APD125, a Selective Serotonin 5-HT$_{2A}$ Receptor Inverse Agonist, Significantly Improves Sleep Maintenance in Primary Insomnia

Russell Rosenberg, PhD[1]; David J. Seiden, MD[2]; Steven G. Hull, MD[3]; Milton Erman, MD[4]; Howard Schwartz, MD[5]; Christen Anderson, MD, PhD[6]; Warren Prosser, MBA[6]; William Shanahan, MD[6]; Matilde Sanchez, PhD[6]; Emil Chuang, MD[6]; Thomas Roth, PhD[7]

NeuroTrials Research and Atlanta School of Sleep Medicine, Atlanta, GA; [2]Broward Research Group, Pembroke Pines, FL; [3]Vince and Associates, Overland Park, KS; [4]Avastra USA, San Diego, CA; [5]Miami Research Associates, Miami, FL; [6]Arena Pharmaceuticals, San Diego, CA; [7]Henry Ford Hospital, Detroit, MI

Introduction: Insomnia is a condition affecting 10% to 15% of the adult population and is characterized by difficulty falling asleep, difficulty staying asleep, or nonrestorative sleep, accompanied by daytime impairment or distress. This study evaluates APD125, a selective inverse agonist of the 5-HT$_{2A}$ receptor, for treatment of chronic insomnia, with particular emphasis on sleep maintenance. In phase 1 studies, APD125 improved sleep maintenance and was well tolerated.

Methodology: Adult subjects (n = 173) with DSM-IV defined primary insomnia were randomized into a multicenter, double-blind, placebo-controlled, 3-way crossover study to compare 2 doses of APD125 (10 mg and 40 mg) with placebo. Each treatment period was 7 days with a 7- to 9-day washout period between treatments. Polysomnographic recordings were performed at the initial 2 screening nights and at nights (N) 1/2 and N 6/7 of each treatment period.

Results: APD125 was associated with significant improvements in key sleep maintenance parameters measured by PSG. Wake time after sleep onset decreased (SEM) by 52.5 (3.2) min (10 mg) and 53.5 (3.5) min (40 mg) from baseline to N 1/2 vs. 37.8 (3.4) min for placebo, ($P < 0.0001$ for both doses vs placebo), and by 51.7 (3.4) min ($P = 0.01$) and 48.0 (3.6) min ($P = 0.2$) at N 6/7 vs. 44.0 (3.8) min for placebo. Significant APD125 effects on wake time during sleep were also seen ($P < 0.0001$ N 1/2, $P < 0.001$ N 6/7). The number of arousals and number of awakenings decreased significantly with APD125 treatment compared to placebo. Slow wave sleep showed a statistically significant dose-dependent increase. There was no significant decrease in latency to persistent sleep. No serious adverse events were reported, and no meaningful differences in adverse event profiles were observed between either dose of APD125 and placebo. APD125 was not associated with next-day psychomotor impairment as measured by Digit Span, Digit Symbol Copy, and Digit Symbol Coding Tests.

Conclusions: APD125 produced statistically significant improvements in objective parameters of sleep maintenance and sleep consolidation and was well tolerated in adults with primary chronic insomnia.

Keywords: Insomnia treatment, serotonin 5-HT$_{2A}$ receptor antagonist, polysomnography, slow wave sleep, sleep maintenance

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THE PREVALENCE OF INSOMNIA COMPLAINTS IN DEVELOPED COUNTRIES IS ESTIMATED TO BE 25% TO 35% IN SEVERAL GENERAL POPULATION SURVEYS[1-3] and includes 30 to 45 million Americans who have a diagnosis of insomnia.[4] The DSM-IV defines insomnia as difficulty initiating or maintaining sleep or nonrestorative sleep associated with significant distress or impairment in social, occupational, or other important areas of functioning.[5] The majority of drugs approved to treat insomnia exert their effects by activating benzodiazepine receptors located on gamma amino butyric acid (GABA)$_A$ receptor complexes, leading to increased inhibition of several pathways involved in sleep-wake regulation, which in turn causes drowsiness and facilitates sleep.[6-8] These benzodiazepine receptor agonists (BzRAs) are effective in promoting sleep, and those with longer half-lives are also effective in maintaining sleep.[9,10] However, BzRAs are associated with central nervous system side effects and possible dependency in at-risk populations.[11-16] As a result, much recent research has focused on developing safer sleep agents[2,17,18]; some of the newer agents under evaluation are designed to increase slow wave sleep (SWS) in an effort to improve sleep quality and maintenance.

The serotonergic pathway is one of the key pathways that contribute to wakefulness.[19-21] Some atypical selective serotonin reuptake inhibitors have been shown to increase SWS, particularly those that bind to the serotonin (5-HT) 2A receptor.[20,22,23] Importantly, it has been suggested that increasing SWS and reducing arousals and stage shifts may improve sleep maintenance.[20,24-26] APD125, a potent and selective inverse agonist for 5-HT$_{2A}$ receptors, belongs to a new class of compounds under investigation for the treatment of insomnia. Inverse agonists differ from neutral antagonists, which affect only ligand-dependent receptor activation and have no effect on constitutive receptor signaling. The potential benefit of an inverse agonist is that, unlike a ligand-dependent neutral agonist, it can block receptor activity in the presence or absence of the native ligand.[27-28]

In previous phase 1 clinical trials, APD125 significantly improved polysomnographic (PSG) parameters of sleep in normal volunteers in the nap model of transient insomnia, resulting in increased SWS, decreased number of awakenings (NAW), and decreased arousal index.[29] Moreover, APD125 was non-sedating: drowsiness and clinically significant adverse cognitive or

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Address correspondence to: Russell Rosenberg, PhD, Director, NeuroTrials and Atlanta School of Sleep Medicine and Technology, 1100 Johnson Ferry Rd, Suite 580, Atlanta, GA 30342; Tel: (678) 651-2006; Cell: (770) 639-0707; E-mail: russell.rosenberg@atlantasleep.com

psychomotor effects were not observed by Leeds psychomotor testing, Bond and Lader visual analog scale, or memory consolidation testing either at T_{max} during daytime dosing or in the morning following nighttime dosing. This is in contrast to compounds whose primary action is on the GABA receptor complexes, where cognitive and psychomotor impairment is observed during peak plasma levels.[30]

The present study was conducted to test the primary hypothesis that APD125 reduces wake time after sleep onset (WASO) in subjects with primary insomnia as compared to placebo during a 7-day treatment period. Secondarily, effects of APD125 on other parameters of sleep maintenance including SWS and NAW were evaluated. Other objectives were to assess the tolerability and safety of APD125 in a primary insomnia population, and to evaluate study drug effects on a panel of other objective and subjective sleep parameters.

METHODS

This study was conducted between February and June 2007 at 24 sleep research centers in the United States. Institutional review boards at each site approved the protocol and informed consent documents. The research was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Subjects were recruited by individual sites via advertising or from an existing database of patients with a diagnosis of insomnia. Subjects with primary insomnia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria, who fulfilled the entry requirements were randomized into a double-blind, placebo-controlled, 3-way crossover study to compare 2 doses of APD125 (10 mg and 40 mg) with placebo. The key inclusion criteria were: age 18-64 years; history of being awake during the night ≥ 1 h after initially falling asleep occurring ≥ 3 nights per week for at least one month prior to study entry; and a Pittsburgh Sleep Quality Index ≥ 5. Exclusion criteria were: comorbid sleep, medical, or psychiatric disorder; consumption of > 2 alcoholic drinks or > 5 caffeinated beverages per day; and the inability to refrain from smoking prior to bedtime. Subjects who had evidence of sleep apnea or periodic limb movement disorder as evidenced by apnea-hypopnea index or periodic limb movement index > 10 during the first screening PSG were also excluded from participation in the study. Drugs and herbal remedies known to affect the sleep-wake cycle, such as benzodiazepines, antihistamines, and psychoactive agents were subject to appropriate washout periods. Once the initial inclusion and exclusion criteria were met, subjects were scheduled for 2 consecutive screening nights of PSG monitoring at the sleep laboratory to establish baseline sleep parameters and determine eligibility for randomization into the double-blind phase of the study. Single-blind placebo was administered one hour prior to lights out on both nights. Screening PSGs were reviewed and scored at a central reading site to determine subject eligibility for randomization. Subjects were required to have an average WASO ≥ 60 min during the 2 screening PSGs, with neither PSG night less than 45 min. Additionally, the average latency to persistent sleep must have been ≥ 20 min, with neither night less than 15 min.

Each treatment period following randomization was 7 days, with a 7- to 9-day washout period between treatments. Subjects spent nights 1 and 2 combined (N 1/2) and nights 6 and 7 combined (N 6/7) of each treatment period in the sleep laboratory, reporting to the laboratory 2 h prior to their usual bedtime. They were discharged the following morning after study procedures were completed; nights 3-5 for each period were spent at home. Subjects were given study medication approximately 1 h prior to bedtime/lights out each night during each of the 3 treatment periods. PSG readings were performed at N 1/2 and N 6/7 for each treatment period. Efficacy was measured objectively by averaging PSG values for N 1/2 and similarly, averaging PSG values N 6/7 to obtain the end of treatment effects; these results were then compared to the average screening/baseline PSG values. Efficacy was also measured subjectively using self-assessment questionnaires that were completed each morning following PSG evaluation. Patient-reported measures were captured daily using telephone diaries (Interactive Voice Response System) to record data concerning sleep patterns and quality of sleep.

Sleep Related Measures

Objective measures of sleep were evaluated from the scored PSGs. Subjects were required to routinely have lights out in the laboratory between 21:00 and 00:00, with actual lights out time based on habitual home sleep pattern. Recording began at lights out and concluded 8 h later (at lights on). All PSG data were captured utilizing computerized PSG recording instruments, and the information was converted into electronic European data format. The recordings included: 2 electrooculographic leads, 2 (submental) electromyographic (EMG) leads, 4 monopolar electroencephalographic channels (C3A2, C4A1, O1A2, O2A1), and 1 electrocardiographic (lead V5) channel. In addition, on the first screening night, a tibialis EMG (nondominant leg) and respiratory flow measurement channels were also included. The digital recordings were blinded as to the treatment night and treatment allocation and were scored visually in 30-sec intervals (epochs) by a reader at a central laboratory according to the criteria of Rechtschaffen and Kales.[31] Every 10th PSG was scored by a second scorer to maintain quality control between central readers. Prior to each study site initiation, sites were required to provide a recording of a PSG for certification of standardization and quality of PSG. Additionally, each site was certified prior to subject assessments.

The primary efficacy outcome measure was WASO, defined as the number of minutes spent awake following the onset of persistent sleep to the end of the recording period. Other key objective sleep maintenance parameters were as follows: wake time during sleep (WTDS), defined as the number of minutes spent awake after the onset of persistent sleep and prior to the last epoch of Stage 1, 2, 3-4, or REM; number of arousals, defined as shifts to stage 1 or a single epoch of wake from a deeper stage of sleep, and NAW, defined as the number of times, after onset of persistent sleep, that there was a wake lasting ≥ 1 minute. Awakenings had to be separated by Stage 2, 3-4, or rapid eye movement (REM) sleep to be counted as separate events. Other standard objective sleep parameters measured included wake time by hourly bins, total sleep time (TST), sleep efficiency, and latency to persistent sleep (defined as the number of minutes from the beginning of the recording to the start of the first 10 contiguous non-wake [Stage 2, 3, or 4] minutes). The

amount of SWS and the other sleep stages were also analyzed. Subjective sleep measures included sleep latency, subjective number of awakenings, subjective total sleep time (sTST), and sleep quality. Sleep quality was rated on a 5-point Likert-like scale.

Safety Assessments

Safety was assessed by monitoring adverse events (AEs), vital signs, 12-lead ECGs, clinical laboratory results, and physical examination findings. All AEs reported during the washout period were attributed to the treatment assignment that was just completed. Possible study medication discontinuation effects were monitored by additional patient diary questions adapted from the Benzodiazepine Withdrawal Symptom Questionnaire. Cognitive function was tested using Digit Span, Digit Symbol Copy, and Digit Symbol Coding Tests at approximately 60 to 90 min after awakening each morning following a PSG night. Finally, a subject neurological impairment assessment that included the Romberg Test, heel-to-toe walking, and finger-to-nose test was also completed each morning prior to discharge from the sleep laboratory.

Statistical Analyses

To address the primary hypothesis, the mean change from baseline to N 6/7 in average PSG WASO at each APD125 dose was compared to that of placebo. The comparison was made using the analysis of covariance (ANCOVA) model with treatment, treatment sequence, and period as fixed effects, and subject as a random effect. Baseline was defined as the average of values obtained at screening visits, PSG1 and PSG2. The PSG WASO was observed prior to the first dose of study medication (average of PSG1 and PSG2); age and weight were included in the model as covariates. The least-squares (LS) means of APD125 and placebo treatment groups and estimates of the treatment differences with their associated 95% confidence intervals were estimated using the ANCOVA model. Similar analyses were performed for the other PSG and subjective efficacy endpoints. As this was a proof of concept study to explore the possible effects of APD125, no adjustments for multiplicity were made. Cognitive function scores were also analyzed with an ANCOVA model with treatment, treatment sequence, and period as fixed effects; subject as a random effect; and age, weight, and screening value as covariates.

The modified intent-to-treat population (all subjects who received ≥ 1 dose of study medication and completed ≥1 on-treatment efficacy evaluation) was used for the analysis of primary and secondary efficacy variables. Dropouts were not replaced. A single efficacy measure was used when only a single data point was available for any efficacy PSG pair. If both paired measurements were missing, the subject was not included in the efficacy analysis for that measure in that treatment period.

RESULTS

One hundred seventy-three subjects met inclusion and exclusion criteria and screening PSG parameters, and were randomized into the double-blind portion of the study. The mean age of the participants was 45.1 ± 11.8 years. There were 106 females and 67 males, with 45.7% Caucasians, 25.4% Hispanics, and 26% African Americans. One hundred forty-seven subjects (85%) completed the study; the most common reasons for study discontinuation were: noncompliance (n = 7), adverse event (n = 6), and subject decision (n = 5).

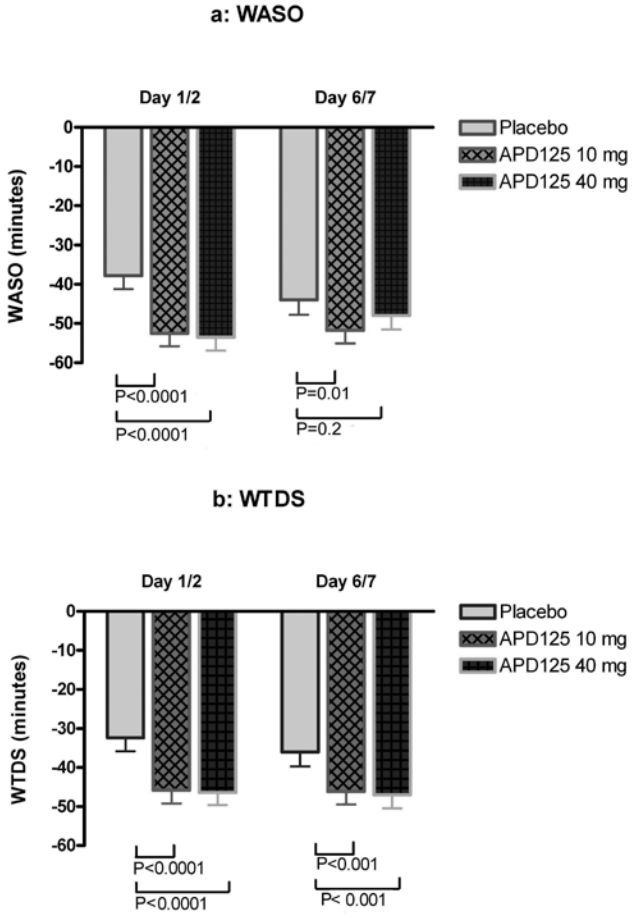

Figure 1—Change from Baseline in WASO and WTDS at Nights 1/2 and 6/7

APD125 was associated with significant improvements in the majority of the PSG sleep maintenance parameters. WASO decreased by a LS mean (SEM) of 52.5 (3.2) and 53.5 (3.5) min from baseline to N 1/2 for the 10 mg and 40 mg doses, respectively ($P < 0.0001$ for both vs placebo), and by 51.7 (3.4) min ($P = 0.01$) and 48.0 (3.6) min ($P = 0.2$) at N 6/7, respectively. This was compared to a placebo response of 37.8 (3.4) min at N 1/2 and 44.0 (3.8) min at N 6/7 (Figure 1a). Larger placebo adjusted APD125 effects were seen at N 6/7 with WTDS than with WASO; WTDS decreased by 45.8 (3.5) min and 46.4 (3.2) min at N 1/2 ($P < 0.0001$) and 46.1 (3.3) min ($P < 0.001$) and 46.9 (3.5) min ($P < 0.001$) at N 6/7 for the 10 mg and 40 mg doses, respectively, compared to a placebo response of 32.4 (3.4) min at N 1/2 and 36.0 (3.8) min at N 6/7 for placebo (Figure 1b). No statistically significant difference was observed between the 10 mg and 40 mg doses with either measure at either timepoint. To further understand the effects of APD125, wake time divided into hourly bins was determined. As seen in Figure 2, statistically significant reductions in wake time were observed from hours 3 to 6 at N 1/2, and similar decreases in wake time

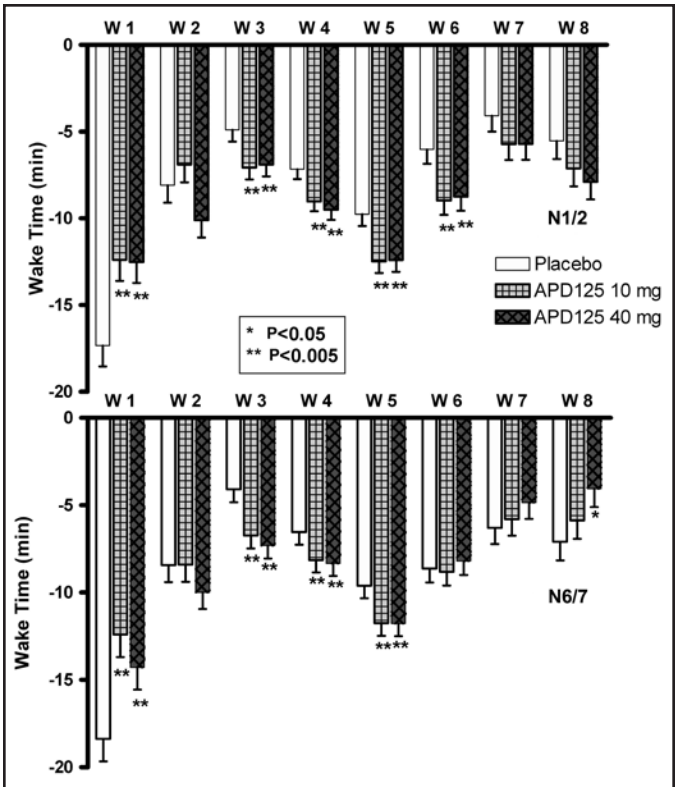

Figure 2—Wake time by hourly bins

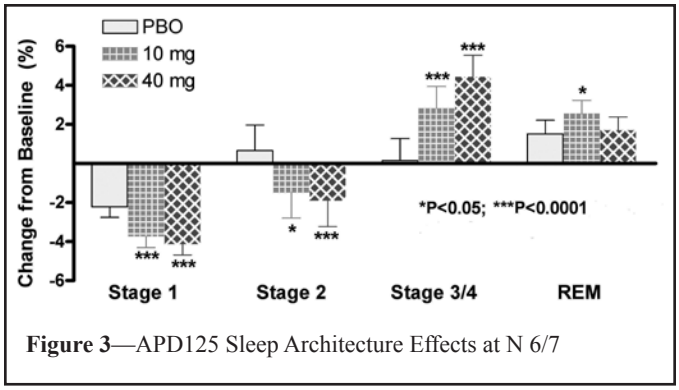

Figure 3—APD125 Sleep Architecture Effects at N 6/7

were seen from hours 3 to 5 at N 6/7.

Statistically significant reductions in the number of arousals ($P < 0.0001$) and NAW ($P < 0.0001$) were observed for both doses of APD125 and at both timepoints (Table 1). A dose response relationship was observed for number of arousals and NAW at N 1/2 and to a lesser extent at N 6/7 ($P = 0.04$ for both). As shown in Figure 3, the percentage of time spent in SWS was statistically increased for both doses of APD125 at N 6/7 ($P < 0.0001$). This was associated with a corresponding reduction in time spent in Stages 1 and 2 sleep. A similar result was observed at N 1/2. Similar to the number of arousals and NAW data, a dose response relationship was observed for %SWS at N 1/2 ($P = 0.02$) and N 6/7 ($P < 0.005$) (data not shown).

No decrease in PSG-determined latency to persistent sleep was observed at either APD125 dose when compared to placebo (Table 1). Statistically significant improvements in some of the more global objective measurements of sleep and in subjective measurements were observed. TST and sleep efficiency increased significantly compared with placebo for APD125 40 mg at N 1/2. The changes in the subjective sleep measures shown in Table 2 were generally consistent with the findings from the PSG parameters. No difference in subjective sleep latency was observed with either dose or at either timepoint. While only the APD125 40 mg dose at N1/2 showed a statistical increase in sTST, a statistically significant decrease in NAW was seen for both timepoints with the APD125 40 mg dose and at N 1/2 with the APD125 10 mg dose. For sleep quality a statistical differentiation was observed at N 1/2 with the 40 mg dose ($P = 0.01$).

Both doses of APD125 were well tolerated. There were no serious adverse events reported in the study. Six subjects had AEs that resulted in either discontinuation of study drug or withdrawal from the study. Of the 6 subjects, AEs occurred in 3 subjects during treatment with placebo, 1 subject during treatment with 10 mg of APD125, and 2 subjects during treatment with 40 mg of APD125. In 4 of these 6 subjects the reason for discontinuation or withdrawal was an increase in serum creatine phosphokinase (CPK); 2 of these occurred during placebo treatment. In each case, CPK elevation was preceded by a period of vigorous exertion. The other causes for study discontinuation were somnolence, fatigue, and dyspnea in a subject during the placebo period, and a mild elevation in serum creatinine that improved with increased fluid intake in a subject during the 40 mg of APD125 treatment period. Table 3 summarizes the treatment-emergent AEs with ≥ 2 occurrences in one or both active treatment periods. The total number of subjects who experienced an AE was low, and similar numbers were observed during APD125 and placebo treatment periods. One of the theoretical risks of this compound is bleeding due to the inhibitory effects of $5HT_{2A}$ receptor blockage on serotonin-mediated amplification of platelet aggregation.[32] In this study, no significant bleeding was reported.

Cognitive tests included the Digit Span Test using the total score of both forward and backward forms, the Digit Symbol Copy Test, and the Digit Symbol Coding Test which included time to completion. Treatment with APD125 at either dose did not result in a significant change in cognitive function on any of the variables tested (Table 4). Motor function was assessed as part of the next morning neurological examination and did not show a negative effect. The Benzodiazepine Withdrawal Symptom Questionnaire showed no evidence of withdrawal with either of the doses tested. Finally, with the exception of the clinical laboratory abnormalities already noted, no clinically meaningful changes in vital signs, hematology, coagulation, chemistry, or ECG parameters were observed during APD125 treatment as compared to placebo.

DISCUSSION

APD125, a selective $5HT_{2A}$ inverse agonist, is a member of a novel therapeutic class under clinical investigation for the treatment of insomnia. Unlike the $GABA_A$ agonists, the $5HT_{2A}$ inverse agonists/antagonists are non-hypnotic and non-sedating; psychomotor impairment and somnolence are not observed, even at peak drug levels. They promote sleep maintenance by decreasing the number of awakenings, sleep stage shifts, and arousals.[22,29,33] In this phase 2 trial, APD125 treatment was associated with significant improvement in many commonly used measures of sleep maintenance, including WASO, WTDS, NAW, and number of arousals. However, APD125 did not decrease sleep onset latency.

Table 1—Response to APD125: Additional PSG Parameters of Sleep

Values = Mean (SD)	Screening	Placebo	APD125 10 mg	APD125 40 mg
Number of arousals[1]				
Nights 1/2 (n)	46.7 (17.8)	50.4 (18.0)	41.2 (16.1)	38.7 (14.5)
P value vs placebo			<0.0001	<0.0001
Nights 6/7 (n)	46.7 (17.8)	49.4 (18.9)	42.3 (15.4)	40.3 (14.6)
P value vs placebo			<0.0001	<0.0001
Number of awakenings[2]				
Nights 1/2 (n)	10.4 (3.9)	10.5 (4.5)	8.1 (3.8)	7.4 (3.7)
P value vs placebo			<0.0001	<0.0001
Nights 6/7 (n)	10.4 (3.9)	9.6 (4.7)	8.2 (4.0)	8.0 (3.9)
P value vs placebo			<0.0001	<0.0001
% time spent in SWS				
Nights 1/2 (%)	11.53 (10.57)	11.74 (11.24)	15.37 (15.19)	16.80 (16.96)
P value vs placebo			<0.0001	<0.0001
Nights 6/7 (%)	11.53 (10.57)	12.07 (11.24)	14.35 (14.23)	16.14 (15.93)
P value vs placebo			<0.0001	<0.0001
Total sleep time				
Nights 1/2 (min)	312.02 (55.51)	374.27 (51.46)	381.63 (52.05)	387.80 (48.99)
P value vs placebo			0.0644	0.0031
Nights 6/7 (min)	312.02 (55.51)	382.92 (54.42)	381.48 (53.18)	384.09 (55.29)
P value vs placebo			0.8150	0.8772
Sleep efficiency				
Nights 1/2 (%)	65.04 (11.57)	78.01 (10.72)	79.55 (10.82)	80.82 (10.22)
P value vs placebo			0.0632	0.0033
Nights 6/7 (%)	65.04 (11.57)	79.82 (11.34)	79.54 (11.06)	80.05 (11.51)
P value vs placebo			0.8401	0.8819
Latency to persistent sleep				
Nights 1/2 (min)	66.13 (36.16)	38.72 (31.97)	47.23 (43.32)	41.67 (31.84)
P value vs placebo			0.0010	0.1492
Nights 6/7 (min)	66.13 (36.16)	37.85 (35.11)	44.96 (39.10)	39.82 (34.78)
P value vs placebo			0.0141	0.3597

[1]Number of arousals: number of entries to Stage 1 plus number of entries to wake.
[2]Number of awakenings: number of times, after onset of persistent sleep that there is an entry to wake ≥60 seconds. Each entry to be counted must be separated by at least two consecutive epochs of Stage 2, 3-4, or REM sleep.

The WASO change for APD125 is comparable to that reported in the literature for zolpidem MR and eszopiclone, both FDA-approved $GABA_A$ agonists indicated for sleep onset and sleep maintenance. Zolpidem-MR also demonstrated statistically significant reduction in the NAW, as did the higher dose (3 mg) of eszopiclone, although neither showed any consistent effect on deep sleep (Stages 3 and 4).[9,10,34] Based on the findings of the present trial, APD125 may differ from $GABA_A$ agonists primarily in its ability to promote SWS and reduce the number of awakenings and arousals in the absence of sedation.

An unexpected finding from the present study was the unusually high placebo response observed with a number of the commonly used PSG parameters, particularly WASO, WTDS, and TST. This may be an unintended effect of the strict PSG inclusion criteria, which required a screening/baseline WASO average > 60 min. As a result, the natural fluctuations in insomnia severity over the course of the study may have been skewed toward improvement, thus potentially contributing to the "placebo response" by regression to the mean. Objective improvements in sleep maintenance and consolidation were corroborated by subjective improvements, but a strong placebo effect was again evident, and placebo subjective responses generally increased from N 1/2 to N 6/7, resulting in more robust differentiation of APD125 from placebo at the earlier timepoint (Table 2). Although it is possible that tachyphylaxis, a phenomenon observed with some sleep agents, may be an explanation for these observations, this is unlikely since the objective PSG measures associated with APD125 tended to remain consistent over the 7 days of treatment.

To date, APD125 has been very well tolerated, with no treatment-emergent serious adverse events in any studies. The overall adverse events have been infrequent and mild, and no consistent changes in laboratory or ECG parameters have been observed. The most common complaints in this study were somnolence and fatigue, but the numbers were not appreciably different among the active and placebo treatment periods.

Most sleep agents currently available are highly effective in initiating sleep; those that have longer half-lives can also exert an effect on sleep maintenance. However, the longer acting BzRAs may be associated with next day residual effects such as memory impairment[35,36] and/or impaired psychomotor function, especially if the prescribed 8 hours of sleep is not achieved.[37] Therefore, the half-life of a BzRA is critically important in balancing a positive effect on sleep maintenance with the poten-

Table 2—Response to APD125: Subjective Parameters of Sleep-Measured Each Morning Following the PSG Nights

Values = Mean (SD)	Screening	Placebo	APD125 10 mg	APD125 40 mg
Sleep latency				
Nights 1/2 (hours)	1.37 (0.86)	1.02 (0.73)	1.03 (0.71)	1.02 (0.68)
P value vs placebo			0.4783	0.5713
Nights 6/7 (hours)	1.37 (0.86)	0.95 (0.71)	1.00 (0.67)	0.93 (0.62)
P value vs placebo			0.2494	0.5852
sNAW				
Nights 1/2 (n)	3.0 (1.4)	2.7 (1.7)	2.4 (1.6)	2.3 (1.3)
P value vs placebo			0.0029	0.0002
Nights 6/7 (n)	3.0 (1.4)	2.4 (1.5)	2.3 (1.5)	2.2 (1.4)
P value vs placebo			0.2051	0.0426
sTST				
Nights 1/2 (hours)	4.96 (1.12)	5.59 (1.13)	5.67 (1.14)	5.81 (1.05)
P value vs placebo			0.7014	0.0101
Nights 6/7 (hours)	4.96 (1.12)	5.76 (1.14)	5.79 (1.11)	5.85 (1.01)
P value vs placebo			0.7706	0.2113
Sleep quality index				
Nights 1/2	3.5 (0.9)	2.9 (1.0)	2.8 (1.0)	2.7 (1.1)
P value vs placebo			0.2775	0.0140
Nights 6/7	3.5 (0.9)	2.8 (1.0)	2.7 (1.1)	2.7 (1.1)
P value vs placebo			0.3628	0.1840

tial for next-morning adverse effects. Inverse agonism of the $5HT_{2A}$ receptor appears to produce sleep maintenance without residual psychomotor impairment upon wakening. The half-life of APD125 ranges from 3.9 to 10.7 hours at doses of 10 and 40 mg, respectively.[29] Even with the relatively long half-life at 40 mg, APD125 appears to be non-sedating, suggesting that the occurrence of next morning residual effects is a lesser consideration than for BzRAs. Indeed, in phase 1 studies, APD125 showed no clinically important psychomotor impairment, even at peak blood levels. The present study reconfirms the phase 1 finding that showed bedtime use of APD125 was not associated with next-morning cognitive or psychomotor impairment. Because APD125 reduces NAW and increases SWS, it may provide particular benefit to the elderly population, many of whom experience frequent nighttime awakenings[38] and reduced SWS, and who may be more sensitive to the adverse effects of BzRAs.[39] APD125 may represent an alternative to sedative hypnotics for insomnia patients with a primary complaint of sleep maintenance difficulty. These theoretical benefits will have to be tested in additional clinical trials. Other patient populations that may potentially benefit from APD125 include patients with sleep disturbance that is characterized by sleep fragmentation, for example, patients with pain syndromes,[40,41,42] and perimenopausal women with hot flashes.[43,44]

In this study, APD125 improved PSG and subjective parameters of sleep maintenance with few side effects. No clear dose response was observed. A key question that remains to be answered is whether promoting SWS and reducing the number of arousals and awakenings will result in a subjectively better quality of sleep or a more restorative sleep. A separate study that specifically focuses on subjective endpoints and sleep quality is underway.

In conclusion, this study represents the largest study published to date for a $5HT_{2A}$ antagonist/inverse agonist compound for the treatment of primary insomnia. APD125 was well tolerated and significantly improved objective sleep parameters, including WASO, SWS, NAW, and number of arousals. Further, the present data confirm that selective blockade of the $5HT_{2A}$ pathway can significantly improve sleep maintenance parameters and support further investigation of APD125 as a potential

Table 3—Treatment-Emergent Adverse Events With ≥ 2 Events in One or Both Active Groups

	Placebo (N = 163) n (%)	APD125 10 mg (N = 162) n (%)	APD125 40 mg (N = 166) n (%)
Total number of patients with at least 1 AE	48 (29.4)	52 (32.1)	43 (25.9)
Somnolence	12 (7.4)	13 (8.0)	7 (4.2)
Fatigue	7 (4.3)	6 (3.7)	10 (6.0)
Headache	4 (2.5)	4 (2.5)	7 (4.2)
Amnesia	2 (1.2)	2 (1.2)	4 (2.4)
Diarrhea	1 (0.6)	2 (1.2)	4 (2.4)
Dizziness	1 (0.6)	1 (0.6)	5 (3.0)
Anorexia	3 (1.8)	3 (1.9)	1 (0.6)
Depression	3 (1.8)	2 (1.2)	2 (1.2)
Blood creatine phosphokinase increased	2 (1.2)	2 (1.2)	2 (1.2)
Upper respiratory tract infection	3 (1.8)	3 (1.9)	0 (0.0)
Nausea	1 (0.6)	2 (1.2)	2 (1.2)
Contusion	1 (0.6)	2 (1.2)	1 (0.6)
Nasopharyngitis	1 (0.6)	2 (1.2)	1 (0.6)
Epistaxis	0 (0.0)	2 (1.2)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	2 (1.2)
Increased appetite	0 (0.0)	2 (1.2)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	2 (1.2)
Vomiting	0 (0.0)	0 (0.0)	2 (1.2)

Table 4—Response to APD125: Cognitive Function Measured the Morning Following PSG Nights 2 and 7 (Mornings 3 and 8, Respectively)

Cognitive Function Values = Mean (SD)	Screening	Placebo	APD125 10mg	APD125 40mg
Digit Span Test - Frontward				
Morning 3	11.4 (2.3)	11.9 (2.5)	11.7 (2.6)	11.7 (2.4)
P value vs placebo			0.1540	0.2578
Morning 8		12.0 (2.5)	12.1 (2.4)	12.0 (2.6)
P value vs placebo			0.9918	0.8322
Digit Span Test - Backward				
Morning 3	6.7 (2.8)	7.5 (2.9)	7.4 (2.8)	7.4 (2.8)
P value vs placebo			0.5093	0.9082
Morning 8		7.6 (2.8)	7.6 (2.9)	7.8 (2.6)
P value vs placebo			0.8810	0.1618
Digit Span Total Score				
Morning 3	18.1 (4.4)	19.4 (4.7)	19.1 (4.7)	19.1 (4.7)
P value vs placebo			0.2178	0.5012
Morning 8		19.6 (4.6)	19.7 (4.8)	19.8 (4.7)
P value vs placebo			0.8947	0.3801
Digit Symbol Copy Test				
Morning 3	107.4 (24.5)	112.1 (21.8)	110.7 (23.3)	112.8 (20.7)
P value vs placebo			0.3803	0.6543
Morning 8		112.4 (21.0)	114.2 (20.2)	111.4 (23.9)
P value vs placebo			0.2348	0.5713
Digit Symbol Coding Test				
Morning 3	71.2 (19.2)	76.0 (20.2)	74.4 (19.9)	75.8 (18.5)
P value vs placebo			0.3039	0.7207
Morning 8		77.5 (21.0)	77.8 (18.6)	77.0 (18.9)
P value vs placebo			0.8419	0.9627
Completion Time for Digit Coding				
Morning 3	118.6 (11.8)	119.9 (1.4)	120.0 (0.0)	119.3 (8.5)
P value vs placebo			0.8808	0.3018
Morning 8		120.0 (0.0)	119.3 (8.7)	119.3 (8.6)
P value vs placebo			0.3672	0.4103

treatment for chronic primary insomnia.

ABBREVIATIONS

WASO	Wake time after sleep onset
WTDS	Wake time during sleep
N 1/2	Nights 1 and 2, combined
N 6/7	Nights 6 and 7, combined
CI	Confidence interval
LS	Least squares
ITT	Intent to treat
REM	Rapid eye movement
PSG	Polysomnography
SWS	Slow Wave Sleep
NAW	Number of awakenings
TST	Total sleep time
BzRA	Benzodiazepine receptor agonists

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The Arena 004 sleep study group
Bogan, Richard K. MD, Columbia, SC
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Hudson, John Douglas MD, Austin, TX
Lankford, D. Alan MD, Atlanta, GA
Mayleben, David W. MD, Cincinnati, OH,
Rice, Kathleen M. PhD, New York, NY
Rosenberg, Russell PhD, Atlanta, GA
Scharf, Martin PhD, Cincinnati, OH
Hull, Steven MD, Overland Park, KS
Thein, Stephen MD, San Diego, CA
Furman, Yury MD, Los Angeles, CA
Wells, Charles C. Jr. MD, Macon, GA
Graci, Gina PhD, Chicago, IL
Flescher, Jonathan MD, Raleigh, NC
Schwartz, Howard MD, South Miami, FL
Safirstein, Beth MD, Hallandale Beach, FL
Bird, C. David MD, Colorado Springs, CO
Salah, Jack MD, Jacksonville, FL
Emsellem, Helene MD, Chevy Chase, MD
Orr, William PhD, Oklahoma City, OK
Seiden, David J. MD, Pembroke Pines, FL
Erman, Milton K. MD, San Diego, CA
Summers, Brock H. MD, Burbank, CA
Simon, Stuart MD, Austell, GA

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