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ORIGINAL ARTICLE

# The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy*

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***Key words:*** **Alertness – Armodafinil – Fatigue – Memory – Narcolepsy – Sleepiness – Wakefulness**



## ABSTRACT

*Objective:* This study assessed the efficacy and safety of armodafinil, the longer half-life enantiomer of modafinil, for the treatment of excessive sleepiness in patients with narcolepsy.

*Research design and methods:* This was a multicenter double-blind study with 196 patients (aged 18–65 years) randomized to receive armodafinil 150 mg ($n = 65$), armodafinil 250 mg ($n = 67$), or placebo ($n = 64$) once daily for 12 weeks.

*Main outcome measures:* Efficacy was assessed using the Maintenance of Wakefulness Test (MWT) (six 20-min subtests across the day), the Clinical Global Impression of Change (CGI-C), subjective measures of sleepiness (Epworth Sleepiness Scale), patient diaries, and evaluations of cognitive performance (Cognitive Drug Research) and fatigue (Brief Fatigue Inventory).

*Results:* Armodafinil significantly increased MWT mean sleep latency (at 0900–1500) compared with placebo. The mean change from baseline at final visit for armodafinil was an increase of 1.3, 2.6, and 1.9 min in the 150-mg, 250-mg, and combined groups, respectively, compared with a decrease of 1.9 min for placebo ($p < 0.01$ for all three comparisons). Mean late-day MWT latency (1500–1900) was also significantly improved (difference of armodafinil combined group relative to placebo at final visit: 2.8 min, $p = 0.0358$). The proportions of patients who showed at least minimal improvement in the CGI-C rating from baseline to final visit in the armodafinil 150-mg, 250-mg, and combined groups were 69%, 73%, and 71%, respectively, compared with 33% for placebo ($p < 0.0001$). Both doses were associated with statistically significant improvements in memory, attention, and fatigue ($p < 0.05$). The most common adverse events in patients receiving armodafinil were headache, nausea, and dizziness.

*Conclusions:* Armodafinil significantly improved ability to sustain wakefulness throughout the day in patients with narcolepsy. Armodafinil also significantly improved overall clinical condition, memory, attention, and fatigue when compared with placebo.

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## Introduction

Narcolepsy is a lifelong, often disabling neurological sleep disorder characterized by excessive daytime sleepiness, cataplexy, and abnormal manifestations of rapid eye movement sleep. Patients with narcolepsy typically also have attentional deficits and other deficits of cognitive functions such as impaired concentration, learning, and memory[1,2].

Two variants of primary narcolepsy are now recognized, narcolepsy with cataplexy and narcolepsy without cataplexy[3]. The prevalence of narcolepsy with cataplexy varies from 0.02% to 0.07% in North America and Western Europe[4]. A deficiency in the hypothalamic peptide hypocretin is found in almost all cases of narcolepsy with cataplexy[5], and a tight association with the human leukocyte antigen (HLA) DQB1*0602 suggests that an autoimmune process may be involved in hypocretin cell loss[6]. Less is known about the prevalence and etiology of narcolepsy without cataplexy. A deficiency of hypocretin is not typically associated with this type of narcolepsy[7]. Although HLA DQB1*0602 is more commonly observed in narcolepsy without cataplexy relative to the general population, the association is not as strong as when cataplexy is present[8].

The wake-promoting agent modafinil has been shown to be effective and well tolerated in the treatment of excessive sleepiness (ES) associated with narcolepsy[9–13]. However, some patients still experience late-day sleepiness with the use of once-daily modafinil therapy and may require multiple doses[14,15].

Modafinil is a racemic compound containing equal amounts of the enantiomers *R*-modafinil and *S*-modafinil. Pharmacokinetic studies have shown that *R*-modafinil has a longer half-life than *S*-modafinil (10–14 vs. 3–4 h)[16–18]. Additionally, it has been reported that the elimination of *S*-modafinil is three times faster than that of *R*-modafinil[17]. Because of differences in half-life and rate of clearance, the proportion of circulating *R*-modafinil with chronic administration of racemic modafinil can be up to three times greater than circulating *S*-modafinil[16–18]. While peak concentration with *R*-modafinil is lower compared with modafinil, the half-life of the racemic compound is attributable to *R*-modafinil. Because *R*-modafinil has this longer half-life, its administration results in higher plasma concentrations later in the waking day compared with modafinil on a 'mg-to-mg' basis[19]. In the present study, *R*-modafinil, also known as armodafinil, administered once daily was investigated to determine its effect on wakefulness, measures of memory and attention, and fatigue throughout the day in patients with ES associated with narcolepsy.

## Patients and methods

### General study procedures

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled study conducted at 47 centers in the United States (30), Canada (3), France (3), Australia (4), Germany (3), and Russia (4). The study protocol was approved by the local Institutional Review Boards and national/local health authorities and was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation[20]. Patients participated in a clinical screening visit to assess eligibility. Patients who met initial criteria returned to the sleep clinic for additional laboratory screening, which included assessment of the severity of ES as determined by the Multiple Sleep Latency Test (MSLT). A subsequent baseline visit was used to establish pretreatment levels of cognitive impairment, fatigue, and ability to maintain wakefulness as determined by the Maintenance of Wakefulness Test (MWT), and to conduct baseline polysomnography. After randomization, patients were evaluated at 4-week intervals using the same assessments.

### Patient selection

In total, 326 men and women between the ages of 18 and 65 years, with a diagnosis of narcolepsy according to *International Classification of Sleep Disorders* criteria[3], were screened for this study. All patients provided written informed consent. Eligible patients had to be free of medical or psychiatric disorders, other than narcolepsy, that could have caused ES, and had to be able to complete self-rating scales and computer-based testing. Female patients of childbearing potential were required to have a negative serum pregnancy test at screening and use a medically accepted method of birth control. Steroidal contraceptives had to be used in conjunction with a barrier method. Patients with self-reported cataplexy on stable doses of anticataplectic medications other than sodium oxybate were permitted to participate in the study.

Patients were excluded if they had any clinically significant uncontrolled medical or psychiatric illnesses (treated or untreated); had a probable diagnosis of a current sleep disorder other than narcolepsy in the opinion of the investigator; consumed > 600 mg/day of caffeine; had a history of alcohol, narcotic, or other drug abuse as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition[21]; had any disorder that might interfere with drug absorption, distribution, metabolism, or excretion (no specific criteria; determined by investigator); or had a known sensitivity to stimulants or modafinil. In addition, patients were excluded if they used drugs disallowed

by the protocol (modafinil, melatonin, sodium oxybate, lithium, St. John's wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, monoamine oxidase inhibitors, anticoagulants, anticonvulsants, and barbiturates) or if they used clinically significant amounts of nonprescription drugs within 7 days of the screening visit. Anticataplectic drugs (i.e., clomipramine, moclobemide, selective serotonin reuptake inhibitors, venlafaxine, and viloxazine), other than sodium oxybate, were permitted if they did not contribute to patients' sleepiness and if doses were stable for at least 1 month prior to baseline. $Alpha_1$ antagonists or muscarinic receptor antagonists known to exacerbate cataplexy were also permitted. Pregnant or lactating women were also excluded.

A mean sleep latency ≤ 6 min on the MSLT[22] and a Clinical Global Impression of Severity of Illness (CGI-S)[23] rating ≥ 4 (moderately ill) were also required for inclusion in the study. The MSLT was scored at a central site (St. John's/St. Luke's Hospital [St. Louis, MO]) by qualified personnel under the supervision of one of the authors (JKW).

Eligible patients were randomized 1:1:1 to receive armodafinil 150 mg, armodafinil 250 mg (Cephalon, Inc., Frazer, PA), or placebo once daily for 12 weeks. Randomization was performed using a central randomization process that employed an interactive voice response system to ensure overall balance among treatment groups within each country. The patients were not randomized within each study center because of the large number of planned centers participating in this study. Patients and investigators remained blinded to treatment assignment throughout the study.

Study medication was administered before 0800 (approximately 30 min before breakfast) throughout the study. During laboratory visits, the medication was administered at approximately 0700 (± 15 min). Armodafinil was initiated at a dose of 50 mg/day in all patients; doses were increased to 100 mg/day on day 2 and titrated upward in 50-mg increments every 2 days until the final dose was achieved. Patients randomized to armodafinil 150 mg also received two placebo tablets. Matching placebo was titrated to five tablets in a similar manner. Patients entered the time they took study medication into their diary daily. The diary data were reviewed by site personnel, and patients were counseled appropriately if they were not following the protocol instructions. Checks of compliance, including review of patient diaries and drug accountability records, were performed by the investigator.

## Assessments

Laboratory assessments were conducted at baseline and at weeks 4, 8, and 12 of the double-blind treatment period. Patients were asked to sleep in the sleep laboratory without undergoing observation or polysomnographic recording or at a nearby hotel the evening before each scheduled visit to assure adequate sleep prior to the MWT, and assessments began the following morning. Although patients were encouraged to get a full night of sleep (8 h) the night before assessments began, this was not regimented.

### *Maintenance of Wakefulness Test*

The MWT[24,25] objectively assesses the ability to remain awake for a defined period of time. Patients are placed in a darkened room in a semi-reclined position and instructed to remain awake. Six 20-min subtests were conducted at 2-h intervals from 0900 to 1900. Electroencephalogram, electro-oculogram, and electromyogram measures were used to determine sleep latency, which was defined as the time from lights out to the first of three consecutive epochs of stage 1 sleep or one epoch of any other sleep stage. Recordings for MWT continued until the patient reached unequivocal sleep or the end of 20 min. If the patient fell asleep, he or she was awakened, removed from the darkened room, and instructed to remain awake until the next subtest. If a patient did not fall asleep during a subtest, the subtest was terminated after 20 min and a sleep latency value of 20 min was assigned. The MWT was scored at a central site (Henry Ford Hospital [Detroit, MI]) by qualified personnel under the supervision of one of the authors (TR).

### *Clinical Global Impression Scales*

Severity of illness was classified at baseline by the investigator by using the CGI-S[23]. The Clinical Global Impression of Change (CGI-C) was used to assess change in illness compared with baseline during study visits (weeks 4, 8, and 12) using a 7-point scale with possible ratings of 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', or 'very much worse'[23].

### *Cognitive Drug Research computerized assessment battery*

The Cognitive Drug Research (CDR) system[26–29] was used to assess major domains of attention and memory and included the following tests: simple reaction time, choice reaction time, digit vigilance, articulatory working memory, word recall (immediate and delayed), word recognition, and picture recognition. The entire battery of tests took just over 25 min to complete. Four CDR composite scores were derived from the measures from these tests. Power of attention[29,30], which reflects

the ability to focus attention, is derived from the speed-of-response scores from three attention tests: simple reaction time, choice reaction time, and digit vigilance. Continuity of attention[29,30], which reflects the ability to sustain attention, is derived from the accuracy measures in choice reaction time and digit vigilance. Quality of episodic secondary memory[26,29] reflects the ability to store, retain, and retrieve information and is derived by combining the accuracy scores from the four recall and recognition tasks. Finally, speed of memory[29] reflects the time taken to retrieve information from memory and is formed by combining the speed scores for correctly identifying previously presented information in the working and recognition memory tasks. The CDR tests were administered at 0930, 1130, 1330, 1530, 1730, and 1930 at baseline and at the same times during the visits at weeks 4, 8, and 12. Parallel forms of the tests were administered on each of the 24 occasions. Furthermore, the tests were administered four times during the day at one screening visit prior to the study to overcome practice effects[31].

### *Epworth Sleepiness Scale*

The Epworth Sleepiness Scale (ESS)[32] was administered at baseline and before the first MWT subtest of each visit. Total scores range from 0 to 24, with higher scores indicating greater sleepiness. An ESS score ≥ 10 indicates ES.

### *Brief Fatigue Inventory*

The 9-item Brief Fatigue Inventory (BFI)[33] was administered at baseline and before the first MWT subtest of each visit to assess patient-rated global fatigue (average of all questions) and worst fatigue during the past 24 h (item number 3). Patients rated each item using an 11-point scale (0–10), with higher scores indicating greater fatigue severity or impact.

### *Polysomnography*

Nocturnal polysomnographic evaluation was obtained after the daytime MWT at baseline and final visit. Patients were required to remain in bed for a maximum of 8 h. Polysomnography began within 30 min of the patients' usual bedtime but not earlier than 2130. Polysomnography was scored at a central site (Henry Ford Hospital [Detroit, MI]) by qualified personnel under the supervision of one of the authors (TR).

### *Patient diaries*

Patients completed daily electronic diaries, which recorded level of daytime sleepiness; frequency of unintended sleep episodes; number of intentional naps; number of mistakes/near misses/accidents; and caffeine use. The daily diaries were also used to obtain information on night-time sleep, cataplexy, and taking of study medication.

## Safety assessments

The safety and tolerability of study medication were determined from adverse events, vital signs (assessed at approximately 3 h and 13 h post dose), serum chemistry and hematology, urinalysis, physical examination findings, and electrocardiogram performed at the laboratory visits. Weight and vital signs were collected at baseline and at final visit approximately 24 h post last dose. Investigators rated the adverse event severity and the relationship of each adverse event to study medication. Safety and tolerability assessments also included examination of the mean change from baseline in nocturnal polysomnography at final visit (week 12 or the last post-baseline visit). Subjective estimates of night-time sleep were obtained with daily electronic diaries.

## Statistical analyses

The co-primary efficacy variables were the baseline assessment to final visit changes in mean sleep latency on the MWT 0900–1500 and the proportion of patients with at least minimal improvement on the CGI-C, as assessed at the final visit. Secondary efficacy variables included mean changes from baseline in the MWT 1500–1900 mean sleep latency; attention and memory as assessed by the CDR (average of first four test sessions at 0930, 1130, 1330, and 1530); ESS scores; CGI-C ratings; BFI (score for global fatigue and score for worst fatigue over the previous 24 h); and data from diaries (sleepiness, mistakes/near misses/accidents, and caffeine use). Analyses of all efficacy variables at weeks 4, 8, and 12 used observed cases, and the final visit analyses were performed using the last observation carried forward.

A sample size of 128 patients in the armodafinil combined group was calculated to provide 80% power to detect a 2.5-min difference in the mean sleep latency on the MWT (subtests at 0900, 1100, 1300, and 1500) between the armodafinil combined group and placebo. A common standard deviation (SD) of 5.0 min was assumed. This sample size also yielded at least 80% power to detect a difference of 25% between the armodafinil combined group and placebo in the proportion of patients reporting at least minimal improvement in CGI-C ratings, assuming a 37% rate in the placebo group. The number of statistical comparisons was minimized by using a closed testing procedure such that comparisons between individual armodafinil dose groups and placebo were made only if the difference

between the armodafinil combined group and placebo was statistically significant. Approximately 210 patients were targeted for enrollment to obtain 192 evaluable patients (i.e., who had at least one post-baseline MWT assessment and one post-baseline CGI-C assessment).

Safety analyses included all randomized patients who received study medication or placebo, and efficacy analyses included all patients in the safety analysis set who had at least one post-baseline measurement on both the MWT and CGI-C. Demographic and baseline characteristics were compared for continuous variables using analysis of variance with the treatment group as a factor. Categorical variables for CGI-S were compared using Pearson's chi-square test. If cell sizes were too small (i.e., < 5 patients per cell), the Fisher exact test was used. All the continuous efficacy variables of mean sleep latency from the MWT (average of daytime and late-day tests), total scores from ESS, CDR variables (power of attention, continuity of attention, quality of episodic secondary memory, and speed of memory for daytime tests), and BFI (worst fatigue and global fatigue) were analyzed using the change from baseline at each visit (weeks 4, 8, and 12 or final visit). All of these variables were analyzed using analysis of covariance (ANCOVA) with treatment and country as factors and the corresponding baseline values as a covariate, and separate analyses were performed at each visit. Pairwise comparisons were performed using appropriate contrasts in the ANCOVA. The categorical variables of proportion of patients with at least minimal improvement in the CGI-C rating and the proportion of patients with ESS total score < 10 were analyzed using the Cochran–Mantel–Haenszel chi-square test adjusted for country, and separate analyses were performed at each visit (week 4, 8, and 12 or final visit). Pairwise comparisons were made for these categorical variables. Diary variables for ES and number of mistakes/near misses/accidents were analyzed using the Kruskal–Wallis nonparametric test. The variables from cataplexy attacks, caffeine consumption, nocturnal polysomnography, adverse events, and all safety evaluations were summarized using descriptive statistics. All tests of significance were 2-tailed, and the 5% level of significance was used.

## Results

### Patient characteristics and disposition

Of the 326 patients screened, 196 met the study entry criteria and were randomized to armodafinil or placebo. Of the 196 patients, 194 (99%) were included in the safety analysis. Two patients were randomized but excluded from the safety analysis: one withdrew consent (armodafinil 150-mg group), and the other was lost to follow-up (placebo group) prior to taking study medication. At baseline, the placebo and armodafinil 150-mg and 250-mg groups were generally well matched, although patients in the armodafinil 250-mg group were significantly younger than patients in the other groups ($p < 0.05$; Table 1). At screening, CGI-S ratings were similar across groups, with the majority of patients enrolled having marked or severe illness, and no differences were found between groups in MSLT (Table 1). The most frequently used concomitant

***Table 1.*** *Demographic and clinical characteristics of patients receiving placebo, armodafinil 150 mg, or armodafinil 250 mg once daily (safety analysis sample*) at study entry*

| Characteristic | Placebo ($n$ = 63) | Armodafinil | | $p$ value† |
|---|---|---|---|---|
| | | 150 mg ($n$ = 64) | 250 mg ($n$ = 67) | |
| Age, years (mean [SD]) | 39.2 (12.0) | 40.4 (12.5) | 35.0 (12.5) | 0.0355 |
| Sex, $n$ (%) | | | | 0.3017 |
| Women | 31 (49) | 36 (56) | 42 (63) | |
| Race, $n$ (%) | | | | 0.7737 |
| White | 49 (78) | 44 (69) | 48 (72) | |
| Black | 10 (16) | 13 (20) | 9 (13) | |
| Other‡ | 1 (2) | 5 (8) | 7 (10) | |
| Missing | 3 (5) | 2 (3) | 3 (4) | |
| BMI, kg/m$^2$ (mean [SD]) | 28.3 (5.3) | 29.6 (6.7) | 28.3 (6.9) | 0.4120 |
| CGI-S, $n$ (%) | | | | 0.7672 |
| Moderately ill | 18 (29) | 19 (30) | 25 (37) | |
| Markedly ill | 34 (54) | 32 (50) | 29 (43) | |
| Severely ill | 11 (17) | 11 (17) | 12 (18) | |
| Most extremely ill | 0 (0) | 2 (3) | 1 (1) | |
| Sleep latency, min (MSLT; mean [SD]) | 2.6 (1.5) | 2.7 (2.1) | 2.8 (1.9) | 0.8469 |
| Cataplexy (%) | 65 | 69 | 66 | 0.8944 |

BMI = body mass index; CGI-S = Clinical Global Impression of Severity of Illness; MSLT = Multiple Sleep Latency Test
*Safety analysis sample defined as all randomized patients who received study medication or placebo
†$p$ value for overall treatment comparison
‡Other includes Asian, American Indian or Alaskan native, Pacific Islander, Hispanic, Filipino, Eurasian, and mixed race

medications included non-opioid analgesics/anti-inflammatory agents (armodafinil, 34%; placebo, 41%), vitamins/nutritional supplements (armodafinil, 20%; placebo, 19%), and metabolic/endocrine agents (armodafinil, 20%; placebo, 19%). Patient disposition and information regarding patient withdrawal are summarized in Figure 1. Baseline values for selected efficacy variables are shown in Table 2.

## Maintenance of Wakefulness Test

At the final visit, mean MWT 0900–1500 sleep latency increased 1.3, 2.6, and 1.9 min from baseline in the 150-mg, 250-mg, and armodafinil combined groups, respectively, and decreased 1.9 min from baseline in the placebo group. Treatment differences relative to placebo were 3.2, 4.5, and 3.8 min in the

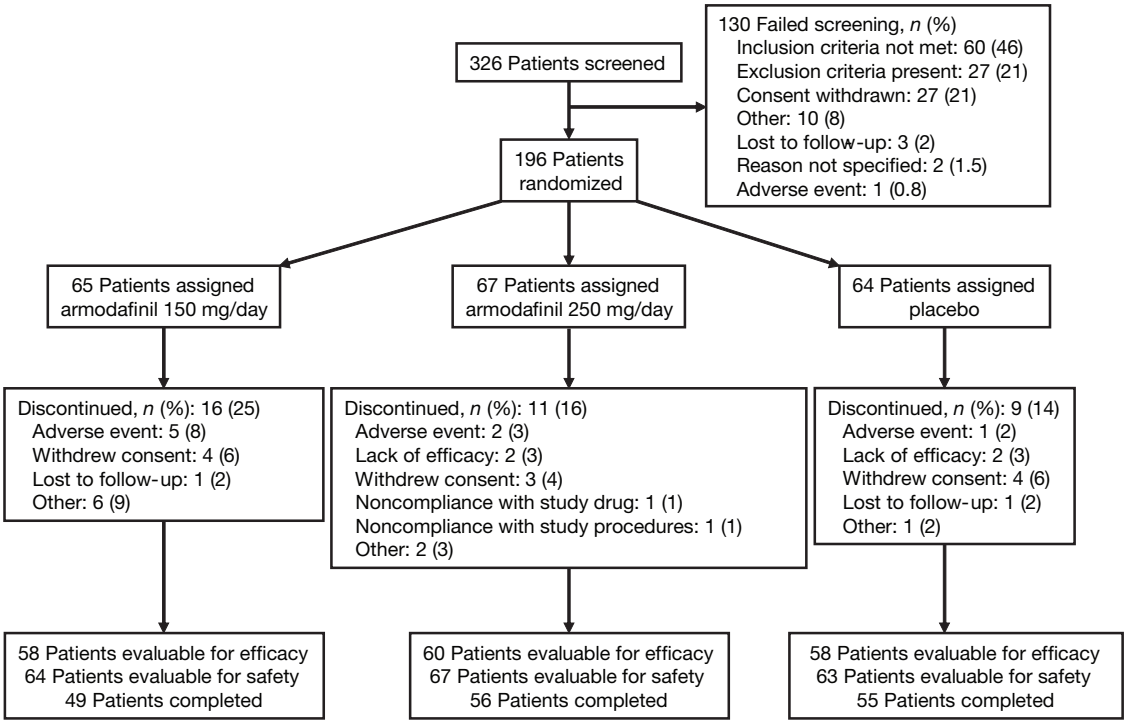



***Figure 1.*** *Patient disposition and withdrawals*

***Table 2.*** *Selected baseline test scores for patients receiving placebo, armodafinil 150 mg, or armodafinil 250 mg once daily (efficacy analysis sample*)*

| Characteristic | Placebo ($n$ = 58) | Armodafinil | | $p$ value† |
|---|---|---|---|---|
| | | 150 mg ($n$ = 58) | 250 mg ($n$ = 60) | |
| Mean (SD) MWT 0900–1500 sleep latency, min (MWT) | 12.5 (6.6) | 12.1 (6.6) | 9.5 (6.1) | 0.0236 |
| Mean (SD) MWT 1500–1900 sleep latency, min (MWT later time points) | 12.9 (6.6) | 12.2 (6.8) | 10.5 (6.6) | 0.1400 |
| Mean (SD) ESS score | 17.5 (3.9) | 17.3 (3.4) | 15.7 (4.7) | 0.0371 |
| Mean (SD) BFI score | | | | |
| Global fatigue | 5.7 (2.1) | 5.7 (2.1) | 5.5 (1.9) | 0.7395 |
| Worst fatigue | 7.9 (2.3) | 7.8 (2.2) | 7.7 (2.2) | 0.8563 |
| Mean (SD) diary-derived variables | | | | |
| Number of unintended sleep episodes per day | 2.2 (1.8) | 2.3 (2.0) | 1.7 (1.5) | 0.2015 |
| Number of daily naps | 1.4 (1.1) | 1.3 (0.9) | 1.3 (1.0) | 0.6039 |
| Number of mistakes/near misses/accidents | 1.0 (1.5) | 1.4 (2.1) | 1.5 (2.0) | 0.3811 |
| Night-time sleep efficiency‡ | 90.8 (10.0) | 90.9 (9.3) | 92.3 (8.6) | 0.6440 |
| Night-time sleep latency, min‡ | 17.0 (26.3) | 12.1 (12.3) | 11.9 (10.3) | 0.4506 |
| Number of caffeinated drinks | 13.9 (12.9) | 15.8 (13.4) | 16.5 (17.4) | 0.7204 |

BFI = Brief Fatigue Inventory; CGI-C = Clinical Global Impression of Change; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test

*Efficacy analysis sample defined as all patients in the safety analysis set who had at least one post-baseline measurement on both the MWT and CGI-C

†$p$ value for overall treatment comparison

‡Effect on sleep based on diary data. Data from the safety analysis sample

150-mg, 250-mg, and armodafinil combined groups, respectively ($p < 0.01$ for all comparisons). Relative to placebo, the improvement in wakefulness observed in both armodafinil dose groups was significant at the first visit at week 4 and was sustained throughout the study for the 150-mg dose group, whereas numerical improvements in the 250-mg dose group did not achieve statistical significance at weeks 8 and 12 (Figure 2a). The difference in age for the different treatment groups at the time of randomization had no effect on the MWT results as verified by ANCOVA using age as a covariate.

Mean MWT 1500–1900 sleep latency at the final visit increased 1.5, 1.6, and 1.6 minutes in the 150-mg, 250-mg, and armodafinil combined groups, respectively, and decreased 1.2 min from baseline in the placebo group. Treatment differences relative to placebo were 2.7, 2.8, and 2.8 min, for the 150-mg, 250-mg, and armodafinil combined groups, respectively. The differences for the armodafinil combined group versus placebo and the 150-mg group versus placebo were significant ($p < 0.05$ for both comparisons) (Figure 2b). The armodafinil groups, individually and collectively, also had numerically longer mean MWT 1500–1900 sleep latencies when compared with placebo at weeks 4, 8, and 12. These differences did not achieve statistical significance. The change in mean MWT sleep latency from baseline with armodafinil over time is reflected in Figure 3.

## Clinical Global Impression of Change

The proportion of patients with at least minimal improvement in their CGI-C rating was significantly higher for the armodafinil 150-mg, 250-mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs. placebo at final visit; Figure 4). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33%, and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo.

## Cognitive Drug Research battery

At final visit, power of attention was significantly improved in the armodafinil 150-mg/day and armodafinil combined groups compared with placebo ($p < 0.05$). Although there were numerical differences in favor of both armodafinil dose groups and the combined group compared with placebo at each visit, statistical significance was not observed until the final visit. Effects on mean continuity of attention were numerically improved for the armodafinil groups compared with placebo, but the difference did not achieve statistical significance.

At final visit, armodafinil (both doses and the combined group) demonstrated significantly greater improvements in quality of episodic secondary memory relative to placebo ($p < 0.05$; Table 3). Improvement was observed at the week 4 visit and was maintained throughout the study. Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory relative to placebo ($p < 0.05$) at final visit.

## Epworth Sleepiness Scale

Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared with placebo at weeks 8 ($p < 0.01$ for all comparisons) and 12 ($p < 0.01$) and at final visit (mean ± SD change from baseline: 150 mg/day, –4.1 ± 5.13, $p$ =0.0044; 250 mg/day, –3.8 ± 4.73, $p$ = 0.0015; combined group, –3.9 ± 4.91, $p$ = 0.0006). At week 4, there was a statistically significant difference in favor of patients receiving armodafinil 150 mg/day ($p$ = 0.0402). In patients receiving armodafinil 250 mg/day, the difference was not statistically significant ($p$ = 0.0760). At the final visit, 21% of patients in the armodafinil 150-mg/day group ($p$ = 0.0312) and 28% of patients in the armodafinil 250-mg/day group ($p$ = 0.0023) had an ESS score < 10, compared with only 7% of patients in the placebo group.

## Brief Fatigue Inventory

Improvements in global fatigue in the armodafinil 150-mg/day, 250-mg/day, and combined armodafinil group at final visit were statistically greater than placebo (mean change from baseline: 150 mg/day, –1.5 ± 2.14, $p$ = 0.0007; 250 mg/day, –1.3 ± 2.09, $p$ = 0.0018; combined group, –1.4 ± 2.11, $p$ = 0.0002; placebo, –0.3 ± 1.89). There was a trend toward improvement from baseline in mean worst fatigue scores over the previous 24 h at final visit, but the differences with armodafinil (all groups) versus placebo were not statistically significant ($p > 0.05$).

## Electronic diary–derived data

Treatment with armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction seen in the placebo group

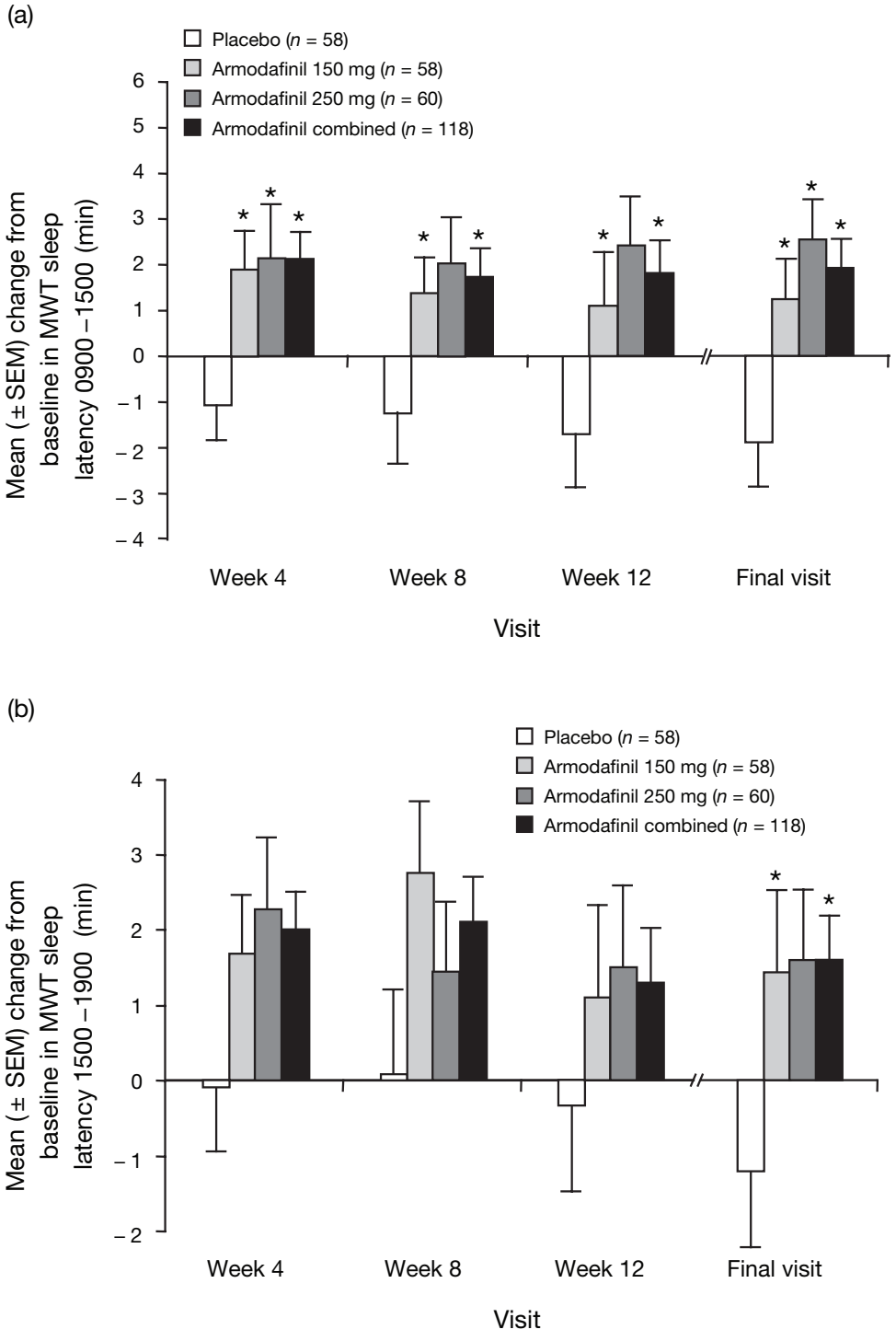


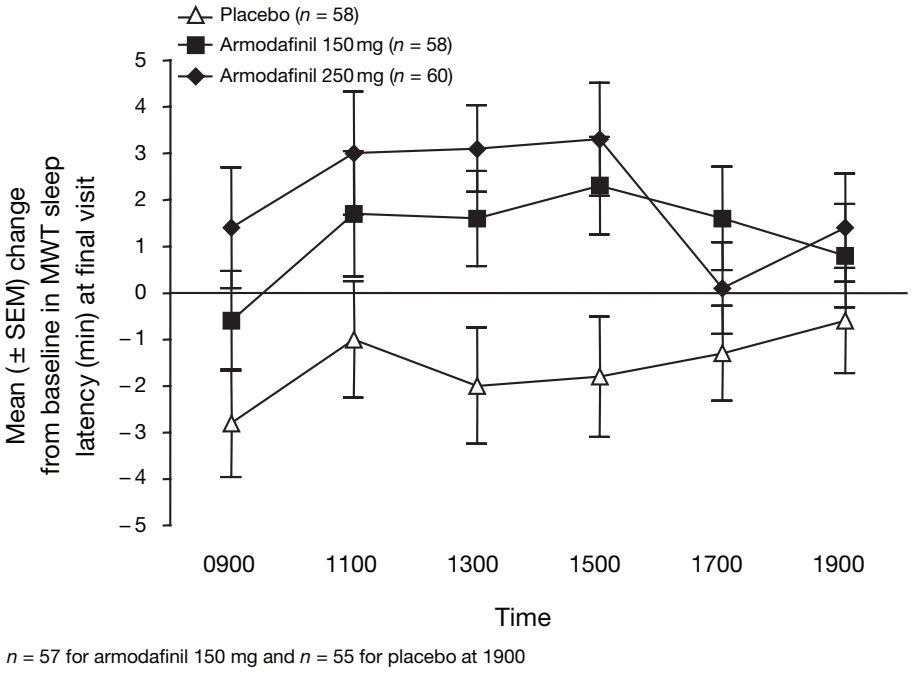

***Figure 2.*** *Change in mean (± SEM) Maintenance of Wakefulness Test (MWT) sleep latency from baseline with armodafinil. (a) MWT sleep latency at 0900–1500; (b) late-day MWT sleep latency (1500–1900). SEM = standard error of the mean.* *p < *0.05 versus placebo*

($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150-mg, armodafinil 250-mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150-mg/day and 250-mg/day groups, respectively, compared with a 10% reduction in the placebo group. These differences, however, did not achieve statistical significance ($p = 0.1792$ for overall treatment comparison). Caffeine use, which was measured by the number of caffeinated drinks consumed each day, remained similar in the armodafinil and placebo groups (mean change from baseline, –0.7, –1.6, and 0.6 for armodafinil 150 mg, armodafinil 250 mg, and placebo, respectively).

*Table 3. Attention and memory scores for patients receiving placebo, armodafinil 150 mg, or armodafinil 250 mg once daily at baseline and final visit*

| | Placebo ($n$ = 58) | Armodafinil 150 mg ($n$ = 58) | Armodafinil 250 mg ($n$ = 60) |
|---|---|---|---|
| Mean (SD) power of attention (ms) | | | |
| Baseline | 1618.0 (852.0) | 1524.4 (686.0) | 1349.5 (349.1) |
| Final visit | 1766.0 (1492.6) | 1444.3 (328.3) | 1384.6 (387.7) |
| Change from baseline | 158.0 (850.1) | –80.1 (532.6) | –3.5 (346.9) |
| 95% confidence interval | – | –463, –12 | –384, 72 |
| $p$ value | – | 0.0389 | 0.1776 |
| Mean (SD) continuity of attention (units) | | | |
| Baseline | 86.6 (8.0) | 86.0 (7.6) | 88.1 (6.4) |
| Final visit | 86.6 (9.3) | 88.2 (6.8) | 87.6 (13.2) |
| Change from baseline | –0.3 (4.9) | 2.2 (5.4) | –0.4 (14.2) |
| 95% confidence interval | – | –1, 6 | –3, 4 |
| $p$ value | – | 0.2054 | 0.8788 |
| Mean (SD) quality of episodic secondary memory (units) | | | |
| Baseline | 163.3 (56.1) | 159.3 (56.8) | 166.4 (48.3) |
| Final visit | 165.7 (59.8) | 180.1 (53.2) | 182.9 (57.5) |
| Change from baseline | 1.0 (29.1) | 20.7 (34.5) | 16.5 (46.5) |
| 95% confidence interval | – | 5, 32 | 3, 30 |
| $p$ value | – | 0.0062 | 0.0168 |
| Mean (SD) speed of memory (ms) | | | |
| Baseline | 3411.0 (1217.4) | 3225.2 (971.1) | 2822.4 (783.5) |
| Final visit | 3386.4 (1358.4) | 3060.7 (982.1) | 2589.3 (603.2) |
| Change from baseline | –6.3 (1180.7) | –164.5 (862.0) | –233.2 (569.3) |
| 95% confidence interval | – | –520, 85 | –730, –116 |
| $p$ value | – | 0.1567 | 0.0072 |






$n$ = 57 for armodafinil 150 mg and $n$ = 55 for placebo at 1900

***Figure 3.*** *Change in mean (± SEM) Maintenance of Wakefulness Test (MWT) sleep latency from baseline with armodafinil throughout the day (0900–1900)*

## Safety and tolerability

Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil (Table 4). Review of the adverse event profile did not suggest that armodafinil had any negative effect on mood in this study. Most adverse events were considered by the investigator to be mild or moderate in severity (defined as no or some limitation of usual activities), occurred with greatest frequency during the first 2 weeks of therapy, and were self-limiting. Adverse

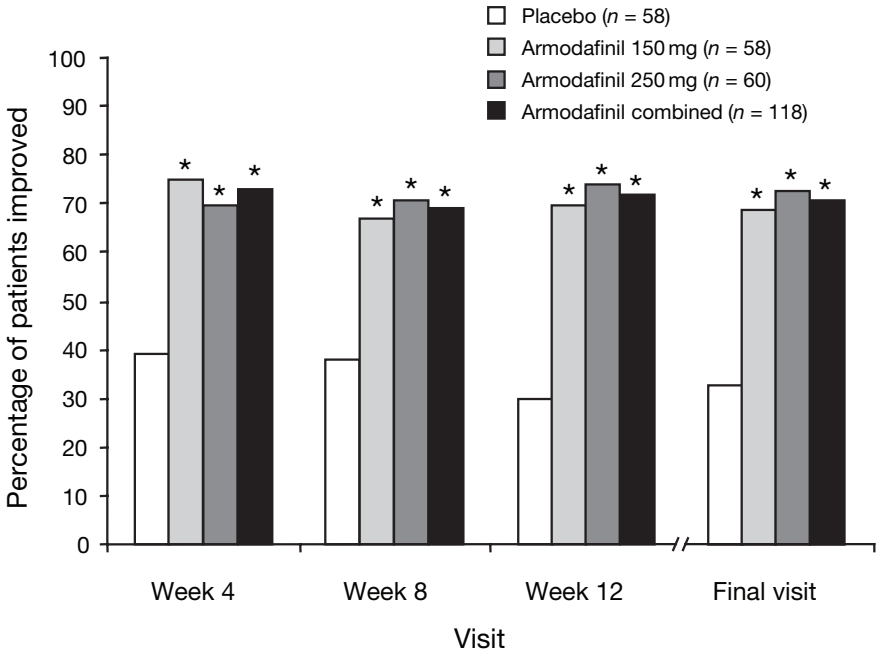



***Figure 4.*** *Percentage of patients with improved overall clinical condition as assessed by CGI-C by treatment visit. CGI-C = Clinical Global Impression of Change. *p < 0.01 versus placebo*

***Table 4.*** *Number of patients (%) with adverse events occurring in ≥ 5% of patients receiving armodafinil and more frequently than in patients receiving placebo*

| Adverse event | Placebo (*n* = 63) | Armodafinil | |
|---|---|---|---|
| | | 150 mg (*n* = 64) | 250 mg (*n* = 67) |
| Headache | 7 (11) | 10 (16) | 19 (28) |
| Nausea | 0 | 9 (14) | 5 (7) |
| Dizziness | 0 | 5 (8) | 2 (3) |
| Decreased appetite | 0 | 2 (3) | 4 (6) |
| Diarrhea | 1 (2) | 3 (5) | 2 (3) |
| Dyspepsia | 1 (2) | 3 (5) | 0 |

events that led to withdrawal occurred in eight patients (five patients in the armodafinil 150-mg/day group, two patients in the armodafinil 250-mg/day group, and one patient who received placebo). The reasons leading to withdrawal, regardless of cause, in patients receiving armodafinil 150 mg included severe acute urticaria with angioedema (*n* = 1), headache and depression (*n* = 1), insomnia (*n* = 1), diarrhea (*n* = 1), and disorientation and headache (*n* = 1). In the armodafinil 250-mg/day group, reasons for withdrawal were dizziness and abnormal behavior (*n* = 1), and sleep disorder and urticaria (*n* = 1). In the placebo group, reasons for withdrawal were myalgia, skin odor abnormal, somnolence, and headache (*n* = 1). One serious adverse event (severe acute urticaria with angioedema) was reported in a patient who received armodafinil 150 mg/day. This adverse event was considered by the investigator unlikely to be related to armodafinil because of the patient's medical history (intermittent poison ivy, cat and egg allergies, and childhood bee venom allergies) and the course of the event was not typical of a drug-related reaction (i.e., event recurred and persisted despite discontinuation of armodafinil). There were no significant changes in physical examination or weight for patients receiving armodafinil.

## Clinical laboratory tests

In general, the groups were comparable for laboratory parameters, including chemistry, hematology, and urinalysis. For alkaline phosphatase, the mean ± SD change from baseline to final visit was 2.5 ± 8.78 U/L for armodafinil 150 mg, 6.3 ± 9.59 U/L for armodafinil 250 mg, and –0.7 ± 8.66 U/L for placebo. For gamma-glutamyl transpeptidase (GGT), the change was 3.4 ± 10.41 U/L for armodafinil 150 mg, 10.7 ± 15.92 U/L for armodafinil 250 mg, and 0.9 ± 9.48 U/L for placebo. An increase in alkaline phosphatase and GGT values was noted at week 4, and there appeared to be a dose relationship for the changes in both parameters. No mean changes in other liver function tests (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) from baseline to final visit were observed in any group. Decreases in mean values for uric acid from baseline to final visit were observed in both the armodafinil and placebo groups. In addition to mean changes from baseline, clinically significant abnormal values defined a priori (GGT and aspartate aminotransferase, > 3 times the upper limit of normal; uric acid, ≥ 625 or ≥ 506 µmol/L for men and women,

respectively; total bilirubin, ≥ 34.2 µmol/L) for clinical laboratory tests at any time during the study were reported for four patients receiving armodafinil 250 mg (two patients for GGT and two for uric acid levels), two patients receiving armodafinil 150 mg (one for total bilirubin and one for aspartate aminotransferase), and three patients receiving placebo (two for uric acid and one for GGT). However, five of the six patients receiving armodafinil had baseline values that met the clinically significant value or were above the reference range.

### Vital signs

Numerical increases in systolic blood pressure and heart rate were observed. For mean morning vital signs (3 h post dose), these effects were statistically significant only for mean morning heart rate between the armodafinil 250-mg and placebo groups (5.3 ± 11.5 vs. 0.8 ± 10.1 mmHg, $p = 0.0193$). A relatively higher proportion of patients receiving armodafinil compared with patients receiving placebo had morning vital sign measurements characterized a priori as clinically significant (Table 5). No numerical differences were seen for mean changes versus baseline in the evening (13 h post dose) heart rate and blood pressure for armodafinil and placebo. There was a small but statistically significant difference for the armodafinil combined group compared with placebo in 24-h mean diastolic blood pressure (0.4 ± 9.32 vs. –2.6 ± 10.25 mmHg, respectively, $p = 0.0294$).

### Electrocardiography

Values for mean PR, QRS, QT, and QTc interval (Bazett or Fridericia) were comparable in the armodafinil and placebo groups throughout the study. The proportion of patients with new electrocardiogram findings was similar between patients receiving armodafinil and those receiving placebo.

### Sleep characteristics and cataplexy

Night-time sleep was not adversely affected by armodafinil. There were no significant effects on any sleep initiation, continuity, or sleep stage variable as assessed by polysomnography (Table 6). Similarly, data obtained from daily patient sleep diaries showed no significant adverse effect on sleep in patients receiving armodafinil compared with patients receiving placebo. There was also no change in the incidence of self-reported cataplexy (mean ± SD change from baseline to final visit, armodafinil 150 mg, 0.0 ± 1.14; armodafinil 250 mg, –0.2 ± 0.66; armodafinil combined group, –0.1 ± 0.93; placebo, –0.1 ± 0.56).

## Discussion

This study of armodafinil, the first in patients with ES associated with narcolepsy, indicates that armodafinil improved patients' ability to sustain wakefulness. Patients participating in this study were representative of patients with ES associated with narcolepsy. At screening, the mean sleep latency on the screening MSLT was < 3 min, which indicates marked or severe ES. Once-daily treatment with armodafinil 150 mg or 250 mg produced statistically significant improvements in both objective (MWT) and subjective (ESS) measures of wakefulness. The clinical relevance of these findings was validated by the positive effects of armodafinil treatment on the clinician-rated measure of improvement in overall clinical condition, the CGI-C. Almost three quarters (71%) of the patients who received armodafinil had improvement

***Table 5.*** *Morning vital sign measurements* at baseline and final visit*

| Vital sign | Placebo ($n = 63$) | Armodafinil | |
|---|---|---|---|
| | | 150 mg ($n = 64$) | 250 mg ($n = 67$) |
| Heart rate, bpm | | | |
| Baseline, mean (SD) | 69.0 (11.32) | 67.8 (10.98) | 68.3 (12.03) |
| Mean change (SD) | 0.8 (10.08) | 3.3 (10.05) | 5.3 (11.50)† |
| Patients with ≥ 120 bpm and increase ≥ 15 bpm, *n* | 0 | 0 | 0 |
| Systolic blood pressure, mmHg | | | |
| Baseline, mean (SD) | 118.6 (16.64) | 120.9 (12.91) | 115.9 (12.07) |
| Mean change (SD) | 0.9 (14.78) | 1.2 (12.42) | 4.3 (11.87) |
| Patients with ≥ 140 and increase ≥ 10%, *n* (%) | 5 (8) | 8 (13) | 9 (13) |
| Diastolic blood pressure, mmHg | | | |
| Baseline, mean (SD) | 74.6 (10.64) | 75.3 (9.47) | 72.9 (9.47) |
| Mean change (SD) | –0.7 (8.87) | 1.6 (10.65) | 1.5 (9.99) |
| Patients with ≥ 90 and increase ≥ 10%, *n* (%) | 4 (6) | 8 (13) | 6 (9) |

*Measured approximately 3 h post study drug administration
†$p = 0.0193$ versus placebo

*Table 6. Mean (SD) nocturnal polysomnography variables at baseline and final visit*

| Variable | Placebo ($n$ = 63) | Armodafinil | |
|---|---|---|---|
| | | 150 mg ($n$ = 64) | 250 mg ($n$ = 67) |
| Latency to persistent sleep*, min | | | |
| Baseline | 15.1 (14.9) | 16.7 (19.0) | 15.9 (16.2) |
| Final visit | 21.9 (27.3) | 15.5 (19.0) | 16.8 (17.2) |
| Number of arousals | | | |
| Baseline | 21.7 (13.5) | 23.7 (11.9) | 21.6 (13.7) |
| Final visit | 20.4 (13.7) | 23.5 (14.8) | 21.7 (14.1) |
| Number of awakenings | | | |
| Baseline | 10.7 (6.3) | 11.3 (6.0) | 8.6 (6.5) |
| Final visit | 11.0 (6.8) | 12.1 (6.1) | 8.8 (7.1) |
| Sleep efficiency, % | | | |
| Baseline | 81.3 (12.8) | 82.9 (11.9) | 85.8 (12.0) |
| Final visit | 80.9 (12.7) | 80.2 (13.2) | 86.5 (11.5) |
| Total sleep time, min | | | |
| Baseline | 389.6 (61.7) | 396.5 (57.1) | 406.2 (58.6) |
| Final visit | 381.4 (79.4) | 374.6 (76.5) | 414.1 (54.8) |
| Wake after sleep onset, min | | | |
| Baseline | 78.2 (61.4) | 69.6 (54.1) | 55.5 (54.0) |
| Final visit | 72.1 (55.2) | 83.8 (58.7) | 52.5 (51.2) |
| Stage 1, % | | | |
| Baseline | 12.8 (8.1) | 13.3 (6.9) | 11.9 (6.7) |
| Final visit | 12.2 (7.8) | 14.0 (8.4) | 11.7 (6.8) |
| Stage 2, % | | | |
| Baseline | 56.1 (12.1) | 58.1 (9.8) | 56.1 (9.8) |
| Final visit | 56.6 (11.8) | 57.0 (11.3) | 55.6 (10.6) |
| Stage 3/4, % | | | |
| Baseline | 11.7 (11.4) | 9.3 (8.1) | 13.5 (8.7) |
| Final visit | 12.0 (10.9) | 11.1 (10.0) | 13.8 (8.6) |
| REM sleep, % | | | |
| Baseline | 19.3 (7.0) | 19.3 (6.2) | 18.4 (6.7) |
| Final visit | 19.2 (8.4) | 17.9 (6.8) | 18.9 (7.2) |
| REM sleep latency, min | | | |
| Baseline | 58.3 (39.1) | 71.0 (49.5) | 73.2 (58.5) |
| Final visit | 63.0 (41.6) | 53.5 (49.4) | 67.6 (63.8) |

REM = rapid eye movement
*Defined as the time from lights out to the first of three consecutive epochs of stage 1 sleep or one epoch of any other sleep stage
The difference between treatment groups at final visit was not statistically significant for any nocturnal polysomnography variable



in their clinical condition, compared with one third (33%) of patients receiving placebo. Fatigue scores were also improved with armodafinil, although this may reflect a close association of ratings of fatigue and sleepiness, rather than be considered an independent effect.

Significant improvements in mean MWT sleep latency were observed at both early (0900–1500) and late (1500–1900) time points at final visit. These results on the prespecified analyses show that once-daily armodafinil improves the ability to sustain wakefulness throughout the day. This finding is consistent with the pharmacodynamic profile of armodafinil shown in a previous study in healthy volunteers[19]. In the current study, analysis of individual MWT subtest sleep latencies across the day at final visit revealed a greater wake-promoting effect of both doses of armodafinil compared with placebo. In those patients receiving armodafinil 150 mg, differences in wakefulness versus placebo were shown at each MWT subtest. For the 250-mg dose group, the sleep latency was greater than that seen with placebo at each MWT subtest but was unexpectedly close to baseline values at the 1700 MWT. The latter unexpected finding may be due to sampling error, given that improvements in sleep latency were seen with armodafinil 250 mg for tests from 0900 to 1500 and at 1900, and also with armodafinil 150 mg across the day. As is routinely observed in clinical studies of patients with narcolepsy, patients who received placebo had a reduction in measures of alertness, including MWT sleep latency, which may reflect adaptation or habituation to the testing procedures, further unmasking ES.

Patients' self-reports showed that armodafinil significantly improved alertness, as measured by the ESS; reduced the number of naps and unintentional sleep

episodes, as recorded in the daily diaries; and reduced global fatigue.

Narcolepsy is associated with cognitive deficits in attention and memory[1]. In the present study, armodafinil improved both attention and memory. A significant improvement was seen in power of attention, indicating that the compound was able to improve patients' ability to focus concentration. Significant improvement was also seen in the quality of episodic secondary memory, indicating that patients treated with armodafinil were better able to store, retain, and retrieve both verbal and pictorial information. Speed of memory was also significantly improved, indicating that, in addition to being more accurate, patients were also faster at retrieving information. Armodafinil was thus able to significantly reduce cognitive impairments typically experienced by patients with narcolepsy.

The majority of the effects of armodafinil on wakefulness, overall clinical condition, memory, attention, and fatigue were shown at the first post-baseline visit (week 4) and were sustained throughout the study. Although a statistical difference in age was observed between groups, the difference was not considered clinically meaningful and did not impact efficacy and safety assessments.

The incidence of adverse events with armodafinil 150 mg and 250 mg was low, and the events were similar in nature to those previously noted in clinical studies of modafinil[9,10,12,13]. Headache and nausea were the most commonly reported adverse events with armodafinil. Armodafinil did not have clinically relevant effects on weight or night-time sleep. The effects of armodafinil on measures of cardiovascular function (i.e., blood pressure and heart rate) were dose dependent. The clinical significance of small mean changes in heart rate and blood pressure is not clear. There were numerical increases in mean GGT and alkaline phosphatase; however, these changes were not considered to be clinically significant.

Although the study enrolled fewer patients than the estimated number of patients in the protocol, the decision to end enrollment was based on the review of variability in the blinded data, which allowed the sample size to be cut to 58 patients in each arm. Post hoc power calculations show that the enrolled sample of 118 patients in the armodafinil combined group and 58 in the placebo group had at least 90% power to detect the observed difference of 3.8 min on the MWT (assuming that the SD was 6.6) and at least 95% power to detect a difference of 38% between the armodafinil combined group and placebo in the proportion of patients reporting at least minimal improvement in CGI-C ratings (assuming a 33% rate in the placebo group). The inclusion of the 1500 time point in the prespecified analyses for the primary measure and the assessment of late-day wakefulness represents a limitation. Although both doses of armodafinil significantly improved wakefulness at final visit, it is not possible to draw conclusions regarding the dose proportionality of armodafinil in patients with narcolepsy because the study was not powered to detect differences between the doses. In addition, there was a difference in baseline MWT sleep latency between the 150- and 250-mg groups. Thus, additional research is needed to clarify the dose proportionality of armodafinil in the narcolepsy population. It should also be noted that the effects of armodafinil on aspects of memory may represent a signal that the drug may directly influence some memory processes but cannot be considered as definitive evidence. Additional research specifically assessing the effects of armodafinil on memory is warranted.

## Conclusion

In patients with ES associated with narcolepsy, armodafinil, at doses of 150 or 250 mg/day, significantly improved wakefulness throughout the day, clinician ratings of overall clinical condition, and some measures of memory and attention compared with placebo.

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## References


1. Naumann A, Daum I. Narcolepsy: pathophysiology and neuropsychological changes. Behav Neurol 2003;14:89-98
2. Rieger M, Mayer G, Gauggel S. Attention deficits in patients with narcolepsy. Sleep 2003;26:36-43
3. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed. Diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine; 2005
4. Hublin C, Partinen M, Kaprio J, Koskenvuo M, Guilleminault C. Epidemiology of narcolepsy. Sleep 1994;17:S7-S12
5. Dauvilliers Y, Baumann CR, Carlander B, et al. CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and other hypersomnias and neurological conditions. J Neurol Neurosurg Psychiatry 2003;74:1667-73
6. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998;50:S16-S22
7. Mignot E. Pathophysiology of narcolepsy. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine, 3rd ed. Philadelphia: Saunders; 2000. p. 663-75
8. Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. Sleep 1997;20:1012-20
9. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97
10. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000;54: 1166-75
11. Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997;49:444-51
12. Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med 2000;1:231-43
13. Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med 2000;1:109-16
14. Schwartz JR, Feldman NT, Bogan RK, Nelson MT, Hughes RJ. Dosing regimen effects of modafinil for improving daytime wakefulness in patients with narcolepsy. Clin Neuropharmacol 2003;26:252-7
15. Schwartz JR, Nelson MT, Schwartz ER, Hughes RJ. Effects of modafinil on wakefulness and executive function in patients with narcolepsy experiencing late-day sleepiness. Clin Neuropharmacol 2004;27:74-9
16. Robertson Jr P, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 2003;42:123-37
17. Wong YN, King SP, Simcoe D, et al. Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 1999;39:281-8
18. Wong YN, Simcoe D, Hartman LN, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. J Clin Pharmacol 1999;39:30-40
19. Dinges DF, Arora S, Darwish M, Niebler GE. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. Curr Med Res Opin 2006;22:159-67
20. US Department of Health and Human Services. Guidance for industry. E6 good clinical practice: consolidated guidance. Rockville (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; 1996
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington (DC): American Psychiatric Association; 1994
22. Thorpy MJ. The clinical use of the Multiple Sleep Latency Test. The Standards of Practice Committee of the American Sleep Disorders Association. Sleep 1992;15:268-76
23. Guy W, ed. Clinical global impressions. In: ECDEU assessment manual for psychopharmacology. Rockville (MD): US Dept of Health and Human Services, National Institute of Mental Health; 1976. p. 218-22
24. Mitler MM, Gujavarty KS, Browman CP. Maintenance of Wakefulness Test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol 1982;53:658-61
25. Doghramji K, Mitler MM, Sangal RB, et al. A normative study of the Maintenance of Wakefulness Test (MWT). Electroencephalogr Clin Neurophysiol 1997;103:554-62
26. Simpson P, Wesnes K, Christmas L. A computerised system for the assessment of drug-induced performance changes in young, elderly or demented populations. Br J Clin Pharmacol 1989;27:711P-712P
27. Wesnes K, Simmons D, Rook M, Simpson P. A double-blind placebo controlled trial of tanakan in the treatment of idiopathic cognitive impairment in the elderly. Hum Psychopharmacol 1987;2:159-69
28. Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle-aged volunteers. Psychopharmacology (Berl) 2000;152:353-61
29. Wesnes KA, McKeith IG, Ferrara R, et al. Effects of rivastigmine on cognitive function in dementia with Lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. Dement Geriatr Cogn Disord 2002;13:183-92
30. Wesnes KA, McKeith I, Edgar C, Emre M, Lane R. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology 2005;65:1654-6
31. Wesnes K, Pincock C. Practice effects on cognitive tasks: a major problem? Lancet Neurol 2002;1:473
32. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5
33. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 1999;85:1186-96



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