ORIGINAL ARTICLE

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Armodafinil for Excessive Sleepiness Associated With Jet Lag Disorder

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OBJECTIVE: **To assess the effect of armodafinil, the longer-lasting isomer of modafinil, on jet lag disorder.**

PARTICIPANTS AND METHODS: **This double-blind, randomized, parallel-group, multicenter study was conducted between September 18, 2008, and February 9, 2009. Adults with a history of jet lag symptoms on previous flights through multiple time zones flew from the United States to France (a 6-hour time zone change) for a 3-day laboratory-based study period. Participants received armodafinil (50 or 150 mg/d) or placebo each morning. Wakefulness was assessed by the coprimary outcomes, mean sleep latency on the Multiple Sleep Latency Test (MSLT) (average of all MSLT sessions across days 1 and 2) and Patient Global Impression of Severity in relation to jet lag symptoms (averaged across days 1 and 2).**

RESULTS: **A total of 427 participants received armodafinil at 50 mg/d (n=142), armodafinil at 150 mg/d (n=143), or placebo (n=142). Armodafinil at 150 mg/d provided a significant benefit in sleep latency on the MSLT (days 1-2: mean, 11.7 minutes vs 4.8 minutes for placebo; *P*<.001) and participants' perception of their overall condition in relation to jet lag symptoms (Patient Global Impression of Severity, days 1-2: mean, 1.6 vs 1.9 for placebo; *P*<.05). The most frequently reported adverse events for armodafinil at 150 mg/d were headache (27%), nausea (13%), diarrhea (5%), circadian rhythm sleep disorder (5%), and palpitations (5%).**

CONCLUSION: **Armodafinil increased wakefulness after eastward travel through 6 time zones.**

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ANCOVA = analysis of covariance; KSS = Karolinska Sleepiness Scale; MSLT = Multiple Sleep Latency Test; NPSG = nocturnal polysomnography; PGI-S = Patient Global Impression of Severity; STAI = State and Trait Anxiety Inventory; SWD = shift work disorder

Jet lag disorder is a circadian rhythm sleep disorder that occurs as a consequence of rapid travel through multiple time zones.[1] The traveler may experience excessive sleepiness, fatigue, insomnia, irritability, gastrointestinal disturbance, or other symptoms after arrival at the destination.[2-4] Jet lag symptoms arise from the desynchronization between the body's circadian rhythm, which is synchronous with the location of departure, and the new sleep/wake cycle required at the destination.[1-4] Effects tend to be more severe when a greater number of time zones are traversed, and following eastbound travel.[2,5,6] Although the percentage of people flying across multiple time zones who develop jet lag disorder is unclear, it is estimated that possibly up to two-thirds of all travelers experience jet lag and may experience symptoms such as excessive sleepiness during the day or insomnia.[2] A treatment for excessive sleepiness that promotes daytime wakefulness may be especially beneficial to travelers who have a limited amount of time at their destination, precluding a circadian readjustment.

Armodafinil, the longer-lasting *R*-isomer of racemic modafinil,[7] is a wakefulness-promoting medication. The terminal half-life of the *R*-isomer is approximately 15 hours, compared with 3 to 4 hours for the *S*-isomer.[8,9] In a study of patients with shift work disorder (SWD), another circadian rhythm disorder, armodafinil 150 mg/d significantly improved wakefulness and clinicians' perception of patients' overall condition, compared with placebo.[10] The primary objective of this study was to evaluate armodafinil (50 mg/d and 150 mg/d) for treatment of excessive sleepiness associated with jet lag disorder due to eastbound travel in a population of travelers with a history of jet lag symptoms.

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PARTICIPANTS AND METHODS

This randomized, double-blind, placebo-controlled, parallel-group study was conducted between September 18, 2008, and February 9, 2009. Sites were selected based on the requirement that participants undergo a 6-hour time zone change. Specific sites were chosen based on their expertise and on logistic considerations, such as being close to an appropriate airport that accommodated private chartered jets and having the capacity required to conduct the study. The protocol was approved by the central institutional review board in the United States and regional independent ethics committees in France, and complied with the International Conference on Harmonisation's Good Clinical Practice Consolidated Guidance[11] and applicable laws and regulations. Study participants provided written informed consent at the origination study centers and reconfirmed their consent at the destination study centers.

Participants were screened at 2 visits during a 1- to 8-week period and, if eligible, flew overnight (day 0) on a nonstop, private chartered flight simulating coach-class accommodations from their origination study center in the United States (New York, NY; Atlanta, GA; Columbia, SC; or Crestview Hills, KY) to their destination study center in France (Rouffach or Toulouse). The flight duration was 8.0 to 10.5 hours, and the difference between time zones was 6 hours. Before participants boarded the plane, a breathalyzer test, urine drug screen, and pregnancy test were administered. Passengers were randomly assigned seats, which could not be reclined more than 37°, and were not allowed to consume alcohol or caffeine during the trip. Cabin lights were turned off after dinner and turned back on before breakfast, as is customary on commercial flights. Study participants were not given instructions regarding sleep and may or may not have slept during the flight. They were served a light breakfast approximately 1 hour before landing. After arriving early the following morning, participants were transported by chartered vehicle to the destination study center (arriving at approximately 7:00 AM) where they stayed for the entire 3-day study period (days 1-3; Figure 1).

During the 3-day study period in France, participants remained indoors (to limit confounding variables, such as access to caffeine, and because of logistic constraints) and slept and ate in accordance with the local time zone. They were exposed to natural light through windows, and the overall degree of light exposure (artificial or natural) was not specified by the protocol, except during nocturnal polysomnography (NPSG) and the Multiple Sleep Latency Test (MSLT). Snacks, decaffeinated drinks, and juices were available throughout the day. Study participants slept in single rooms with lights turned out at 10:00 PM±30 minutes; their wake-up time was 8 hours later.

Participants flew back to their origination study center in the United States on the morning of day 4. A final evaluation was performed after arrival at the origination study center in the United States. Participants were also contacted via telephone approximately 48 hours and 7 days after discharge from the origination study center for follow-up of adverse events.

Men and women (18-65 years old) who previously experienced symptoms consistent with the diagnostic criteria for jet lag disorder (as defined by *The International Classification of Sleep Disorders*, Second Edition[1]) were enrolled at the 4 origination study centers in the United States. Participants were required to have experienced jet lag symptoms after jet travel (with a time zone change of ≤6 hours) at least once in the past 5 years. All participants were required to report sleeping 6.5 to 9 hours per night, on average, during the month preceding screening, at screening visits, and on the day of departure from the origination city (day 0). In addition, participants had to have a self-reported bedtime between 9:00 PM and 12:00 AM during the month preceding screening and during the 2 nights before day 0. Major exclusion criteria included traveling across time zones with a 4-hour or greater difference within 2 weeks before the end of the screening period or traveling outside the origination time zone within 1 week before the end of the screening period. Participants were also excluded if they had a history (ie, in the preceding 12 months) or diagnosis of narcolepsy, obstructive sleep apnea, or SWD; any history of hypersomnia, insomnia, or sleep disorder; a history of deep venous thrombosis; or any current diagnosis of a clinically relevant medical disorder. Participants with a history of any psychiatric disorder that would affect study participation or with an Epworth Sleepiness Scale score of 10 or higher, MSLT score lower than 8 minutes, or State and Trait Anxiety Inventory (STAI) score greater than 50 on either of the 2 scales (trait or state anxiety) were excluded. Participants were excluded for taking medications that might influence sleep (eg, hypnotics, melatonin, and stimulants) within 7 days before completing screening and for caffeine intake greater than 300 mg/d within 2 weeks before completing screening. Participants with any history of substance abuse or dependence (except nicotine dependence >5 years ago), any use of nicotine within 3 months, or current alcohol consumption greater than 14 units/week were excluded. Alcohol consumption was prohibited during the study period.

Eligible participants were randomized in a 1:1:1 ratio to receive either 50 mg or 150 mg of armodafinil or placebo once daily. The 150-mg dose was the dose evaluated in relation to the primary efficacy assessment; the 50-mg dose was evaluated as a minimally effective dose in secondary assessments. Armodafinil was provided in tablets of 50 mg/d that were identical in appearance to placebo tablets.

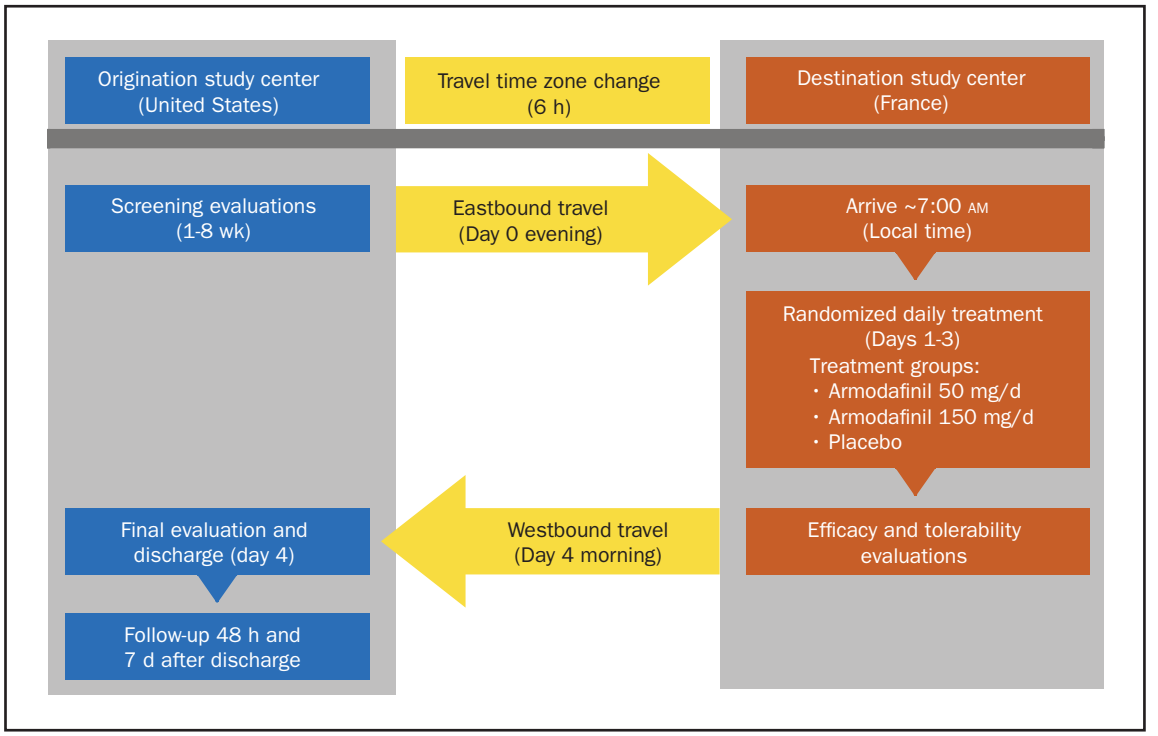

FIGURE 1. Study design.

At approximately 8:00 AM on each of the 3 laboratory study days, participants were given 3 tablets of study drug (of which 0, 1, or 3 were armodafinil at 50 mg/d), 1 from each of 3 bottles prelabeled with their randomization number. The sponsor generated the randomization code, as well as packaged and labeled the study medication. Randomization was performed in blocks of 3 and stratified according to destination site. The participants, the investigators and their study site personnel, and the study sponsor's personnel were blinded to identification of treatment.

Efficacy

Wakefulness was assessed using 2 prespecified coprimary outcomes, the mean score on the MSLT[12] and participants' rating of their overall condition (in relation to their jet lag symptoms) using the Patient Global Impression of Severity (PGI-S),[13] both of which were averaged across days 1 and 2 when, on the basis of the number of time zones crossed, participants' sleepiness and jet lag symptoms were expected to be maximal.[4,14] Secondary outcomes included scores on the MSLT and PGI-S ratings from individual days 1 to 3, and the Karolinska Sleepiness Scale (KSS) scores averaged across days 1 and 2 and from individual days 1 to 3.

The MSLT is a validated, objective assessment of excessive sleepiness,[12] the key characteristic of jet lag as defined by *The International Classification of Sleep Disorders*.[1] This measure has been used in studies of other circadian sleep disorders, including SWD.[10] As specified in the MSLT protocol, participants are instructed to attempt to fall asleep while lying quietly in a darkened room. Four 20-minute (maximum) MSLT sessions were performed. Each MSLT session was performed during a 20-minute period at individual test times: 10:00 AM, 12:00 PM, 2:00 PM, and 4:00 PM at screening visit 2 (to determine eligibility for inclusion in the study) and during the 3 laboratory days. After a participant fell asleep, he or she was immediately awakened and kept awake for the rest of the period.[12] If a participant did not fall asleep in the given time, the MSLT was terminated after 20 minutes.[12]

The PGI-S is a scale that allows individuals to assess their overall condition.[13] Participants were asked to assess how they felt overall in relation to their jet lag symptoms. Participants were instructed to rate their overall condition according to 7 categories: normal (shows no sign of illness), borderline ill, mildly (slightly) ill, moderately ill, markedly ill, severely ill, and extremely ill. Study site personnel described the term *ill* as follows: "*Ill* refers to symptoms of jet lag and any other symptoms. Excessive sleepiness is one of the symptoms of jet lag. Irritability, malaise, gastrointestinal disturbance, and difficulty maintaining one's usual level of performance are other symptoms of jet lag."

The PGI-S was assessed at screening visit 2 and during the 3 laboratory days, just before the first MSLT session.

The KSS is a validated, participant-rated instrument for measuring excessive sleepiness based on a scale of 1 to 9 (with 1 indicating "very alert" and 9 indicating "very sleepy, great effort to stay awake, fighting sleep").[15] The KSS was administered before each MSLT session at screening visit 2, and before each MSLT session and at bedtime on the 3 laboratory days.

Efficacy data (MSLT, PGI-S, and KSS), collected at screening visit 2, served as the baseline for statistical analyses.

Safety and Tolerability

The STAI,[16] Mini International Neuropsychiatric Interview,[17] and the Columbia Suicide History Scale[18] were performed at screening to assess participants' psychiatric status. The state anxiety subscale of the STAI was performed at screening, on each of the 3 laboratory days after the last MSLT session, and at any other time if clinically indicated. Clinical laboratory tests (chemistry, hematology, and urinalysis) and physical examination were performed at screening, and the final evaluation was performed on discharge (day 4). Nocturnal polysomnography was performed at screening and on nights 1 and 2. All safety screening assessments occurred at the first screening visit except NPSG, which was performed at the second (overnight) screening visit. Adverse events and vital signs were monitored on all study days.

Statistical Analyses

Sample size was calculated on the basis of findings from a clinical study of armodafinil for excessive sleepiness associated with SWD.[19] A sample size of 133 evaluable participants per treatment group was expected to provide at least 90% power to detect a 1.6-minute difference (assuming a pooled SD of 4.0) in sleep latency on the MSLT and a 1-point mean treatment difference in PGI-S rating (assuming a pooled SD of 2.5). The power to test the joint hypothesis was calculated as at least 81%.

Scores on the MSLT across days 1 and 2 (ie, average of all 8 test sessions across days 1 and 2) were analyzed using analysis of covariance (ANCOVA), with treatment as the main factor and baseline MSLT value as the covariate. A Cochran-Mantel-Haenszel test was used to analyze mean PGI-S ratings on days 1 and 2. The primary comparison was that made between the group who received armodafinil at 150 mg/d and the placebo group for both these outcomes. Type 1 error was controlled at the 0.05 level for the analyses of primary efficacy variables. The secondary outcomes, mean KSS score (average of 4 sessions given before each MSLT) and MSLT scores on days 1, 2, and 3, were analyzed using ANCOVA, with treatment as the main factor and baseline value as covariate. The PGI-S was analyzed using a Cochran-Mantel-Haenszel test on days 1, 2, and 3. Data from NPSG were also analyzed using ANCOVA. Adverse events were analyzed using the Fisher exact test. Statistical analyses completed for all secondary outcome measures were not adjusted for multiplicity; therefore, nominal *P* values are reported. All other tolerability outcomes are summarized with descriptive statistics.

The safety analysis set included all randomized participants who took at least one dose of study medication, and the efficacy analysis set included all participants in the safety analysis set who had at least one postbaseline, primary efficacy assessment on day 1 or 2.

RESULTS

A total of 427 participants were randomized as follows: 142 received armodafinil at 50 mg/d, 143 received armodafinil at 150 mg/d, and 142 received placebo (Figure 2). With regard to age, the treatment groups were similar (*P*=.23) (Table 1).

Post hoc analyses confirmed that statistical differences in mean body weight and race did not impact the outcome of the study. One participant withdrew due to an adverse event before any efficacy assessments. When weight was added as a covariate in the MSLT analysis, it was not found to influence the primary result significantly. Similarly, when the PGI-S was analyzed controlling for weight, the treatment difference between the 150-mg and the placebo groups was unaffected. A difference was observed in regard to race, in that 11 Asian participants were randomly assigned to the armodafinil treatment groups (10 in the 50-mg group and 1 in the 150-mg group) and none to the placebo group. However, when the participants were grouped as white vs nonwhite, the distribution on the primary end points was similar among the treatment groups.

Efficacy

Statistically significant differences, indicating the benefit of armodafinil treatment of excessive sleepiness and in the participants' perception of their overall condition, at a dosage of 150 mg/d were attained across days 1 and 2 for both primary measures in the study (mean [SD]: 11.7 [4.17] min vs placebo 4.8 [2.69] min; *P*<.001 for MSLT and 1.6 [0.80] vs 1.9 [1.01]; *P*=.04, for PGI-S; Figure 3). Across days 1 and 2, sleep latency was also significantly increased in the 50 mg/d group; however, the mean PGI-S rating (1.9 [1.07]; *P*=.80; Figure 3) did not differ significantly from that of placebo.

Scores on the MSLT on each of days 1 to 3 demonstrated a significant benefit (ie, mean sleep latencies increased) for both armodafinil dose groups compared with the placebo group (*P*<.001 for both doses vs placebo) (Table 2). Par-

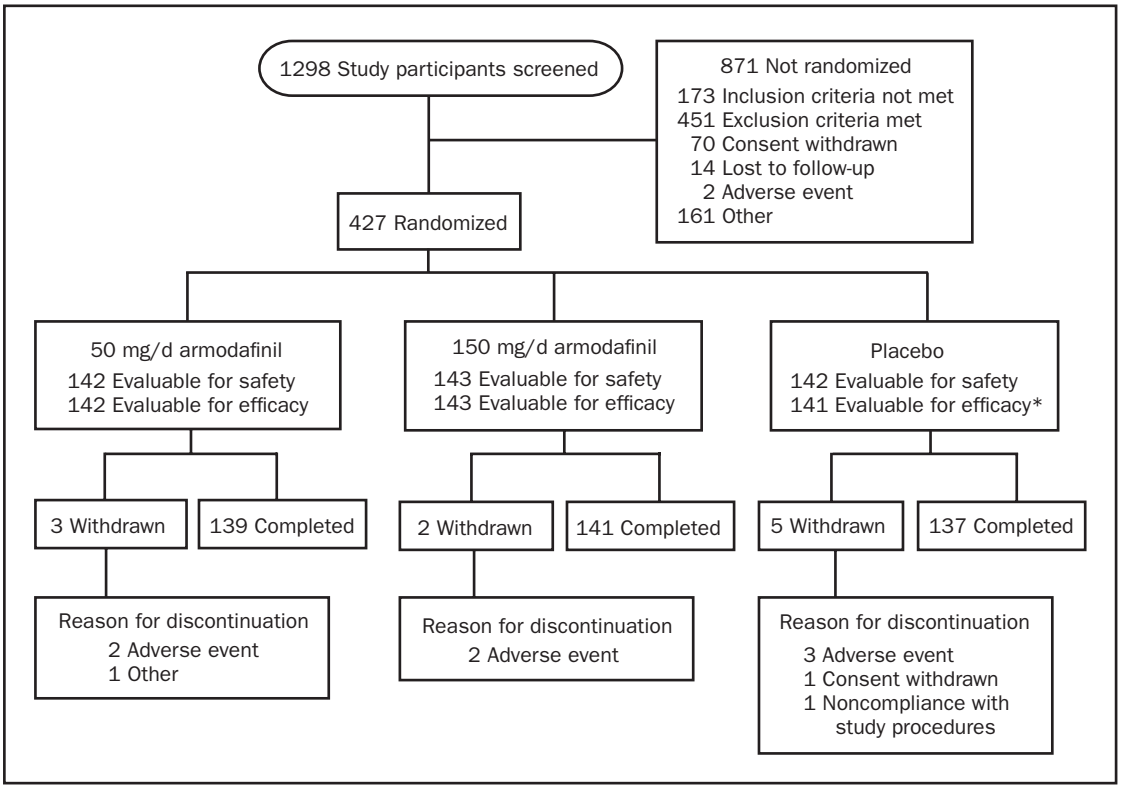

FIGURE 2. Participant disposition.
*One participant did not have any postbaseline efficacy assessments performed.

ticipants' perception of their overall condition in relation to jet lag symptoms (ie, mean PGI-S rating) was significantly better in the group taking 150 mg/d of armodafinil compared with the placebo group on day 1 (P=.005), but significant differences were not observed for days 2 or 3, or between the group taking 50 mg/d and the placebo group (Table 2).

Mean KSS scores, which represent participant-reported measure of sleepiness, decreased, indicating improvement in both the 50-mg and 150-mg groups compared with placebo across days 1 and 2 (P<.001 for both doses vs placebo; Figure 3) and on each of the 3 days individually (P≤.003 for all doses vs placebo; Table 2).

Safety and Tolerability

Headache, nausea, diarrhea, circadian rhythm sleep disorder, and palpitations were the most frequently reported adverse events (Table 3). Most adverse events were mild or moderate; no serious adverse events were reported. Two participants in each of the armodafinil groups and 3 in the placebo group withdrew from the study because of adverse events. Events leading to discontinuation in the armodafinil groups were anxiety (n=1); symptom cluster of nausea, vomiting, and diarrhea (n=1); medical device site reaction (related to electrode placement) (n=1); and ventricular extrasystoles (n=1). In the placebo group, ventricular extrasystoles and medical device site reaction (related to electrode placement) (n=1 each), toxic skin eruption (n=1), and upper abdominal pain (n=1) were causes for study discontinuation.

Mean pulse rate and blood pressure increased from baseline to the final visit in all treatment groups, although these differences were not considered clinically meaningful. Mean changes in heart rate and blood pressure on days 1, 2, and 3 showed a dose-related increase, with changes being generally highest in the group taking 150 mg/d of armodafinil. There were no clinically meaningful changes in mean laboratory values, physical examination findings, anxiety (as indicated by mean scores on the state anxiety subscale of the STAI), or concomitant medication use (data not shown).

For participants in both armodafinil groups, on night 1, differences from the placebo group were seen in most values for mean changes from baseline in total sleep time, latency to persistent sleep, sleep efficiency, and wake after sleep onset (Table 2). Differences on night 2 persisted for participants receiving armodafinil at 150 mg/d compared with those receiving placebo. The observed changes from

TABLE 1. **Baseline Demographics and Disease Characteristics**[a]

	Armodafinil 50 mg/d (n=142)	Armodafinil 150 mg/d (n=143)	Placebo (n=142)	*P* value
Age (y)				
Mean (SD)	36.7 (12.01)	34.6 (10.38)	36.0 (10.06)	.23[b]
Sex, No. (%)				.14[c]
Male	64 (45)	59 (41)	75 (53)	
Female	78 (55)	84 (59)	67 (47)	
Race, No. (%)				.004[d]
White	97 (68)	102 (71)	98 (69)	
Black	34 (24)	38 (27)	41 (29)	
Asian	10 (7)	1 (<1)	0	
Other	1 (<1)	2 (1)	3 (2)	
Weight (kg)				
Mean (SD)	74.2 (15.06)	75.1 (15.43)	79.5 (16.13)	.009[b]
ESS total score				
Mean (SD)	3.8 (2.49)	3.2 (2.30)	3.4 (2.57)	.18[b]
STAIT score				
Mean (SD)	25.8 (5.25)	25.3 (5.12)	25.7 (4.98)	.71[b]
MSLT[e] sleep latency (min)				
Mean (SD)	15.2 (3.82)	15.3 (3.83)	15.0 (4.16)	.74[b]
PGI-S rating[e]				
Mean (SD)	1.0 (0.08)	1.0 (0.14)	1.0 (0.19)	.64[b]
KSS score[e]				
Mean (SD)	3.3 (1.16)	3.1 (1.04)	3.1 (1.21)	.41[b]

[a] ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; MSLT = Multiple Sleep Latency Test; PGI-S = Patient Global Impression of Severity; STAIT = State and Trait Anxiety Inventory–Trait Anxiety.
[b] Comparison across all treatments from an analysis of variance with treatment group as a factor.
[c] Comparison across all treatments from Pearson χ^2 test.
[d] Comparison across all treatments from Fisher exact test.
[e] Includes study participants in efficacy analysis set only.

baseline to night 1 for the armodafinil 150 mg/d group in all 4 parameters were similar to the changes from baseline to night 2 for the placebo group. Mean values for all NPSG measures were within the normal range by night 2 for all 3 groups.[20] Insomnia was reported as an adverse event by 2 participants in the group receiving armodafinil at 50 mg/d, 1 in the group receiving armodafinil at 150 mg/d, and none in the placebo group.

DISCUSSION

The excessive sleepiness associated with jet lag disorder is significant in travelers who cross multiple time zones. After arriving at their destination study centers on day 1, participants who received placebo experienced excessive sleepiness that was well within the range defined as pathological (MSLT score <5 minutes)[12] and similar to that reported in patients with moderate to severe narcolepsy (MSLT score <3 minutes).[21] Compared with the placebo group, the mean sleep latency of participants receiving armodafinil (50 mg/d or 150 mg/d) was significantly longer on day 1; however, in the 50-mg/d group, average sleep latency still was within the range thought to reflect moderate sleepiness (5-10

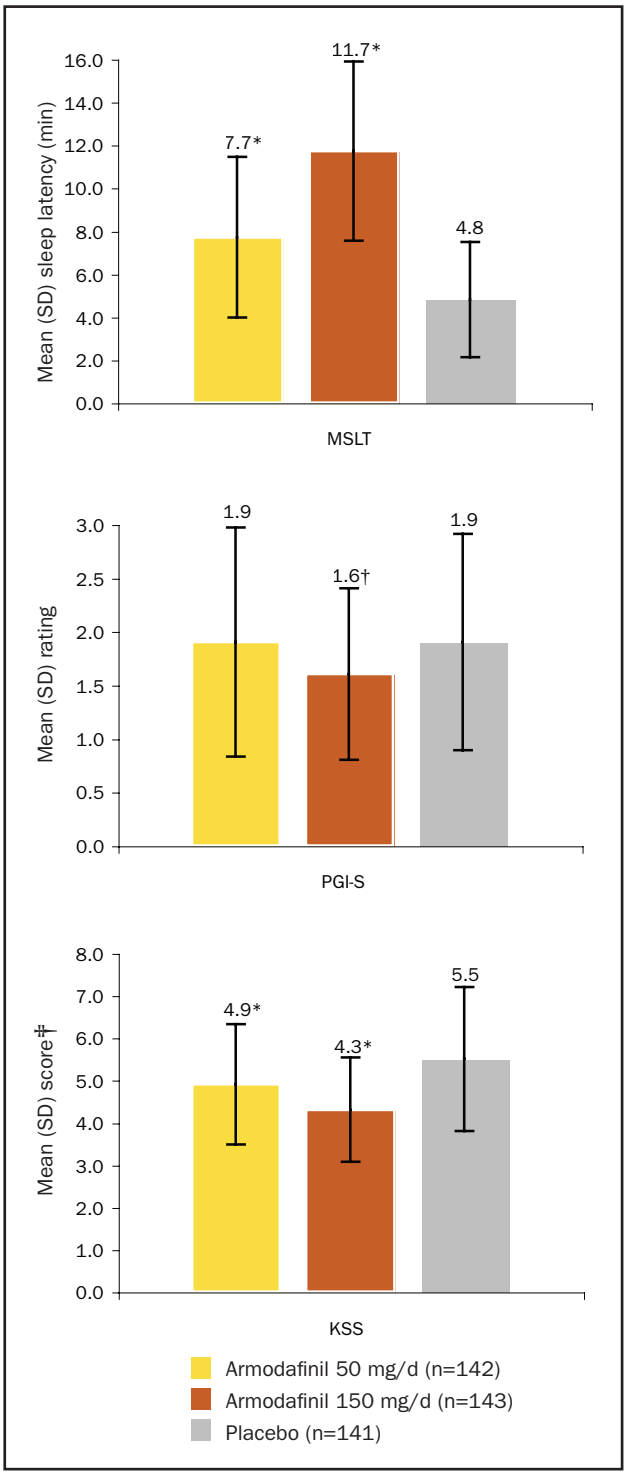

FIGURE 3. Mean (SD) scores on the Multiple Sleep Latency Test (MSLT), Patient Global Impression of Severity (PGI-S), and Karolinska Sleepiness Scale (KSS) across days 1 and 2.
* *P*<.001, analysis of covariance.
† *P*=.04, Cochran-Mantel-Haenszel test.
‡ Average of the 4 KSS assessments performed before the MSLT (daytime assessments).

TABLE 2: **Mean (SD) Scores on the Multiple Sleep Latency Test (MSLT), Patient Global Impression of Severity (PGI-S), Karolinska Sleepiness Scale (KSS), and Nocturnal Polysomnography**

Variable	Armodafinil 50 mg/d (n=142)	*P* value[a]	Armodafinil 150 mg/d (n=143)	*P* value[a]	Placebo (n=141)
		Daytime measures			
MSLT (min)					
Baseline	15.2 (3.82)		15.3 (3.83)		15.0 (4.17)
Day 1	5.6 (3.68)	<.001	9.7 (5.05)	<.001	3.4 (2.52)
Day 2	9.9 (4.76)	<.001	13.8 (4.51)	<.001	6.2 (3.75)
Day 3	12.1 (4.73)	<.001	14.8 (4.80)	<.001	8.2 (4.42)
PGI-S					
Baseline	1.0 (0.08)		1.0 (0.14)		1.0 (0.19)
Day 1	2.2 (1.41)	.79	1.7 (1.10)	.005	2.1 (1.39)
Day 2	1.6 (1.03)	.82	1.5 (0.83)	.58	1.6 (0.95)
Day 3	1.2 (0.58)	.16	1.4 (0.71)	.91	1.4 (0.74)
KSS[b]					
Baseline	3.3 (1.16)		3.1 (1.04)		3.1 (1.21)
Day 1	5.7 (1.74)	.001	4.8 (1.66)	<.001	6.3 (1.95)
Day 2	4.0 (1.42)	<.001	3.7 (1.25)	<.001	4.7 (1.70)
Day 3	3.6 (1.17)	.002	3.6 (1.17)	.003	4.0 (1.53)
		Nocturnal polysomnography			
Variable	Armodafinil 50 mg/d (n=142)	*P* value[a]	Armodafinil 150 mg/d (n=143)	*P* value[a]	Placebo (n=142)
Total sleep time (min)					
Baseline	400.7 (33.23)		408.7 (36.60)		409.4 (33.02)
Night 1	409.7 (63.80)	.01	403.5 (59.77)	<.001	429.9 (39.86)
Night 2	390.4 (67.67)	.19	377.7 (81.17)	.002	404.3 (58.46)
Latency to persistent sleep (min)					
Baseline	27.6 (27.26)		24.6 (22.48)		23.9 (20.14)
Night 1	6.8 (8.79)	.73	11.9 (18.88)	<.001	6.1 (9.39)
Night 2	14.7 (21.88)	.62	23.8 (39.42)	.002	13.1 (19.84)
Sleep efficiency (%)					
Baseline	83.5 (6.92)		85.1 (7.63)		85.3 (6.88)
Night 1	85.4 (13.29)	.01	84.1 (12.45)	<.001	89.6 (8.30)
Night 2	81.3 (14.10)	.19	78.8 (16.84)	.002	84.2 (12.18)
Wake after sleep onset (min)					
Baseline	57.8 (30.50)		51.1 (31.18)		52.1 (29.64)
Night 1	65.5 (61.65)	.007	67.8 (53.59)	<.001	46.5 (38.53)
Night 2	78.0 (67.32)	.20	81.9 (73.88)	.048	66.3 (57.42)

[a] Change from baseline, placebo vs armodafinil, from analysis of covariance for all variables except PGI-S, for which a Cochran-Mantel-Haenszel test was used.

[b] The KSS score was the average of the 4 KSS assessments performed before the daytime assessments with the MSLT.

minutes).[1] On day 1 in the group receiving 150 mg/d, mean sleep latency was nearly within the range of normal scores of healthy volunteers who were not sleepy (>10 minutes).[12] By day 2 in this group, the mean was within the normal range, and on day 3, it had returned to baseline (before air travel). Even by day 3, sleep latency in the placebo group remained below normal and at about half the baseline value. Overall, the change in sleep latency appeared to be 1 day ahead of placebo in the group receiving 50 mg/d and 2 days ahead in the group receiving 150 mg/d, relative to returning to the baseline level. This demonstrates that the adjustment to a new circadian time takes days. These data suggest that the use of a wakefulness-promoting medication such as armodafinil during this readjustment time was efficacious for the participants.

Improvements in excessive sleepiness measured objectively with the MSLT were corroborated by significant improvements in subjective ratings as measured by the KSS. Additionally, treatment with armodafinil at 150 mg/d improved participants' perception of their overall condition relative to jet lag symptoms (PGI-S) on days 1 and 2.

Armodafinil was generally well tolerated. No serious adverse events occurred, and the proportion of armodafinil-treated participants who discontinued the study because of adverse events was low (1% in both groups) and similar to those receiving placebo (2%). On the basis of adverse event reports, nighttime sleep did not appear to be adversely affected in a majority of participants: only 3 reported insomnia (all in the armodafinil-treated groups). Regarding objective measures of sleep, minutes of wakefulness after

TABLE 3. **Adverse Events Occurring in at Least 2% of the Armodafinil Group and at a Higher Rate Than in the Placebo Group**

Adverse event, No. (%)	Armodafinil 50 mg/d (n=142)	*P* value[a]	Armodafinil 150 mg/d (n=143)	*P* value[a]	Placebo (n=142)
Headache	24 (17)	.31	39 (27)	.002	17 (12)
Diarrhea	6 (4)	.75	7 (5)	.54	4 (3)
Nausea	4 (3)	1.0	18 (13)	.008	5 (4)
Fatigue	3 (2)	.25	4 (3)	.12	0
Restlessness	3 (2)	.62	3 (2)	.62	1 (<1)
Blood pressure increased	3 (2)	.62	0	.50	1 (<1)
Back pain	3 (2)	1.0	1 (<1)	.62	2 (1)
Vomiting	3 (2)	.25	3 (2)	.25	0
Circadian rhythm sleep disorder	2 (1)	.50	7 (5)	.01	0
Palpitations	1 (<1)	1.0	7 (5)	.01	0
Anxiety	0	1.0	6 (4)	.12	1 (<1)

[a] Comparison of armodafinil vs placebo using Fisher exact test.

sleep onset increased from baseline in all treatment groups (except for placebo on night 1), as would be expected after eastbound travel. Although changes from baseline in most NPSG values differed significantly between the placebo and armodafinil groups (particularly in the group receiving 150 mg/d), they remained within the normal range after treatment.[20] Comparison of NPSG means across nights suggests that participants in the group receiving 150 mg/d were 1 day ahead of participants in the placebo group with regard to the effects of jet lag on sleep. Interestingly, although most NPSG values had returned close to baseline levels by night 2 in the placebo group, daytime excessive sleepiness, as measured by MSLT, remained well below baseline. These findings suggest that nighttime sleep might not fully account for the daytime symptoms of jet lag disorder. Similar findings have been seen in connection with other circadian rhythm disorders.[22]

To our knowledge, this is the first clinical study to evaluate a wakefulness-promoting medication in a population with a history of jet lag symptoms. Other medications have been studied to treat the excessive sleepiness or insomnia symptoms associated with jet lag disorder, such as melatonin, tasimelteon, and slow-release caffeine.[23-27] Both melatonin and tasimelteon have been studied as treatment for transient insomnia, not for daytime excessive sleepiness.[24,26,27] Melatonin has been studied in healthy individuals with jet lag disorder with and without sleep deprivation (N=27 for both studies).[26,27] Tasimelteon was studied in healthy individuals (N=411) in a model of shifted sleep and wake times, but not in jet lag disorder per se.[24] Slow-release caffeine has been evaluated for the treatment of excessive sleepiness associated with jet lag disorder in individuals without a history of jet lag disorder (N=27 for both studies).[23,26] Efficacy measures in these studies were continuous wrist actigraphy or physical performance.[23,26] Because the study designs in the slow-release caffeine studies were different from the current study, comparison of the results is not possible. The current study used both objective and subjective measures of excessive sleepiness (MSLT and KSS, respectively), in addition to a measure of participants' perception of their overall condition (PGI-S), to determine participants' wakefulness for the first 3 days after arrival.

The *International Classification of Sleep Disorders*, Second Edition, defines jet lag as a condition of excessive sleepiness, which is appropriately measured by the MSLT. For this reason, the Maintenance of Wakefulness Test[28] was not assessed in the current study, even though it is a reasonable alternative to the MSLT. Moreover, a recent study of patients with SWD,[10] another circadian rhythm disorder, used the MSLT. Therefore, using MSLT in the current study facilitated interpretation of results in the context of studies of other circadian rhythm disorders. Finally, the MSLT may be more sensitive to this type of analysis, and the normalized data are well characterized.

The current study evaluated individuals who previously had symptoms of jet lag disorder and not a general sample of individuals undergoing jet travel. Adults older than 65 years, smokers, and individuals who consumed more than 300 mg/d of caffeine were excluded. In addition, participants were not allowed to consume alcohol during the study. All participants traveled eastward from similar cities of origination in the same time zone in the eastern United States to similar destinations in France, across the same number of time zones, via private, chartered aircraft (in similar conditions involving actual flights in coach class), and with similar departure and arrival times.

Compared with laboratory-simulated travel, the actual travel undergone in this study provided conditions (eg, air pressure, humidity, restricted movement) that are known to contribute to the development of jet lag disorder. Private, chartered aircraft were used both for reasons of logistics (eg, available flight schedules) and to control potentially confounding variables (eg, seat back position). The possibility that private transportation introduced some bias cannot be ruled out; however, conditions were adjusted to mimic commercial coach-class accommodations. Indeed, if the private, chartered jet was more comfortable than an actual commercial cabin, it is possible that the participants arrived in France somewhat better rested, which could have reduced the potential for improvement with armodafinil treatment.[14,29]

The participants' environment was also controlled throughout the treatment period; they were not permitted to go outside or to leave the study site in order to control light exposure and variability in meal and sleep schedules.

These factors, and the large sample size, would tend to reduce confounding effects and improve the reliability of the data collected. This study may be more generalizable than previous studies because participants were not limited to any specific group, such as airline crew,[30] air force personnel,[23] physicians,[14] or athletes and support staff,[31] but was composed of a heterogeneous group of participants.

CONCLUSION

Excessive sleepiness associated with jet lag disorder due to rapid eastbound travel is common among those who travel. A treatment that improves wakefulness from the time of arrival at the destination could have a substantial impact on the health of those who have jet lag. On the basis of the results of this study, armodafinil at 150 mg/d increases wakefulness after eastbound travel through 6 time zones in those with a history of symptoms of jet lag and is generally well tolerated.

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