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ORIGINAL ARTICLE

Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss*

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Objective: To assess the pharmacodynamics of armodafinil compared with modafinil and placebo on measures of alertness in healthy volunteers undergoing sleep loss.

Research design and methods: In a double-blind, active- and placebo-controlled, parallel-group study, 107 healthy male volunteers (aged 18–40 years) were randomized to receive a single oral dose of armodafinil (100, 150, 200, or 300 mg), modafinil (200 mg), or placebo administered at 19:25 h.

Main outcome measures: The primary outcome was the Maintenance of Wakefulness Test (MWT), administered every 2 hours from 22:00–08:00 h. Secondary outcomes included the Psychomotor Vigilance Task (PVT) and the Karolinska Sleepiness Scale. Blood samples for pharmacokinetic analysis were collected hourly. Adverse events were evaluated throughout the 2-day laboratory stay and by telephone on day 9.

Results: All four doses of armodafinil, and the dose of 200 mg modafinil, improved wakefulness as measured by increased MWT latencies (treatment effect, $p < 0.0001$) and reduced PVT lapses of attention (treatment effect, $p < 0.0001$). The magnitude and duration of these effects at the later time points appeared to be dose and concentration dependent. Armodafinil at 200 mg resulted in comparable C_{max}, a later t_{max}, and higher plasma concentrations 6–14 hours post-drug administration than with 200 mg modafinil. Following armodafinil, longer MWT latencies and fewer PVT lapses 6 to ≈ 14 hours post-drug administration were observed compared with modafinil. Armodafinil doses were well tolerated, with the most common adverse events including abdominal pain, nausea, and headache. There were reports of tachycardia/palpitations. Decreased mean sleep efficiency and increased mean blood pressure were also observed.

Conclusion: Armodafinil improved alertness at all doses studied. Relative to modafinil 200 mg, armodafinil 200 mg showed a comparable peak plasma concentration with higher concentrations 6–14 hours post-drug, and improved wakefulness and sustained attention for a longer time post-dose. Both drugs were well tolerated; however, further research on the efficacy, safety, and tolerability of armodafinil in patients with disorders of excessive sleepiness (ES) is required.

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Introduction

Excessive sleepiness (ES) is a common manifestation of a number of sleep disorders, including narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSA/HS), and shift work sleep disorder (SWSD)[1]. Therapy for hypersomnolence begins, when possible, with treatment of underlying conditions that contribute to its development (e.g. nasal continuous positive airway pressure [nCPAP] for OSA/HS). In addition, ES that is persistent and severe may pose a safety risk and may require the use of pharmacologic therapies such as the wake-promoting agent modafinil, which is approved for the treatment of ES associated with narcolepsy, OSA/HS, and SWSD[2]. Modafinil has been reported to improve wakefulness as measured by sleep latency tests in patients with narcolepsy[3–5], in patients with residual ES following nCPAP treatment for OSA/HS[6,7], and in patients with SWSD[8]. Additionally, improvements in sustained attention measured with the Psychomotor Vigilance Task (PVT) have been reported in OSA/HS and SWSD populations following treatment with modafinil[8,9].

The benefits of modafinil for ES are not maintained throughout the entire waking period in some patients, which may result in the need for dose escalation and split-dosing[10,11]. In two randomized, double-blind studies conducted in patients with ES associated with narcolepsy, improvements in wakefulness as assessed using the Maintenance of Wakefulness Test (MWT) were sustained longer with split modafinil doses of 400 and 600 mg (administration at 07:00 h and 12:00 h) than with administration of once-daily doses of 200 and 400 mg (07:00 h)[10,11]. However, once-daily dosing is often more convenient for patients and may improve adherence to therapy. With this in mind, we examined the pharmacodynamic profile of armodafinil, the levorotatory *R*-enantiomer of modafinil, which is a racemic compound containing equal amounts *R*-modafinil and *S*-modafinil. Pharmacokinetic studies have shown that *R*-modafinil has a half-life of 10–14 hours compared with 3–4 hours for *S*-modafinil[12–14]. In addition, the elimination of *S*-modafinil has been reported to be three times faster than *R*-modafinil[13]. As a result of the differences in half-life and rate of clearance, the chronic use of modafinil results in significant differences in circulating levels of the two enantiomers. Thus, the proportion of *R*-modafinil can be as much as three times greater than the circulating levels of *S*-modafinil[12,14]. Therefore, the majority of the effects observed from racemic modafinil administration are theoretically attributable to *R*-modafinil. We therefore hypothesized that efficacious armodafinil concentrations might be maintained throughout the waking day with once-daily dosing. The present study was designed to assess the pharmacokinetic and pharmacodynamic effect of single doses of armodafinil on MWT and PVT, objective measures of alertness in healthy adults undergoing a model of acute sleep loss.

Patients and methods

Subjects

Male volunteers between 18 and 40 years of age who were able to maintain stable sleep/wake schedules (defined as sleep between 23:00 and 07:00 h ± 1 h, for a total of 8 hours in bed per night) beginning 1 week before study drug administration were eligible. All volunteers were in good health as determined by a medical and psychiatric history, medical examination, electrocardiogram, and laboratory assessments. In addition, volunteers were required to comply with all study restrictions, including abstinence from nicotine, caffeine, and alcohol during the in-clinic phase of the study (described below). Volunteers who smoked ≥ 10 cigarettes per day or consumed > 3 alcoholic drinks per day were excluded. Additional exclusion criteria consisted of the following: average caffeine consumption of > 600 mg daily during the 2 weeks before study enrollment; a sleep disorder (e.g. narcolepsy, OSA/HS, periodic leg movement syndrome) established by history and physical examination at screening; history of working irregular hours, shift work or night-shift work during the month prior to randomization; an Epworth Sleepiness Scale[15] score > 10 at screening; travel across > 1 time zone during the 2 weeks before randomization; and use of any prescribed systemic or topical medication within 2 weeks (or sedating over-the-counter medication within 1 week) of study drug administration.

Study design and dosing

This randomized, double-blind, active- (modafinil) and placebo-controlled, parallel-group study of single oral doses of armodafinil in healthy male volunteers undergoing acute sleep loss was conducted at two research centers located in France and the United Kingdom. The study protocol was approved by the Institutional Review Board at each participating site, and all participants provided written informed consent before undergoing study-screening procedures. The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization[16] and national and local laws and regulations.

Prospective participants underwent screening procedures and assessments at least 1 week prior to

randomization. Sleep patterns prior to the study were monitored in those meeting all selection criteria, using wrist actigraph and a daily sleep diary for 7 days prior to study drug administration. Subjects were admitted to the study clinic on the afternoon before dosing (day –1). For 2 days, participants were confined to the clinic and were provided meals which consisted of a standardized diet devoid of caffeine and alcohol. They were permitted to lie down only for protocol-specified sleep periods, the first of which occurred between 23:00 hours on day –1 to 07:00 h on day 1. Participants remained awake throughout day 1. They were randomized to single doses of armodafinil at either 100, 150, 200, or 300 mg (CEP-10953, Cephalon, Inc., Frazer, PA); a single dose of modafinil at 200 mg (Provigil, Cephalon, Inc., Frazer, PA); or placebo according to a randomization code provided by Cephalon, Inc. The randomization number and the name of the study drug were provided to the study centers in a sealed envelope. The study drug was packaged individually for each subject, with the subject identification number indicated. Subjects received six capsules (armodafinil 50 mg or matching placebo) and two tablets (modafinil 100 mg or matching placebo). To maintain blinding, those randomized to armodafinil also received two placebo tablets and those randomized to modafinil also received six placebo capsules. Medications were dispensed by a pharmacist at each study center.

Study medication was administered at 19:25 h immediately followed by a standardized meal on day 1 (after 12:25 h of wakefulness). Subjects were monitored by qualified personnel at the study centers to ensure they remained awake throughout the night from 19:25 h on day 1 to 11:00 h on day 2 (i.e. for hours 13 through 28 of sustained wakefulness). Pharmacodynamic responses were assessed throughout this period. An 8-hour period of recovery sleep was permitted on day 2 from 11:00–19:00 h. Final assessments and end-of-study procedures were performed between 20:55 and 21:30 h, after which subjects were discharged from the clinic. Seven days after discharge, participants were contacted by telephone to determine if they had experienced adverse events since the time of their discharge from the clinic.

Sampling for pharmacokinetic analysis

Venous blood samples were collected hourly for 14 consecutive hours. Samples were collected immediately before study drug administration at 19:25 h on day 1, then at 19:55 and 20:25 h, and at 1-hour intervals thereafter (i.e. from 20:25–09:25 h). Samples were centrifuged within 1 hour after collection, with the resulting plasma shipped and stored at –20°C until analyzed (Covance Laboratories, Madison, WI). Plasma samples were assayed for *R*-modafinil and (*RS*)-modafinil using validated non-chiral high-performance liquid chromatography with ultraviolet detection. Mean intra-assay precision and accuracy were within ≤ ± 15% (≤ 20% at the lower limit of quantitation) of the acceptance criteria. Predicted drug concentrations were calculated from the equation of the regression line determined by using a weighting factor of (1 / concentration). The quantification ranges of the standard curves were 0.020 to 50.0 µg/mL. The following pharmacokinetic parameters were determined: maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation); time of maximum observed drug concentration (t_{max}) by inspection; and area under the plasma drug concentration versus time curve from 0–14 hours post-drug administration (AUC_{0-14}).

Assessments

The MWT[17,18] was the primary outcome used to objectively assess the pharmacodynamic effect of study medications on the ability to sustain wakefulness during the nocturnal sleep-loss period. For this test, subjects were instructed to sit in a darkened room in a semi-reclined position and try to remain awake. Six 20-minute MWTs were conducted – one every 2 hours – between 22:00 h on day 1 and 08:00 h on day 2 (during the nocturnal period without sleep). Time to unequivocal sleep latency (i.e. minutes to three consecutive epochs of stage 1 or one epoch of stage 2, 3, 4, or rapid eye movement sleep) was the primary MWT outcome. If no sleep occurred within the testing period, sleep latency was recorded as 20 minutes. Once sleep occurred, subjects were awakened. Time to first 10 seconds of sleep was also scored. Polysomnography recordings to determine MWT were scored at a central site using criteria as described by Rechtschaffen and Kales[19].

The Psychomotor Vigilance Task (PVT)[20,21] was used to assess the pharmacodynamic effect of study medications on sustained attention performance during the nocturnal sleep-loss period. This included a standard 10-minute PVT performed at each of seven 2-hour intervals beginning at 21:10 h on day 1 to 09:10 h on day 2. During each 10-minute PVT session, visual stimuli appeared at randomly variable intervals of 2000 to 10 000 milliseconds. The number of performance lapses (i.e. reaction times ≥ 500 ms) and median reaction time were the PVT variables analyzed. The Karolinska Sleepiness Scale (KSS)[22] was used to assess subject-estimated sleepiness hourly from 19:50 h on day 1 to 10:50 h on day 2. Subjects rated their sleepiness on a nine-point scale from 1 (very alert) to

9 (extremely sleepy–fighting sleep). Other assessments included the Cognitive Drug Research test battery, the results of which will be reported elsewhere.

Safety and tolerability during the study were evaluated by monitoring adverse events. Vital signs were monitored at screening and on days –1 and 1 prior to study drug administration and on day 2 until approximately 14 hours after study drug administration. The effect on sleep efficiency was determined by polysomnography, which was recorded during the nocturnal sleep period the night before drug administration to ensure subjects received an adequate night's sleep and during the diurnal sleep period on day 2 following the night of sleep deprivation. Sleep efficiency was defined as total sleep time (h) / total time in bed (h) × 100. Scoring of polysomnographic findings was based on criteria described by Rechtschaffen and Kales[19].

Statistical analysis

The pharmacodynamic effect of study medication on sleep and attention was analyzed with descriptive statistics. In addition, analyses of MWT (average of six tests performed every 2 h from 22:00–08:00 h), PVT (average of six tests performed every 2 h from 23:10–09:10 h), and KSS (average of 16 ratings made once every hour from 19:50–10:50 h) were conducted using analysis of variance (ANOVA) with treatment and study site as factors, and with pair-wise comparisons made using an appropriate contrast. In addition, a test for linear trend from ANOVA with treatment and center as factors was performed on the placebo and armodafinil groups (using a contrast of –0.67, –0.22, 0, 0.22, and 0.67 for placebo and armodafinil 100, 150, 200, and 300 mg, respectively). The pair-wise change from baseline in vital signs (active drug vs. placebo) was compared using nonparametric tests of Wilcoxon rank sum. All tests of armodafinil were two-sided and performed at the 0.05 significance level.

Results

Following screening, 107 healthy male volunteers were randomized to study drug and completed the study (armodafinil 100 mg, $n = 18$; armodafinil 150 mg, $n = 18$; armodafinil 200 mg, $n = 17$; armodafinil 300 mg, $n = 18$; modafinil 200 mg, $n = 18$; or placebo, $n = 18$). All groups were comparable with respect to age, weight, body mass index, and baseline sleep efficiency (Table 1). Average body mass index for each group was within the normal range (18.5–24.9 kg/m^2). Average polysomnographic sleep efficiency at baseline for each group (85.8%–89.3%) was consistent with healthy nocturnal sleepers. None of the subjects discontinued study medication for any reason.

Table 1. *Baseline characteristics of subject volunteers randomized to the six interventions**

	Armodafinil				Placebo ($n = 18$)	Modafinil 200 mg ($n = 18$)
	300 mg ($n = 18$)	200 mg ($n = 17$)	150 mg ($n = 18$)	100 mg ($n = 18$)		
Age (y)	25.8 ± 5.9	27.5 ± 6.3	28.7 ± 6.8	26.8 ± 5.2	27.9 ± 5.2	25.9 ± 5.8
Weight (kg)	71.7 ± 9.3	78.6 ± 12.7	75.6 ± 10.8	76.1 ± 8.6	76.8 ± 12.0	75.7 ± 10.3
BMI (kg/m^2)	23.0 ± 2.4	24.5 ± 2.7	23.6 ± 3.1	23.4 ± 2.2	24.6 ± 3.4	23.6 ± 2.3
Baseline SE (%)†	89.3 ± 6.7	88.2 ± 6.4	88.8 ± 6.9	87.2 ± 9.3	85.8 ± 7.3	86.3 ± 6.1

BMI = body mass index, SE = sleep efficiency
*Mean ± SD
†Baseline night time sleep efficiency from polysomnography ([total sleep time (h) ÷ total time in bed (h)] × 100)

Table 2. *Pharmacokinetic parameters of armodafinil and modafinil following administration of single doses in healthy young men*

	Armodafinil (*R*-modafinil)				Modafinil (*RS*-modafinil)
	300 mg ($n = 18$)	200 mg ($n = 17$)	150 mg ($n = 18$)	100 mg ($n = 18$)	200 mg ($n = 18$)
C_{max} (μg/mL)*	6.37 ± 0.88	4.04 ± 0.69	2.99 ± 0.41	1.97 ± 0.25	4.35 ± 0.94
t_{max} (h)†	5 (3–12)	6 (2–8)	6.5 (3–11)	5.5 (0.5–11)	2 (0.5–6)
AUC_{0-14} (μg·h/mL)*	66.2 ± 8.5	42.4 ± 7.2	29.9 ± 4.6	20.1 ± 3.5	35.0 ± 6.7

AUC_{0-14} = area under the plasma drug concentration versus time curve from 0–14 hours post-drug administration; C_{max} = maximum observed plasma drug concentration by inspection without interpolation; t_{max} = time of maximum observed drug concentration by inspection
*Mean ± SD
†Median (range)

Pharmacokinetics

Systemic exposure was linear over the studied dose range of armodafinil (100–300 mg), as reflected in the increases in C_{max} and AUC_{0-14} as shown in Table 2. Plasma concentrations for the single 200 mg dose of armodafinil and the single 200 mg dose of modafinil up to 14 hours after drug administration are shown in Figure 1. The concentration–time profiles for modafinil 200 mg and armodafinil 200 mg were different despite comparable C_{max} values. The t_{max} for armodafinil occurred approximately 3 to 4 hours later, and the decline from peak concentration was slower, resulting in a higher plasma concentration, as determined by AUC, for the armodafinil 200 mg group when compared with the 200 mg modafinil group (Figure 1).

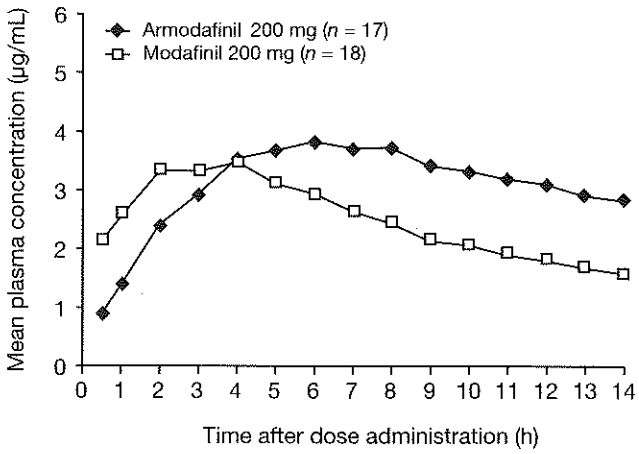

Figure 1. *Concentration–time profiles in healthy young adult volunteers following a single dose of armodafinil 200 mg and a single dose of 200 mg modafinil at 19:25 h (time 0). Concentrations were significantly different at all time points except at 3 and 4 hours post-drug administration (all time points, p < 0.05). The 14th hour after dose was 09:25 h on day 2*

Maintenance of Wakefulness Test

All doses of armodafinil and 200 mg modafinil significantly improved wakefulness, as assessed by mean MWT unequivocal sleep latency, compared with placebo (overall treatment comparison for the average MWT across all six tests, $F = 13.94$ [5, 100], $p < 0.0001$; Table 3). MWT latency to the first 10 seconds of sleep also showed significant drug effects ($p < 0.0001$).

When comparing the effects of 200 mg armodafinil with those of 200 mg modafinil, MWT sleep latencies were numerically longer in the armodafinil 200 mg group than in the modafinil 200 mg group, starting approximately 6 hours after drug administration. These profile differences are displayed in Figure 2A.

Secondary assessments

All doses of armodafinil and 200 mg modafinil significantly improved sustained attention performance on the PVT relative to placebo, with fewer lapses of attention and shorter median reaction time during the period of acute sleep loss (overall treatment effect for comparing the average across all six tests post-administration, $F = 9.05$ [5, 99], $p < 0.0001$ for PVT lapses; $F = 7.92$ [5, 99], $p < 0.0001$ for PVT median reaction time; Table 3).

Comparison of the effects of 200 mg armodafinil with 200 mg modafinil revealed numerically fewer PVT lapses of attention in the armodafinil 200 mg group than those observed in the modafinil 200 mg group beginning approximately 8 hours after drug administration. These profile differences are displayed in Figure 2B.

There was no statistically significant treatment effect for armodafinil or 200 mg modafinil on subject-estimated sleepiness on the KSS throughout the night.

Table 3. *Effects of armodafinil and modafinil on MWT, PVT, and KSS outcomes, as assessed by analysis of variance of average daily values* for placebo, modafinil, and the four doses of armodafinil*

	Armodafinil				Placebo (n = 18)	Modafinil 200 mg (n = 18)
	300 mg (n = 18)	200 mg (n = 17)	150 mg (n = 18)	100 mg (n = 18)		
MWT sleep latency (min)†	18.5 ± 2.19	18.5 ± 2.00	16.8 ± 2.93	16.1 ± 3.68	10.5 ± 4.98	16.4 ± 3.25
MWT latency to 10 s sleep (min)†	16.1 ± 4.41	15.6 ± 3.02	15.0 ± 3.51	14.3 ± 4.35	8.5 ± 4.54	15.1 ± 4.09
PVT lapse frequency†	0.9 ± 1.17	1.4 ± 1.54	1.4 ± 1.71	2.9 ± 3.99	8.8 ± 8.44	3.0 ± 3.33
PVT median RT (ms)†	232 ± 26	240 ± 19	238 ± 24	252 ± 32	293 ± 56	253 ± 34
KSS sleepiness‡	3.7 ± 1.33	3.7 ± 1.33	4.2 ± 1.32	3.8 ± 1.10	4.6 ± 1.07	3.8 ± 1.32

*Mean ± SD. MWT data were averaged over the six tests completed every 2 hours from 22:00–08:00 hours. PVT data were averaged over the six tests completed every 2 hours from 23:10–09:10 hours. KSS data were averaged over the 16 ratings made hourly from 19:50–10:50 hours. *P*-values for overall treatment comparison from an analysis of variance (ANOVA) with treatment and center as factors

†ANOVA, $p < 0.0001$

‡ANOVA, $p = 0.067$

MWT = Maintenance of Wakefulness Test; PVT = Psychomotor Vigilance Task; KSS = Karolinska Sleepiness Scale; RT = Reaction Time

Safety and tolerability

The most frequently occurring adverse events in the armodafinil groups were abdominal pain and nausea, each of which occurred in nine (13%) of subjects. Injection site pain (i.e. pain or discomfort on insertion of the intravenous cannula for blood collection) also was reported in nine (13%) of subjects; however, it was not considered treatment related. Adverse events occurring in > 5% of subjects in the armodafinil arm are shown in Table 4. The incidences of headache and nausea increased with the higher doses of armodafinil.

In the 200 mg modafinil group, headache, dyspepsia, flatulence, nervousness, and sleep disorder each occurred in one subject (6%). In the placebo group, injection site pain was the most common adverse event ($n = 3$; 17%); abdominal pain, asthenia, gastrointestinal disorder, dizziness, somnolence, and urinary frequency each occurred in one subject (6%).

Insomnia occurred in 7% of subjects in the armodafinil group but in none of the subjects in the 200 mg modafinil group or the placebo group. Dizziness occurred in 7% of subjects in the armodafinil groups, none of the subjects in the 200 mg modafinil group, and 6% of the subjects in the placebo group.

Most adverse events reported for any group were mild in severity. Serious adverse events were reported in two subjects during the study: one subject receiving armodafinil 150 mg reported tachycardia and ventricular extrasystoles, and one subject who received placebo reported asymptomatic bigeminy. All adverse events resolved without residual effect. No subjects discontinued from the study prematurely due to adverse events.

An increase from baseline to day 2 in mean systolic blood pressure was noted in the armodafinil 300 mg group ($p = 0.041$, Wilcoxon test). Increases from baseline in mean diastolic blood pressure and heart rate were also noted with increasing doses of armodafinil compared with placebo; however, these effects were not statistically significant (all $p > 0.05$). Table 5 provides the mean ± SD and change from baseline for sitting systolic and diastolic blood pressure and sitting heart rate.

As determined by nocturnal polysomnography, mean sleep efficiency at baseline was similar in all groups (85.8%–89.3%). On day 2, decreases in daytime sleep efficiency were observed with the higher doses of armodafinil as indicated by a statistically significant effect for treatment condition ($F = 3.18$ [5, 101], $p = 0.01$). Mean ± SD daytime sleep efficiencies after receiving study medication were 80.2% ± 14.37% in the placebo group compared with 59.6% ± 21.40%, 69.4% ± 20.44%, 69.1% ± 24.65%, 76.1% ± 15.16%, and 79.6% ± 13.92% in the armodafinil 300 mg, 200 mg, 150 mg, and 100 mg groups, and the modafinil 200 mg group, respectively.

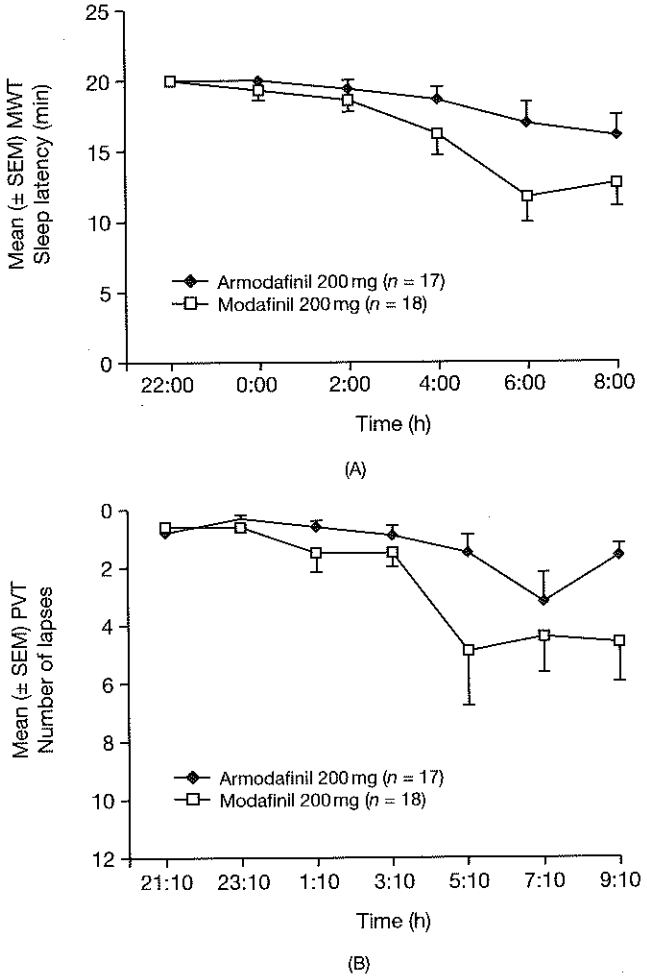

Figure 2. *The alertness-promoting effects across the night of a single dose of armodafinil 200 mg compared with a single dose of 200 mg modafinil at 19:25 h. (A) Mean ± SEM for sleep onset latency from the MWT at 22:00, 00:00, 02:00, 04:00, 06:00, and 08:00 h. Longer latencies indicate greater alertness. Although sleep latencies decreased across the night in both conditions (F = 46.08 [1, 171], p < 0.0001), the change in ability to sustain wakefulness was smaller in the armodafinil 200 mg group than in the modafinil group (F = 5.50 [1, 171], p = 0.02), indicating that armodafinil improved the ability to sustain wakefulness for a longer time throughout the night. (B) Mean ± SEM for lapses of attention (reaction time ≥ 500 ms) during each 10-minute PVT at 21:10, 23:10, 01:10, 03:10, 05:10, 07:10, and 09:10 h. Fewer lapses indicate a greater ability to sustain attention. Although PVT lapses of attention increased across the night in both conditions (F = 26.53 [1, 208], p < 0.0001), the change in ability to sustain attention was smaller in the armodafinil 200 mg group than in the modafinil group (F = 5.06 [1, 208], p = 0.026), indicating that armodafinil improved the ability to sustain attention for a longer time throughout the night*

Table 4. Number (%) of subjects with adverse events occurring in > 5% of subjects receiving armodafinil

	Armodafinil				Placebo (n = 18)	Modafinil 200 mg (n = 18)
	300 mg (n = 18)	200 mg (n = 17)	150 mg (n = 18)	100 mg (n = 18)		
Abdominal pain	2 (11)	4 (24)	1 (6)	2 (11)	1 (6)	0
Dizziness	1 (6)	2 (12)	1 (6)	1 (6)	1 (6)	0
Headache	3 (17)	1 (6)	1 (6)	1 (6)	0	1 (6)
Injection site pain	1 (6)	3 (18)	2 (11)	3 (17)	3 (17)	0
Insomnia	2 (11)	1 (6)	1 (6)	1 (6)	0	0
Nausea	4 (22)	3 (18)	2 (11)	0	0	0
Palpitation	1 (6)	2 (12)	0	2 (11)	0	0
Tachycardia	1 (6)	0	2 (11)	1 (6)	0	0
Urinary frequency	1 (6)	3 (18)	1 (6)	0	1 (6)	0

*Table 5. Effects of armodafinil and modafinil on sitting blood pressure and heart rate before (baseline) and after drug administration and change**

	Armodafinil				Placebo (n = 18)	Modafinil 200 mg (n = 18)
	300 mg (n = 18)	200 mg (n = 17)	150 mg (n = 18)	100 mg (n = 18)		
Systolic BP (mmHg)						
Baseline (B)	118.9 ± 10.5	117.6 ± 6.9	120.1 ± 10.9	116.3 ± 8.8	115.1 ± 10.7	119.8 ± 12.2
Day 2 (D2)	126.2 ± 11.8	121.2 ± 12.8	120.0 ± 10.8	118.4 ± 10.2	117.4 ± 9.5	120.8 ± 9.8
Change (B – D2)	7.3 ± 9.2†	3.6 ± 13.7	–0.1 ± 8.0	2.1 ± 11.8	2.3 ± 6.3	0.9 ± 6.7
Diastolic BP (mmHg)						
Baseline (B)	70.7 ± 9.0	69.9 ± 7.8	67.9 ± 7.6	69.6 ± 8.1	68.8 ± 9.0	71.5 ± 8.9
Day 2 (D2)	75.2 ± 9.1	74.5 ± 7.6	71.2 ± 8.1	70.9 ± 7.2	70.1 ± 6.1	73.1 ± 10.4
Change (B – D2)	4.5 ± 9.3	4.6 ± 6.7	3.3 ± 6.8	1.4 ± 7.0	1.3 ± 7.6	1.6 ± 9.8
Heart rate (BPM)						
Baseline (B)	62.2 ± 9.0	67.9 ± 9.6	61.9 ± 7.3	61.6 ± 11.7	60.8 ± 9.3	63.8 ± 7.6
Day 2 (D2)	77.1 ± 14.3	80.6 ± 16.1	74.8 ± 15.9	72.9 ± 14.5	68.9 ± 8.7	73.6 ± 14.9
Change (B – D2)	14.9 ± 10.3	12.7 ± 13.7	12.8 ± 12.7	11.3 ± 11.4	8.2 ± 7.9	9.8 ± 16.0

B – D2 = baseline to day 2; BP = blood pressure; BPM = beats per minute; D2 = day 2
*All values are mean ± SD
†p = 0.041

Discussion

The MWT[17,18] and PVT[20,21] are validated objective measures used to evaluate an individual's ability to sustain wakefulness and to sustain attention (i.e. vigilance and reaction time), respectively. The KSS[22] is a validated subjective test that is used to measure subject-estimated sleepiness. These assessments have been widely used in studies of modafinil in clinical populations to assess alertness and performance[8,9,23,24]. This is the first study to show that, in a model of acute sleep loss in healthy subjects, armodafinil, the enantiomer of modafinil with the longer half-life, had significant effects on MWT and PVT. These effects were observed throughout the sleep deprivation period for up to 13.5 hours post-administration. These observations are consistent with reported effects of modafinil; for example, modafinil 200 mg significantly improved alertness, as determined by MWT, and vigilance and reaction time, as determined by PVT, in 19 healthy volunteers during a period of four consecutive simulated night shifts[23]. Similar to the present study, subject-estimated sleepiness was not consistently different between modafinil and placebo[23].

In the present study, placebo was associated with the highest level of subject-estimated sleepiness as determined by the KSS. However, the effects of armodafinil and modafinil on subjective sleepiness did not achieve statistical significance. In contrast, both objective measures of alertness – the MWT (i.e. time to unequivocal sleep latency and time to first 10 seconds of sleep) and the PVT (i.e. number of lapses and median reaction time) – showed significant changes across doses of armodafinil (100–300 mg), as well as after 200 mg modafinil, relative to placebo. The magnitude and duration of armodafinil's effects on objective alertness and attention appeared to be dose and concentration dependent.

Direct comparison of armodafinil 200 mg to modafinil 200 mg showed longer wake-promoting and

attention-sustaining effects for armodafinil, beginning approximately 6–8 hours post-administration. These differences appear to reflect the different pharmacokinetic profiles of the compounds, particularly the maintenance of higher plasma concentrations for a longer period of time after dosing with armodafinil versus modafinil. Although the drugs also differed in the time to reach peak plasma concentrations when administered with food (t_{max}, 5–6 h for armodafinil and 2 h for modafinil), this difference did not appear to influence the onset of wake-promoting effects; significant effects relative to placebo were observed at the earliest time point for both compounds.

Armodafinil was generally well tolerated by the healthy volunteers participating in this study. Headache and nausea were the most frequently occurring treatment-related adverse events following the administration of armodafinil, both of which appeared to be dose related. Insomnia was reported in five subjects (7%) who received armodafinil. Because of the small number of subjects in this study, the dose-response relationship for insomnia with armodafinil is unclear. Also, it is difficult to ascertain whether the effects observed with armodafinil on sleep and cardiovascular measures are clinically relevant.

Polysomnography findings indicated that there was an inverse relationship among armodafinil doses and daytime sleep efficiency in this population of healthy sleep-deprived volunteers. These adverse effects appear to have been the result of the maintenance of armodafinil plasma concentrations into the diurnal recovery sleep period in this study from 11:00–19:00 h on day 2. The effects of armodafinil on measures of cardiovascular function (i.e. blood pressure and heart rate) were also dose dependent. The 300 mg dose of armodafinil was associated with statistically significant increases in systolic blood pressure. Large randomized, placebo-controlled studies of armodafinil in patients with disorders of ES are required to establish the efficacy, tolerability, and safety profile of armodafinil.

Conclusion

Armodafinil improved alertness at all doses studied. Relative to modafinil 200 mg, armodafinil 200 mg showed a comparable peak plasma concentration with higher concentrations 6–14 hours post-drug, and improved wakefulness and sustained attention performance for longer periods post-dose. Both drugs were well tolerated. Further research with armodafinil in patients with disorders of ES is required.

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Armodafinil

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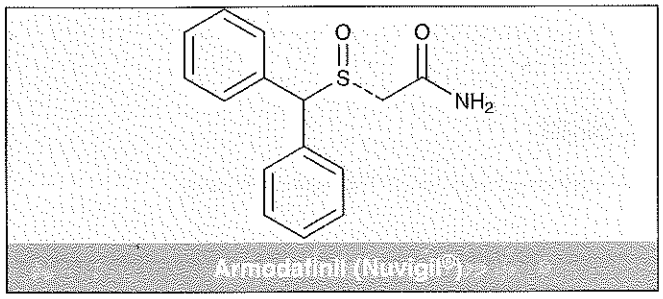
Contents

Abstract

- Armodafinil is the *R*-enantiomer of modafinil, a wake-promoting agent, that primarily affects areas of the brain involved in controlling wakefulness.
- Once-daily armodafinil was effective in improving wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA) [despite treatment of the underlying condition], narcolepsy or shift work sleep disorder (SWSD) in four large (n > 195), double-blind, multinational trials of 12 weeks' duration.
- Compared with placebo, mean sleep latency (coprimary endpoint) was significantly improved with armodafinil 150 or 250 mg once daily in patients with OSA or narcolepsy, and with armodafinil 150 mg once daily in patients with SWSD, as assessed by the Multiple Sleep Latency Test (MSLT) or the Maintenance of Wakefulness Test (MWT).
- Furthermore, a significantly higher proportion of armodafinil than placebo recipients achieved a response (at least a minimal improvement) on the Clinical Global Impressions of Change (CGI-C) scale at study end in these four trials (coprimary endpoint).
- Once-daily armodafinil was generally well tolerated in adult patients with excessive sleepiness associated with OSA (despite treatment of the underlying condition), narcolepsy or SWSD.

Features and properties of armodafinil (Nuvigil®)

Indications		
To improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (despite treatment of the underlying condition), narcolepsy or shift work sleep disorder		
Mechanism of action		
Affects areas of the brain involved in controlling wakefulness		
Dosage and administration		
Dose	150 or 250 mg	
Frequency	Once daily	
Route	Oral	
Pharmacokinetic profile (single 150 or 250 mg dose in healthy volunteers)		
	150 mg	250 mg
Mean peak plasma concentration [μg/mL]	2.99	5.9
Median time to peak plasma concentration [h]	6.5	1.5
Mean area under the plasma concentration-time curve from time zero to 14 hours (150 mg) or infinity (250 mg) [μg • h/mL]	29.9	129.2
Adverse events (incidence ≥5% and higher than placebo)		
Headache, nausea, dizziness, insomnia		



Excessive sleepiness, while often due to insufficient night-time sleep, can be a symptom of many sleep disorders and other diseases, including obstructive sleep apnoea/hypopnoea syndrome (OSA), narcolepsy and shift work sleep disorder (SWSD).[1] The most common underlying cause of excessive sleepiness among patients referred to specialists is OSA.[1]

OSA is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, causing brief arousal from sleep.[2] Patients do not feel refreshed when they wake, and excessive sleepiness is very common. Narcolepsy is classified as a hypersomnia of central nervous origin, and is characterized by excessive daytime sleepiness with or without cataplexy.[2] Patients nap during the day and awake feeling refreshed, but are sleepy again within 2–3 hours. SWSD is classified as a circadian rhythm sleep disorder, with symptoms of insomnia or excessive sleepiness occurring transiently in relation to work schedules.[2] It is characterized by fatigue and functional impairment.

Initial treatment recommendations involve treatment of underlying causes (wherever possible), lifestyle interventions, and psychological and/or drug therapy (if required).[1] Historically, stimulants (sympathomimetics, amfetamines and amfetamine-like compounds) were used to treat excessive sleepiness associated with a sleeping disorder.[3] However, these have a potential for drug abuse, which was believed to be inseparable from the stimulant effects of the drugs.[3] Caffeine is known to sustain performance and alertness, though its role has been limited in some individuals because of unacceptable acute side effects including tremor, gastrointestinal symptoms and palpitations.[4]

The wake-promoting agent modafinil is an orally administered benzhydrylsulfinylacetamide.[5] It is a racemic compound containing equal amounts of *R*-modafinil and *S*-modafinil, with demonstrated efficacy in improving wakefulness and performance in patients with excessive sleepiness associated with OSA despite nasal continuous positive airway pressure therapy (nCPAP) and in patients with narcolepsy or SWSD[6] (partially reviewed by Keating and Raffin[5]). Recipients of modafinil experienced clinical improvement with no adverse effect on daytime sleep.[5]

Armodafinil (Nuvigil®) is the *R*-isomer of modafinil.[7] It has a half-life that is approximately three to four times longer than that of the *S*-isomer and may provide longer-lasting wake-promoting effects than those of modafinil when given once daily.[8,9]

This article provides an overview of the pharmacological properties of oral armodafinil and reviews the clinical trial data available on the efficacy and tolerability of the drug in patients with excessive sleepiness associated with OSA (despite treatment of the underlying condition), narcolepsy or SWSD. Medical literature on the use of armodafinil to improve wakefulness in these patients was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Where data for the pharmacodynamic properties of armodafinil are limited, discussion focuses on the racemic compound modafinil, as reported in the manufacturer's prescribing information for armodafinil.[10]

- Although the exact mechanism by which armodafinil promotes wakefulness is unknown, it appears that the drug primarily affects areas of the brain involved in controlling wakefulness.[11] Armodafinil is classified as a non-narcotic schedule IV compound.[3]
- The pharmacodynamic profile of armodafinil differs from that of sympathomimetic amines (e.g. amfetamine and methylphenidate), although

armodafinil has wake-promoting actions similar to these agents.[10]

- At pharmacologically relevant concentrations, armodafinil does not bind to most of the potentially relevant receptors for sleep/wake regulation (e.g. serotonin, dopamine and adenosine receptors) or transporters of neurotransmitters or enzymes involved in sleep/wake regulation (e.g. serotonin, noradrenaline [norepinephrine] and phosphodiesterase VI transporters).[10]
- Armodafinil is not a direct- or indirect-acting dopamine receptor agonist; however, *in vitro*, it binds to the dopamine transporter, thereby inhibiting dopamine reuptake.[10] Modafinil requires dopamine transporters for its wake-promoting action and binds to the dopamine reuptake site, resulting in an increase in extracellular dopamine.[10]
- Modafinil does not appear to be a direct or indirect α_1-adrenergic agonist, although it has been suggested that the mechanism whereby it promotes wakefulness requires an intact α_1-adrenergic system;[5] modafinil action was attenuated by prazosin, an α_1-adrenergic antagonist.[10] Modafinil appears to enhance the inhibitory effect of noradrenaline on sleep-promoting neurons in the brain.[5]
- Small, but consistent increases in heart rate and systolic and diastolic blood pressure (SBP and DBP) were evident in placebo-controlled studies of armodafinil (see section 3 for study design details).[10] The average increase in heart rate compared with placebo was 0.9–3.5 beats per minute; the average increase in SBP and DBP was 1.2–4.3 mmHg.[10]
- The abuse potential of armodafinil has not been investigated; however, it is likely to be similar to that of modafinil.[10] The potential for abuse and dependency appears to be lower for modafinil than amfetamine-like stimulants.[12]
- Armodafinil significantly increases the expression of Fos, a marker of neuronal activation.[11] The number of Fos-labelled neurons increased in brain arousal centres in rats administered a wake-promoting dose of armodafinil compared with those administered vehicle.
- In a rat model, intraperitoneal armodafinil dose dependently increased wakefulness when compared with vehicle (abstract presentation).[13] Moreover, there was no induction of hyperthermia or increased locomotor activity at a dose that produced a degree of wake-enhancement similar to that produced by the stimulant *d*-metamfetamine; nor was armodafinil-induced wakefulness followed by acute rebound hypersomnolence, all of which were observed during *d*-metamfetamine administration.[13]
- In 107 healthy volunteers, relative to placebo, a single dose (100–300 mg) of armodafinil significantly ($p < 0.0001$) improved wakefulness in a randomized, double-blind study ($n = 17–18$ /group).[7] In addition, while both armodafinil 200 mg and modafinil 200 mg were associated with a decrease (after the initial increase) in sleep latency across the night, the change in latency was significantly ($p = 0.02$) smaller with armodafinil than with modafinil.[7] For discussion of the effects of armodafinil in patients with OSA (despite treatment of the underlying condition), narcolepsy and SWSD see section 3.

2. Pharmacokinetic Profile

The pharmacokinetics of armodafinil have only been investigated in healthy volunteers.[7,9,14] Where data for armodafinil are not available, data for modafinil (from the armodafinil prescribing information[10]) are reported, as these data should be applicable to armodafinil as well. The pharmacokinetics of the modafinil isomer *R*-modafinil (when modafinil was administered) are also reported and compared with those of the other isomer *S*-modafinil.[9] Discussion focuses on recommended dosages (section 5).

- Oral armodafinil is rapidly absorbed and exhibits linear pharmacokinetics after single and multiple 50–400 mg doses.[14] As armodafinil is insoluble, intravenous administration was not possible, thus preventing determination of absolute oral bioavailability.[10] Over 12 weeks of treatment, no time-dependent pharmacokinetic changes were observed,[10] and steady state was reached within 7 days.[14] The

steady-state systemic exposure is 1.8-fold higher than that after a single dose.[14]

- After a single dose of armodafinil 150 mg, values for the mean maximum plasma concentration (C_{max}), mean area under the plasma concentration-time curve from time zero to 14 hours (AUC_{14}) and median time to attain C_{max} (t_{max}) were 2.99 μg/mL, 29.9 μg • h/mL and 6.5 (range 3–11) hours, respectively.[7] Multiple-dose data are not available for this dosage.
- Single (day 1) and multiple (day 7) doses of armodafinil 250 mg/day resulted in a mean C_{max} of 5.9 and 9.2 μg/mL and a mean AUC from time zero to infinity (AUC_{∞}; single dose) and over time period τ (AUC_{τ}; multiple doses) of 129.2 and 148.3 μg • h/mL.[14] The median t_{max} values were 1.5 (range 0.5–6.0) and 2 (range 0.5–6.0) hours, respectively.
- In a study investigating a once-daily dose of modafinil (200–800 mg) for 7 days, *R*-modafinil was rapidly absorbed and widely distributed in body tissues.[9] Steady-state plasma levels were attained after the third dose for *R*-modafinil, compared with the first dose for *S*-modafinil, and the elimination of *R*-modafinil was approximately three times slower than that of the *S*-enantiomer (terminal elimination half-life of 13–16 vs 4.0–4.2 hours after a single dose [day 1] and 15–16 vs 4.3–4.9 hours after multiple doses [day 7]).[9]
- When administered with food, the overall bioavailability of armodafinil is not affected; however, as the t_{max} is delayed by ≈2–4 hours,[14] it is possible that food may affect the onset and time course of armodafinil pharmacological action.[10]
- The apparent volume of distribution after a single dose of armodafinil (normalized to 50 mg) is ≈42 L.[14] While armodafinil protein-binding data are not available, approximately 60% of modafinil is bound to plasma protein *in vitro*, predominantly to albumin.[10]
- Armodafinil metabolism data are not available. However, modafinil is metabolized primarily by the liver; <10% of the parent compound is excreted in the urine.[10] By 11 days post-dose, 80% of a radiolabelled dose of modafinil was excreted in the urine and 1% in the faeces.
- Armodafinil undergoes hydrolytic deamidation, *S*-oxidation and aromatic ring hydroxylation followed by glucuronide conjugation of the hydroxylated products.[10] The most prominent pathway is amide hydrolysis; the second most prominent is sulfone formation by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5. Two metabolites of armodafinil reach appreciable concentrations in plasma: *R*-modafinil acid and modafinil sulfone.[10]
- The apparent terminal elimination half-life of armodafinil is ≈15 hours, and the oral clearance at steady state is ≈33 mL/min.[10,14]

Special Patient Populations

- There are no sex-based differences in the pharmacokinetic profile of armodafinil.[10]
- Pharmacokinetic data for armodafinil in other special patient populations are not available; therefore, relevant data for modafinil are discussed.[10]
- It was considered unlikely that the changes in the oral clearance or C_{max} values of modafinil in elderly patients (67–87 years) versus historically matched younger adults would be of clinical significance, as they may have been due to potential effects from the multiple concomitant medications taken.[10] However, oral clearance may be reduced in this population.
- Exposure to the inactive metabolite modafinil acid, but not modafinil, was increased after a single modafinil 200 mg dose in patients with severe chronic renal failure (creatinine clearance ≤20 mL/min [≤1.2 L/h]), though the clinical relevance of this is unknown.[10]
- Dosage reductions are recommended in patients with severe hepatic impairment with or without cirrhosis, since clearance of modafinil has been shown to be reduced relative to that of healthy participants.[10]

Drug Interactions

- As there are multiple pathways by which armodafinil is metabolized and as a non-CYP-related pathway is the most rapid metabolic pathway, the likelihood of concomitant medications substantially altering the overall pharmacokinetics of armodafinil via CYP inhibition is low.[10]
- Armodafinil 250 mg/day did not induce CYP1A2, moderately induced CYP3A4 and moderately inhibited CYP2C19.[15] Thus, the pharmacokinetics of drugs that are substrates of CYP3A4/5 (e.g. steroidal contraceptives, midazolam, ciclosporin and triazolam) or CYP2C19 (e.g. omeprazole, diazepam and phenytoin) may be affected when co-administered with armodafinil. These drugs may therefore require dosage adjustments (section 5).
- There is also a potential for drug interactions between armodafinil and drugs that are inhibited, induced or metabolized by CYP2B6 and CYP2C9. Data are lacking for armodafinil; however, modafinil modestly induces CYP2B6 and suppresses CYP2C9 in *in vitro* studies.[16]
- The potential for armodafinil interactions with highly protein-bound drugs is considered minimal.[10] Caution should be used when co-administering armodafinil and monoamine oxidase inhibitors, as data specific to drug-drug interaction potential are not available.[10]
- Armodafinil most likely has no clinically relevant effects on the pharmacokinetic profile of CNS active drugs, such as methylphenidate and dexamfetamine. When these drugs were coadministered with modafinil in a pharmacokinetic model, no clinically relevant effects on the concomitant drugs were observed; however, modafinil absorption was delayed for ≈1 hour.[10]
- Concomitant modafinil had no effect on the pharmacokinetic profile of *R*- or *S*-warfarin, though it is recommended that prothrombin times or the international normalized ratio are monitored more frequently when armodafinil and warfarin are coadministered.[10]

3. Therapeutic Efficacy

The efficacy of armodafinil has been investigated in four 12-week, randomized, double-blind, placebo-controlled, multinational studies. Eligible patients (aged 18–65 years) were diagnosed with OSA,[20,21] narcolepsy[19] or SWSD[18] according to International Classification of Sleep Disorders criteria and had a Clinical Global Impressions of

Table I. Definition and description of efficacy rating scale and other relevant abbreviations used in clinical studies

Term	Definition	Description
CGI-C	Clinical Global Impressions of Change scale	Seven-point scale for rating the change in severity of illness, taking into account the total clinical experience. Rating is from 1 (very much improved) to 7 (very much worsened)
CGI-S	Clinical Global Impressions of Severity scale	Seven-point scale for rating the severity of illness, taking into account the total clinical experience. Rating is from 1 (normal) to 7 (extremely ill)
ESS	Epworth Sleepiness Scale	Eight-item rating scale measuring the likelihood of falling asleep in certain situations. Each item is rated from 0 (would never doze) to 3 (high chance of dozing); final score 0–24
KSS	Karolinska Sleepiness Scale	Nine-point scale for rating the level of sleepiness in the 5 minutes before the test. Rating is from 1 (very alert) to 9 (very sleepy, great effort to stay awake, fighting sleep)
MSLT	Multiple Sleep Latency Test	An objective assessment of sleepiness. The patient is instructed to lie quietly and attempt to sleep in five 20-minute naps at 2-hour intervals. Sleep latency is the time taken to reach either three consecutive 30-second epochs of stage 1 sleep or any single 30-second epoch of stage 2, 3, 4 or REM sleep[17,18]
MWT	Maintenance of Wakefulness Test	An objective measure of sleepiness. The patient is instructed to try to remain awake in a darkened room while in a semireclined position in six 20-[19] or 30-[20,21] minute periods at 2-hour intervals. Sleep latency is the time taken to reach either three consecutive epochs of stage 1 sleep or any epoch of stage 2, 3, 4 or REM sleep

REM = rapid eye movement.

Severity (CGI-S) scale score ≥4 (representing moderately ill or worse).[18-21] Patients received armodafinil 150[18-21] or 250[19,21] mg once daily or matching placebo.[18-21] Dosage was initiated at 50 mg/day and increased to 100 mg/day on day 2, followed by 50 mg/day increments every second day until the target dosage was achieved.[18-21] Treatment was administered in the morning in the studies in patients with OSA[20,21] or narcolepsy[19] and before the start of the night shift in the study in patients with SWSD.[18]

Key efficacy measures (including acronyms and definitions) used in the trials are listed in table I. The primary endpoints were the change from baseline to final visit in MWT (using the first 4 of 6 subtests)[19-21] or MSLT (using the last 4 of 5 subtests)[18]-assessed mean sleep latency, and the CGI-C scale response rate (response was defined as at least a minimal improvement on the CGI-C at the final visit).[18-21] Other endpoints included ESS[19-21] and KSS[18] scores and the change from baseline to final visit in MWT-assessed mean late-day sleep latency (using the last three of the six subtests).[19-21]

Efficacy assessments were based on the modified intent-to-treat (mITT) population using last-observation-carried-forward (LOCF) imputation.[18-21] Where stated, patient characteristics were generally comparable between treatment groups in each study.[19-21] The study in patients with narcolepsy reported a significant difference in age between groups at baseline; however, this was shown to have no effect on MWT results.[19]

In Patients with Obstructive Sleep Apnoea/Hypopnoea Syndrome

Patients diagnosed with OSA were required to have an ESS score ≥10, despite effective (Apnoea-Hypopnoea Index score ≤10 on night-time polysomnography) and regular (≥4 h/night on 70% of nights in a 2-week period) use of nCPAP treatment for ≥4 weeks.[20,21] Exclusion criteria included: medical or psychiatric disorders other than OSA that could cause excessive sleepiness;[20,21] other clinically significant, uncontrolled medical or psychiatric disorders;[20,21] caffeine consumption exceeding 600 mg/day;[20,21] or current use of drugs disallowed by the protocol.[20]

At baseline, 49–60% of patients in the armodafinil and placebo groups had a CGI-S rating of 'moderately ill', 26–33% were 'markedly ill', 10–17% were 'severely ill' and 2% were 'among the most extremely ill'.[20,21] Baseline ESS sleepiness scores in these patients were 15.3–16.0 and mean MWT-assessed sleep latencies were 21.5–23.7 min.[20,21]

- Armodafinil was associated with improved ($p < 0.001$) wakefulness in terms of mean MWT-assessed sleep latency compared with placebo in patients with OSA who were receiving adjunctive nCPAP therapy (coprimary endpoint) [figure 1a].[20,21] A significant ($p < 0.05$) difference from placebo was evident from week 4 onward in armodafinil 250 mg/day recipients,[21] and, for the most part, in armodafinil 150 mg/day recipients (except at the week 8 timepoint in one study[21]).[20,21] No significant difference between armodafinil 150 mg/day and armodafinil 250 mg/day recipients in mean MWT-assessed sleep latency was observed.[21]
- The proportion of patients classified as at least minimally improved on the CGI-C was significantly ($p < 0.01$) greater in armodafinil 150 and 250 mg/day than placebo recipients (coprimary endpoint) [figure 1b].[20,21]
- With regard to late-day MWT-assessed sleep latency, no significant differences between armodafinil 150 or 250 mg/day and placebo were found at the final visit in the individual studies (figure 2).[20,21] However, a pooled analysis of the two studies revealed that armodafinil 150 mg/day significantly ($p < 0.05$) improved wakefulness relative to placebo with regard to late-day MWT-assessed latency (+1.2 vs −0.3 minutes; extrapolated from graph).[22]
- Both armodafinil 150 and 250 mg/day recipients demonstrated significant ($p < 0.01$) improvements in patient-estimated sleepiness versus those receiving placebo.[20,21] The changes in ESS scores from baseline to final visit were −5.3[20]

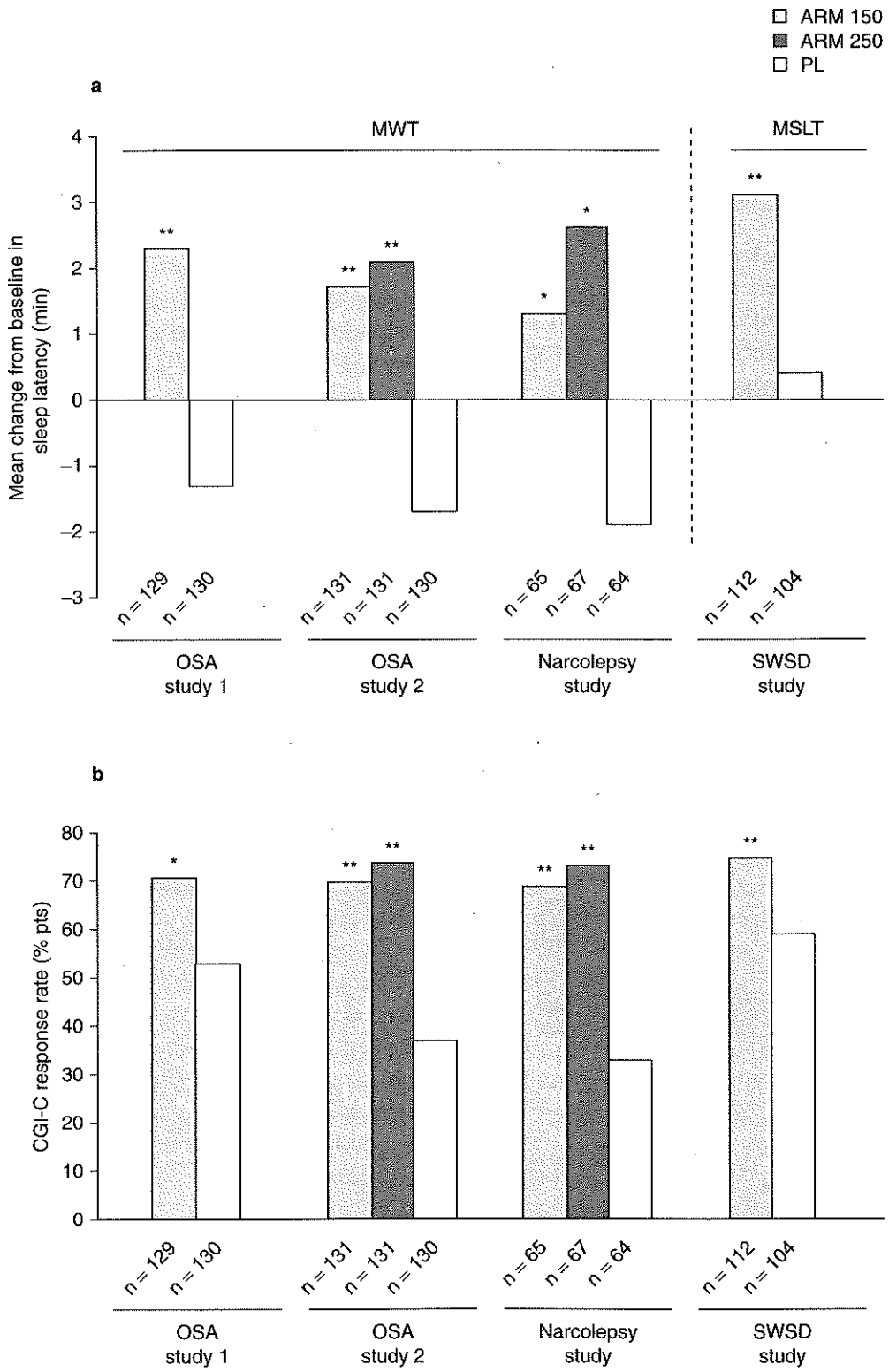


Fig. 1. Primary efficacy of armodafinil (ARM) vs placebo (PL). Twelve-week, randomized, double-blind, multinational studies in patients (pts) with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA; OSA study 1[20] and OSA study 2[21]) [despite treatment of the underlying condition], narcolepsy[19] or shift work sleep disorder (SWSD).[18] (**a**) Mean change from baseline to last visit in sleep latency (coprimary endpoint), measured using the first 4 of 6 Maintenance of Wakefulness Test (MWT) subtests (baseline values in OSA pts of 21.5–23.7 min[20,21] and in narcolepsy pts of 9.5–12.5 min[19]) or the last 4 of 5 Multiple Sleep Latency Test (MSLT) subtests (baseline values 2.3 [ARM 150] and 2.4 [PL] min).[18] (**b**) Clinical Global Impressions of Change (CGI-C) scale response rate (coprimary endpoint); response was defined as at least a minimal improvement on the CGI-C at the final visit. Pts were randomized to once-daily treatment with ARM 150 (ARM 150)[18-21] or 250 (ARM 250)[19,21] mg/day or matching PL.[18-21] * $p < 0.01$, ** $p \leq 0.001$ vs PL.

and −5.5[21] in armodafinil 150 mg/day recipients, −5.5 in armodafinil 250 mg/day recipients[21] and −3.0[20] and −3.3[21] in placebo recipients (extrapolated from graphs).

In Patients with Narcolepsy

Patients with narcolepsy were required to have an MSLT-assessed mean sleep latency of ≤6 minutes.[19] Exclusion criteria included: medical or psychiatric disorders other than narcolepsy that could cause excessive sleepiness; other clinically significant, uncontrolled medical or psychiatric disorders; caffeine consumption exceeding 600 mg/day; or current use of drugs disallowed by the protocol.[19] Patients who reported cataplexy while on stable doses of anticataplectic medication (excluding sodium oxybate) were not excluded; however, anticataplectic medication was only permitted if it did not contribute to patient sleepiness and if the dosage was stable for ≥1 month.[19]

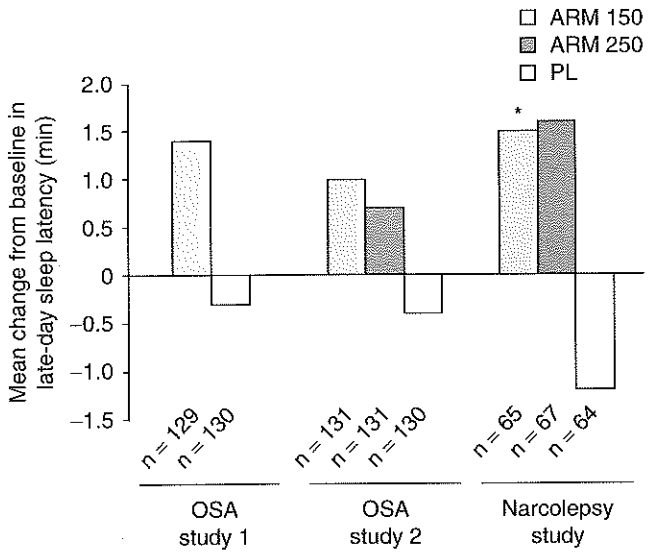


Fig. 2. Efficacy of armodafinil (ARM) vs placebo (PL). Twelve-week, randomized, double-blind, multinational studies in patients (pts) with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA; OSA study 1[20] and OSA study 2[21]) [despite treatment of the underlying condition] or narcolepsy.[19] Mean change from baseline to last visit in late-day sleep latency, measured using the final three of six Maintenance of Wakefulness Test (MWT) subtests (baseline values in OSA pts of 23.4–25.4 min[20,21] and in narcolepsy pts of 10.5–12.9 min[19]). Pts were randomized to once-daily treatment with ARM 150 (ARM 150)[19-21] or 250 (ARM 250)[19,21] mg/day or matching PL.[19-21] * $p < 0.05$ vs PL.

At baseline, 29–37% of patients in the armodafinil and placebo groups had a CGI-S rating of 'moderately ill', 43–54% were 'markedly ill', 17–18% were 'severely ill' and 0–3% were 'among the most extremely ill'.[19] Baseline ESS sleepiness scores in these patients were 15.7–17.5 and mean MWT-assessed sleep latencies were 9.5–12.5 min.[19]

- In patients with narcolepsy, recipients of armodafinil 150 and 250 mg/day experienced a significantly ($p < 0.01$) greater improvement in mean MWT-assessed sleep latency and had higher ($p < 0.001$) CGI-C response rates than placebo recipients (coprimary endpoints) [figure 1].[19]
- Furthermore, the significant ($p < 0.05$) improvement from baseline in mean sleep latency compared with placebo recipients was observed from the first visit at week 4 till study end in armodafinil 150 mg/day recipients; armodafinil 250 mg/day recipients only significantly ($p < 0.05$) differed from placebo at week 4 and at the final visit.[19]
- Mean late-day MWT-assessed latency was also significantly ($p < 0.05$) improved among armodafinil 150 mg/day versus placebo recipients at the final visit; armodafinil 250 mg/day recipients did not differ significantly from placebo recipients for this endpoint (figure 2).[19]
- Both armodafinil 150 and 250 mg/day recipients demonstrated a significant ($p < 0.01$) improvement in patient-estimated sleepiness versus those receiving placebo[19] (change in ESS scores from baseline to final visit of −4.1[19] and −3.8,[19] respectively; change in ESS score among placebo recipients was −1.9[23]).

In Patients with Shift Work Sleep Disorder

Patients with SWSD were required to have an MSLT-assessed mean sleep latency of ≤6 minutes and a sleep efficiency of ≤87.5% on daytime polysomnography, to have complained of excessive sleepiness during night shifts for ≥3 months and were working for ≥5 nights per month (shift duration ≥6 and ≤12 hours); night shifts had to be consecutive for ≥3 nights.[18] Exclusion criteria included: clinically significant, uncontrolled medical

or psychiatric disorders; current sleep disorder other than SWSD; caffeine consumption exceeding 600 mg/day; or current use of drugs disallowed by the protocol.[18]

At baseline, 56% of armodafinil and 57% of placebo recipients had a CGI-S rating of 'moderately ill', 34% and 36% were 'markedly ill', 9% and 7% were 'severely ill', and <1% were 'among the most extremely ill'.[18] Baseline KSS sleepiness scores were 7.4 (in armodafinil recipients) and 7.3 (in placebo recipients) and mean MSLT-assessed sleep latencies were 2.3 and 2.4 minutes.[18]

- At final visit, armodafinil recipients showed significant ($p < 0.001$) improvement in wakefulness in terms of mean MSLT-assessed sleep latency compared with placebo recipients in patients with SWSD (coprimary endpoint) [figure 1a].[18] Moreover, a significant ($p < 0.05$) improvement from baseline in mean sleep latency in armodafinil compared with placebo recipients was observed from the first visit at week 4 till study end and throughout the night at final visit.[18]
- A greater ($p = 0.001$) proportion of armodafinil than placebo recipients showed an overall improvement in clinical condition as assessed by the CGI-C (coprimary endpoint) [figure 1b].[18]
- Patients receiving armodafinil also showed significant improvement in patient-estimated sleepiness compared with those receiving placebo.[18] The mean change from baseline in KSS score at study end was −1.8 for armodafinil recipients versus −1.0 for placebo recipients ($p < 0.01$); a significant improvement in sleepiness was apparent from week 4 till study end ($p < 0.01$).[18]

4. Tolerability

Armodafinil was generally well tolerated in clinical trials discussed in section 3, with the focus in this section being on a descriptive analysis of data pooled from all four placebo-controlled trials, as presented in the prescribing information.[10]

- Common (≥5% of armodafinil recipients) treatment-emergent adverse events that occurred more frequently in the armodafinil than placebo group during 12 weeks' treatment are summarized in figure 3.[10] Treatment-emergent adverse events were generally mild to moderate in severity. No serious adverse events considered treatment related were reported in the clinical trials.[18-21]

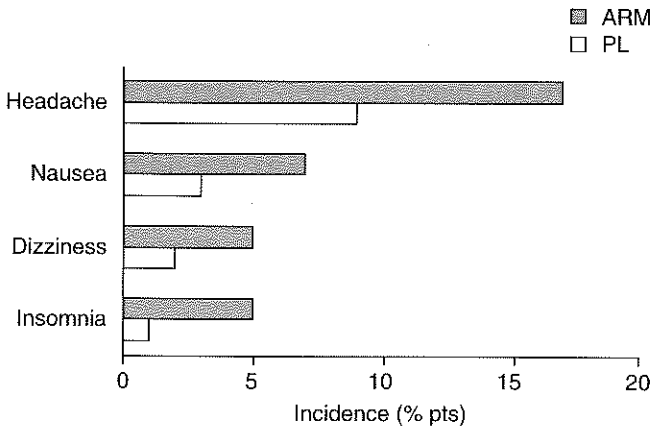


Fig. 3. Tolerability profile of armodafinil (ARM). Treatment-emergent adverse events that occurred in ≥5% of ARM 150 or 250 mg once-daily recipients (n = 645) and more frequently in ARM than in placebo (PL) recipients (n = 445) in a pooled analysis[10] of four 12-week, randomized, double-blind trials in patients (pts) with obstructive sleep apnoea (despite treatment of the underlying condition),[20,21] narcolepsy[19] or shift work sleep disorder.[18] Descriptive analysis only.

- Discontinuation of treatment as a result of adverse events occurred in 7% of armodafinil and 4% of placebo recipients; the most common adverse event leading to discontinuation was headache.[10] Adverse events that were potentially dose dependent were headache, rash, depression, dry mouth, insomnia and nausea.[10]
- Most laboratory parameters were generally similar in armodafinil and placebo groups.[10] Mean plasma gamma glutamyltransferase and alkaline phosphatase levels were higher than baseline in armodafinil recipients, although no change from baseline was observed in placebo recipients.[10] No ECG abnormalities were evident during armodafinil treatment.[10]
- While no serious skin rashes have been reported in clinical trials of armodafinil, those investigating modafinil have reported serious rash (including one paediatric case of possible Stevens-Johnson Syndrome) requiring hospitalization and discontinuation of treatment.[10] Armodafinil has been associated with benign rashes. As it is difficult to determine the severity of rashes, armodafinil should be discontinued at first sign of rash.
- As armodafinil is closely related to modafinil, multi-organ hypersensitivity reactions and

psychiatric symptoms cannot be ruled out.[10] Also, among all patients exposed to armodafinil, there has been one report each of angioedema and hypersensitivity (with rash, dysphagia and bronchospasm). Therapy should be discontinued in these instances.

5. Dosage and Administration

In patients with excessive sleepiness associated with OSA or narcolepsy, the recommended dosage of armodafinil in the US is 150 or 250 mg/day, given as a single dose in the morning.[10] Patients with OSA are expected to be receiving adjunctive therapy with standard treatment for the underlying disorder, for example, nCPAP. In patients with SWSD, the recommended dosage is 150 mg/day, administered ≈1 hour before the start of the work shift. Long-term use of armodafinil has not been investigated with regard to efficacy; therefore, periodical re-evaluations may be required when used for extended durations, to assess long-term benefit to the patient.[10]

Dosage adjustment may be required in patients receiving concomitant medications that are substrates for CYP3A4 or CYP3A5 (e.g. steroidal contraceptives, triazolam or ciclosporin) or drugs that are largely eliminated via CYP2C19 metabolism (e.g. diazepam, propranolol or phenytoin).[10,15] Patients with severe hepatic disease should receive a reduced dosage, as, potentially, should elderly patients.[10]

As patients may have more than one sleep disorder that is contributing to the excessive sleepiness, prescribers must pay careful attention to diagnosis and treatment.[10]

Armodafinil has not been studied in paediatric patients, nor is it approved in this patient group for any indication.[10]

Local prescribing information should be consulted for detailed information, including further contraindications, precautions, drug interactions and use in special patient populations.

6. Armodafinil: Current Status

Armodafinil is approved in the US to improve wakefulness in adult patients with excessive sleepiness associated with OSA (in conjunction with standard treatment[s] for underlying obstruction), narcolepsy or SWSD.[10] Armodafinil was more effective than placebo at improving sleep latency, was associated with higher CGI-C response rates and was generally well tolerated in four well designed studies in patients with excessive sleepiness associated with OSA (despite nCPAP therapy), narcolepsy or SWSD.

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