NEW RESEARCH

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SCIENTIFIC INVESTIGATIONS

Effects of Armodafinil on Simulated Driving and Self-Report Measures in Obstructive Sleep Apnea Patients prior to Treatment with Continuous Positive Airway Pressure

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Study Objectives: Obstructive sleep apnea (OSA) has been associated with an increased risk of motor vehicle crashes. This driving risk can be reduced (≥ 50%) by treatment with continuous positive airway pressure (CPAP). However residual excessive daytime sleepiness (EDS) can persist for some patients who regularly use CPAP. The current study was designed to assess the effect of armodafinil on simulated driving performance and subsequent CPAP treatment compliance in newly diagnosed OSA patients with EDS during a 2-week "waiting period" prior to initiation of CPAP.

Methods: Sixty-nine newly diagnosed OSA patients, awaiting CPAP therapy, were randomized (1:1) to placebo or armodafinil (150 mg/day) treatment. Simulated driving tests and self-report measures were completed at baseline, after 2 weeks of drug treatment, and following 6 weeks of CPAP treatment. CPAP compliance was evaluated at the end of 6 weeks of CPAP.

Results: Compared to placebo, armodafinil improved simulated driving safety performance in OSA patients awaiting CPAP therapy ($p = 0.03$). Improvement was seen in lane position deviation ($p = 0.002$) and number of lane excursions ($p = 0.02$). Improvement was also observed on measures of sleepiness using the Epworth Sleepiness Scale (ESS) and sleep related quality of life. Following 6 weeks of CPAP, there was also significant improvement observed on multiple measures of simulated driving performance. CPAP compliance did not differ between armodafinil-treated and placebo-treated patients ($p = 0.80$).

Conclusions: Armodafinil was found to improve simulated driving performance in OSA patients with EDS prior to initiation of CPAP. Treatment with armodafinil showed no effect on subsequent CPAP compliance.

Keywords: CPAP, OSA, driving simulation, ESS, armodafinil

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Obstructive sleep apnea syndrome (OSA) is the most common medical disorder causing excessive daytime sleepiness (EDS).[1] Untreated individuals with OSA have an increased risk of motor vehicle crashes. This increased risk of crashes was first recognized in the 1980s and has since been reported by multiple investigators.[2,3] In this regard, a meta-analysis has shown a 3.71-fold increase in the relative risk for motor vehicle crashes for individuals with untreated OSA.[4]

Sleepiness related crashes generally result from falling asleep while driving or from impairment of the cognitive, perceptual, or motor abilities essential to the complex task of driving. The impact of sleepiness on driving performance has been demonstrated by driving simulator studies investigating the effects of sleep deprivation and CNS sedatives.[5] In general, these studies have demonstrated that drivers with OSA perform worse than matched controls on driving simulators.[6] Using the AusEd driving simulator, investigators found that OSA patients performed worse than controls on 4 of 5 outcomes: lane position variability, crash frequency, and performance on measures of divided attention.[7] Researchers using the STI driving simulator found poor simulated driving performance in OSA patients was related to EEG evidence of attention lapses.[8] Lane position variability was the most sensitive measure for assessing and quantifying impairment. In a study investigating simulated versus real driving that evaluated the effects of fatigue and sleepiness, the investigators concluded that for some variables (e.g., fatigue and lane crossings) the two methodologies were comparable.[9]

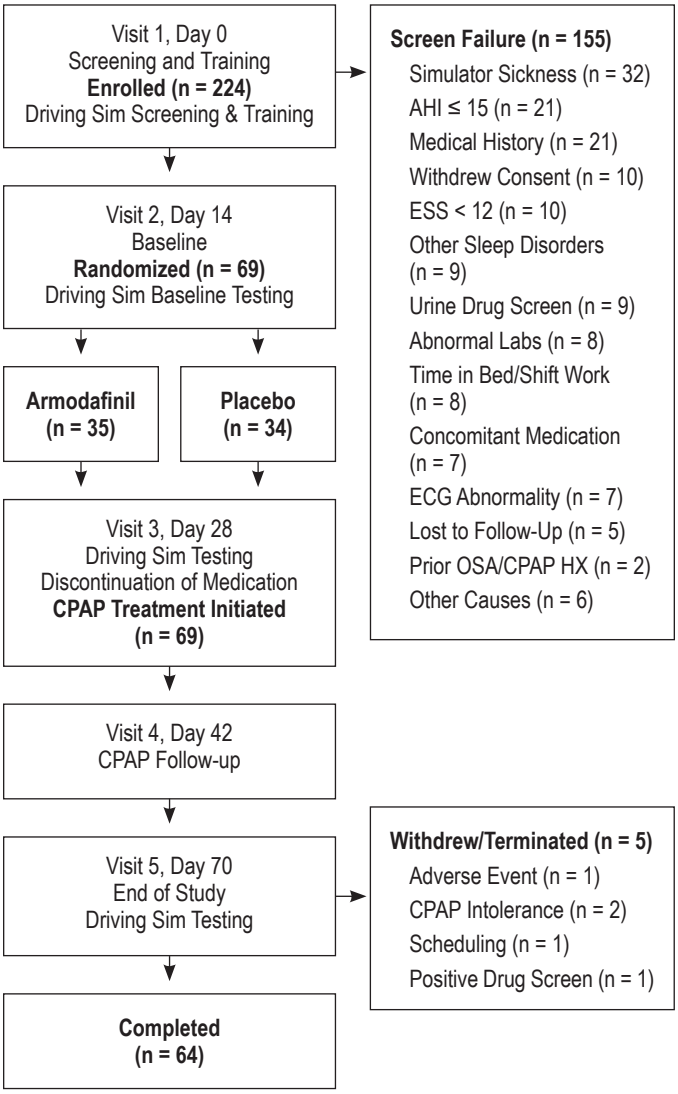
It is now well recognized that the risk of motor vehicle crashes for OSA patients is significantly decreased following treatment with nasal continuous positive airway pressure (CPAP).[10] It has been estimated that there is at least a 50% reduction in crash risk.[2,11] Improved driving safety is also reflected in bet-

BRIEF SUMMARY

Current Knowledge/Study Rationale: This study investigated a strategy for improving driving safety in OSA patients during the interval between the first contact of the clinician with the patient and the initiation of CPAP. The study was designed to assess the effect of armodafinil on simulated driving performance prior to the initiation of CPAP treatment and to determine the impact of this treatment on subsequent CPAP compliance.

Study Impact: Results demonstrate that 2 weeks of treatment with armodafinil improved simulated driving performance prior to the initiation of CPAP therapy and had no impact on subsequent CPAP compliance. The study also provided evidence of the marked improvement in driving performance following 6 weeks of treatment with CPAP (after discontinuation of the drug treatment phase of the study).

Figure 1—Study Design and Subject Disposition



ter driving performance on simulated driving tests following CPAP treatment.[12-15] However, some OSA patients, in spite of receiving therapeutic CPAP, continue to experience EDS. For these individuals, modafinil has been shown to be an effective treatment for residual EDS.[16,17]

Investigators have also examined the effect of modafinil on the simulated driving performance of OSA patients. It has been reported that speed deviation was reduced by 14% following treatment with modafinil (200 mg) in partially sleep-deprived OSA patients.[18] Another study investigated the effect of modafinil (300 mg) on sleep-restricted normal adults.[19] For these individuals, modafinil was found to reduce lane position deviation, off- road incidents, and reaction time on a divided attention task. More recently, investigators have evaluated the effects of modafinil (200 mg) on the treatment of residual EDS in OSA patients following acute withdrawal from CPAP. In the preliminary study, improvements in driving performance were reported following treatment with modafinil; however, these findings did not reach statistical significance when compared to placebo treatment.[20] When the same research group conducted a larger crossover study in the same patient population following acutely interrupted CPAP therapy, they were able to show that modafinil indeed prevented the decline in simulated driving performance, neurocognitive performance, and subjective sleepiness compared to placebo treatment.[21]

The current study was designed to assess the effects of 150 mg of armodafinil (the R-enantiomer of modafinil) on simulated driving performance in newly diagnosed OSA patients with excessive daytime sleepiness (ESS ≥ 12) during a 2-week period prior to initiating CPAP therapy. We chose an ESS ≥ 12 to obtain a study population with more clinically significant illness that might put them at risk for motor vehicle accidents. Unlike those who participated in the studies conducted by Williams et al.,[20,21] our patients were CPAP naïve and studied for a different purpose. In clinical practice, patients newly diagnosed with OSA often must wait for weeks before initiating CPAP therapy. Delays can be the result of scheduling, waiting for insurance approval, or other causes. The obvious concern is that these patients are at higher risk for driving related accidents.[2,3] In this regard, practitioners have asked whether it would be advisable to start a newly diagnosed OSA patient on a stimulant medication approved for treatment of residual EDS (e.g., armodafinil) while they are awaiting initiation of CPAP treatment.[22] However, an additional concern is that prior use of stimulant treatment might negatively impact subsequent CPAP compliance. Therefore, in addition to determining the effect of armodafinil on simulated driving performance, the present study was designed to assess whether treatment with armodafinil, prior to initiation of CPAP, would affect subsequent CPAP compliance. Finally, the present study was also designed to assess simulated driving performance following 6 weeks of CPAP therapy.

METHODS

Patients

The study was advertised in local newspapers and was described in a local television news story. A total of 69 previously untreated OSA patients were enrolled in the study. Male and female subjects eligible for participation were 21-64 years of age, with a diagnosis of OSA confirmed by nocturnal polysomnogram (PSG) (apnea-hypopnea index [AHI] > 15), and with excessive daytime sleepiness (ESS ≥ 12). All subjects were newly diagnosed and awaiting CPAP therapy. Subjects were required to have a valid driver's license and to have been actively engaged in driving for the past 3 years. Exclusion criteria included any unstable medical condition, circadian rhythm disorder, restless leg syndrome, narcolepsy, other significant sleep disorders, irregular sleep schedules, use of sedating antihistamines, selective serotonin reuptake inhibitors, muscle relaxants or hypnotics, consumption of more than 600 mg of caffeine per day, alcohol abuse, simulator sickness, and medical conditions or use of medications contraindicated for use of armodafinil.[23] Subjects were admitted and randomized without regard for their driving history.

Study Design

The study design is shown in **Figure 1**. This was a double-blind, placebo-controlled, randomized, single-site study. The study was reviewed and approved by an institutional review board. All sub-

jects gave written informed consent. This study was conducted in compliance with Good Clinical Practice, according to the International Conference on Harmonization Tripartite Guideline.

There were two phases to this study. In the first 2-week phase, subjects with OSA and EDS were randomized (1:1) to treatment with armodafinil (150 mg) or placebo. In the second phase, all subjects completing the first phase were treated for 6 weeks with CPAP.

During the 2-week screening period, the diagnosis of OSA was confirmed by nocturnal polysomnogram (AHI > 5) and subjects had to demonstrate at least moderate EDS (ESS ≥ 12). During the screening period subjects were given a brief introduction to the driving simulator (approximately 10 min). Upon completion of this screening drive, subjects were orally administered the Simulator Sickness Questionnaire (SSQ).[24] Subjects with scores > 20 on the SSQ Nausea, Disorientation, Oculomotor, or Total scale were excluded. Subjects who passed the screening were shown an instructional orientation slideshow. This was followed by a 20-min training scenario, which provided additional standardized instructions for the scenarios used in the study. This was followed by an additional 20-min practice driving session.

Eligible subjects returned for their baseline visit (Visit 2). During the baseline visit, all study measures were administered. The driving simulation test was administered at approximately 10:00 and consisted of a 20-min vigilance driving scenario (VIG), a 20-min urban scenario (URB), and a 40-min country vigilance scenario (CV). Prior to beginning the driving simulation test, subjects completed a 10-min warm-up drive to reacquaint them with the driving controls.

Study medication was dispensed following completion of baseline testing. Subjects were randomly assigned on a 1:1 basis to receive armodafinil or matching placebo once daily in the morning (i.e., before 08:00 and 30 min prior to breakfast). Subjects were titrated to a fixed dose of 150 mg of armodafinil: 50 mg of armodafinil for the first 2 days of dosing, 100 mg of armodafinil for the second 2 days of dosing, and 150 mg of armodafinil for the remainder of the dosing period (10 to 24 days). A computer-generated randomization schedule was prepared using SAS Version 9.1.3 PROC PLAN.

Following the 14-day dosing period, subjects returned for Visit 3 procedures. A final dose of the study medication was dispensed at the clinic. Armodafinil dosing compliance was monitored by "pill count" on Visit 3 of the study (see **Figure 1**). Self-report measures (ESS, Functional Outcomes of Sleep Questionnaire [FOSQ], and Medical Outcomes Study 6-item Cognitive Functioning Scale [MOS-CF6]) were completed prior to beginning the driving tasks. In addition, subjects completed a 10-min warm-up drive. At approximately 10:00am, the subjects drove the 3 scenarios. Subjects returned on the evening of the same day or on the following day for a nocturnal polysomnogram with CPAP titration and were given instructions on proper use of CPAP. Two weeks following initiation of CPAP, subjects returned to the clinic for a follow-up clinic appointment (Visit 4), which addressed compliance and further instruction on proper use of CPAP as needed.

The final testing visit (Visit 5) was conducted after 4 additional weeks (6 weeks total) of CPAP. Subjects completed the same testing procedures that were completed at the baseline visit and following discontinuation of the study medication.

After completion of driving simulator testing, subjects were administered a battery of neuropsychological tests including measures of vigilance, psychomotor functioning, memory, and executive functions, including the computer-based cognitive test (CogScreen) used in the Apnea Positive Pressure Long-term Efficacy Study (APPLES).[25] Results of the effects of armodafinil and CPAP on these cognitive measures will be reported separately.

Adverse events were monitored throughout the study, with severity (mild, moderate, or severe) and relationship to study medication rated by the investigator. Concomitant medications were recorded. Physical examinations (screening and end of study or final visit), vital sign measurements, and standard hematologic laboratory tests and chemistries were performed.

Cognitive Research Corporation Driving Simulator (CRCDS)

The CRCDS is a PC-based driving simulator which incorporates the Systems Technologies Inc. STISIM (Model 100W) software, three 21-inch LCD monitors to provide a wide field of view (105°), and a full-size steering wheel and pedals (ECCI Trackstar 6000GT). The CRCDS complies with current regulatory guidelines (U.S. FDA 21 CFR Part 11), which specify data integrity and system validation requirements. Two equivalent CRCDS simulators were used to conduct the study. The STISIM software used in the CRCDS has previously been used in studies of stimulant effects on driving performance[26] and to study the effects of obstructive sleep apnea.[8]

The specific driving scenarios chosen for the study were designed to be sensitive to the known driving difficulties of untreated patients with OSA and are comparable to those used in prior studies of OSA patients. The subjects began by driving the VIG scenario, a 20-min scenario consisting of a 2-lane, rural highway with rolling hills, occasional oncoming traffic, a single crash likely event, and a secondary (divided-attention) vigilance task. For this task, subjects were instructed to rapidly press a button on the steering wheel when an infrequently presented target stimulus appeared in boxes at the upper left and right sides of the screen. The second scenario was the 20-min URB scenario. This scenario has considerably more traffic, pedestrians, and 3 crash likely events. The final drive was the CV scenario, a 40-min drive consisting of a 2-lane, rural highway with curves and hills but no sharp turns or stops, minimal oncoming traffic, no crash likely events, and a set speed limit (55 miles per hour). Driving data for the CV scenario was grouped into five 8-min time blocks (Epochs 1-5) to evaluate the effect of time-on-task.[27]

Self-Report Measures

The self-report measures selected for the study are among the most commonly used measures to assess outcome in sleep research, and included the Epworth Sleepiness Scale (ESS),[28] the Functional Outcomes of Sleep Questionnaire (FOSQ),[29] and the Medical Outcomes Study 6-item Cognitive Functioning Scale (MOS-CF6).[30]

CPAP Compliance

The Smart Card installed in the CPAP machine (Resmed Elite) was used to provide a measure of CPAP treatment com-

pliance (i.e., mean hours at pressure). Compliance data were obtained for the final 2 weeks of the 6-week period of CPAP treatment.

Statistical Analysis

The primary and secondary efficacy endpoints were conducted on the modified intent-to-treat (mITT) population, defined as all randomized subjects who missed no more than 3 doses of armodafinil and who completed all assessments at end of treatment with armodafinil or placebo (Visit 3). All analyses were prespecified in a Statistical Analysis Plan. Baseline characteristics were assessed for the two medication treatment groups.

The primary efficacy analysis was conducted on the Driving Safety Score (DSS)[26] at Visit 3 and compared to baseline (Visit 2) using an analysis of covariance (ANCOVA) with treatment, center (i.e., research site), and treatment × center as fixed effects, and baseline score as the covariate. The DSS is expressed as the mean z-score derived from predefined safety related critical elements (i.e. Total Tickets URB, Total Collisions CV, percent distance exceeded speed tolerance [ES Distance CV], number of times out of driving lane [Out of Lane CV], percent of time exceeded speed tolerance [ES Time CV], number of times over-cornering [Excessive Ay CV], and lane position deviation [Lane Deviation CV; also referred to as standard deviation of lateral position SDLP]).

Recent research on OSA and driving suggested the need to also examine a modified Driving Safety Score (mDSS),[26] which was specified *a priori*. The mDSS is based upon performance on the CV scenario and consists of the following elements; total collisions, time to first collision, number of times out of driving lane (Out of Lane), and lane position deviation during the final 8 min of the scenario (Lane Deviation E5).

The driving related secondary efficacy variables included the components of the DSS and mDSS, lane position deviation by epoch, average speed by epoch and overall, speed deviation by epoch and overall, total crashes by epoch and overall, and out of lane score by epoch and overall. For the URB scenario, additional secondary endpoints included lane position deviation, speed deviation for the construction zone, total collisions outside the construction zone, and total crashes in the construction zone. For the VIG scenario, additional secondary endpoints included out of lane score, total collisions, divided attention correct responses, divided attention omission errors, divided attention commission errors, divided attention reaction time, and total tickets. Driving simulator scores were obtained for each of the 3 driving scenarios at Visit 2 (baseline), following 2 weeks of armodafinil or placebo (Visit 3), and following 6 weeks of CPAP (Visit 5).

Results for the ESS and other self-report measures were analyzed using appropriate nonparametric methods. For categorical secondary efficacy variables, a Cochran-Mantel-Haenszel (CMH) Type 2 (ANOVA mean score) statistic using center as stratum was used for treatment comparison of ordinal variables, while a CMH Type I statistic was used for treatment comparison of nominal variables.

Treatment groups were compared on the measure of CPAP compliance (mean hours at pressure during weeks 5 and 6 of CPAP treatment). Treatment groups were also compared with respect to dropout rates to determine if the use of a pharmacologic agent as a "bridging" therapy affects the rate at which patients present for PSG/titration.

RESULTS

Clinical Population

Two hundred twenty-four (224) participants were screened, and 69 were randomized. The most common cause for screen failure was simulator sickness (n = 32; 14.3% of the subjects who were screened), followed by failure to meet the PSG criteria (i.e., AHI ≤ 15; n = 21; 9.4%), failure to meet the medical history criteria (n = 21, 9.4%), low ESS score (n = 10; 4.5%), withdrawal of consent (n = 10; 4.5%), and positive urine drug screen (n = 9; 4.0%). One subject was excluded from the efficacy analysis (the mITT population) due to unwillingness to perform the driving simulation test at the end of Period 1. The same subject withdrew from the study at the beginning of Period 2 due to a work schedule conflict. Four other subjects discontinued during Period 2; one withdrew due to a treatment unrelated adverse event (cataract worsening); one for a positive urine drug screen, and 2 subjects could not tolerate CPAP. In the mITT population, 34 subjects were randomized to each of the 2 treatments. Treatment related adverse events are reported in **Table 1**.

The subject demographics are summarized in **Table 2**. Sixty-nine (69) subjects were randomized to armodafinil or matching placebo treatment for 14 days. The mean age of participants was 46.1 ± 9.8 years (range 23 to 64). The majority of subjects were males (85.5%). The distribution by race shows that 71.0% were non-Hispanic Caucasian, 18.8% African American, 8.7% Hispanic, and 1.4% Asian. College education (13 or more years of school) was reported by 72.4% of participants. Of the remaining subjects, 21.7% had completed high school and 5.8% had not graduated from high school. The mean AHI at baseline was 43.12 ± 26.1 (range 15.07-114.6), and the mean body mass index (BMI) was 37.0 ± 7.5. The mean ESS score at baseline was 16.8 ± 3.0 (range 12 to 24). There were no significant differences between treatment groups on any of these variables.

Simulated Driving Performance

Effect of Armodafinil

There was significant improvement in the DSS (p = 0.03) for subjects who received armodafinil compared to those treated with placebo (see **Table 3**). For the DSS, a lower value indicates safer driving. Subjects who received armodafinil had a significantly lower DSS following treatment. In contrast, for subjects who were treated with placebo, the DSS increased from Baseline to Visit 3.

Of the 7 variables (see **Table 3**) that comprise the DSS, a significant difference between armodafinil and placebo was found for Out of Lane CV (p = 0.02) and Lane Deviation CV (p = 0.002). Except for the 2 speeding variables (ES Time CV and ES Distance CV), which showed no response to treatment, the 3 remaining DSS variables; Excessive Ay CV (cornering speed), Total Tickets URB, and Total Crashes CV demonstrate numerically better performance for the armodafinil group than the placebo group.

Table 1—Treatment-related, treatment-emergent adverse events by system organ class (mITT)

	Placebo (n = 35)	Armodafinil (n = 34)
Cardiac Disorders	1 (2.9%)	2 (5.9%)
Palpitations	1 (2.9%)	2 (5.9%)
Gastrointestinal Disorders	1 (2.9%)	4 (11.8%)
Abdominal Pain	0 (0.0%)	2 (5.9%)
Diarrhea	1 (2.9%)	0 (0.0%)
Dry Mouth	0 (0.0%)	1 (2.9%)
Nausea	0 (0.0%)	1 (2.9%)
Tongue Biting	0 (0.0%)	1 (2.9%)
General Disorders and Administration Site Conditions	1 (2.9%)	0 (0.0%)
Feeling Jittery	1 (2.9%)	0 (0.0%)
Nervous System Disorders	2 (5.7%)	4 (11.8%)
Dizziness	0 (0.0%)	1 (2.9%)
Headache	2 (5.7%)	2 (5.9%)
Hypoesthesia	0 (0.0%)	1 (2.9%)
Psychiatric Disorders	2 (5.7%)	6 (17.6%)
Abnormal Dreams	0 (0.0%)	1 (2.9%)
Affect Labiality	1 (2.9%)	0 (0.0%)
Anxiety	0 (0.0%)	2 (5.9%)
Depressed Mood	0 (0.0%)	1 (2.9%)
Insomnia	0 (0.0%)	2 (5.9%)
Irritability	0 (0.0%)	1 (2.9%)
Mood Altered	1 (2.9%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	0 (0.0%)	1 (2.9%)
Rash	0 (0.0%)	1 (2.9%)
Vascular Disorders	0 (0.0%)	1 (2.9%)
Hypertension	0 (0.0%)	1 (2.9%)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. Patients with more than one occurrence in a category are only counted once.

Table 2—Demography of the safety population

Characteristic	Placebo (N = 35)	Armodafinil (N = 34)	Overall (N = 69)
Age (y)			
N	35	34	69
Mean	46.0	46.2	46.1
SD	8.5	11.2	9.8
Gender			
Male	29 (82.9%)	30 (88.2%)	59 (85.5%)
Female	6 (17.1%)	4 (11.8%)	10 (14.5%)
Race			
Caucasian	25 (71.4%)	24 (70.6%)	49 (71.0%)
Black	8 (22.9%)	5 (14.7%)	13 (18.8%)
Hispanic	1 (2.9%)	5 (14.7%)	6 (8.7%)
Asian	1 (2.9%)	0 (0.0%)	1 (1.4%)
Weight (lb)			
Mean	249.7	255.9	252.8
SD	55.8	57.3	56.2
Height (in)			
Mean	69.4	69.0	69.2
SD	3.8	3.2	3.5
BMI			
Mean	36.3	37.8	37.0
SD	6.8	8.1	7.5
Education (y)			
< 12	3 (8.6%)	1 (2.9%)	4 (5.8%)
12	7 (20.0%)	8 (23.5%)	15 (21.7%)
13-15	10 (28.6%)	14 (41.2%)	24 (34.8%)
16	8 (22.9%)	9 (26.5%)	17 (24.6%)
> 16	7 (20.0%)	2 (5.9%)	9 (13.0%)

SD, standard deviation; BMI, body mass index.

Additional driving variables demonstrating a significant difference of $p \leq 0.10$ between armodafinil and placebo are found in **Table 4**. Of those comparisons, only Speed Deviation CV ($p = 0.005$) and Total Tickets V ($p = 0.04$) were found to be statistically significant ($p \leq 0.05$). A trend towards significance was found for Time to First Crash CV ($p = 0.09$) and the Divided Attention Reaction Time VIG ($p = 0.08$) measure.

Analysis of time-on-task variables for the lengthy CV shows treatment group differences or trends favoring armodafinil for the second 8-min epoch (Lane Deviation E2, $p = 0.001$; Average Speed E2, $p = 0.08$; Speed Deviation E2, $p = 0.004$; Total Crashes E2, $p = 0.06$; and Out of Lane E2, $p = 0.06$). For the first 8-min epoch there was significantly better performance on the measure of Lane Deviation E1 ($p = 0.006$). In addition, for the measure of Speed Deviation, there was significantly better performance for the fourth 8-min epoch (Speed Deviation E4, $p = 0.017$).

Effect of CPAP

Evaluation of the impact of CPAP was complicated by the unanticipated brief interval between screening and baseline (i.e., < 24 h for 23 of 69 subjects). Experience in our laboratory has shown that the time between driving sessions significantly impacts simulated driving performance (i.e., very short intervals result in inflated retest scores). As a result of the unequal time interval between Visit 1 and Visit 2 (< 24 h), compared to the time between Visit 2 and Visit 3 (generally 2 weeks), the driving simulator results from the Baseline session (Visit 2) were not considered to be optimal for evaluating the effects of CPAP. Based on the interval between visits and the lack of a confounding treatment, assessment of the effect of CPAP on simulated driving performance was based on a comparison of the driving results from Visit 3 (end of drug treatment) and Visit 5 (after 4 weeks of CPAP treatment) for those subjects who were randomized to placebo.

The results for CPAP treatment on driving simulator performance are summarized in **Table 5**. The DSS showed a trend for improved performance with CPAP treatment ($p = 0.07$). Significant improvement was seen for Lane Deviation CV ($p = 0.01$). Only 1 of the DSS components, Total Tickets URB, failed to show a numerical benefit of CPAP treatment. All other DSS components showed a trend for improved performance ($p = 0.06$ to $p = 0.15$) with CPAP treatment. Many other driving simulator parameters showed significant improvement with CPAP, including; Time to First Crash CV ($p = 0.045$), Speed Deviation CV ($p = 0.02$), Crashes in the Construction Zone URB ($p = 0.03$),

Table 3—DSS driving variables: change from Baseline to Visit 3 (mITT)

Driving Variable	Placebo (n = 34)	Armodafinil (n = 34)	p-value
DSS	0.42 (1.03)	0.07 (0.49)	0.03*
DSS Components			
Lane Deviation CV	0.21 (0.37)	-0.09 (0.42)	0.002
Out of Lane CV	9.6 (18.3)	-0.2 (20.3)	0.02
Excessive AY CV	26.4 (73.5)	4.8 (36.7)	0.13
ES Distance CV	0.01 (0.02)	0.00 (0.01)	0.25
Total Crashes CV	0.9 (3.0)	0.6 (4.5)	0.31
Total Tickets URB	0.5 (1.3)	0.2 (1.1)	0.43
ES Time CV	0.00 (0.02)	0.00 (0.01)	0.58

CV, country vigilance scenario, URB, urban scenario, ES, exceeded speed. *p ≤ 0.05.

Table 4—Additional driving variables (p-values < 0.10): change from baseline to Visit 3 (mITT)

Driving Variable	Placebo (n = 34)	Armodafinil (n = 34)	p-value
Lane Deviation CV E1	0.20 (0.42)	-0.05 (0.27)	0.006*
Lane Deviation CV E2	0.24 (0.51)	-0.14 (0.44)	0.001*
Speed Deviation CV	0.81 (1.99)	-0.44 (1.79)	0.005*
Speed Deviation CV E2	1.26 (3.34)	-0.79 (2.23)	0.004*
Speed Deviation CV E4	1.36 (4.03)	-0.89 (3.06)	0.017*
Time to First Crash CV	-177 (670)	52.9 (656)	0.0923*
Total Tickets VIG	0.47 (1.48)	-0.15 (1.13)	0.0358*
Average Speed CV E2	-0.69 (2.38)	0.15 (2.22)	0.0784
Total Crashes CV E2	0.2 (0.8)	0.0 (0.4)	0.0593
Out of Lane CV E2	2.2 (4.7)	0.0 (4.7)	0.0602
Divided Attention Reaction Time VIG	0.14 (0.25)	0.01 (0.30)	0.0792

For country vigilance scenario: E1 = 0-7:59 min, E2 = 8-15:59 min, E3 = 16-23:59 min, E4 = 24-31:59 min, E5 = 32-40 min. CV, country vigilance scenario, VIG, vigilance scenario. *p ≤ 0.05.

Table 5—Driving variables: paired comparisons of CPAP effect, Visit 3 (pre-CPAP treatment) vs. Visit 5 (post-CPAP treatment)

Driving Variable	T-value	df	p-value[1]
Driving Safety Score	-1.90	32	0.0660
Modified Driving Safety Score	-2.16	32	0.0381*
Lane Position Deviation CV	-2.57	32	0.0149*
E1	-2.21	32	0.0342*
E2	-2.57	32	0.0151*
E3	-1.80	32	0.0808
E5	-1.88	32	0.0687
Average Speed CV E2	1.63	32	0.1125
Speed Deviation CV E2	-2.42	32	0.0212*
Speed Deviation CV E5	-1.32	32	0.1972
Total Crashes CV	-1.49	32	0.1453
E1	-1.44	32	0.1605
E2	-1.60	32	0.1186
Time to First Crash CV	2.09	32	0.0447*
Total Crashes VIG	-1.98	32	0.0564
Total Crashes CZ URB	-2.21	32	0.0342*
Out of Lane CV	-1.97	32	0.0579
E1	-1.33	32	0.1930
E2	-2.43	32	0.0210*
E3	-1.43	32	0.1622
E4	-1.82	32	0.0778
E5	-1.56	32	0.1295
Out of Lane VIG	-2.24	32	0.0319*
Divided Attn Correct VIG	1.71	32	0.0974
Divided Attn Omissions VIG	-1.71	32	0.0974
Divided Attn Reaction Time VIG	-2.40	32	0.0222*
Total Tickets URB	-0.25	32	0.8007
Total Tickets VIG	-2.97	32	0.0056*
Average Speed CV	1.38	32	0.1765
Excessive Ay CV	-1.88	32	0.0689
ES Distance CV	-1.59	32	0.1214
ES Time CV	-1.59	32	0.1214
Speed Deviation CV	-2.26	32	0.0307*

[1]Paired T-test for Visit 5 versus Visit 3. For country vigilance scenario: E1 = 0-7:59 min, E2 = 8-15:59 min, E3 = 16-23:59 min, E4 = 24-31:59 min, E5 = 32-40 min. CV, country vigilance scenario; URB, urban scenario; VIG, vigilance scenario; CZ, construction zone. *p ≤ 0.05.

Out of Lane VIG (p = 0.03), Divided Attention Reaction Time VIG (p = 0.02), and Total Tickets VIG (p = 0.01). Analysis of time-on-task for the 40-min CV drive shows that for the five 8-min blocks (E1- E5), the most significant impact of CPAP was evident during the second 8-min block.

Analysis of the impact of CPAP compliance on simulated driving shows strong correlations between primary and secondary driving variables and hours of CPAP use. Correlations > 0.20 are shown in **Table 6**. CPAP compliance accounted for 26% of the variance (rho = 0.51) in the DSS.

The relationship between baseline driving performance and PSG measures (AHI, mean O_2, minimum O_2 saturation, and arousal index) is shown in **Table 7**. This analysis shows that baseline AHI had the most impact on simulated driving performance, followed by minimum O_2 saturation and mean O_2.

Patient Reported Outcomes

Following treatment with armodafinil, there was a trend for improved self-reported sleepiness on the ESS (p = 0.066). Following CPAP, the improvement in ESS score was highly significant (p < 0.0001). ESS scores at Visit 5 were correlated with CPAP compliance (r = 0.33).

The FOSQ was administered to assess changes in quality of life. Following treatment with armodafinil, there was a significant improvement compared to placebo in 2 of the 5 FOSQ domains: General Productivity (p = 0.01) and Social Outcome (p = 0.005). Treatment with CPAP resulted in significant improvements in 3 FOSQ domains: General Productivity (p < 0.0001), Social Outcome (p < 0.0001), and Vigilance (p < 0.0001). FOSQ scores at Visit 5 for these 3 domains were correlated with CPAP compliance: General Productivity, r = 0.20; Social Outcome, r = 0.23; and Vigilance, r = 0.24.

Table 6—Correlations between CPAP compliance and driving variables

Spearman Correlation Coefficients > 0.20 for Additional Driving Variables	
DSS	**Rho**
Driving Safety Score	-0.5084
Lane Position Deviation CV	-0.4414
E1	-0.3988
E2	-0.4648
E3	-0.5432
E4	-0.4738
E5	-0.4752
Speed Deviation CV	-0.4550
E2	-0.3567
E3	-0.5245
E4	-0.4265
E5	-0.4857
Total Crashes CV	-0.4470
E3	-0.3646
E5	-0.3019
Out of Lane CV	-0.4734
E1	-0.5026
E2	-0.3459
E3	-0.4303
E4	-0.3477
E5	-0.2755
Lane Position Deviation CZ URB	-0.3448
Average Speed CZ URB	0.2265
Speed Deviation CZ URB	-0.2788
Excessive Ay CV	-0.2890
Total Tickets URB	-0.3448
Divided Attention Reaction Time	-0.3943

For country vigilance scenario: E1 = 0-7:59 min, E2 = 8-15:59 min, E3 = 16-23:59 min, E4 = 24-31:59 min, E5 = 32-40 min. CV, country vigilance scenario; URB, urban scenario; CZ, construction zone.

Table 7—Correlations between baseline PSG and baseline driving variables, Spearman correlation coefficients ≥ 0.15

	PSG Variable		
	AHI	**Minimum O_2 Saturation**	**Mean O_2**
DSS			
Out of Lane	0.19	-0.16	
Excessive Ay	0.15		
Other Driving Variables			
Country Vigilance			
Lane Position E2	0.17		
Lane Position E5	0.17		
Out of Lane	0.19		
Av Speed E1	0.18		-0.24
Speed Dev		-0.15	
Speed Dev E2		-0.20	
Speed Dev E4			0.16
Total Crashes E2	0.21	-0.23	
Total Crashes E4		0.18	0.15
First Crash		-0.28	
Out of Lane E2			0.22
Out of Lane E4	0.23		
Out of Lane E5		0.18	0.15
Urban			
Ave Speed CZ	0.16		
Speed Dev CZ			0.18
Crashes in CZ			0.25
Crashes non CZ	0.15		
Vigilance			
Out of Lane		-0.27	
DA Correct Responses	-0.17	0.19	
DA Omission Errors	0.17	-0.19	
DA Commission Errors			0.21

For country vigilance scenario: E1 = 0-7:59 min, E2 = 8-15:59 min, E3 = 16-23:59 min, E4 = 24-31:59 min, E5 = 32-40 min. CZ, construction zone, DA, divided attention.

The MOS-CF6 was administered at Baseline, Visit 3, and Visit 5. At Baseline, the placebo group reported more difficulty with cognitive functioning (65.4 ± 17.3) than subjects who were randomized to the armodafinil group (74.7 ± 13.6). Specifically, the placebo group reported more difficulty with problem solving, concentration, disorganization, and memory. At Visit 3, both groups reported less difficulty with cognitive functioning. However, the improvement for the placebo group (8.6 ± 18.1) was somewhat less ($p = 0.06$) than the improvement reported by the armodafinil group (9.3 ± 12.1). In contrast, CPAP treatment resulted in a highly significant reduction in self-reported cognitive function difficulty ($p < 0.0001$). The overall change from baseline in MOS-CF6 score for the mITT population following CPAP treatment was 17.4 ± 14.6.

After finishing the CV, subjects responded to 2 visual analog scales: (1) "How well do you think you drove for the last 60 minutes?" and (2) "How motivated did you feel to drive at your best during the last 60 minutes of driving?" From Baseline to Visit 3, subjects receiving placebo reported a decline (-10.9 mm) in their driving performance. In contrast, subjects receiving armodafinil reported an improvement (+1.9 mm) in their driving performance ($p = 0.002$). CPAP treatment resulted in a marked positive increase in "How well do you think you drove for the last 60 minutes?" (+12.5 mm, $p = 0.0023$). In response to the visual analog scale (VAS) measuring motivation, subjects receiving placebo reported a decline (-8.3 mm) in motivation. By comparison, those receiving armodafinil reported increased motivation (+4.3 mm, $p = 0.0031$). Following CPAP treatment, there was an improvement in motivation compared to baseline (+4.9 mm); however, the increase did not reach statistical significance ($p = 0.107$).

CPAP Compliance

The compliance results for the final 2 weeks of CPAP treatment were used to compare treatment compliance for the armodafinil and placebo groups. Results showed that hours of CPAP compliance did not differ for those subjects who had pre-

viously been treated with armodafinil compared to those who had received placebo (p = 0.80).

Clinician Assessment: CGI-s and CGI-c

The Principal Investigator, who was blind to both treatment group assignment and to CPAP compliance results, completed the Clinical Global Impression of Severity (CGI-s) rating at baseline and both the Clinical Global Impression of Change (CGI-c) and the CGI-s at subsequent visits. Mean CGI-s scores and score distributions were comparable at Baseline for the 2 treatment groups (placebo = 4.91; armodafinil = 5.06; 5 = markedly ill). Following treatment with armodafinil or placebo, the mean CGI-c score for the placebo group was 3.09 and for the armodafinil group 2.79. Although, numerically the change from baseline is more favorable for the armodafinil group, the difference between groups is statistically nonsignificant (p = 0.34). At the end of CPAP treatment, there was no difference in CGI-c scores between the 2 treatment groups (p = 0.82). However, for both groups there was a marked improvement in CGI-s (p < 0.0001) compared to Baseline. Of the 68 subjects in the mITT population, 41 (60%) were rated as normal, 14 (21%) were rated as borderline ill, and 4 (6%) were rated as mildly ill at the end of the study. At Baseline, the lowest rating was moderately ill (19%). Following CPAP, only 4 (6%) were rated as moderately ill, and 1 subject was rated as markedly ill (compared to 63% at baseline).

DISCUSSION

A primary objective of this study was to determine whether use of a new wake-promoting agent, armodafinil, prior to initiation of nasal continuous positive airway pressure (CPAP) therapy, would improve the simulated driving performance of patients with excessive daytime sleepiness (EDS) secondary to obstructive sleep apnea (OSA). Another objective of the study was to assess the impact of treatment with armodafinil prior to CPAP treatment on compliance with CPAP treatment.

The results demonstrate that armodafinil improved simulated driving performance prior to initiation of CPAP therapy. This improvement in driving performance was evident in the composite DSS, which was the primary study endpoint (p = 0.03). The DSS was shown to be sensitive to other stimulant agents in a prior study.[26] In addition, according to the VAS, subjects appeared to be aware of their improved driving performance in response to treatment with armodafinil compared to placebo (p = 0.002).

The specific driving simulator measures which were most sensitive to the beneficial effects of armodafinil on driving performance were lane position deviation (p = 0.002), lane excursions (p = 0.02; Out of Lane), speed deviation (p = 0.005; Speed Variability), and total tickets (p = 0.036). Armodafinil also showed a trend to improvement (compared to placebo) on measures of reaction time on a divided attention task (p = 0.08) and time to first crash (p = 0.09).

Evaluation of the impact of CPAP on simulated driving was complicated by the unanticipated short interval (i.e., < 24 h) between the screening visit and the baseline visit. To eliminate this effect we assessed the impact of CPAP treatment by comparing the driving simulation results for Visit 3 (end of drug treatment) and Visit 5 (end of CPAP treatment) for the subjects randomized to placebo. Subjects who were randomized to armodafinil were excluded from this analysis to avoid the confounding effect of drug treatment.

In spite of the reduction in the number of subjects (n = 32), due to the exclusion of those treated with armodafinil, the results replicate the improvement in simulated driving performance previously shown following CPAP treatment.[2,14]

The DSS showed a trend for improved performance following CPAP (p = 0.07). The only DSS component significantly affected by CPAP treatment was Lane Deviation (p = 0.01). This is consistent with the literature demonstrating SDLP to be the most sensitive measure to treatment with CPAP treatment. The Out of Lane measure and the Excessive Ay (cornering speed) measures showed a trend for better performance following CPAP (p = 0.06, and p = 0.07, respectively).

The mDSS, which is based on recent simulation research with OSA patients, showed significant improvement following CPAP (p = 0.038). The four mDSS components which showed a significant effect of CPAP include: Time to First Crash (p = 0.045), Out of Lane (p = 0.06), Lane Position Deviation E5 (p = 0.07), and Total Crashes (p = 0.15).

In addition to the driving measures already mentioned, the beneficial effect of CPAP was also evident on measures of speed deviation (p = 0.03), speeding violations on the vigilance scenario (p = 0.006), divided attention reaction time (p = 0.02), lane excursions on the vigilance scenario (p = 0.03), and crashes in the urban scenario construction zone (p = 0.03). Furthermore, subjects reported awareness of their improved driving performance following treatment with CPAP (p = 0.0023).

As expected, the benefits of CPAP are dependent upon treatment compliance. More than 25% of the variance in the DSS (rho = 0.55) at Visit 5 can be accounted for by CPAP compliance (i.e., hours of CPAP use in the last 2 weeks of the study). The strongest correlations between CPAP compliance and driving variables were found for measures of lane position deviation, speed deviation, and lane excursions. The benefit of CPAP on simulated driving performance is most evident on measures that assess weaving (i.e., maintenance of lane position) and speed control.

The results of the current study also touched on the question of the underlying causes of the driving problems associated with OSA. Regression analyses revealed that simulated driving performance was most strongly associated with baseline AHI, followed by minimum O_2 saturation and mean O_2 level.

Patient reported outcome scores also demonstrate the value of treatment with armodafinil prior to initiation of CPAP. The improvement in self-reported sleepiness approached significance on the ESS (p = 0.066). Following two weeks of armodafinil, subjects reported significant improvement on sleep-related quality of life outcome scales (FOSQ Productivity, p < 0.001; and FOSQ Social Outcome, p < 0.001). On the other hand, the clinician-based ratings (CGI scales) showed a numerical advantage but not a statistically significant treatment difference in disease severity. Although subjects were less sleepy, they were still judged by the clinician as showing moderate disease severity.

Consistent with the benefits seen on measures of driving performance, the patient reported outcome measures and clinician

ratings showed marked benefits of CPAP. The ESS dropped significantly following CPAP ($p < 0.0001$). ESS improvement was correlated with compliance ($r = -0.33$). Significant improvement was seen in three FOSQ domains (General Productivity, $p < 0.0001$), Social Outcome ($p < 0.0001$), and Vigilance ($p < 0.0001$). Similarly, CPAP treatment resulted in improved scores on the MOS-CF6. Subjects reported significantly less cognitive difficulties following CPAP ($p < 0.0001$). These benefits were also evident in the clinician's rating of the patient's condition following CPAP. Specifically, the clinician rating of disease severity (CGI-s) dropped significantly following CPAP ($p < 0.0001$).

Although treatment with armodafinil improved simulated driving performance in OSA patients, it is not our intention to encourage use of armodafinil as a substitute for treatment with CPAP. Our study was conducted to identify a safe alternative to CPAP during the waiting prior to the initiation of CPAP therapy (i.e., bridging therapy). However, it should be noted that treatment with armodafinil prior to initiation of CPAP did not have an impact on CPAP compliance ($p = 0.80$). This may allay the concerns that some practitioners may have as to whether treatment prior to initiation of CPAP would discourage subsequent use of CPAP treatment.

In summary, armodafinil was found to improve simulated driving performance in OSA patients with EDS prior to initiation of CPAP. The improvement in driving performance was most evident on measures of lane position control (including the number of lane excursions) and speed control. Subjects treated with armodafinil showed awareness of their improved driving performance. Treatment with armodafinil was not found to impact subsequent CPAP compliance. The improvement seen on driving simulator parameters in this study following CPAP is comparable to that reported in prior studies. Although the purpose of the current study was not to compare armodafinil to CPAP, a review of the study results shows a comparable effect size on DSS for treatment with armodafinil and treatment with CPAP (armodafinil vs. placebo, $d = 0.42$; Baseline vs. CPAP, $d = 0.40$).

ABBREVIATIONS

AHI, apnea-hypopnea index
ANCOVA, analysis of covariance
APPLES, Apnea Positive Pressure Long-term Efficacy Study
BMI, body mass index
CGI, clinical global impression
CGI-c, clinical global impression of change
CGI-s, clinical global impression of severity
CMH, Cochran-Mantel-Haenszel
CNS, central nervous system
CPAP, continuous positive airway pressure
CRCDS, Cognitive Research Corporation Driving Simulator
CV, country vigilance driving scenario
DSS, Driving Safety Score
EDS, excessive daytime sleepiness
EEG, electroencephalogram
ESS, Epworth Sleepiness Scale
FOSQ, Functional Outcomes Sleep Questionnaire
mDSS, modified Driving Safety Score
mITT, modified intent-to-treat
MOS-CF6, Medical Outcomes Study 6-item Cognitive Functioning Scale
MWT, maintenance wakefulness test
nCPAP, nasal continuous positive airway pressure
OSA, obstructive sleep apnea
PSG, polysomnogram
PVT, psychomotor vigilance test
SDLP, standard deviation of lateral position
SSQ, simulator sickness questionnaire
STI, Systems Technology, Inc.
URB, urban driving scenario
VAS, visual analog scale
VIG, vigilance driving scenario

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DISCLOSURE STATEMENT

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The use of armodafinil (Nuvigil) in this clinical trial is considered off-label, since the approved FDA labeling states that: "In OSA, Nuvigil is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Nuvigil."