNTs for pitolisant were 3–5 for the treatment of excessive daytime sleepiness and 3–4 for the treatment of cataplexy.

Conclusions The results of this analysis demonstrate the robust efficacy of pitolisant for the reduction in both excessive daytime sleepiness and cataplexy. These large effect sizes and low NNTs provide further evidence supporting the strength of the clinical response to pitolisant in the treatment of adults with narcolepsy.

Clinical Trial Registration ClinicalTrials.gov identifiers: NCT01067222 (February 2010), NCT01800045 (February 2013).

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Key Points

When evaluating the results of randomized controlled trials, the clinical impact of a treatment can be assessed using effect size metrics such as Cohen's *d* and number needed to treat (NNT).

In conjunction with the primary results from placebo-controlled studies, the large Cohen's *d* values and low NNTs observed in this analysis demonstrate the robust efficacy of pitolisant for the reduction in both excessive daytime sleepiness and cataplexy in adults with narcolepsy.

The strength of this evidence suggests that pitolisant should be considered as a first-line treatment in adult patients with narcolepsy.

1 Introduction

Narcolepsy is a chronic, debilitating neurological disorder characterized by symptoms that are indicative of sleep–wake state instability (e.g., excessive daytime sleepiness [EDS], cataplexy, hypnagogic hallucinations, sleep paralysis, disrupted night-time sleep) [1, 2]. In patients with narcolepsy, EDS is typically characterized by repeated episodes of an irrepressible need to sleep, and/or unintended lapses into drowsiness or sleep but may also manifest with automatic behaviors and lapses in attention [2, 3]. Excessive daytime sleepiness is required for the diagnosis of narcolepsy; cataplexy (the sudden, brief loss of muscle tone usually triggered by emotion) and other manifestations of rapid eye movement sleep dysregulation (e.g., hypnagogic hallucinations, sleep paralysis) also occur in some patients [3]. There are two phenotypes of narcolepsy: narcolepsy type 1, which is diagnosed based on the presence of cataplexy attacks and/or low levels of hypocretin in cerebrospinal fluid, and narcolepsy type 2, in which cataplexy is absent [3]. Narcolepsy type 1 is caused by the selective loss of hypocretin-producing neurons in the lateral hypothalamus, whereas the pathophysiology of narcolepsy type 2 is less well understood [4]. Narcolepsy type 1 is associated with genetic (e.g., human leukocyte antigen DQB1*06:02) and environmental (e.g., infection) factors that may activate immunologic pathways, leading to the destruction of hypocretin-producing neurons [2, 5].

Although hypocretin-based therapies such as hypocretin-2 receptor agonists are currently in clinical development [6, 7], at present, there are no approved agents that restore hypocretin function in patients with narcolepsy [8]. Available

treatments are symptom driven and are thought to modulate various neurotransmitter systems that regulate wakefulness and sleep (e.g., norepinephrine, serotonin, dopamine, histamine, γ -aminobutyric acid) or play a role in the pathophysiology of cataplexy (e.g., norepinephrine, serotonin) [8–11]. Histamine, a wake-promoting neurotransmitter produced by neurons that originate in the tuberomammillary nucleus of the posterior hypothalamus, plays an important role in the regulation of sleep and wakefulness [12, 13]. Preclinical research has demonstrated that histamine is essential for normal sleep–wake behavior; in addition, histamine may stabilize sleep–wake transitions [12, 14]. Binding of histamine at postsynaptic histamine 1 receptors in the brain promotes wakefulness and suppresses sleep [12, 15]. Histamine binding at presynaptic histamine 3 (H_3) autoreceptors decreases the synthesis and release of histamine [16–18], and histamine binding at presynaptic H_3 heteroreceptors inhibits the release of other neurotransmitters (e.g., norepinephrine, serotonin, acetylcholine, dopamine) [17, 19].

Pitolisant, a selective H_3 receptor antagonist/inverse agonist, is a first-in-class medication with a novel mechanism of action for the treatment of patients with narcolepsy [20, 21]. Pitolisant blocks the inhibitory effect of histamine on endogenous histamine release and increases the synthesis and release of histamine in the brain [16, 22, 23]. Pitolisant also increases the release of other neurotransmitters (e.g., norepinephrine, dopamine, acetylcholine) in the cerebral cortex [23, 24]. Thus, the mechanism of action for pitolisant in the treatment of narcolepsy is thought to involve both direct effects via the histaminergic system and indirect effects via other neurotransmitter systems [10, 11]. Pitolisant is approved by the US Food and Drug Administration for the treatment of EDS or cataplexy in adult patients with narcolepsy [25] and by the European Medicines Agency for the treatment of narcolepsy with or without cataplexy in adults [26]. The efficacy of pitolisant for reducing EDS and cataplexy in adults with narcolepsy has been demonstrated in randomized placebo-controlled trials (RCTs) [25, 27, 28] with additional information on safety and efficacy provided by a long-term open-label study [29].

When evaluating the clinical relevance of RCT results, response to treatment can be quantified using metrics such as effect size; Cohen's *d*, for example, reflects the magnitude of the drug–placebo difference for an outcome measure [30]. Number needed to treat (NNT) is a derived statistic calculated from observed response rates; it can provide additional information regarding the number of patients that are likely to benefit from a treatment intervention [30, 31]. NNT suggests the number of patients that need to be treated with one agent (e.g., study medication) instead of another (e.g., placebo) to obtain a positive clinical outcome for one additional person [30, 31]. Information about the effect sizes of narcolepsy treatments may be useful for enhancing clinical

decision making. The objective of this analysis was to evaluate the clinical impact of pitolisant for the treatment of EDS and cataplexy in adults with narcolepsy by using effect size metrics (Cohen's d , NNT) to quantify the clinical relevance of RCT results and express them in a clinically meaningful way.

2 Methods

This post hoc analysis included data from two randomized, double-blind, placebo-controlled trials that evaluated the efficacy and safety of pitolisant in the treatment of adults with narcolepsy: HARMONY 1 (NCT01067222) and HARMONY CTP (NCT01800045) [27, 28]. HARMONY 1 was conducted at 24 centers in Europe between May 2009 and June 2010. HARMONY CTP was conducted at 16 centers in Europe between April 2013 and January 2015. The studies included a 1-week (HARMONY 1) or 2-week (HARMONY CTP) baseline period followed by a 7-week (HARMONY CTP) or 8-week (HARMONY 1) treatment period. Study conduct was consistent with Good Clinical Practice guidelines and the Declaration of Helsinki. Each study was approved by an institutional review board or independent ethics committee at each study site, and all patients provided written informed consent prior to study enrollment. The primary results of each study have been reported elsewhere [27, 28].

2.1 Patients

All patients were adults (aged ≥ 18 years) with a diagnosis of narcolepsy according to *International Classification of Sleep Disorders, 2nd Edition* criteria: narcolepsy with or without cataplexy in HARMONY 1 and narcolepsy with cataplexy in HARMONY CTP. Excessive daytime sleepiness was present in all patients, as documented by an Epworth Sleepiness Scale (ESS) score of ≥ 14 in HARMONY 1 or ≥ 12 in HARMONY CTP. All patients in HARMONY CTP also had three or more attacks of cataplexy per week at baseline. Key exclusion criteria included other conditions that may cause EDS (e.g., sleep apnea, periodic limb movement disorder, circadian rhythm sleep–wake disorders), substance abuse or dependence (within the past year), severe hepatic or renal impairment, and significant cardiovascular abnormality.

2.2 Treatment

This analysis included patients who were randomly assigned to receive pitolisant or placebo. Study medication was individually titrated over a 3-week period, with a possible maximum pitolisant dose of 35.6 mg/day; the dose

administered at the beginning of week 4 remained stable for the remainder of the treatment period. Stimulants and other wake-promoting medications (e.g., amphetamines, methylphenidate, modafinil) were prohibited. Concomitant use of other antiepileptic medications (e.g., sodium oxybate, antidepressants other than tricyclic antidepressants) was permitted if the dose had been stable for ≥ 1 month prior to screening and remained unchanged during the study.

2.3 Assessments

Excessive daytime sleepiness was assessed using the ESS: an eight-item, validated, patient-report questionnaire that assesses the propensity to doze off or fall asleep in real-world situations [32]. The total ESS score ranges from 0 to 24; scores ≤ 10 are considered to be within the normal range, scores > 10 are indicative of EDS, and scores ≥ 16 denote severe EDS [32, 33]. The ESS was administered at baseline and at scheduled study visits during the treatment period (weeks 2, 3, 7, and 8 in HARMONY 1; weeks 2, 3, 6, and 7 in HARMONY CTP). The weekly rate of cataplexy (WRC) attacks was calculated for the baseline period and weekly thereafter using information recorded in patient diaries. End-of-treatment assessments occurred at week 8 in HARMONY 1 and week 7 in HARMONY CTP.

2.4 Statistical Analysis

To evaluate the clinical impact of treatment, effect sizes were calculated using ESS scores (HARMONY 1, HARMONY CTP) and WRC (HARMONY CTP). Least-squares (LS) mean change from baseline was obtained from analysis of covariance models that included fixed effects for treatment and baseline and a random effect for study site. Cohen's d was derived from the LS mean difference between treatment groups (pitolisant vs placebo). NNTs were calculated from response rates. For both studies, treatment response was defined for EDS in two ways: (a) reduction in ESS score ≥ 3 or final ESS score ≤ 10 and (b) final ESS score ≤ 10 (i.e., within the normal range). For HARMONY CTP, treatment response was defined for cataplexy as a $\geq 25\%$, $\geq 50\%$, or $\geq 75\%$ reduction in WRC. The NNT was computed as the inverse of the drug–placebo difference in response rates rounded upward to the next higher whole number [31]. For the ESS score, the final value used in each analysis was the average of the last two study visits; for WRC, the final value was the average during the stable dose period in HARMONY CTP (weeks 4–7). All analyses used a last observation carried forward approach.

3 Results

The analysis population included the intent-to-treat population from each study: 61 patients in HARMONY 1 (pitolisant, $n = 31$; placebo, $n = 30$) and 105 patients in HARMONY CTP (pitolisant, $n = 54$; placebo, $n = 51$). Baseline characteristics were similar across the two studies (Table 1). At baseline, the mean ESS score was 17.8 in the pitolisant group and 18.9 in the placebo group in HARMONY 1, and 17.4 and 17.3, respectively, in HARMONY CTP, which is representative of severe EDS [32]. In HARMONY CTP, the frequency of cataplexy attacks at baseline was 11.7 per week, on average, in the pitolisant group and 9.6 per week in the placebo group. Pitolisant was titrated to the maximum recommended dose (35.6 mg/day) in 61.3% of patients in HARMONY 1 and 64.8% of patients in HARMONY CTP. Concomitant antiepileptic medications were used by four patients (7.4%) in the pitolisant group (selective serotonin reuptake inhibitor, $n = 3$; sodium oxybate, $n = 1$) and eight patients (15.7%) in the placebo group (selective serotonin reuptake inhibitor, $n = 1$; serotonin and norepinephrine reuptake inhibitor, $n = 5$; norepinephrine reuptake inhibitor, $n = 1$; sodium oxybate, $n = 1$) in HARMONY CTP.

Large effect sizes, as measured using Cohen's d , were observed for pitolisant in the treatment of EDS (Fig. 1) and cataplexy (Fig. 2). For changes in ESS scores from baseline to the end of treatment, the LS mean (standard error) difference for pitolisant vs placebo was -3.1 (1.3) in HARMONY 1 ($p = 0.022$) and -3.4 (0.8) in HARMONY CTP ($p < 0.001$). In a pooled analysis using data from both studies (pitolisant, $n = 85$; placebo, $n = 81$), the LS mean change in ESS score from baseline to end of treatment was -5.6 in the pitolisant group and -2.3 in the placebo group (LS mean treatment difference, -3.3 ; $p < 0.001$; Cohen's $d = 0.73$). For changes in WRC from baseline to the stable dose treatment period, the LS mean (standard error) difference for pitolisant vs placebo was -6.2 (1.4) in HARMONY CTP ($p < 0.001$).

Response rates for EDS (Fig. 3) and WRC (Fig. 4) were consistently greater for pitolisant compared with placebo, regardless of how treatment response was defined. NNT values for pitolisant ranged from 3 to 5 in the treatment of EDS (Fig. 3). In a pooled analysis using ESS data from both studies, treatment response defined as an ESS score reduction ≥ 3 or a final ESS score ≤ 10 was observed in 68.3% of the pitolisant group vs 37.5% of the placebo group (NNT = 4). An ESS score of ≤ 10 (within the normal range) was noted at the end of treatment in 41.5% of patients receiving pitolisant vs 16.3% of patients receiving placebo (NNT = 4). For pitolisant in the treatment of cataplexy, NNT values ranged from 3 to 4 in HARMONY CTP (Fig. 4).

4 Discussion

The statistical superiority of one intervention over another is commonly evaluated using statistical significance (p -value) in clinical trials; however, this does not necessarily reflect the clinical relevance of the intervention. Measures of effect size provide clinicians with metrics for appraising the magnitude of response in a clinical trial [30, 34]. This post hoc analysis used effect sizes (i.e., Cohen's d , NNT) to capture the magnitude of response to pitolisant from the clinical trial results in the treatment of adult patients with narcolepsy. The therapeutic effects of pitolisant vs placebo resulted in large values for Cohen's d (0.61 and 0.86 for EDS, 0.86 for cataplexy) and single-digit NNT values (3–5 for EDS, 3–4 for cataplexy). The primary efficacy analyses demonstrated a significantly greater mean change from baseline for pitolisant vs placebo on measures of EDS and cataplexy, which was important for establishing treatment efficacy [27, 28]. The findings of this analysis provide further evidence of the robust therapeutic effects of pitolisant in the treatment of EDS and cataplexy, with symptom reduction of a magnitude that was clinically meaningful for many patients.

Table 1 Demographic and baseline characteristics

Characteristic	HARMONY 1		HARMONY CTP	
	Pitolisant ($n = 31$)	Placebo ($n = 30$)	Pitolisant ($n = 54$)	Placebo ($n = 51$)
Age, years, median (range)	33.0 (19–65)	39.5 (19–75)	34.0 (18–64)	39.0 (18–66)
Male sex, n (%)	20 (64.5)	13 (43.3)	26 (48.1)	27 (52.9)
BMI, kg/m ² , mean (SD)	30.4 (8.3)	28.2 (6.0)	27.2 (5.2)	28.8 (6.0)
Baseline score, mean (SD)				
ESS score	17.8 (2.5)	18.9 (2.5)	17.4 (3.3)	17.3 (3.2)
WRC	–	–	11.7 (10.0)	9.6 (9.5)

BMI body mass index, ESS Epworth Sleepiness Scale, SD standard deviation, WRC weekly rate of cataplexy.

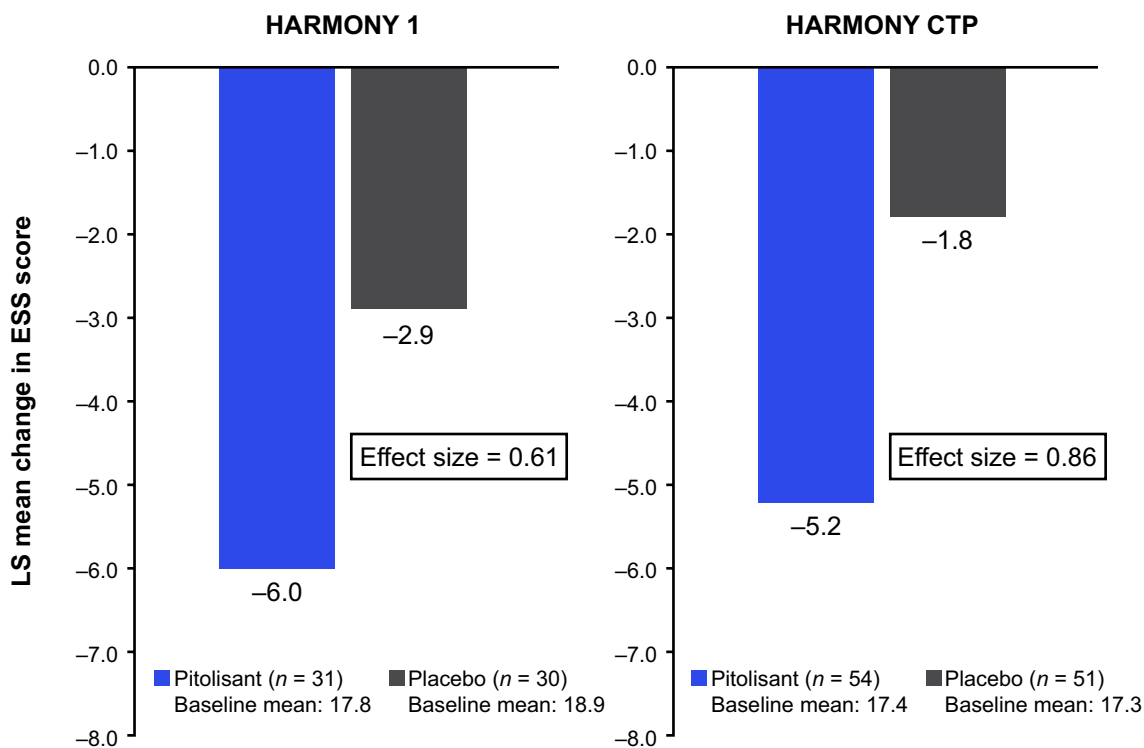
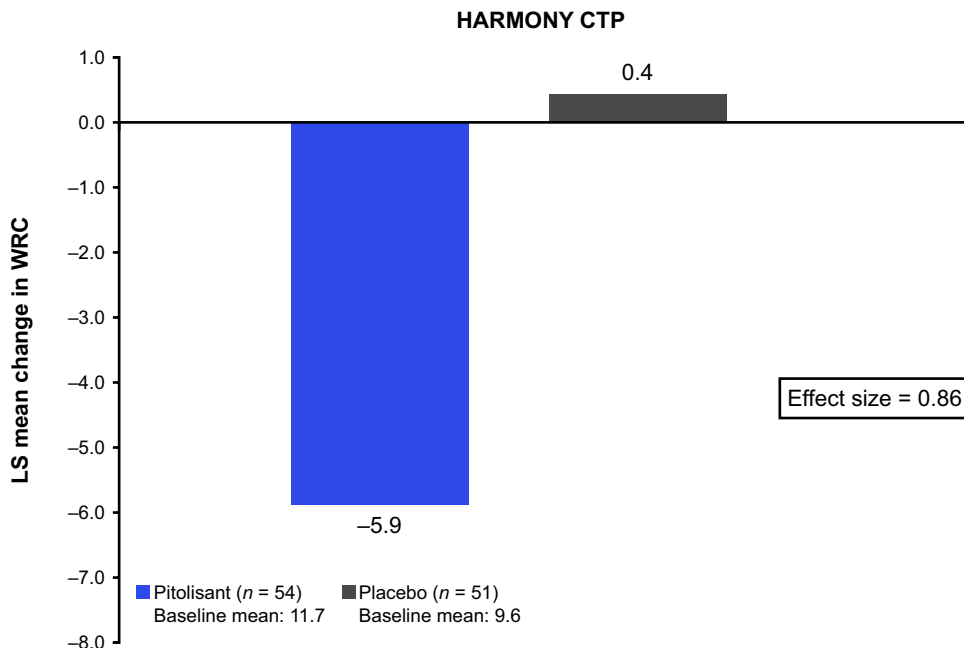


Fig. 1 Effect size, assessed using Cohen’s *d*, for pitolisant in the treatment of excessive daytime sleepiness in HARMONY 1 and HARMONY CTP. End of treatment defined as the mean of the last two

assessments (last observation carried forward). *ESS* Epworth Sleepiness Scale, *LS* least-squares

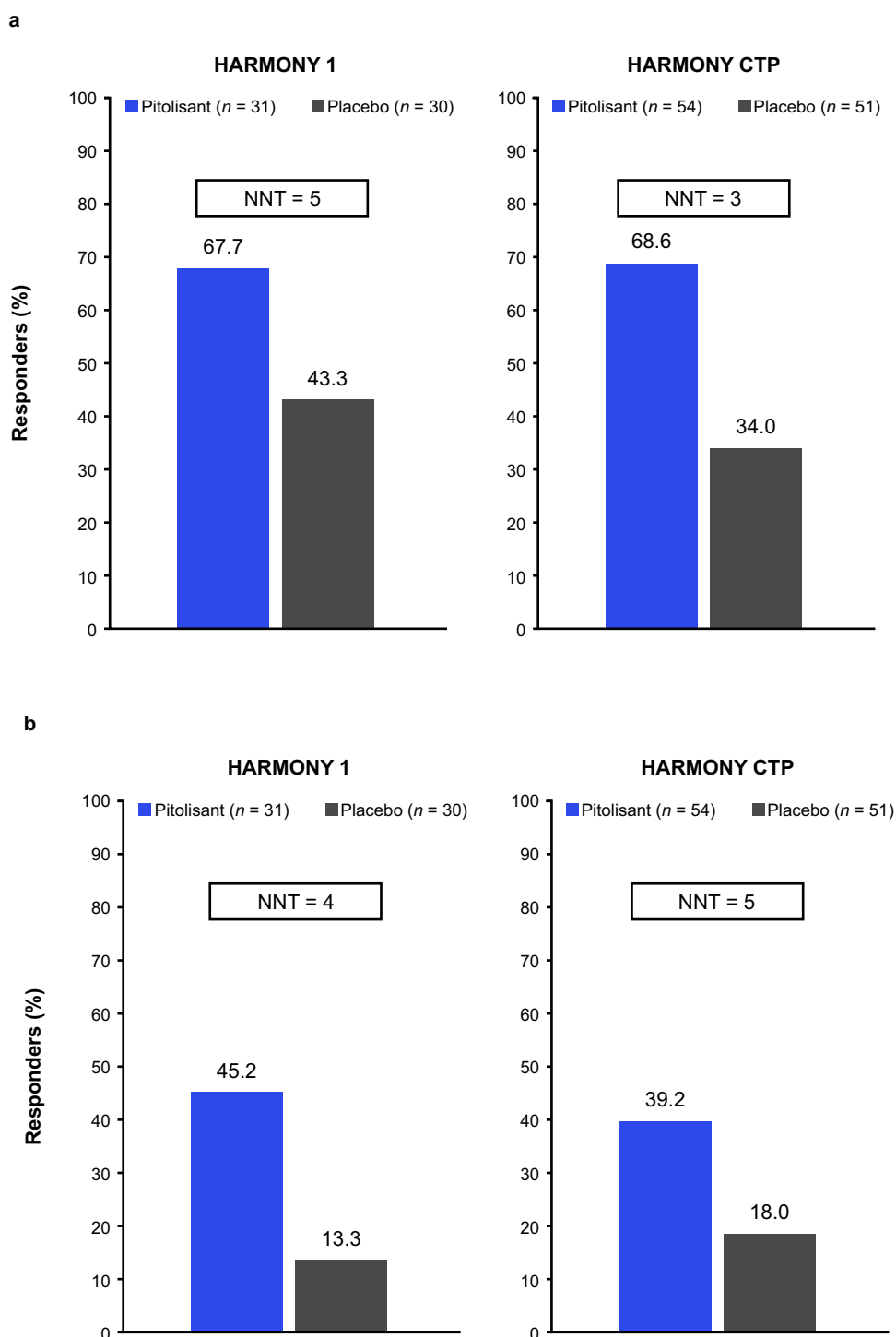
Fig. 2 Effect size, assessed using Cohen’s *d*, for pitolisant in the treatment of cataplexy (HARMONY CTP). End of treatment defined as the stable dose period (last observation carried forward). *LS* least-squares, *WRC* weekly rate of cataplexy



Cohen’s *d*, one of the commonly used metrics of effect size, describes the standardized mean difference of an effect and can be used to compare across studies [30, 35]. The standard interpretation for Cohen’s *d* is that a value

of 0.2 represents a small effect size, 0.5 a medium effect size, and 0.8 a large effect size [30, 34]. In this analysis, medium-to-large Cohen’s *d* values were observed for pitolisant in the treatment of EDS and cataplexy, and these

Fig. 3 Number needed to treat (NNT) for pitolisant in the treatment of excessive daytime sleepiness in HARMONY 1 and HARMONY CTP for treatment response defined in two ways: **a** Epworth Sleepiness Scale score reduction ≥ 3 or final Epworth Sleepiness Scale score ≤ 10 and **b** final Epworth Sleepiness Scale score ≤ 10



values were similar to those reported for sodium oxybate for treatment of EDS in patients with narcolepsy [36]. It is important to note, however, that cross-study comparisons should be interpreted with caution because differences in study design (e.g., fixed dose vs flexible dose, variations in inclusion/exclusion criteria) may influence Cohen's *d* values.

The NNT may be a particularly useful and clinically applicable measure when evaluating the effectiveness of therapeutic interventions, including treatments for neurological disorders [37]. Single-digit NNTs are considered to be clinically meaningful, with lower NNTs indicative of more robust treatment effects [30]. In this analysis, the NNT for achieving ESS score normalization with pitolisant

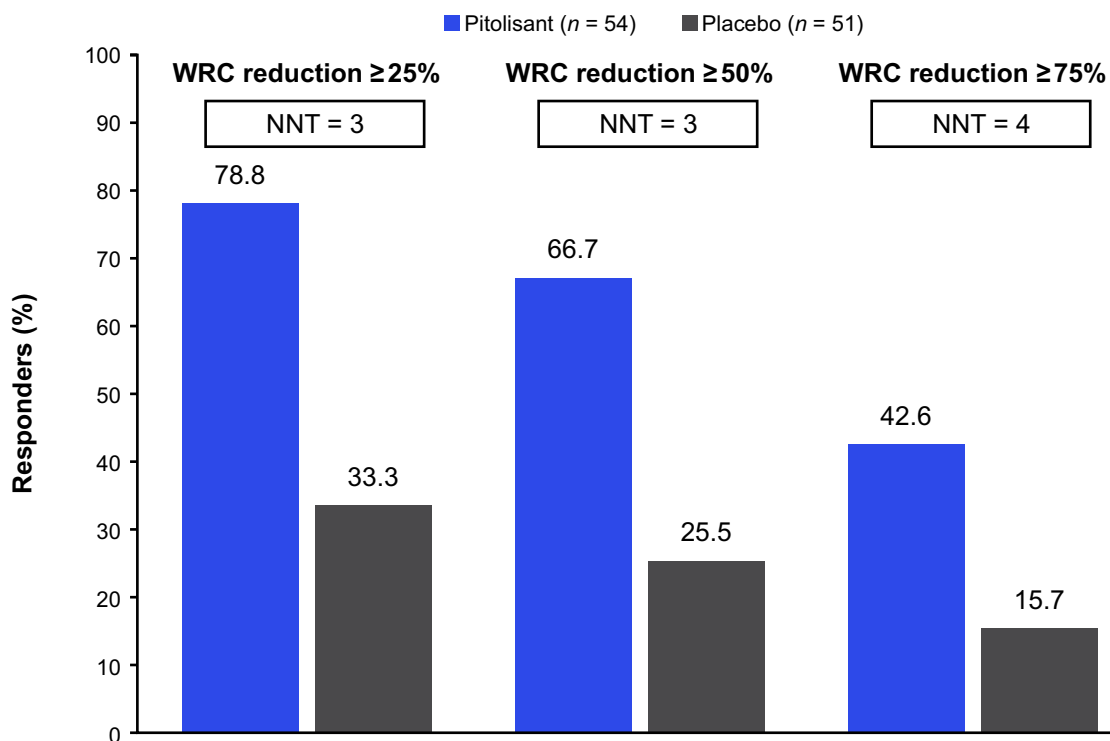


Fig. 4 Number needed to treat (NNT) for pitolisant in the treatment of cataplexy (HARMONY CTP) for treatment response defined as a $\geq 25\%$, $\geq 50\%$, and $\geq 75\%$ reduction in the weekly rate of cataplexy (WRC)

was 4 (HARMONY 1) or 5 (HARMONY CTP), which is comparable to the NNTs observed in studies of other commonly used narcolepsy medications at approved doses (e.g., solriamfetol, armodafinil) [38, 39]. In addition to ESS score normalization, other thresholds have been used to identify a clinically meaningful change on the ESS (e.g., a $> 20\%$ or $> 25\%$ reduction in the total score [40, 41]). In the present analysis, an ESS score decrease of ≥ 3 (or an ESS score in the normal range) was used to define a clinically meaningful reduction in EDS, with an NNT of 3 (HARMONY CTP) or 5 (HARMONY 1) observed for pitolisant in attaining this outcome. A change in the frequency of cataplexy was evaluated using three different thresholds; for a reduction in WRC of $\geq 50\%$ (which is consistent with a clinically meaningful change as identified in a separate analysis of narcolepsy study data [40]), the NNT for pitolisant was 3.

The NNT has been used to evaluate the effectiveness of treatments for other neurological disorders [42]. The NNTs reported for widely recognized standard-of-care treatments for epilepsy (e.g., topiramate, levetiracetam, sodium valproate, zonisamide, lamotrigine, gabapentin) and migraine (oral triptans) have been in the range of 4–12 [43–45], which is comparable to (or higher than) those observed in this analysis of pitolisant for the treatment of EDS and cataplexy.

Additional considerations when evaluating the clinical impact of a treatment for narcolepsy include the time

to onset of a therapeutic response, effectiveness across the range of symptom severity, and safety/tolerability. In a post hoc analysis evaluating the time to onset of clinical response for pitolisant (up to a possible maximum dose of 35.6 mg/day), an initial response was observed for both EDS and cataplexy within 2–3 weeks of starting treatment, which is during the recommended titration period, with larger response rates observed as the dose of pitolisant was increased [46]. In a pooled post hoc analysis of patients with a high burden of symptoms at baseline (i.e., ESS score of ≥ 16 or WRC ≥ 15), the LS mean change in ESS score was significantly greater for pitolisant (-6.1) vs placebo (-2.3 ; $p < 0.001$) as was the LS mean change in WRC (-14.5 vs -0.1 ; $p = 0.004$), indicating that pitolisant was effective in the treatment of patients with more severe narcolepsy symptoms [47].

Pitolisant is generally well tolerated in patients with narcolepsy; across clinical trials, the most common adverse events (incidence $\geq 5\%$ in pitolisant-treated patients and two or more times the rate with placebo) were insomnia (6% vs 2%), nausea (6% vs 3%), and anxiety (5% vs 1%), and the rate of discontinuation because of adverse events was comparable for pitolisant (3.9%) and placebo (3.5%) [25]. In addition, pitolisant demonstrated minimal to no potential for abuse in a clinical human abuse potential study [48] and was approved by the US Food and Drug Administration

without being scheduled as a controlled substance. The 2 to 3 weeks' time to the onset of therapeutic response, effectiveness across the range of symptom severity, and favorable safety and tolerability profile further corroborate the robust clinical impact of pitolisant in the treatment of narcolepsy [25, 47, 48].

This analysis has several limitations that should be noted. As this was a post hoc analysis, these outcomes were not prespecified and the studies were not powered to evaluate them. The data for this analysis were obtained from rigorously designed studies, and generalizability to patients in real-world treatment settings is unknown.

5 Conclusions

In conjunction with the primary results from RCTs, the results of this analysis demonstrate the robust efficacy of pitolisant for the reduction in both EDS and cataplexy in adults with narcolepsy. The large effect sizes and low NNTs observed in this analysis add to the evidence that the results of the pitolisant RCTs demonstrate clinically meaningful reductions in EDS and cataplexy. The strength of this evidence suggests that pitolisant should be considered as a first-line treatment in adult patients with narcolepsy.

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Declarations

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Conflicts of interest/competing interests GJM reports serving on advisory boards and on the speakers' bureau for Harmony Biosciences and Jazz Pharmaceuticals. CWD, DZ, MD, and JMD are employees of Harmony Biosciences. JCS is a co-founder of Bioprojet Pharma.

Availability of data and material The datasets generated and/or analyzed for the current study are not publicly available.

Code availability Not applicable.

Authors' contributions GJM: data analysis and interpretation, and review and editing of the article; CWD: conceptualization, data analysis and interpretation, and review and editing of the article; DZ: conceptualization, data analysis and interpretation, and review and editing of the article; MD: data analysis and interpretation, and review and

editing of the article; JCS: data analysis and interpretation, and review and editing of the article; and JMD: data analysis and interpretation, and review and editing of the article. All authors provided input into the drafting of the manuscript, reviewed and approved the final version, and agree to be accountable for the work presented in the article.

Ethics approval Both studies (NCT01067222, NCT01800045) were conducted in accordance 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 at each study site.

Consent to participate All patients provided written informed consent before study enrollment.

Consent for publication Not applicable.

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