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The Effects of Armodafinil on Clinical Condition Late (0400 to 0800) in Shift, Including the Commute Home, and on Functioning in Patients With Excessive Sleepiness Associated With Shift Work Disorder

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Background

- An estimated 21 million people in the United States, or nearly 1 in 5 members of the labor force, work shifts outside the normal work day (6 AM to 6 PM).[1]
  - — Shift workers are at approximately 3 times greater risk for occupational accidents compared with individuals who work traditional daytime shifts.[2]
  - — Shift workers often experience chronic sleep problems and are almost twice as likely to fall asleep at work compared with individuals who work traditional daytime shifts.[2]
- Shift work disorder (SWD) is a circadian rhythm sleep disorder that can occur in people who work shifts during the normal sleep period.[3]
  - — Key symptoms of SWD, excessive sleepiness and/or insomnia, are reported by up to 45% of shift workers.[4]
  - — It is estimated that 10% to 23% of shift workers have SWD.[4,5]
- Excessive sleepiness associated with SWD has been shown to impair patient functioning, such as overall global function, alertness, cognition, and performance.[4]
- Armodafinil, the *R*- and longer-lasting isomer of modafinil, significantly improves wakefulness in patients with excessive sleepiness related to SWD as assessed by the Clinical Global Impression of Change (CGI-C)[7] and the Karolinska Sleepiness Scale (KSS).[8]
- The current study examined the effect of armodafinil on wakefulness and global functioning in patients with SWD. This was, to our knowledge, the largest interventional study ever conducted in patients with SWD.

Methods

Study Design

- This was a 6-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group study evaluating armodafinil 150 mg in patients with SWD.
  - — Armodafinil or placebo was given 30 to 60 minutes before the start of the night shift on nights worked.
  - — Armodafinil was titrated from 50 mg on the first night shift worked, to 100 mg on nights 2 and 3, and to 150 mg thereafter.
  - — Patient evaluations were conducted at baseline, 3 weeks, and 6 weeks or final postbaseline visit.
- The tolerability analysis included all patients who received ≥1 dose of study drug.
- The efficacy analysis included those in the tolerability analysis with ≥1 postbaseline CGI-C assessment.[7]
- The study was conducted in compliance with the Good Clinical Practice: Consolidated Guidance. Patients provided written informed consent and an independent ethics committee or institutional review board at each center approved the protocol.

Population

Key Inclusion Criteria

- Aged 18 to 65 years
- Diagnosis of SWD (≥1 month) by *International Classification of Sleep Disorders*, 2nd edition[3] and *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM IV-TR)*[9]
- Worked ≥5 night shifts per month between 10 PM and 8 AM (≥6 hours in duration)
- Rating of at least "moderately ill" for excessive sleepiness (score of ≥4 on the Clinical Global Impression of Severity of Illness)[7]
- Impaired patient function as shown by a score <70 on the Global Assessment of Functioning (GAF) from the *DSM IV-TR*[9]
- A score of ≥6 ("some signs of sleepiness") on the KSS[8]

Key Exclusion Criteria

- Obstructive sleep apnea (apnea/hypopnea index >5) or any sleep disorder other than SWD
- Prior use of modafinil or armodafinil
- Other medications or conditions causing functional impairment or contributing to excessive sleepiness

Assessments

Primary Efficacy Assessment

- The proportion of patients with at least minimal improvement of clinical condition, as related to late-in-shift sleepiness (defined as 4 AM to 8 AM), measured immediately after the shift by the CGI-C at the final visit.
  - — CGI-C measures clinician-rated change in disease severity from "very much improved" to "very much worse."[7]

Secondary Efficacy Assessments

- The key secondary assessment was mean change in patient functioning, as measured by change from baseline in GAF score at the final visit.
  - — GAF is a clinician-rated 0 to 100 scale measuring overall psychological, social, and occupational functioning, with higher scores indicating better functioning.[9]
- Other secondary assessments include mean change from baseline in late-in-shift KSS scores on the last night worked (average of scores at 4, 6, and 8 AM) at Week 3 and Week 6 or final visit.
  - — KSS is a patient-rated scale of sleepiness from 1 (very alert) to 9 (very sleepy, great effort to stay awake, fighting sleep).[8]
- Tolerability was also assessed.

Statistical Analysis

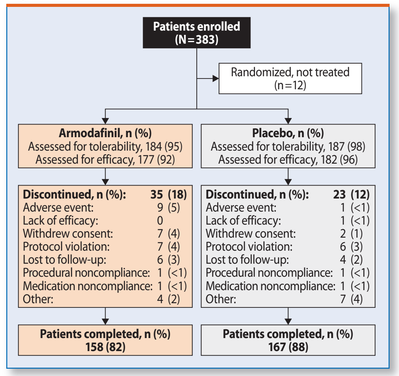
- Continuous baseline characteristics and demographic variables were compared using analysis of variance (ANOVA) with treatment as a factor.
- Categorical variables were compared using a Pearson's Chi-square test.
- The primary efficacy variable was analyzed using a Cochran-Mantel-Haenszel test controlling for baseline shift-work duration. All tests were 2-tailed, at a significance level of 0.05.
- Continuous secondary efficacy variables were analyzed by analysis of covariance (ANCOVA) with treatment and baseline shift-work duration as factors and baseline as a covariate.
- Final-visit analysis used the last observation carried forward methodology.

Results

Patients

- Of 383 randomized patients, 325 (85%) completed the study (**Figure 1**).

Figure 1. Patient Disposition



- The most commonly represented occupations were in the fields of healthcare, protective services, and transportation (**Table 1**).
- Baseline characteristics were similar between the 2 groups (**Table 1**).

Efficacy

- The proportion of patients with improved late-in-shift CGI-C was significantly greater in the armodafinil group compared with the placebo group at final visit, as well as at weeks 3 and 6 ($P<0.0001$ at all time points; **Figure 2**).
  - — More patients in the armodafinil group were rated as "much improved" and "very much improved" compared with placebo (**Figure 3**).

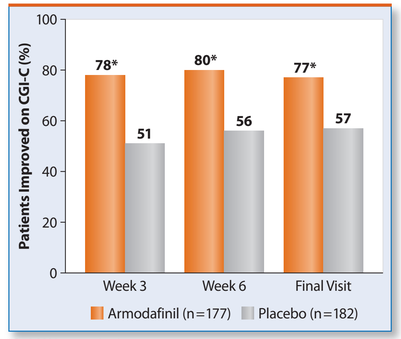
Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic		Armodafinil (n=193)	Placebo (n=190)
Age, years; mean (SD)		36.7 (10.71)	36.1 (10.75)
Female, n (%)		85 (44)	90 (47)
Race, n (%)	White	128 (66)	141 (74)
	Black	50 (26)	42 (22)
	Asian	15 (8)	4 (2)
	Other	0	3 (2)
BMI, kg/m²; mean (SD)		28.6 (5.73)	28.3 (5.23)
Duration of shift;[a] n (%)	≤9 h	132 (68)	147 (77)
	>9 h	60 (31)	43 (23)
Job status, n (%)	Full time	182 (94)	181 (95)
	Part time	11 (6)	9 (5)
Type of shift work, n (%)			
Permanent shift worker		182 (94)	175 (92)
Rotating shift worker		11 (6)	15 (8)
Patients' occupations, n (%)			
Healthcare practitioner and technical		25 (13)	31 (16)
Protective services		24 (12)	32 (17)
Healthcare support		22 (11)	15 (8)
Transportation and material moving		19 (10)	21 (11)
Office and administrative support		15 (8)	15 (8)
Sales and related		13 (7)	13 (7)
Management		12 (6)	13 (7)
Manufacturing		10 (5)	5 (3)
Other		53 (28)	45 (23)
CGI-S rating, n (%)			
Moderately ill		111 (58)	96 (51)
Markedly ill		63 (33)	55 (29)
Severely ill		18 (9)	39 (21)
Among the most extremely ill		1 (<1)	0
GAF score, mean (SD)		63.1 (4.28)	62.7 (4.39)
KSS score, mean (SD)		7.4 (0.92)	7.5 (0.82)

[a]Data not available for 1 patient receiving armodafinil.

BMI, body mass index; CGI-S, Clinical Global Impression of Severity of Illness; GAF, Global Assessment of Function; KSS, Karolinska Sleepiness Scale; SD, standard deviation.

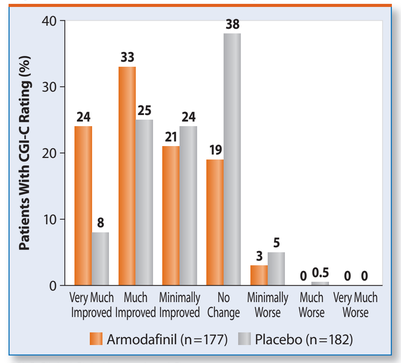
Figure 2. Proportion of Patients With Improvement in Late-in-Shift CGI-C



*$P<0.0001$ versus placebo.

CGI-C, Clinical Global Impression of Change.

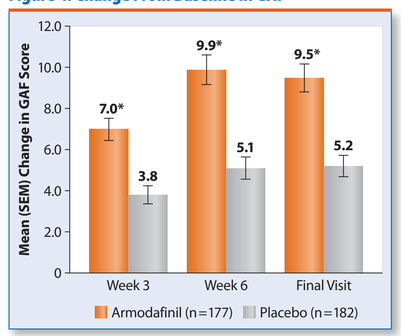
Figure 3. Late-in-Shift CGI-C Ratings at Final Visit



CGI-C, Clinical Global Impression of Change.

- Functional improvement assessed by the GAF was also significantly greater in the armodafinil group compared with the placebo group ($P<0.0001$ at all time points; **Figure 4**).
  - — At the final visit, mean (SEM) change in GAF score for the armodafinil group was 9.5 (0.67) compared with 5.2 (0.51) for the placebo group.

Figure 4. Change From Baseline in GAF

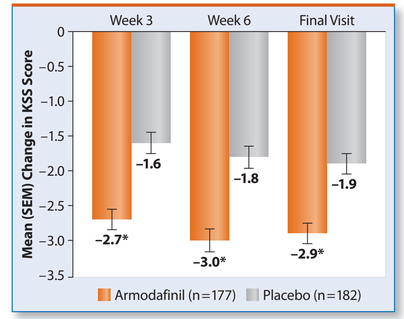


*$P<0.0001$ versus placebo.

GAF, Global Assessment of Function Scale; SEM, standard error of the mean.

- The decrease in late-in-shift subjective sleepiness, as assessed using the KSS, was significantly greater in the armodafinil group compared with the placebo group ($P<0.0001$ at all time points; **Figure 5**).
  - — At the final visit, mean (SEM) change in late-in-shift KSS score for the armodafinil group was −2.9 (0.15) compared with the placebo group −1.9 (0.15).

Figure 5. Change From Baseline in Late-in-Shift KSS Scores



*$P<0.0001$ versus placebo.

KSS, Karolinska Sleepiness Scale; SEM, standard error of the mean.

Safety and Tolerability

- The most common adverse events are shown in **Table 2**.

Table 2. Adverse Events Reported in ≥5% of Patients Receiving Armodafinil and More Frequently Than in Patients Receiving Placebo

Adverse Event, n (%)	Armodafinil (n=184)	Placebo (n=187)
Headache	28 (15)	13 (7)
Nausea	20 (11)	7 (4)
Insomnia	12 (7)	3 (2)

- One serious adverse event occurred during the study (nephrolithiasis in a patient in the placebo group).
- The most common adverse events leading to discontinuation were headache (n=5 [3%] in the armodafinil group and n=1 [<1%] in the placebo group) and nausea (n=3 [2%] in the armodafinil group).

Conclusions

- In this large study of patients working actual night shifts, armodafinil significantly improved shift-workers' wakefulness late in shift during the critical circadian nadir period from 4 AM to 8 AM, as measured by the CGI-C and KSS.
- Armodafinil significantly improved functional status, as measured by the GAF.
- Armodafinil was generally well tolerated. No new safety signals were identified during this study.

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