Cover Page

Official Study Title: Three Approaches to Maintenance Therapy for Chronic Insomnia in Older Adults

NCT Number: NCT03774810

Date: 04/12/2022

The Effects of Solriamfetol and CBT-I (alone and in combination) on Sleep Continuity, Sleepiness, Fatigue, and Performance in Patients with Insomnia Disorder.

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Regulatory Sponsor	This work is supported by Axsome Pharmaceuticals
NIH Grant Number	*N/A*
Investigational Product:	Solriamfetol
Protocol Number:	850945
IND/ IDE Number: *[If applicable]*	*N/A*
ClinicalTrials.gov Number	*In process*
Title	The Effects of Solriamfetol and CBT-I (alone and in combination) on Sleep Continuity, Sleepiness, Fatigue, and Performance in Patients with Insomnia Disorder.
Short Title	Solriamfetol and CBT-I
Study Summary	Medication is FDA approved. The objective of this project is to test the efficacy of solriamfetol for treating insomnia (alone and in combination with CBT-I). Ultimately, this study will test whether wake extension (regardless of how it is achieved) will consolidate sleep and improve sleep continuity.
Methodology	Please see investigational plan for more information
Study Duration	12-18 months
Study Center(s)	One site only: Penn Behavioral Sleep Medicine Program
Objectives	1. To investigate the effects of solriamfetol on sleep continuity, alone and in combination with CBT-I. 2. Assess the effects of solriamfetol on daytime sleepiness, fatigue, adherence with “sleep rescheduling”, and on daytime performance
Number of Subjects	We will enroll and complete 40 subjects with Insomnia Disorder (60 recruited and a min. of 40 completed subjects).

Main Inclusion and Exclusion Criteria	Subjects. Subjects will be between the ages of 25-65 years old and have a stable sleep/wake schedule (no shift work) with a preferred sleep phase between 9:00 PM and 9:00 AM. Inclusion Criteria. Adults $\geq$ 25 and $\leq$ 65 years of age with chronic insomnia who meet DSM-5 criteria for Insomnia Disorder and ICSD-3 criteria for Psychophysiologic insomnia. In addition, all subjects will have a sleep initiation and/or a sleep maintenance complaint ($\geq$ 30 min. to fall asleep and/or $\geq$ 30 min. of wakefulness during the night) with a problem frequency $\geq$ 3 nights/wk and problem duration $\geq$ 3 mo. This profile must be evident at both intake (based on retrospective reports) and as an average profile from the two weeks of baseline diaries (based on prospective sampling). Exclusion Criteria for All Subjects. In brief, the exclusionary criteria are currently in treatment for insomnia, unstable medical or psychiatric illness, night shift work, and/or a history of other sleep disorders.
Investigational Product (drug, biologic, device, etc.)	Solriamfetol (trade name: Sunosi), 75mg.
Duration of administration (if applicable)	4 weeks
Reference therapy	Cognitive Behavioral Therapy for Insomnia (CBT-I)
Statistical Methodology	A 2x2 mixed model design. The two factors will be 1) treatment (+/- solriamfetol and +/- CBT-I) and 2) Time (pre-post assessment, with additional follow-up data).
Safety Evaluations	Daily diary assessments of side effects, weekly symptom checklists to monitor the health status of subjects (upon disbursement of medication). We will utilize a side-effect check list based on the package insert for Solriamfetol.
Data and Safety Monitoring Plan	We will establish a four-person advisory board comprised of a second MD sleep medicine specialist, a clinical psychologist, a nurse sleep scientist, and a biostatistician. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflicts of interest with the trial. Collaborators of the PIs will not be eligible to serve on the advisory board. The board will receive reports from the study team every six months with information about the progress of recruitment, the demographic characteristics of participants, serious adverse events, the number of dropouts, and participants' reasons for dropping out, and any protocol amendments. These meetings will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

BACKGROUND AND STUDY RATIONALE

1. Introduction

Background and Relevant Literature

Presently, treatment for insomnia (in the case of cognitive behavioral treatment for insomnia [CBT-I]) focuses on limiting time in bed to reduce night-time wakefulness, thereby improving sleep continuity and daytime performance. The proposed project approaches insomnia treatment differently: the same outcomes may be achieved by enhancing and/or extending wakefulness during the day. The current proposal will test whether enhancing daytime wakefulness using a wake-promoting medication, solriamfetol, can improve sleep continuity and daytime performance, both as a stand-alone and in combination with CBT-I.

The current pharmacological approach for the treatment of insomnia is largely sedative medications, which promote sleep and have some benefit, but considerably limited efficacy compared to cognitive behavioral treatment for insomnia (CBT-I). Part of the mechanism of action for CBT-I is that over the course of 2-6 weeks of behavioral treatment, time in bed is severely limited, which has the intended outcome of increasing homeostatic sleep drive and thereby reducing night-time wakefulness. The current unknown is whether implementing this mechanism via wake-promoting medication can achieve efficacious outcomes. It is expected (given a common mechanism [wake extension]) that both CBT-I and treatment with solriamfetol [SFTRL] will improve sleep continuity, and that such effects will potentially be additive. Preliminary work by our group with another wake promoting medication suggests that such outcomes are feasible (PMID: 15283007). If successful, this unique treatment approach may provide an important alternative for patients that do not tolerate sleep restriction during CBT-I or for whom the transient iatrogenic sleepiness of CBT-I represents an unacceptable risk (e.g., surgeons, pilots, etc.).

2. Name and Description of the Investigational Product

Solriamfetol (trade name Sunosi), is a norepinephrine-dopamine reuptake inhibitor available in 75mg and 150mg tablets for oral administration during the day. Solriamfetol's primary indication is to treat excessive daytime sleepiness (EDS) in patients diagnosed with OSA or Narcolepsy. It binds to the dopamine transporter and the norepinephrine transporter with affinities (Ki) of 14.2 μM and 3.7 μM, respectively), does not undergo significant metabolism in humans, and has a Tmax of ~2 hours (range 1.25–3.0 hours) and a T1/2 of ~7.1 hours. The pharmacokinetic profile of solriamfetol, along with the absence of active metabolites, makes it unlikely that there are accumulation effects with multiple doses over days. See the attachment for a copy of the package insert for solriamfetol.

Solriamfetol will be provided by Axsome Pharmaceuticals (no cost), and managed by, the Investigational Drug Services of the University of Pennsylvania. An over encapsulation technique will be used to ensure that the drug doses and placebo formulations appear identical. The first five participants will be enrolled slowly to observe whether any adverse responses occur (e.g., taking longer to fall asleep after medication administration at 2pm) that would necessitate protocol modifications, for instance to the timing of medication dosing, if not amount.

Solriamfetol or placebo will be administered at 2pm daily for 4 weeks. Dosage will (for all subjects) start at 75mg. This dosage was chosen through weighing up the need to extend wake/delay bedtime to consolidate sleep and improve sleep continuity (necessitating a later timing of dose than typical), without inadvertently enhancing wake to the point where it extends sleep latency. Rather than downwardly titrate the medication, the timing of dosing will be altered where required (for example, timing advanced to 1pm or 12pm). Changes in dose timing will occur when the study staff (therapist, PI, and medical collaborator) deem it to be optimal (i.e., in response to extended sleep latency). Subjects in the SRFT + CBT-I arm will also be eligible for changes in dose timing if they report being unable to adhere to the prescribed time to bed (PTTB) component of CBT-I. As noted above, medication use will also include a 1-week placebo run-in and a 3-week placebo "run-out" (eight weeks' total). The timing of the first administration of SRFTL will (for those receiving CBT-I) align with the start of sleep restriction (Session 2).

All study medication will be provided by Axsome Pharmaceuticals (no cost) and will be received, stored, and packaged by the University of Pennsylvania Investigational Drug Service (IDS). IDS will create blister packs for each patient that are identical and will allocate active medication and placebo according to treatment condition. This will enable double blinding of the study. All doses will be over-encapsulated, and all daily doses will be delivered as a single capsule. The use of blister

packs will also allow us to not only track adherence but to identify the patterning of medication use. Blister packs will be returned once a month when subjects will be evaluated and provided the next month's medication supply. The study CRC will dispense and receive the foil packs. The pattern of used and unused data will be coded.

2.1 Nonclinical and Clinical Data To Date

The use of solriamfetol to treat EDS has been evaluated and extensively profiled in the literature. Given the shared EDS phenotype between narcolepsy, OSA, and insomnia, such data support that solriamfetol may be useful in those patients who cannot or do not tolerate the iatrogenic effects of sleepiness in CBT-I. Three such studies are listed below:

Krystal, A. D., Benca, R. M., Rosenberg, R., Schweitzer, P. K., Malhotra, A., Babson, K., ... & Strohl, K. P. (2022). Solriamfetol treatment of excessive daytime sleepiness in participants with narcolepsy or obstructive sleep apnea with a history of depression. Journal of psychiatric research, 155, 202-210.

Subedi, R., Singh, R., Thakur, R. K., Bibek, K. C., Jha, D., & Ray, B. K. (2020). Efficacy and safety of solriamfetol for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea: a systematic review and meta-analysis of clinical trials. Sleep Medicine, 75, 510-521.

Servid, S. (2012). New Drug Evaluation: solriamfetol tablets, oral.

2.2 Human Pharmacokinetics The time to peak levels of solriamfetol is about 2 hours (range 1.25–3.0 hours). Solriamfetol is minimally metabolized in humans. Its elimination half-life is about 7.1 hours.

2.3 Clinical Studies in Adults Please see section 1.2.1

2.4 Clinical Studies in Children N/A

2.5 Dose Rationale (if applicable) 75mg was chosen through weighing up the need to extend wake/delay bedtime to consolidate sleep and improve sleep continuity (necessitating a later timing of dose than typical), without inadvertently enhancing wake to the point where it extends sleep latency. Rather than downwardly titrate the medication, the timing of dosing will be altered where required (for example, timing advanced to 1pm or 12pm). Changes in dose timing will occur when the study staff (therapist, PI, and medical collaborator) deem it to be optimal (i.e., in response to extended sleep latency). Subjects in the SRFT + CBT-I arm will also be eligible for changes in dose timing if they report being unable to adhere to the prescribed time to bed (PTTB) component of CBT-I.

3 Study Objectives

As noted above, the current proposal is for a one-year study to investigate whether solriamfetol can improve sleep continuity and daytime performance, alone and in combination with CBT-I. It is expected (given a common mechanism [wake extension]) that both CBT-I and treatment with solriamfetol will improve sleep continuity, and that such effects will potentially be additive.

3.1 Primary Objective(s)

To investigate the effects of solriamfetol on sleep continuity, alone and in combination with CBT-I.

3.2 Secondary Objectives (if applicable)

Assess the effects of solriamfetol on daytime sleepiness, fatigue, adherence with "sleep rescheduling", and on daytime performance

4. Investigational Plan

All subjects will be monitored for 2 weeks prior to treatment, for 8 weeks during treatment, and for 2 weeks following treatment. Additionally, subjects will complete two questionnaires complete two questionnaires (Insomnia Severity Index [ISI] and Retrospective Sleep Continuity Assessment Questionnaire [RSCAQ]) 3 months after completing treatment.3 months after completing treatment. Subjects receiving solriamfetol will take medication at 2pm daily for 4 weeks. Medication use will also include a 1-week placebo run-in and a 3-week placebo "run-out" (8 weeks' total). Note: This design was used for our prior trials of CBT-I with wake promoting medications. Subjects receiving CBT-I will have 8 weekly

sessions (up to 90 minutes in duration). Daily sleep diaries will be administered to assess for differences in sleep continuity between conditions and over time. Self-report weekly assessments will also be administered and will include standard retrospective measures of insomnia (ISI), sleepiness (Epworth Sleepiness Scale, ESS), depression (PHQ-9), fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue Scale [*FACIT-Fatigue*], PROMIS-Short Form 7a, and Brief Fatigue Inventory [BFI]), treatment acceptability (MITAS)), and daytime function (Functional Outcomes of Sleep-10 item, FOSQ-10). Daytime function will also be objectively assessed daily via Ecological Momentary Assessment and at the end of baseline treatment, and post treatment periods using a PVT phone-based app. Self-report assessments will be accomplished on-line via RedCap software and subjects will also be asked to complete weekly and monthly questionnaires via Hypknowledge (a PHT Penn Health Tech Clinical Research Tool) site.

Treatment Regimen (as noted above)

The first five participants will be enrolled slowly to observe whether any adverse responses occur (e.g., taking longer to fall asleep after medication administration at 2pm) that would necessitate protocol modifications, for instance to the timing of medication dosing, if not amount.

Medication: Solriamfetol (SRFTL) or placebo (PLA) will be administered at 2pm daily for 4 weeks. Dosage will (for all subjects) start at 75mg. This dosage was chosen through weighing up the need to extend wake/delay bedtime to consolidate sleep and improve sleep continuity (necessitating a later timing of dose than typical), without inadvertently enhancing wake to the point where it extends sleep latency. Rather than downwardly titrate the medication, the timing of dosing will be altered where required (for example, timing advanced to 1pm or 12pm). Changes in dose timing will occur when the study staff (therapist, PI, and medical collaborator) deem it to be optimal (i.e., in response to extended sleep latency). Subjects in the SRFT + CBT-I arm will also be eligible for changes in dose timing if they report being unable to adhere to the prescribed time to bed (PTTB) component of CBT-I. As noted above, medication use will also include a 1-week placebo run-in and a 3-week placebo "run-out" (eight weeks' total). The timing of the first administration of SRFTL will (for those receiving CBT-I) align with the start of sleep restriction (Session 2).

All study medication will be provided by Axsome Pharmaceuticals (no cost) and will be received, stored, and packaged by the University of Pennsylvania Investigational Drug Service (IDS). DS will create blister packs for each patient that are identical and will allocate active medication and placebo according to treatment condition. This will enable double blinding of the study. All doses will be over-encapsulated, and all daily doses will be delivered as a single capsule. The use of blister packs will also allow us to not only track adherence but to identify the patterning of medication use.

Cognitive Behavioral Therapy: Treatment will be conducted by a master therapist via a HIPAA compliant video link (Zoom), with 1-2 members of our established cohort of CBT-I experts (n=17) serving as backup therapists. Sessions 1-8 will follow our published protocol (published in 2005 by Springer). Each session will be conducted individually and have a singular focus per session. All sessions following the delivery of sleep restriction therapy & stimulus control instructions (post Session 2) will include, as needed, management of non-adherence and/or time-in-bed titration. The Session specific itinerary will be as follows.

Session 1: evaluation and orientation
Session 2: data acquisition and delivery of sleep restriction therapy & stimulus control instructions
Session 3: review of sleep hygiene
Session 4: management of non-adherence and/or time-in-bed titration only
Session 5: cognitive therapy [de-catastrophization]
Session 6: management of non-adherence and/or time-in-bed titration only
Session 7: management of non-adherence and/or time-in-bed titration only
Session 8: review of treatment progress and relapse prevention.

All treatment will be delivered by a single master therapist (DA Posner PhD CBSM). Dr. Posner has more than 27 years' experience with CBT-I, he is one of the authors of our published treatment manual (1), and he is also a co-author of a second CBT-I treatment manual (2). He was a consultant for the VA's rollout of CBT-I, he jointly conducts the Penn 3-day Basic and Advanced CBT-I courses, and he regularly conducts on-site one-day CBT-I workshops. As a final testament to his expertise, he was one of the first individuals to be certified in behavioral sleep medicine and one of the first to receive the SBSM's Distinguished Career Achievement Award.

***5.* General Design**
A double blind 2x2 mixed model design. The two factors will be 1) treatment (+/- solriamfetol and +/- CBT-I) and 2) Time (pre-post assessment, with additional follow-up data). Patients with insomnia will be randomly assigned to treatment condition.

5.1 Screening
Participants with insomnia will be recruited via established recruitment approaches. Advertising includes social media strategies, which have been found to be maximally productive (e.g., Google and Facebook Ads where the catchment is limited to within 60 miles of Philadelphia). Potential participants will be provided with contact information and a link to our screening page (www.sleeplessinphilly.com), which has proved successful in past studies. The study CRC and/or PI will review the screening form and contact the participant via e-mail to let them know whether or not they pass this screening stage. If so, participants will provide physician assent to confirm eligibility. If they are eligible, the CRC and/or the PI will follow-up with the participant via HIPAA compliant telehealth to complete the consent and provide more information about the study.

Please note that the intake questionnaires to be used include a set of measures that are validated and a set of measures that are specific to our laboratory. Subjects that are still eligible after the intake interview will be instructed to obtain their PCP's assent to participate in the study.

Following the intake, all subjects that remain eligible for the proposed study will complete two more assessments prior to being enrolled in the proposed experiment. First, each subject will complete two weeks of daily sleep diaries to confirm 1) their retrospective estimates regarding the type, severity, and frequency of their insomnia and 2) that they are compliant with the daily task of completing the daily diaries. Second, each subject will undergo a Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study) study to rule out the presence of occult sleep disorders (sleep disorders for which the patient does not exhibit the typical signs and symptoms). This sleep study will be equivalent to the quality of a clinical PSG. These screenings will be conducted according to the Penn CSI Sleep Research Laboratory's standards. The recording montage consists of 14 electrophysiological signals. The basic montage includes 2 EOGs referenced to a single mastoid [LOC & ROC], 6 EEGs referenced to linked mastoids [F3, F4,C3,C4,O1,&O2,], 1 bipolar mentalis EMG, an EKG, 2 bipolar tibial EMGs, a nasal/oral airflow thermocouple, 2 respiratory effort sensors, and an oximeter measure of blood oxygen saturation. All 14 signals will be recorded with SD32 amplifiers and use Sandman v10 acquisition software to transmit data directly to the control room where the PSG can be monitored online and simultaneously recorded to PCs located in the control room. PSG data will be scored according to Rechtschaffen, and Kale's standards and the sleep continuity and sleep architecture variables will be calculated using lab standard definitions. Additionally, AI/AHI indices will be calculated according to AASM criteria. Subjects with an AI (vs. AHI) of >10 will be ineligible for the proposed study.

5.2 Study Intervention Phase
See section 3.0 – Investigation Plan.

5.3 Phase II (if applicable include and add details about open label study phase if appropriate)
See section 3.0 – Investigation Plan.

5.4 Follow Up Phase
Three months after completion of treatment, subjects will complete two questionnaires (Insomnia Severity Index [ISI] and Retrospective Sleep Continuity Assessment Questionnaire [RSCAQ]).

5.5 Allocation to Interventional Group
The study statistician and/or staff member of the Investigational Drug Services will execute the randomization procedures.

5.6 Study Endpoints
<u>Primary hypothesis</u>

1. Patients administered solriamfetol will have significantly greater improvements in sleep continuity (total wake time [TWT]) from baseline to post-treatment compared to patients administered placebos. Note: the study is powered for this hypothesis.

5.6.1 Primary Study Endpoints
As noted in section 3.2

5.6.2 Secondary Study Endpoints

1. Patients treated with CBT-I will have significantly greater improvements in sleep continuity from baseline to post-treatment compared to patients not administered CBT-I.

2. Patients treated with CBT-I in combination with solriamfetol with have significantly greater improvements in sleep continuity from baseline to post-treatment compared to patients treated with CBT-I alone.
3. **Exploratory hypotheses:** Patients treated with CBT-I in combination with solriamfetol will have significantly greater adherence with sleep restriction (i.e., sleep rescheduling, prescribed time to bed [PTTB]) and on daytime performance measures (e.g., ESS, FSS, etc.) compared to CBT-I alone.

i. Primary Safety Endpoints [if applicable]

As noted above, side effects will be assessed in several ways: daily assessments via the sleep diaries, weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected).

6. Study Population and Duration of Participation

Subjects 25 to 65 years old (inclusive) and who have a stable sleep/wake schedule (no shift work) with a preferred sleep phase between 10:00 PM and 8:00 AM. The recruitment sample will be populated by 40 completed subjects. The study duration will be 12 weeks, with a one-time follow-up at 3 months post-treatment.

a. Inclusion Criteria

Participants will meet the diagnostic criteria for Insomnia Disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM–5). The complaint of disturbed sleep will meet the following criteria:

- $\geq$ 30 minutes to fall asleep (SL) and/or $\geq$ 2 awakenings per night of $\geq$ 15 minutes duration and/or wake after sleep onset (WASO) time of $\geq$ 30 minutes where total sleep time (TST) did not exceed 6 hours (unless sleep efficiency [SE] is $\leq$ 80%).
- The problem is present for $\geq$ 3 nights per week.
- The problem duration exceeds $\geq$ 6 months.
- The complaint of impaired daytime function must include, although not limited to, the report of daytime fatigue, sleepiness, or both.

Additional inclusion criteria are as follows.

1. Aged 25 to 65 years (inclusive).
2. Have a preferred regular sleep phase between 10:00 PM and 8:00 AM.

b. Exclusion Criteria

Please note that all subjects will have to receive physician assent before being enrolled into the study.

Use of medication expressly for the purpose of falling or staying asleep (e.g., trazadone/ desyrel, melatonin, Tylenol PM, Nyquil, Benadryl).
Assessed with patient Hx
While medication can be used while participating in CBT-I, it is recommended that medications taken for sleep be discontinued.

Night shift work
Assessed with patient Hx
To ensure enrolled subjects are on a normal sleep schedule

Compromised renal function
Assessed with patient Hx
Will ascertain physician assent
To ensure the safety of the subject as Solriamfetol has been found to be contraindicated in those with renal impairment.

Use of MAOIs
Assessed with patient Hx
Will ascertain physician assent
To ensure safety as MAOIs are contraindicated with the concurrent use of solriamfetol

Major Coronary Artery Disease and/or uncontrolled (with meds) Hypertension
Assessed with patient Hx
Will ascertain physician assent
To ensure safety as solriamfetol is contraindicated in patients with these disorders

Planning to become pregnant, pregnant, and/or breastfeeding
Assessed with patient Hx (will ensure use of birth control methods on the screening form)
To ensure safety as solriamfetol has not been demonstrated to be safe for use while pregnant and/or breast feeding.

Unstable medical or psychiatric illness
Assessed with the patient Hx, PHQ-9, and the GAD-7
Assessed with a History and Physical, an EKG, and a clinical chemistries panel
To ensure that the insomnia is not comorbid with unstable medical or psychiatric illness (e.g., Bipolar Disorder)

Symptoms suggestive of sleep disorders other than insomnia
Assessed with the Sleep Disorders Symptoms Checklist (SDS-CL).
To ensure that the insomnia is not comorbid with other intrinsic sleep disorders

Polysomnographic data indicating sleep disorders other than insomnia
Assessed with Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study).
Subjects w/ an AI of >10 are excluded from the study

Subjects w/ an abnormal Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study) are excluded from the study
To ensure that the insomnia is not comorbid with other intrinsic sleep disorders.

Evidence of active illicit substance use, abuse, or dependence
Assessed with the patient Hx
Assessed with the AUDIT and CAGE
To ensure that the insomnia is not comorbid with alcoholism or substance abuse

Use of CNS active medications that are for treatment of insomnia or are thought to have caused insomnia as a side effect
Assessed by self-report
To ensure that the clinical effects observed in this study are not obscured by other medications

Inadequate language comprehension
Assessed informally by the Clinical Research Coordinator during Intake Interview
To ensure the quality of self-report data as all the measures are in English.

Current or past experience with CBT-I
Assessed with patient Hx
To evaluate why CBT-I was potentially unsuccessful in the past

No access to the computers, I-Pads, or the internet
Since the primary recruitment methods are via the internet, this is likely to be a non-issue.

c. Subject Recruitment

A broad strategy will be employed to recruit subjects so that our annual recruitment goals can be met or exceeded. The primary methods will be use of our volunteer database (presently more than 3500 individuals), ResearchMatch, Craigslist, and an Electronic Medical Records (EMR) query through the University of Pennsylvania Data Analytics Center (DAC). DAC EMR data consists of individuals diagnosed with Insomnia and/or individuals who have receive one or more prescriptions for Insomnia. These strategies will be supplemented with local advertisements on cable TV, radio, city newspapers, local sleep centers, recruitment boards on Penn's campus, other community centers (e.g., senior citizen living centers), and

places of business (e.g., restaurants). All recruitment emails will be sent via REDCap's utility for group emails, and no individual will ever be contacted more than three times.

Additionally, compensation will be pro-rated for each component of the study for a total of $500 per participant. Specifically, each participant will receive $50 for completing the screening visit, $25 for fully completing baseline sleep diaries, $200 for fully completing all sleep diaries and questionnaires during the treatment period (8 weeks), $100 for completing the study, and $125 for completing the follow-up assessment.

d. Duration of Study Participation

All subjects will be monitored for 2 weeks prior to treatment, for 8 weeks during treatment, and for 2 weeks following treatment. Subjects receiving solriamfetol will take medication at 2pm daily for 4 weeks. Medication use will also include a 1-week placebo run-in and a 3-week placebo "run-out" (8 weeks' total). Additionally, follow-up questionnaires will be completed 3 months after end of treatment (Insomnia Severity Index [ISI] and Retrospective Sleep Continuity Assessment Questionnaire [RSCAQ]).

e. Total Number of Subjects and Sites

40 subjects recruited and completed Phase-1 at one site (Penn).

f. Vulnerable Populations:

The study does not involve any of the following populations:

- Pregnant women
- Fetuses or neonates
- Prisoners
- Children

No subjects, including the economically disadvantaged, employees, and/or students at Penn, will be unduly influenced, encouraged, or coerced into participating in this study. These populations will not be targeted or excluded. IF they are encountered and would like to participate, the appropriate measures will be taken in order to allow them the opportunity to provide consent.

7. Study Intervention (Study drug, device, biologic, vaccine, food etc.)

Solriamfetol, 75mg

a. Description

Solriamfetol (trade name Sunosi), is a norepinephrine-dopamine reuptake inhibitor available in 75mg and 150mg tablets for oral administration during the day. Solriamfetol's primary indication is to treat excessive daytime sleepiness (EDS) in patients diagnosed with OSA or Narcolepsy. It binds to the dopamine transporter and the norepinephrine transporter with affinities (Ki) of 14.2 µM and 3.7 µM, respectively), does not undergo significant metabolism in humans, and has a Tmax of ~2 hours (range 1.25–3.0 hours) and a T1/2 of ~7.1 hours. The pharmacokinetic profile of solriamfetol, along with the absence of active metabolites, makes it unlikely that there are accumulation effects with multiple doses over days. See the attachment for a copy of the package insert for solriamfetol.

b. Intervention Regimen

A 2x2 mixed model design. The two factors will be 1) <u>treatment</u> (+/- solriamfetol and +/- CBT-I) and 2) <u>Time</u> (pre-post assessment, with additional follow-up data). Patients with insomnia will be randomly assigned to treatment condition.

c. Receipt

Solriamfetol will be provided (at no cost) by Axsome, and managed by, the Investigational Drug Services of the University of Pennsylvania.

d. Storage

Formulation and storage will be accomplished by Investigational Drug Services of the University of Pennsylvania.

e. Preparation and Packaging

An over encapsulation technique will be used to ensure that the drug doses and placebo formulations appear identical. Over encapsulation will be accomplished by using green and yellow capsules. While over encapsulation may slow the absorption of study medication, this should not pose a risk to participants nor compromise the experimental design as the slower absorption is constant to condition. Treatment will consist of 75mg of solriamfetol or one or more of inactive ingredients in solriamfetol tablets (hydroxypropyl, cellulose, and magnesium stearate.). All subjects will be instructed to

take the medication or placebo at 2pm for 4 weeks. IDS will create blister packs for each patient that are identical and will allocate active medication and placebo according to treatment condition. This will enable double blinding of the study. All doses will be over-encapsulated, and all daily doses will be delivered as a single capsule. The use of blister packs will also allow us to not only track adherence but to identify the patterning of medication use.

f. Blinding

Blinding will be accomplished by the Investigational Drug Services (IDS) of the University of Pennsylvania. As noted above, placement of medication will be coded per pack (so as to allow for the post hoc assessment of which nights of the week were medication and which were placebo).

g. Administration and Accountability

The study CRC will dispense and receive the foil packs. The pattern of used and unused medication will be captured by xeroxing or photographing each foil pack. Once a subject has completed their participation in the study (i.e., they have either completed the study, experienced treatment non-response or relapse, or withdrew from the study) they will be given the option to either (a) come to our office at 3535 Market St. and return the blister packs to the CRC, who will bring them to IDS for destruction or (b) take the blister-packs to a local pharmacy and record a video of themselves placing the blister-packs in a safe drug disposal box, and share the video with study staff. This can be done via email or by uploading the video via REDCap (see example link: https://redcap.med.upenn.edu/surveys/?s=XE4T3MKRTPNL7JY7). The video will not include the subject's face or other identifying information. This will ensure that the medication is properly disposed of, and that this disposal is documented. Note: the study's informed consent already mentions that we cannot guarantee the security of email correspondence, and that email privacy is based on the email provider's user agreement. We will remind subjects of this so they can consider this factor when deciding whether to return the medication to our office (no video required) or to their local pharmacy's drug disposal box (video required).

h. Subject Compliance Monitoring

Pill use will be tracked per week via the sleep diary. These data will be compared to, and corroborated with, the foil pack data.

i. Return or Destruction of Investigational Product

Blister packs will be returned once the subject has completed the study. Following the archiving of the pill pack (pill utilization pattern captured by xeroxing or photograph) the study CRC will return the foil packs and remaining capsules to Investigational Drug Services of the University of Pennsylvania for destruction.

8. Study Procedures

All subjects will receive medication and complete daily sleep diaries and weekly questionnaires.

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☐ Yes ☒ No

Check of all that apply:

☐ 1.5T MRI
☐ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/or coils?
(See Experimental Device Clause)

☐ Yes ☒ No ☐ Unsure

Does your study include pregnant women?
(See Pregnancy Clause and Justification)

☐ Yes ☒ No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

The following are examples of procedures involving ionizing radiation:
(Refer to appendix 17.3 for radiotracers, radiation use and 17.5 for nuclear medicine guidance and language)

- X-rays (examples: CT scan, chest x-ray, hand/wrist x-ray, abdomen x-ray, DEXA, pQCT, Fluoroscopy/Angiography)
- Nuclear Medicine scans (examples: FDG-PET, PET/CT, Tc-99m, SPECT, MUGA, bone scan)

If you are unsure please contact Will Davidson in EHRS (wed@ehrs.upenn.edu).

Ultrasound

☐ Yes ☒ No

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ *Apheresis/plasma exchange*
☐ *Leukapheresis*
☐ *Bone Marrow Biopsy or Aspirate*
☐ *Use of AP clinical specimens*
☐ *Biopsies- check those which apply*

☐ *Blood draw*

a. Screening

- Informed Consent
- Questionnaires
- Two weeks of prospective assessment with sleep diaries
- PCP assent
- Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study)

b. Study Intervention Phase

See section 3.0 – Investigation Plan.

c. Rescue Therapy [if applicable] N/A

d. Unscheduled Visits

All subjects may contact the study coordinator at any time by email or phone to make an appointment or to discuss questions or concerns.

e. Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to medication use. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events.

i. Data Collection and Follow-up for Withdrawn Subjects

"Subjects who withdraw consent to participate in the study will be asked to return their foil packs. Please see section 5g".

f. Early Termination Visits

See section; Subject Withdrawal

g. Subject Contact

Subjects will be contacted through phone, email, and via HIPAA compliant Zoom. Identifying information, such as names, will not be used.

Axsome Study - Table of Instruments						
Instrument Name	Abbreviation	Pre	Daily	Weekly	Post	Follow-up (3 mo.)
Sleep Disorder Symptom Checklist	SDS-CL-25	X			X	
Insomnia Severity Index	ISI	X		X	X	X
Retrospective Sleep Continuity Assessment Questionnaire	RSCAQ					X
Daily Sleep Diary	DSD		X			
Epworth Sleepiness Scale	ESS	X		X	X	
Brief Fatigue Inventory	BFI	X		X	X	
Functional Assessment of Chronic Illness Therapy – Fatigue Scale	FACIT-F	X		X	X	
PROMIS-SF 7a	PROMIS	X		X	X	
Functional Outcomes of Sleep Questionnaire	FOSQ-10	X			X	
Profile of Mood State Questionnaire	POMS	X			X	
Patient Health Questionnaire	PHQ-9	X		X	X	
Medical Symptom Checklist	MSCL	X		X	X	
Morin Insomnia Treatment Acceptability Scale	MITAS				X	
Ecological Momentary Assessment	EMA		X			
Psychomotor Vigilance Test	PVT		X			

9. Study Evaluations, Measurements, and Schedule

a. Medical Record Review N/A

b. Physical Examination N/A. Physician Assent will be ascertained.

c. Vital Signs N/A. Physician Assent will be ascertained.

d. Laboratory Evaluations

The primary lab evaluation at screening is the Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study).

e. Pregnancy Testing

An effective method of birth control (as determined by their physician and intake) is required for women who are pre-menopausal. There are no requirements regarding the specific form of contraception that must be used. Subjects must agree to continue to use this method of birth control during the entire course of the study. If a subject does become pregnant during the study, they will be disenrolled. Outcome data on incidental pregnancies will not be collected.

f. Other Evaluations, Measures N/A

g. Efficacy Evaluations

The primary efficacy evaluation is accomplished with on-line prospective sampling, e.g., daily sleep diaries and the completion of weekly questionnaires.

h. *Pharmacokinetic Evaluation N/A*

i. Genetic Testing (only if applicable) N/A

j. Safety Evaluations

As noted above, side effects will be assessed in several ways: daily assessments via the sleep diaries and weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected).

10. Statistical Plan

k. Primary Endpoint

The primary endpoint is total wake time (time spent awake in bed) at the end of post-treatment, as measured via a web based self-report Sleep Diary.

l. Secondary Endpoints

1. Patients treated with CBT-I will have significantly greater improvements in sleep continuity from baseline to post-treatment compared to patients not administered CBT-I.

2. Patients treated with CBT-I in combination with solriamfetol with have significantly greater improvements in sleep continuity from baseline to post-treatment compared to patients treated with CBT-I alone.

3. Exploratory hypotheses: Patients treated with CBT-I in combination with solriamfetol will have significantly greater adherence with sleep restriction (i.e., sleep rescheduling, prescribed time to bed [PTTB]) and on daytime performance measures (e.g., ESS, FSS, etc.) compared to CBT-I alone.

m. Sample Size and Power Determination

To detect a clinically significant difference in self-reported total wake time of 30 minutes between the four treatment groups at the end of post-treatment using an ANOVA test, this study will require 10 subjects per group x 4 groups = 40 treatment completers. These calculations assume a standard deviation in total wake time of 19 minutes, with 80% power to detect the clinically significant change at an alpha level of .05. A total of 60 subjects will be recruited to obtain a sample of 40 subjects that complete the study due to attrition.

n. Statistical Methods

Primary analyses will be conducted on an intention to treat basis and the trial conducted and reported according to CONSORT guidelines. Variable distributions will be examined to investigate homoscedasticity, outliers and normality, and corrected where appropriate using data transformations. The primary analysis is a 4(condition: +/- solriamfetol and +/- CBT-I) x 2(time: pre- and post-treatment) mixed ANOVA on absolute and percent change in total wake time ([TWT], time spent awake per night). If the interaction between condition and time is significant, Dunnett multiple comparisons will be conducted to further investigate differences in TWT between active treatment conditions versus the control condition to test Hypotheses 1-3. These analyses will be unadjusted in the first instance and then adjusted for covariates (primarily, age and sex).

An interim unadjusted analysis as per above will be conducted after 50% of the target sample have completed post-treatment (i.e., when N=20).

Secondary analyses include examining the interaction between treatment condition and time on other outcomes, including sleep continuity assessed via Sleep Diary (SL, WASO, EMA, TST, SE), insomnia (ISI), daytime sleepiness (ESS and KSS), fatigue (FSS and modified KSS), and daytime function (FOSQ-10, POMS, and PVT). Additionally, compliance to the medication (adherence to daily pill administration, as assessed via blister packs) and to sleep restriction (adherence to prescribed time to bed) will be investigated as covariates.

i. Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

ii. Pharmacokinetic Analysis **N/A**

iii. Interim Analysis **N/A**

iv. Safety Analysis

Side effects and adverse events will be assessed in several ways: daily assessments via the sleep diaries, and with a weekly evaluation using a medical symptoms checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected),

An adverse event will be defined as 1) any behavioral or health complaint spontaneously reported during the study, 2) an above threshold score on the study clinical assessment instruments (ESS, PHQ-9, or GAD-7), and/or a 20% increase in the medical symptom check list scores (frequency or severity).

o. Subject Population(s) for Analysis

- All-randomized population.
- All-treated population
- Protocol-compliant population

11. Safety and Adverse Events (as stated in the IRB template)

p. Definitions

i. Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

ii. Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

q. Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though grouped under one diagnosis.
All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

r. Relationship of AE to Study

The relationship of each adverse event to the study procedures will be classified in terms of the event's potential relationship to the study (definitely related, probably related, possibly related, unlikely or unrelated).

s. Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

The occurrence of adverse events will be reported to the study's medical collaborators, advisory board chair, Penn IRB, and our contacts at Axsome.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- *Study identifier*
- *Study Center*
- *Subject number*
- *A description of the event*
- *Date of onset*
- *Current status*
- *Whether study intervention was discontinued*
- *The reason why the event is classified as serious*
- *Investigator assessment of the association between the event and study intervention*

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

i. Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable.

ii. Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor (Axsome) by telephone and email within 24 hours of the event. Specifically, the SAE will be reported to our program officer. "*To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events to the therapist, CRC, and/or the PI via e-mail or phone*

Study PI: Michael Perlis, mperlis@upenn.edu,
CRC: Mark Seewald, mark.seewald@pennmedicine.upenn.edu

Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events will be provided promptly to the study sponsor.

t. Investigator Reporting: Notifying the Penn IRB

Penn IRB will be notified in accordance with the requirements and timelines as specified by the IRB.

i. Sponsor reporting: Notifying the FDA (applies only to Penn sponsor –investigator IND/IDE holders)
N/A

ii. Sponsor reporting: Notifying participating investigators N/A

u. Unblinding Procedures

In the event of an SAE, Investigational Drug Services of the University of Pennsylvania will unblind the subject's status with respect to treatment condition. This information will be provided to the subject, and with permission, the subject's clinical providers (or emergency care providers) within 24 hours or less.

v. Stopping Rules

The advisory board chair will be notified of any serious adverse events that occur, regardless of whether they are thought to be study-related, within 24 hours of project staff learning of their occurrence. The advisory board chair will decide, independent of the study investigators, whether the study should be discontinued.

w. Medical Monitoring

The medical monitoring will be accomplished by our collaborating physician, Dr. Michael Thase.

i. Data and Safety Monitoring Plan

Please see below.

Data Safety Monitoring Board

We will establish a four-person advisory board comprised of a second MD sleep medicine specialist, clinical psychologist, a nurse sleep scientist, and a biostatistician. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflicts of interest with the trial. Collaborators of the PIs will not be eligible to

serve on the advisory board. The board will receive reports from the study team every six months with information about the progress of recruitment, the demographic characteristics of participants, serious adverse events, the number of dropouts, and participants' reasons for dropping out, and any protocol amendments. These meetings will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

12. Study Administration, Data Handling and Record Keeping

x. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

In the case of the present study all self-report data will be acquired through RedCap and Hypknowledge. Files containing PHI (that is not stored in the EMR) will be stored on a secure shared drive on the Penn Network. Only authorized study staff will have access to this shared drive.

y. Data Collection and Management

All data will be collected via Redcap and Hypknowledge. Data download will only be available to the PI and/or his designates. Files containing PHI will be stored on a secure shared drive on the Penn network. Only authorized study staff will have access to this shared drive.

z. Records Retention

All electronic data will be maintained for a period equal to that required by the study sponsor. Longer term database management will occur, but all subject identifiers will be removed.

13. Study Monitoring, Auditing, and Inspecting

The study materials and databases will be available to the study sponsor, the advisory board, and/or Penn IRB should a data audit be deemed necessary.

aa. Study Monitoring Plan

See DSMB section.

bb. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

14. Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

cc. Risks

Risks of Cognitive Behavioral Therapy for Insomnia (CBT-I):

CBT-I may result in temporary increases in daytime fatigue and/or sleepiness, and/or memory and concentration difficulties.

dd. Risks of Solriamfetol:

The most commonly observed side effects of Solriamfetol are headache, nausea, dizziness, palpitations, abdominal pain, feeling jittery, chest discomfort, decreased appetite, anxiety, insomnia irritability, dry mouth, and diarrhea. These effects generally happen with an incident rate of <2%. Headaches however were found to occur in up to 5% of patients using the medication (these are placebo-adjusted rates).

Please note that solriamfetol can cause increased blood pressure, heart rate, increased risk for exacerbation of bipolar disorder and/or psychosis. Physician assent will be obtained prior to enrollment and any subjects who present with the aforementioned medical and/or psychiatric diagnoses will be excluded.

12.1.1 Possible Drug Interactions

Possible drug interactions with solriamfetol include:

- MAOIs (must have stopped the medication > 14 days ago)

ee. Benefits

As indicated in the research plan, participants in this study will likely experience improved sleep (less insomnia). The results of this study, it is hoped, will provide a novel approach to the treatment of insomnia that is as or more effective than traditional approaches and/or makes traditional treatments easier to follow.

ff. Risk Benefit Assessment

1. Risks:
Non-invasive procedures are proposed. It is possible that completion of questionnaires may cause some discomfort for participants due to the content of questions asked. Subjects may experience higher than normal levels of sleepiness due to the nature of CBT-I. The use of the internet for completion of study measures also introduces potential risks for confidentiality of personal data.

2. Benefits:
There may be no known benefits for participants in this study. This project serves to benefit the research community by providing data on insomnia treatment mechanisms. Subjects may experience a decrease in their insomnia and fatigue symptoms. The risks to the participants are believed to be outweighed by the benefit of conducting the research.

10. Informed Consent Process / HIPAA Authorization

Overview
Consent is done on an individual basis during the initial evaluation by a designated staff member via HIPAA compliant Zoom. Subjects will be asked to complete the consent in a private area. For the informed consent process, the details of the consent form are discussed, and the subject is encouraged to ask questions about study participation and any other details described in the consent form. Once signed, the subject is provided a copy of the consent form to keep.

Children and Adolescents
N/A

Adult Subjects Not Competent to Give Consent
Only competent adults will be included in this study.

i. *Alterations to Typical Consent Process (only include if applicable)* ***N/A***

1. *Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible per IRB SOPs)* **N/A**

2. Waiver of Written Documentation of Consent N/A

3. Waiver of Written Documentation of Consent where the research is subject to FDA regulations **N/A**

4. Waiver of HIPAA Authorization **N/A**

j. Study Finances

a. Funding Source

This study is supported by an Axsome Pharmaceuticals

b. Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

c. Subject Stipends or Payments

d. Compensation will be pro-rated for each component of the study for a total of $500 per participant. Specifically, each participant will receive $50 for completing the screening visit, $25 for fully completing baseline sleep diaries, $200 for fully completing all sleep diaries and questionnaires during the treatment period (8 weeks), $100 for completing the study, and $125 for completing the follow-up assessment.

k. Publication Plan

While the primary intent of the study is to garner effect size data, if the inferential statistics are significant with 5-8 subjects per condition, the data will be summarized as a short report for the journal SLEEP or the Journal of Sleep Research.

l. References

Relevant references were placed in text (PMID numbers). Also below.

1: 1. Perlis, M., Jungquist, C., Smith, M. T., & Posner, D. (2005). The cognitive behavioral treatment of insomnia: A treatment manual. Springer. ISBN-10: 0387222529, https://www.amazon.com/Cognitive-Behavioral-Treatment-Insomnia-Session-ebook/dp/B000PC6BGA

m. Attachments

- Sample Consent Form

a. Source Documents

The data is being acquired on-line. The original questionnaires are not retained, though they can be regenerated from the database data.

b. Case Report Forms (CRFs)

The data is being acquired on-line. The original questionnaires are not retained, though they can be regenerated from the database data.