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Pimavanserin tartrate, a 5-HT_{2A} Receptor Inverse Agonist, Increases Slow Wave Sleep as Measured by Polysomnography in Healthy Adult Volunteers

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Abstract

Objective—Determine the effects of pimavanserin tartrate [ACP-103; N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide], a selective serotonin 5-HT_{2A} receptor inverse agonist, on slow wave sleep (SWS), other sleep parameters, and attention/vigilance.

Methods—Forty-five healthy adults were randomized to pimavanserin (1, 2.5, 5, or 20 mg) or placebo in a double-blind fashion (n = 9/group). Pimavanserin or placebo was administered once daily, in the morning, for 13 consecutive days. The effects of pimavanserin were measured after the first dose and again after 13 days. Sleep parameters were measured by polysomnography. Effects on attention/vigilance were measured by a continuous performance task.

Results—Compared to placebo, pimavanserin significantly increased SWS following single and multiple dose administration. Pimavanserin also decreased number of awakenings. PSG variables not affected by pimavanserin included sleep period time, total sleep time, sleep onset latency, number of stage shifts, total time awake, early morning wake, and microarousal index. Changes in sleep architecture parameters, sleep profile parameters, and spectral power density parameters were consistent with a selective increase in SWS. Pimavanserin did not adversely affect performance on the continuous performance test measured on the evening before or morning after polysomnography.

Conclusions—These data suggest that pimavanserin selectively increases slow wave sleep and decreases awakenings, an effect that does not diminish with repeated administration.

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Disclosure/Conflict of Interest

This work was supported by ACADIA Pharmaceuticals. Pimavanserin tartrate is an investigational drug under development by ACADIA. Drs. Vanover, Weiner, Davis, and van Kammen were employees of ACADIA at the time this study was designed and conducted. Dr. Ancoli-Israel was a paid consultant to ACADIA, helping with data analysis and interpretation. Dr. Ancoli-Israel is currently a consultant to Ferring Pharmaceuticals Inc., GlaxoSmithKline, Merck, NeuroVigil, Inc., Neurocrine Biosciences, Pfizer, Respirex, sanofi-aventis, Sepracor, Inc., Schering-Plough. Dr. Vanover is now a paid employee of Intra-Cellular Therapies, Inc. Dr. Weiner is now a paid employee of EMD Serono with no present financial interest in ACADIA or pimavanserin. Dr. Davis is now the President of 3-D Pharmaceutical Consultants. Dr. van Kammen is a paid employee of CHDI Foundation, Inc. and has no paid interest in ACADIA.

Keywords

5-HT_{2A} Receptor Inverse Agonist; Pimavanserin; Polysomnography; Serotonin; Sleep maintenance insomnia; Slow wave sleep

Introduction

With age, the amount of slow wave sleep (SWS) decreases. In the older adult, as the amount of SWS decreases, the amount of lighter levels of sleep increases. These sleep architecture changes potentially result in increased arousals, increased wakefulness, and sleep fragmentation. A recent meta-analysis suggested that most age-related sleep changes occur in early and mid- years of life. In healthy older adults, sleep remains relatively constant from age 60 to the mid-90s, except for sleep efficiency (SE, the amount of sleep given the amount of time in bed) that continues to decrease⁴. Nevertheless, about 50% of elderly (>65 years) complain about their sleep^{1,2}. The most common complaints in the older adults are of frequent awakenings (i.e., sleep maintenance insomnia) rather than trouble falling asleep or excessive daytime sleepiness which are more common in younger adults⁵. Sleep maintenance insomnia is also more common in patients with chronic medical, neurological and psychiatric diseases and in women⁶.

Many pharmacotherapies targeted for disorders of sleep have traditionally focused on sleep initiation. Such therapies include off-label use of antihistamines or sedating antidepressants⁷. Additionally, there are many drugs with Food and Drug Administration (FDA) approval for insomnia characterized by difficulty falling asleep, including benzodiazepines, non-benzodiazepine receptor agonists (BzRAs), and melatonin receptor agonists⁷. Only two of these compounds are indicated for sleep maintenance and both require that patients have about 8 hours available to sleep due to psychomotor sedation.

It should be noted that the soporific qualities, or ability to promote sleep, can be dissociated from psychomotor sedation that results in motor incoordination, ataxia, muscle relaxation, and cognitive impairment^{8,9}. Psychomotor sedation might increase a person's risk of falling¹⁰ and risk of fracture injuries¹¹ during the night and might increase next day cognitive impairment¹². Sedative/hypnotic drugs also have been associated with abnormal thinking, behavioral changes, and complex behaviors such as "sleep-driving" (i.e., driving while not fully awake and subsequent amnesia for the event).

Another alternative to the traditional BzRAs, sedating antidepressants and antihistamines, is a selective 5-HT_{2A} receptor antagonist or inverse agonist. Serotonin (5-HT) neurotransmission plays an important role in sleep and the 5-HT_{2A} receptor subtype is of particular interest. A selective 5-HT_{2A} receptor antagonist, M100907, increases non-rapid eye movement (NREM) sleep in mice, an effect that is abolished in 5-HT_{2A} receptor knockout mice¹⁴. Similarly, pimavanserin has been shown to increase NREM sleep in rats (unpublished observations). In humans, ritanserin, a 5-HT₂ receptor antagonist, has been shown to increase slow wave sleep in healthy volunteers after a single dose^{15,16,17,18} and after repeated administration¹⁹. Ritanserin also increases slow wave sleep in younger²⁰ and older²¹ poor sleepers, and in a variety of patient populations including those with depression²², dysthymic disorder²³, and generalized anxiety disorder²⁴. Another 5-HT₂ receptor antagonist, eplivanserin, also increases slow wave sleep²⁵. Thus, the proof of concept for 5-HT_{2A} receptor regulation of slow wave sleep EEG patterns has been established. Moreover, 5-HT_{2A} receptors may be involved in endocrine, behavioral, and body temperature homeostasis regulation^{26,27,28}, components that might be important during the state of slow wave sleep. Although other mechanisms also may be involved in the

regulation of slow wave sleep, it appears that 5-HT_{2A} receptor antagonism or inverse agonism is sufficient to increase slow wave sleep.

Pimavanserin tartrate [ACP-103; N- (4-fluorophenylmethyl)-N- (1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy) phenylmethyl) carbamide] is a novel 5-HT_{2A} receptor inverse agonist²⁹, that is long acting, with a half-life of about 55 hours³⁰. Treatment of sleep maintenance insomnia by chronic treatment of a long-lasting, non-sedating pharmaceutical agent administered in the morning represents a novel approach. As a first step to verify 5-HT_{2A} receptor inverse agonism in humans using slow wave sleep as a biomarker, pimavanserin was evaluated using polysomnography (PSG) in healthy volunteers. The purpose of the present study was to evaluate the effects of pimavanserin on sleep, as measured by PSG, and on day-time functioning, as measured by a continuous performance task (CPT), before and after a single dose and again after 13 days of repeated administration.

Methods

This was a single-center, randomized, placebo-controlled double-blind study conducted by FORENAP Pharma (France). Forty-five healthy male and female volunteers ranging in age from 40 to 75 years were randomized to one of five study arms: placebo, 1 mg, 2.5 mg, 5 mg, or 20 mg pimavanserin. After signing informed consent, participants underwent screening to ensure eligibility for the study and to exclude underlying medical disorders based on medical history, physical exam, vital signs, height and weight, electrocardiogram (ECG), clinical laboratory evaluations, concomitant medications, and testing for Hepatitis B, Hepatitis C, HIV, urine drug and alcohol levels. A two-night screening/baseline PSG evaluation occurred within 7 days of the clinical screening evaluation.

An Independent Ethics Committee approved the protocol and study related materials. This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, last revision, Tokyo 2004, and in compliance with the protocol, the Good Clinical Practices guidelines (ICH E6), and the local regulatory requirements.

Inclusion criteria included a reported bedtime between 9 pm and midnight, a usual sleep duration >4 hours, and habitual time in bed between 6 and 9 hours per night. With these criteria, subjects with insomnia were not specifically excluded. Women had to be postmenopausal or previously surgically sterilized in order to participate.

Exclusion criteria included a history or current diagnosis of other sleep disorders (such as restless leg syndrome, periodic leg movements with arousals, narcolepsy, rapid eye movement (REM) Behavior Disorder, circadian rhythm sleep disorder, breathing related sleep disorder, or parasomnias), smoking more than 10 cigarettes (or equivalent) per day, a history of alcohol or substance abuse or positive drug or alcohol screen, or drinking more than 5 cups of caffeine containing beverages, more than 1 liter of xanthine containing beverages, or more than 40 g of alcohol per day. Subjects were allowed to maintain their typical intake of caffeine, xanthine, alcohol and cigarettes throughout the study as long as they met these criteria to avoid excessive amounts. Participants with an occupational history that included shift work or recent significant travel across three or more time zones within the prior two weeks or self reported napping of >45 min per day were also excluded. In addition, after a screening PSG, participants with an apnea-hypopnea index > 15 or a periodic leg movement arousal index > 15 were also excluded.

During the assessment period, participants stayed overnight on the clinical unit for one night from Day -1 to Day 2 and one night from Day 13 to Day 14. Participants underwent a one-night PSG evaluation on the evening of Day 1, following the first dose of treatment and a

final one-night PSG evaluation on the evening of Day 13. Between Day 3 and Day 12, participants were at home.

The PSG recordings on Day 1 and Day 13 consisted of an all night recording of sleep parameters including two channels of EEG (C3 and O1 referred to contralateral mastoid), two channels of EOG (with electrode placement at the outer canthi in a superior and inferior position), and a single channel of EMG (with electrode placement in a sub-mental location). Polysomnographic recordings were performed from 23:00 to 07:00. Sleep recordings were scored at 30-s intervals for each stage of sleep using Rechtschaffen and Kales criteria³¹. Percent and duration of each sleep stage (i.e., stage 1, 2, SWS, REM). In addition, sleep period time, total sleep time (total recording duration minus waking duration), sleep onset latency (time from lights off to the first epoch of stage 2), number of stage shifts (number of times sleep stage shifts from one stage to another), total time awake, early morning wake (wake during the last 2 h of time in bed), microarousal index (return to alpha, differentiated from background EEG), number of awakenings after sleep onset and duration of awakenings were also computed.

Sleep diaries were kept by subjects and filled out each morning upon waking. Subjects were asked to answer a series of questions related to bed time, time to fall asleep, number of awakenings, time spent asleep, time spent awake, and time spent napping.

Participants were randomized to either pimavanserin (1, 2.5, 5, or 20 mg) or placebo. Pimavanserin or placebo was taken as an oral solution once a day in the morning (between 7:30 and 9:00 am) for 14 consecutive days. Study staff administered the study treatment during the days spent inpatient and a kit of vials with instructions was sent home with each subject. A 90-min window was allowed for taking the drug each morning to allow flexibility in subjects' schedules at home. Compliance with the dosing regimen was verified by subject verbal reports, by returned (empty) vials and by plasma sampling at the end of the two-week period. Sampling to determine plasma concentrations of pimavanserin occurred pre-dose on Study Day 14 to measure trough level at steady-state.

A Continuous Performance Test (CPT)^{32,33}, used to evaluate attention and vigilance, was administered both during the evening and the morning following the baseline PSG on Day 1 and the evaluation PSG on Day 13. The CPT consisted of a rapid presentation of a numerical train with a target number as point of reference. The task required the participant to push a button rapidly when a target number appears in a number list. The procedure lasted three minutes. Number of targets detected and number of false alarms were assessed.

Safety measures included 3-positional vital signs, ECGs, body temperature, and respiratory rates as well as blood chemistries, hematology, and urinalysis. Safety measures were assessed at screening, baseline (Day -1), Day 1, Day 2, Day 13, and Day 14. Any observed or reported adverse events were recorded. Blood samples were taken on Day -1 (baseline) and on Day 14 (estimated plasma steady-state); prepared plasma samples were frozen at -70°C and later analyzed by Quintiles, Inc. (Kansas City, Missouri, USA), using a validated high performance liquid chromatography/tandem mass spectrometric (LC/MS/MS) assay. An end-of-study clinical safety evaluation occurred two weeks after the termination of treatment administration.

The primary objective of the study was to determine the effects of pimavanserin on slow wave sleep. Secondary objectives included determining the effects of pimavanserin on other PSG measures, on attention/vigilance as assessed by CPT, and to evaluate the safety and tolerability of pimavanserin. A formal power analysis was not conducted, but the sample size was determined based on previous studies showing effects on slow wave sleep testing drugs with a similar mechanism of action^{15,20,25}.

For the primary endpoint of slow wave sleep, change from baseline to the last day of drug administration was assessed by an analysis of covariance with repeated measures (ANCOVA-RM), with the baseline variables as covariates, to detect group differences (pimavanserin versus placebo). For the ANCOVA, two main effects (Treatment, 4 levels and Study Day, 2 levels) and their interaction (Treatment * Study Day) were analyzed. Drug to placebo contrasts were calculated as a whole (Day 1 and Day 13 combined) as well as separately for each Study Day.

For secondary objectives, multivariate analyses of variance (MANOVA) with clusters of sleep parameters as dependent variables were conducted initially to look for overall effects on sleep clusters. The clusters included: Sleep Continuity & other PSG Parameters (e.g., number of awakenings, duration of wake after sleep onset, sleep period time, total sleep time, sleep onset latency, number of stage shifts, total time awake, early morning wake, and microarousal index), Sleep Architecture Parameters (e.g., duration and percent of wake after sleep onset, NREM sleep, SWS, REM sleep, stage1, and stage 2, as well as REM sleep latency, activity, and density), Sleep Profile Parameters (e.g., Number of REM/NREM cycles, Mean duration of REM/NREM cycles, REM 1st third of night, REM 2nd third of night, REM 3rd third of night, REM gravity center or the average of the occurrence of REM weighted by their duration, SWS 1st third, SWS 2nd third, SWS 3rd third, and SWS gravity center, or the average of the occurrence of SWS weighted by their duration), and Spectral Power Density Parameters (e.g., REM: Delta (0.5-3.5 Hz), Theta (4-7.5 Hz), Alpha (8-12.5 Hz), Beta 1 (13-21.5 Hz), Beta 2 (22-30 Hz) and NREM: Slow delta (0.5-1 Hz), Fast delta (1.5-3.5 Hz), Slow wave activity (0.5-3.5 Hz), Theta (4-7.5 Hz), Alpha (8-12.5 Hz), Spindle activity (11.5-15 Hz), Beta 1 (13-21.5 Hz), Beta 2 (22-30 Hz). The spectral power analysis was performed using a Fast Fourier Transform algorithm on consecutive 2-s epochs. Truncated error is reduced by applying a Hanning window and the values for 15 adjacent 2-s epochs were averaged to yield power density values for 30-s periods corresponding to the visual sleep scores. Post-hoc ANCOVA-RM analyses were conducted subsequent to the MANOVAs.

Change from baseline to the last day of drug administration, by group, on the results of the CPT was also analyzed. Additional pharmacodynamic analysis, including the electrographic results obtained on Study Day 1, was performed. SAS® Version 8.2 was used for non-pharmacokinetic parameters and WinNonLin V4.0 was used to compute all pharmacokinetic parameters.

Results

Demographics

Twenty-three (23) men and twenty-two (22) women were included in the study for a total of 45 participants randomized (Table 1). All 45 participants completed the study and were included in data analysis. There were no significant differences across dose groups for age, sex, height, weight or BMI.

Compliance

Compliance with the dosing regimen was reported to be high and was confirmed with the determination of pimavanserin plasma concentrations on the morning of Day 14. The mean plasma steady-state concentrations increased with increased dose and ranged from 1.6 ng/mL to 35.0 ng/mL (Table 2).

Subjective reports

There were no meaningful differences across individuals or groups in reported habitual sleep time or measured sleep parameters at baseline.

Primary analyses

Slow Wave Sleep—Table 3 reports the baseline values across groups for the primary outcome measure slow wave sleep. In order to control for possible effects of baseline values on outcome variables, baseline was included as a covariate in subsequent ANCOVAs.

Results of the ANCOVA on the primary endpoint, slow wave sleep showed a significant effect of Treatment ($p < 0.001$) and no main effect of Study Day nor Treatment by Study Day interaction. This suggests that the Treatment effect was similar across the 2 Study Days and that the 4 treatment conditions were not differently influenced by study day. Figure 1 and Table 3 show the SWS increase seen with pimavanserin administration. No significant difference between Study Days were found. As shown in Figure 2, a positive correlation was observed between SWS duration and pimavanserin plasma level ($r = 0.51$, 95% CI = 0.22 – 0.72; $r^2 = 0.26$, $p = 0.002$).

Secondary Analyses

Sleep Parameters—MANOVA on Treatment by Study Day effects resulted in significant Treatment effects of pimavanserin vs. placebo for all clusters of sleep parameters (e.g., sleep architecture, sleep profile, spectral power density) except “sleep continuity and other PSG” variables, suggesting that pimavanserin significantly influenced, as a whole, most of the sleep parameters under study. A Study Day effect (single versus repeated treatment administration) was observed only for NREM relative parameters for the spectral power density. No Study Day effect was observed for the 4 other clusters suggesting that most of the sleep EEG parameters under study were not influenced by Study Day.

Sleep Continuity & Other PSG Parameters—In agreement with MANOVA results showing no significant effect of Treatment, ANCOVAs performed on each of these sleep parameters taken separately were not significant for Treatment, for Study Day, or for Treatment by Study Day interaction. The sole exception was the number of awakenings for which a significant ($p < 0.05$) effect of Treatment was observed (Figure 3, Table 4), consistent with a shift to deeper sleep. Drug to placebo contrasts indicated that the 4 doses of pimavanserin statistically significantly decreased number of awakenings after sleep onset overall (combination of Day 1 and Day 13) and on Day 1. However, on Day 13, the number of awakenings after sleep onset was not statistically significantly decreased. Other PSG variables that were measured but not affected by pimavanserin included sleep period time, total sleep time, sleep onset latency, number of stage shifts, total time awake, early morning wake, and microarousal index.

Sleep Architecture Parameters—In agreement with MANOVA results showing a significant Treatment effect ($p < 0.001$), ANCOVAs revealed significant Treatment effects for most of the sleep architecture parameters: increased non-REM sleep duration ($p < 0.05$), increased non-REM sleep proportion ($p < 0.01$), decreased stage 2 (duration as well as proportion, $p < 0.05$), and increased slow wave sleep proportion ($p < 0.001$). For all sleep architecture parameters, neither significant Study Day effects nor Treatment by Study Day interactions were found. Pimavanserin had no effect on REM sleep duration, proportion of REM sleep, REM sleep latency, REM activity or REM density.

Sleep Profile Parameters—The MANOVA performed on sleep profile parameters showed a significant Treatment effect ($p < 0.001$). Results of the ANCOVAs revealed that

this Treatment effect mostly related to slow wave sleep parameters since significant Treatment effects were observed on duration of slow wave sleep on the first ($p < 0.01$) and second ($p < 0.001$) third of the night. There were no other Treatment effects for the other sleep profile parameters. For all ANCOVAs, neither significant Study Day effect nor a Treatment by Study Day interaction was observed.

Spectral Power Density Parameters—MANOVAs performed on spectral power density parameters revealed a significant Treatment effect ($p < 0.01$) without Study Day effect during REM sleep and a significant Treatment effect ($p < 0.001$) with a significant Study Day effect ($p < 0.001$) during NREM sleep. For REM sleep parameters, the sole significant ANOVAs Treatment effect was for Beta1 ($p < 0.05$). REM Beta1 was decreased by pimavanserin only on Day 13. For non-REM sleep parameters, pimavanserin significantly increased slow delta ($p < 0.001$), fast delta ($p < 0.001$), slow wave ($p < 0.001$), and theta ($p < 0.001$) activities, and decreased spindle frequency ($p < 0.001$) and Beta1 ($p < 0.001$) activities.

Performance—On the CPT, ANCOVAs indicated an absence of effect of any dose of pimavanserin on the detected targets and false alarm change scores, regardless of evaluation session and group ($p > 0.10$). None of the planned comparisons were significant or approached statistical significance ($p > 0.10$). These results suggest that pimavanserin had no negative effect on performance.

Adverse Effects and Safety—The adverse events, listed by dose, are presented in Table 5. The most frequent treatment-emergent adverse effect was headache with 14% of participants randomised to pimavanserin and 11% of participants randomised to placebo experiencing headache. Other treatment emergent adverse effects included those of gastrointestinal nature (6% of pimavanserin-treated participants and 22% of placebo-treated participants) and general disorders (8% of pimavanserin-treated participants and 33% of placebo-treated participants). All of the adverse events were mild to moderate in nature and there was no dose-relationship for any of the adverse events. There were no severe or serious adverse events. Interestingly, there were 2 participants treated with 5 mg pimavanserin who noted “deeper sleep” and one treated with 1 mg pimavanserin who noted “increased dreams”, whereas none of the participants randomised to placebo reported such changes in sleep-related events. Three events noted for 1 mg pimavanserin (and only 1 for placebo) in the general disorders category were “increased energy” during the day.

There were no clinically significant changes in blood chemistries, hematology, or urinalysis safety measures. All mean vital signs and ECG values were within normal ranges; individual changes in vital signs were considered not clinically significant.

Discussion

Morning administration of pimavanserin resulted in a statistically significant increase of slow wave sleep during the subsequent night in healthy volunteers. This effect was observed after a single administration and was sustained over 13 days with repeated administration. The two highest doses of pimavanserin (5 and 20 mg) had a greater effect on slow wave sleep than the two lowest doses. Doses of 5 mg and 20 mg and associated mean plasma levels ranging from 8.5 to 35.0 ng/mL showed robust and significant increases in parameters directly related to slow wave sleep. Increased plasma levels generally were associated with higher magnitude of effects. These dose dependent observations are consistent with a shift to deeper sleep.

That pimavanserin did not significantly increase total sleep time indicates that the increase in slow wave sleep occurs at the expense of some other sleep stages. Results indicate that the two highest doses of pimavanserin significantly decreased stage 2 sleep and spindle frequency activity, the spectral hallmark of stage 2. All REM sleep parameters were left unchanged by pimavanserin indicating that the drug did not interfere with the REM sleep regulation mechanism. Pimavanserin also did not affect sleep onset latency.

Pimavanserin was administered in the morning due to its relatively long time to peak effect (T_{max}) of about 6 hours and a long half-life of about 55 hours³⁰. Furthermore, pimavanserin is safe and well tolerated when administered in the morning as indicated by the safety parameters, including CPT, measured in the present study when plasma levels of pimavanserin were at or near their peak. Moreover, pimavanserin was shown to be safe and well tolerated at single doses up to and including 300 mg and multiple doses up to 100 mg once daily in the morning for 14 days³⁰, much higher doses than those utilized in the present study. A dose of pimavanserin just before bedtime would need to be sufficiently high to produce effective plasma levels within the first hour. For example, a single dose of 20 mg pimavanserin produces a similar plasma level (9.2 ng/mL)³⁰ as 5 mg pimavanserin produces at plasma steady-state (8.5 ng/mL). It is likely that a higher dose would cross the efficacy plasma level threshold earlier, but lower doses may be sufficient to maintain efficacy across days or weeks.

In the normal population, percent of slow wave sleep decreases with age resulting in a greater percent of stage 1 and stage 2 sleep³⁴. Benzodiazepines can cause an increase in stage 2 sleep and a decrease in slow wave sleep³⁵. Non-benzodiazepine receptor agonists and melatonin receptor agonists have no effect on SWS or other aspects of sleep architecture. In contrast, the present results showed that pimavanserin increased slow wave sleep. It has been suggested that an increase in slow wave sleep might be associated with improved sleep quality³⁶. However, the present study with pimavanserin did not measure quality of sleep nor was it statistically powered to be able to measure such a subjective effect.

One limitation of this study was that the effects of pimavanserin were measured in healthy adults. Additional studies evaluating the efficacy of pimavanserin in patients with insomnia are warranted. Such studies should include both objective (PSG) and subjective assessments in order to gain a clear understanding of efficacy for the treatment of sleep maintenance insomnia.

The increases in slow wave sleep induced by pimavanserin were consistent with the increases in slow wave sleep induced by ritanserin^{15,16,17,18} and eplivanserin²⁵. The results also were consistent with a 5-HT_{2A} receptor mechanism underlying slow wave sleep. Slow wave sleep may act as a useful biomarker for 5-HT_{2A} receptor antagonism or inverse agonism in translational drug development. Additionally, recent review articles support pursuing the role of increased slow wave sleep in the treatment of insomnia^{37,38}.

Another non-benzodiazepine receptor mechanism recently has been identified that also increases slow wave sleep and thus has potential for the treatment of insomnia. Gaboxadol, for example, is an extrasynaptic gamma-aminobutyric acid (GABA) receptor agonist rather than a traditional post-synaptic receptor agonist like the benzodiazepine receptor ligands³⁹. Gaboxadol has been shown to increase total sleep time and decrease the number of awakenings and time spent awake after sleep onset in healthy adults^{40,41} without affecting next day cognitive performance or mood⁴¹. However, the development of gaboxadol has been discontinued. Unlike the selective effect on slow wave sleep that pimavanserin and the 5-HT_{2A} receptor antagonists or inverse agonists have, gaboxadol also decreases the time it

takes to fall asleep and/or the perception of shorter sleep latency^{40,41}. Such GABA receptor modulators may therefore need to be administered shortly before bedtime whereas pimavanserin can be administered at any time of day as it is not sedating and does not induce sleep. In the present study, pimavanserin was administered once daily in the morning; significant effects were measured on sleep with no effect on performance either the evening before or the morning after the PSG nights. Chronic morning treatment of a long-lasting, non-sedating drug would be a new approach to the selective treatment of sleep maintenance insomnia. Only one other drug, low-dose doxepin, an antidepressant drug acting primarily as a histamine H1 antagonist at these low doses, has shown efficacy in the treatment of sleep maintenance insomnia.¹³

Pimavanserin was safe and well-tolerated in healthy adults and showed robust effects on sleep architecture, including increasing slow wave sleep and decreasing awakenings after sleep onset. These data suggest that pimavanserin should be evaluated for the treatment of sleep maintenance insomnia, with the potential to avoid interfering with other aspects of sleep architecture. Despite the limitations of benzodiazepines and agonists at benzodiazepine receptors, these agents remain the most effective and widespread treatments for insomnia. Much more research, including large placebo-controlled randomized clinical trials in patients with insomnia are needed to determine whether pimavanserin demonstrates both objective and subjective improvements in sleep in a patient population. That pimavanserin does not affect sleep latency onset suggests that future trials should target patients with difficulty maintaining sleep rather than patients with difficulty initiating sleep. Further, the dose-response relationships in a patient population need to be determined. Lastly, future research on the implications of a slow onset and long duration of action on the ideal timing of dosing (morning versus evening) need to be conducted.

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Figure 1.

The effects of pimavanserin on duration of slow wave sleep. Total baseline (BL) values are represented by the open bars. This figure shows the absolute change from baseline (min) as a function of dose group. Hatched bars represent the change from baseline of pimavanserin or placebo on day 1 (D1); the black bars show the change from baseline on day 13 (D13). Mean and standard deviations are shown.

Figure 2. Regression of slow wave sleep duration (min) on Day 13 vs. pimavanserin plasma level (ng/mL). Correlation $r = 0.51$, $p = 0.002$.

Figure 3.

The effects of pimavanserin on the number of awakenings after sleep onset. Total baseline (BL) values are represented by the open bars. This figure shows the absolute change from baseline (min) as a function of dose group. Hatched bars represent the change from baseline of pimavanserin or placebo on day 1 (D1); the black bars show the change from baseline on day 13 (D13). Mean and standard deviations are shown.

Table 1

Demographics of study participants (n = 45).

Demographic		Number of Subjects (Percent)
Sex	Female	22 (48.9%)
	Male	23 (51.1%)
Race	Caucasian	45 (100%)

Demographic	Mean ($\pm$ Standard Deviation)
Age (years)	51.8 ($\pm$ 6.9)
Weight (kg)	68.7 ($\pm$ 10.4)
Height (cm)	168.8 ($\pm$ 10.0)
BMI (kg/m ²)	24.1 ($\pm$ 2.7)

Table 2

Plasma concentrations of pimavanserin after 13 days once daily administration. Concentrations given in ng/mL (n=9/dose).

	1 mg	2.5 mg	5 mg	20 mg
Mean	1.63	3.65	8.52	35.03
Median	1.75	3.36	8.72	34.10
SD	0.46	1.07	2.13	10.18
Minimum	0.92	2.07	5.91	21.90
Maximum	2.33	5.55	13.00	52.70

SD = Standard deviation

Table 3

Effects of pimavanserin vs. placebo on duration (min) of slow wave sleep. Mean $\pm$ standard deviations are shown.

	Placebo	Pimavanserin			
Timepoint		1 mg N=9	2.5 mg N=9	5 mg N=9	20 mg N=9
Baseline		67.39 $\pm$ 32.09	63.39 $\pm$ 23.12	54.00 $\pm$ 30.88	57.61 $\pm$ 33.06
Day 1		56.22 $\pm$ 19.12	69.78 $\pm$ 32.14	75.83 $\pm$ 50.91	94.89 $\pm$ 39.84
Dis Mean ¹		17.3	32.4	48.1	57.9
p-value ²		0.178	0.013	<0.001	<0.001
Day 13		64.28 $\pm$ 13.96	68.78 $\pm$ 31.01	73.61 $\pm$ 50.82	99.56 $\pm$ 49.64
Dis Mean ¹		8.3	22.2	44.7	42.8
p-value ²		0.519	0.088	<0.001	<0.001
Overall Treatment Effect					
Dis Mean ¹		12.8	27.3	46.4	50.4
p-value ³		0.160	0.004	<0.001	<0.001
Overall ANCOVA for Treatment p < 0.001					

¹ Dis Mean = difference between least-squares means for each pimavanserin dose and placebo (pimavanserin minus placebo)

² p-value for Treatment effect from ANCOVA model at Timepoint

³ p-value for overall Treatment effect (averaged over Study Day 1 and Study Day 13)

Table 4

Effects of pimavanserin on number of awakenings after sleep onset (n=9/dose). Mean $\pm$ standard deviations are shown.

	Placebo	Pimavanserin			
Timepoint		1 mg	2.5 mg	5 mg	20 mg
Baseline	20.78 $\pm$ 9.51	21.11 $\pm$ 6.41	24.11 $\pm$ 7.20	26.22 $\pm$ 7.28	20.67 $\pm$ 7.94
Day 1	27.89 $\pm$ 10.39	20.22 $\pm$ 3.15	21.44 $\pm$ 6.84	20.67 $\pm$ 6.56	20.89 $\pm$ 11.82
Dls Mean ¹		-7.79	-7.70	-9.27	-6.96
p-value ²		0.017	0.019	0.005	0.032
Day 13	23.11 $\pm$ 5.80	20.78 $\pm$ 5.70	19.78 $\pm$ 6.00	21.78 $\pm$ 6.46	18.89 $\pm$ 6.81
Dls Mean ¹		-2.46	4.59	-3.38	-4.18
p-value ²		0.443	0.157	0.299	0.194
Overall Treatment Effect					
Dls Mean ¹		-5.13	-6.14	-6.32	-5.57
p-value ³		0.026	0.009	0.008	0.016
Overall ANCOVA for Treatment p < 0.05					

¹ Dls Mean = difference between least-squares means for each pimavanserin dose and placebo (pimavanserin minus placebo)

² p-value for Treatment effect from ANCOVA model at Timepoint

³ p-value for overall Treatment effect (averaged over Study Day 1 and Study Day 13)

Table 5

Treatment-emergent adverse events, presented by dose of pimavanserin.

System organ class (SOC)	Placebo N = 9	ACP-103 1 mg N = 9	ACP-103 2.5 mg N = 9	ACP-103 5 mg N = 9	ACP-103 20mg N = 9
Preferred term (PT)					
Gastrointestinal disorders	2	-	-	2	-
Abdominal pain	1	-	-	-	-
Vomiting	1	-	-	-	-
Diarrhoea	-	-	-	1	-
Nausea	-	-	-	1	-
General disorders and administration site conditions	3	3	-	-	-
Asthenia	2	-	-	-	-
Energy increased	1	3	-	-	-
Infections and infestations	1	-	-	1	1
Urinary tract infection	-	-	-	1	-
Rhinitis	1	-	-	-	1
Musculoskeletal and connective tissue disorders	-	-	-	1	-
Myalgia	-	-	-	1	-
Nervous system disorders	1	-	2	3	1
Headache	1	-	1	3	1
Disturbance in attention	-	-	1	-	-
Psychiatric disorders	-	1	-	2	-
Sleep disorder	-	1	-	2	-
Total	7	4	2	9	2