Clinical Trial of Solriamfetol for Excessive Sleepiness Related to Shift Work Disorder

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DETAILED PROTOCOL
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I. BACKGROUND AND SIGNIFICANCE

Shift work has become increasingly common as our 24/7 global society has required more and more workers to do their jobs at irregular hours. According to the National Health Interview Survey in 2010, approximately 28.7% of the American workforce is engaged in work outside a regular day shift (outside 7 AM-to 6 PM) (Alterman et al., 2013). Working irregular hours poses a serious threat to the shift worker's physical, mental, and psychosocial health due to circadian misalignment and misplaced sleep (Boivin & Boureau, 2014; James et al., 2017). The most severe problems faced by shift workers are sleep disturbances and excessive sleepiness (Åkerstedt, 2003). The disruptions caused by shift work are recognized as a circadian rhythm sleep disorder in the International Classification of Sleep Disorders, 3rd Edition (American Academy of Sleep Medicine, 2014), and is called Shift Work Disorder [SWD (Drake et al., 2014; Wickwire et al., 2017)]. SWD is characterized by excessive sleepiness (ES) during wakefulness, accompanied by a reduction of total sleep time and/or insomnia. Several studies have shown that 10-43% of shift workers are diagnosed with SWD, dependent on the criteria used (Drake et al., 2004; Anbazhagan et al., 2016).

One study of 2,570 working adults found that 35.8% of rotating shift workers reported ES, which could occur from excessive build-up of sleep pressure due to prolonged wakefulness and/or curtailed sleep (Drake et al., 2004). Shift workers who suffer from ES associated with SWD are more vulnerable to cognitive impairments, which in turn contributes to their increased risk for occupational performance deficits and motor vehicle crashes while commuting (Drake et al., 2004, Ftouni et al.,2013). In fact, one study has shown that shift workers have nearly 3 times greater risk for occupational accidents compared to day workers (Swanson et al., 2011).

Shift work not only has immediate impacts on workers' on-shift alertness, performance, and safety, it can have longer-term effects on their health and quality of life. Adverse consequences include greater complaints of gastrointestinal disorders, greater likelihood of depression, increased risk of myocardial infarction and cardiovascular disease, as well as greater risk for developing certain cancers and metabolic syndrome (James et al., 2017; Kervezee et al., 2018).

Studies have shown that wake promoting agents can be used to treat ES in shift workers, ranging from caffeine to prescription pharmacological agents (Czeisler et al., 2005; Czeisler et al., 2009; Erman et al., 2011; Howard et al., 2014; Ker et al., 2010; Walsh et al., 2004). Current Food and Drug Administration (FDA)-approved options for SWD patients with ES are modafinil and armodafinil. A three-month, double-blind trial of 209 randomized SWD patients showed that modafinil improves wakefulness and the ability to sustain attention working night shifts without negatively affecting daytime sleep. Furthermore, SWD patients who received modafinil had an improvement in clinical symptoms, reduced levels of sleepiness during night shift and during commute home, and proportionally fewer patients reported motor vehicle accidents or near accidents while commuting home (Czeisler et al., 2005). Czeisler and colleagues (2009) also performed a 12-week randomized, double-blind, placebo-controlled, parallel-group, multicenter study, which showed that armodafinil was well-tolerated and improved clinical conditions, wakefulness, attention and memory during night shifts in SWD patients without jeopardizing daytime sleep and reduced sleepiness during the commute home.

All these previous studies were described in SWD patients working night shifts, yet approximately 3 times as many individuals work shifts that start in the early morning compared with those who work night shifts (Czeisler et al., 2009). These early-morning shift workers are a unique, high-risk group because their early work start times (3:00 AM to 6:00 AM) require the workers to wake up in the middle of the night, close to their circadian nadir, resulting in curtailed sleep and commuting to work during times of high sleepiness. Previous research has shown that early-morning shift starts in particular are associated with increased sleepiness (Knauth, 1993). To our knowledge, no studies have addressed the use of wake promoting agents for ES in early-morning shift workers.

In this clinical trial, we will test whether Solriamfetol (SUNOSI™), a drug approved for the treatment of ES in patients with obstructive sleep apnea (OSA) and narcolepsy (Schweitzer et al.,2019; Thorpy et al., 2019), is effective in: (1) decreasing sleepiness without reducing sleep duration or sleep quality; (2) improving work functioning; and (3) improving quality of life in early-morning shift workers diagnosed with ES associated with SWD.

Summary of Concept
Shift work is associated with excessive sleepiness (ES), sleep disturbances, and performance decrements due to circadian misalignment and misplacement of sleep relative to the 24-hour external environment and internal biological timing. We will test whether solriamfetol is effective in reducing excessive sleepiness without reducing sleep duration and sleep quality, thereby improving global functioning in early-morning shift workers diagnosed with ES associated with shift work disorder (SWD).

II. SPECIFIC AIMS

Hypothesis
- Excessive sleepiness during wakefulness on a workday can be improved by solriamfetol compared with placebo in patients with shift work disorder who work early-morning shifts (H_1: $\mu_{sol} - \mu_{pl} > 0$). The statistical null hypothesis is that solriamfetol does not improve change in MWT scores versus placebo after 4 weeks of treatment (H_0: $\mu_{sol} - \mu_{pl} \leq 0$).

Primary Objective
- Demonstrate improvement of objective sleepiness (assessed with a Maintenance Wakefulness Test (MWT)) in early-morning shift workers after treatment with solriamfetol.

Secondary Objectives
- Demonstrate improvement of subjective sleepiness [assessed with a Karolinska Sleepiness Scale (KSS, Åkerstedt & Gillberg, 1990) in early-morning shift workers after treatment with solriamfetol.
- Demonstrate improvement of clinician's global impression [assessed with Clinical Global Impression-CGI-Change (Guy, 1976)] in early-morning shift workers after treatment with solriamfetol.
- Demonstrate improvement of Patient's Global Impression of Change (Guy, 1976) after treatment with solriamfetol in early-morning shift workers.

Exploratory Objectives
- Demonstrate improvement in work function and daily activity in early-morning shift workers after treatment with solriamfetol, as assessed by Work Productivity and Activity Impairment-Specific Health Problem questionnaire (WPAI-SHP; Reilly et al., 1993; Emsellem et al., 2020).
- Demonstrate improvement in subjective global functioning, as assessed with Functional Outcomes of Sleep Questionnaire (FOSQ-10; Chasens et al., 2009) and Sheehan Disability Scale (SDS; Sheehan & Sheehan, 2008), in early-morning shift workers after treatment with solriamfetol.
- Demonstrate that early-morning shift workers who are treated with solriamfetol do not show significant reduction in objective Total Sleep Time (Actigraphy-TST) or increases in sleep disturbances (Actigraphy-Fragmentation Index).
- Demonstrate improvement of subjective sleepiness (decreased score on modified Epworth Sleepiness Scale (ESS, Johns, 1990, 1997) in early-morning shift workers after treatment with solriamfetol.

III. PARTICIPANT SELECTION

Work schedule and history. Participants must be currently employed and work 20 or more hours per week on 6-12 hour shifts. They must have a work schedule where their start times are between 3am and 7am at least three days per week, and have worked early morning start shifts for at least three months prior to the study.

Participants must show evidence for SWD, either by prior diagnosis or via screening questionnaires (4-item SWD screening questionnaire, modified ESS) followed by SWD confirmation by a clinician.

Medication/drug use. Participants must report no current or recent (within 2 years) history of drug or alcohol dependency, or treatment for drug or alcohol dependency. They must report moderate or no use of caffeine, cigarettes or other nicotine-containing products, cannabis/marijuana, and alcohol by history; and be willing to abstain from products containing cannabis/marijuana for the duration of the screening and while in the study. A positive test for cannabinoid (THC) at screening may be repeated once and if negative the participant will be allowed to enter the study. Participants will be urine drug tested during screening and any positive test for opiates, phencyclidine, cocaine, amphetamines (unless prescribed), or alcohol at screening will be exclusionary.

Participants must report no use of a monoamine oxidase inhibitor (MAOI) in the past 14 days (or five half-lives, whichever is longer) prior to the Baseline Visit, and must not plan to use an MAOI during the study.

Participants must report no use of any investigational drug in the 30 days (or 5 half-lives, whichever is longer) prior to the Baseline visit, and have no plans to use any investigational drug (other than the study drug) during the study.

Participants must report no use of any over-the-counter (OTC) or prescription medication that could affect the evaluation of excessive daytime sleepiness within a time period prior to the Baseline visit corresponding to at least 5 half-lives of the drug(s). Participants must also not plan to use such drug(s) at any point throughout the duration of the study. Examples of excluded medications include OTC sleep aids, stimulants (e.g. methylphenidate, amphetamines, modafinil, and armodafinil), sodium oxybate, pemoline, pitolisant, bupropion, trazodone, vortioxetine, duloxetine, tricyclic antidepressants, hypnotics, benzodiazepines, barbiturates, and opioids.

Participants must report no previous exposure to solriamfetol (JZP-110, ADX-N05, R228060, or YKP-10A).

Evaluation of medical suitability. Participants must be ambulatory and free from any acute or debilitating medical conditions. Medical suitability will be determined by clinical history, physical examination, and clinical biochemical screening tests of blood and urine (see Appendix II for details). Any participant with symptoms of acute or active illness will not be allowed to proceed to the Baseline Visit until the illness is resolved. The following summarizes medical conditions that will be exclusionary.

General: History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect the safety of the participant or interfere with study efficacy, safety, or the ability of the participant to complete the trial based on the judgment of the investigator will be exclusionary.

Laboratory tests: value(s) outside the laboratory reference range that is considered to be clinically significant by the investigator (clinical chemistry, hematology, and urinalysis) will be exclusionary. See Table I.

Sleep Disorders: history of narcolepsy, moderate to severe sleep apnea (respiratory event index ≥ 15), moderate to severe Periodic Limb Movement Disorder (PLMD, PLM index ≥ 25), nocturnal paroxysmal dystonia, REM-sleep behavior disorder, restless legs syndrome (RLS) will be exclusionary. Participants will undergo a home sleep test (HST) to screen for undiagnosed sleep apnea and PLMD.

Cardiovascular Disorders: uncontrolled hypertension (systolic blood pressure >155 or diastolic blood pressure >95mmHg) at Screening or Baseline, clinically significant EKG abnormality in the opinion of the investigator, myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, uncontrolled atrial fibrillation, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator (AICD) or medication therapy, history of heart transplantation, cardiac tumors, pericardial disease, or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant safety in the study will be exclusionary.

Neurologic Disorders: epilepsy and disorders of consciousness, dementia, amnesic disorders, neoplastic diseases of the central nervous system, demyelinating diseases, Parkinson's Disease, muscular dystrophy, myasthenia gravis, periodic paralysis, dermatomyositis, polymyositis, infections of the nervous system, stroke, history of transient ischemic attacks, hydrocephalus, tumors of the pituitary gland, pinealoma, intervertebral disc disease, ataxia, Gilles de la Tourette Syndrome, Huntington's Disease, tardive dyskinesia, history of recurrent migraine or cluster headaches, neuromuscular disease, history of traumatic brain injury or coma will be exclusionary.

Kidney Disorders: presence of renal impairment or calculated creatinine clearance < 60 mL/min, history of renal transplantation will be exclusionary.

Endocrine: Hypothyroidism or hyperthyroidism, unless stabilized by appropriate medication for at least 3 months prior to screening, will be exclusionary.

Gastrointestinal: Participants with a history of any gastric bypass procedure or a history of bariatric surgery within the past year will be excluded.

Participants who report a phenylketonuria (PKU) or a history of hypersensitivity to phenylalanine-derived products will be excluded.

Evaluation of psychiatric/psychological suitability. Participants with a history or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria will be excluded, as will participants with a history of suicide attempt. Participants will be screened with the Beck Depression Scale (BDI), the Beck Anxiety Scale (BAI), and the Columbia Suicide Severity Rating Scale (C-SSRS). Those with evidence of significant depression, anxiety, or suicidality will be excluded and referred for follow-up care.

Evaluation of reproductive suitability. Women who are pregnant or planning to become pregnant will be excluded. Women who are breastfeeding or planning to breastfeed during the study will be excluded.

Women of non-childbearing potential will be included. This includes: premenopausal women with documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy; post-menopausal women.

Women of childbearing potential (WOCBP) must be using a contraceptive method that is highly effective (with a failure rate of <1% per year) and agree to continue using it throughout the study intervention period and for at least 30 days after the last dose of study medication. Allowable methods include: implantable progestogen-only hormone contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS). In addition, the following methods will be allowed after a physician evaluates the potential for contraceptive method failure (e.g., noncompliance, recently initiated): combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal, injectable), progestogen-only hormone contraception associated with inhibition of ovulation (oral, injectable), sexual abstinence (refraining from heterosexual intercourse during the entire study). WOCBP will have a urine pregnancy test at the screening visit and again at the randomization visit (Visits 1 and 3).

Male participants must agree to refrain from donating sperm during the study and for at least 30 days after the last dose of study medication. They must also be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent or must agree to use a male condom with their female partner(s) of childbearing potential who must also use a highly effective contraceptive method with a failure rate of <1% per year.

Inclusion Criteria

1. Men and women
2. Ages 18 to 64 years
3. Early-morning shift workers with a fixed work schedule (start times between 3 AM-7 AM, for at least 3 days per week)

4. ≥ 20 work hours per week, 6-hour to 12-hour shifts
5. ≥ 3-month history of working early morning shifts prior to the study
6. Shift work disorder (as measured by 4-item SWD screening questionnaire and SWD symptoms confirmed by clinician) with excessive sleepiness (as measured by the modified ESS) specifically related to early morning shifts
7. Baseline MWT average sleep latency <20 minutes on the first 4 scheduled naps
8. Body mass index 18.5 to 45 kg/m^2
9. Normal thyroid stimulating hormone (TSH) level
10. Female participants must not be pregnant or breastfeeding.
11. Female participants must either be of non-childbearing potential or using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, and agree to continue its use for at least 30 days after the last dose of study medication.
12. Male participants must agree to refrain from donating sperm and agree to remain abstinent from heterosexual intercourse or to use a male condom with female partners who are on an additional highly effective contraceptive method, both during the study and for at least 30 days after the last dose of study medication.
13. Are willing to refrain from any alcohol and nicotine-containing product use during the 24 hours prior to each MWT visit.
14. Are willing to refrain from any caffeine use on the day of the MWT visits.
15. Are willing and able to comply with the study requirements.

Exclusion Criteria

1. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect the safety of the participant or interfere with study efficacy, safety, or the ability of the participant to complete the trial based on the judgment of the investigator.
2. Presence of renal impairment or calculated creatinine clearance < 60 mL/min.
3. Laboratory value(s) outside the laboratory reference range that is considered to be clinically significant by the investigator (clinical chemistry, hematology, and urinalysis; see Appendix II).
4. Hypothyroidism or hyperthyroidism, unless stabilized by appropriate medication for at least 3 months prior to screening.
5. Clinically significant EKG abnormality in the opinion of the investigator.
6. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, uncontrolled atrial fibrillation, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy, uncontrolled hypertension, systolic blood pressure ≥ 155 mmHg or diastolic blood pressure ≥ 95 mmHg (at Screening or Baseline), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant safety in the study.
7. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
8. Use of an MAOI in the past 14 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.
9. Pregnant or intention to become pregnant.
10. Breast-feeding or plans to breastfeed.
11. On long-term sick leave or with no history of work in the last 12 months
12. Diagnosis with sleep disorder (regardless of treatment status) other than SWD including: OSA, PLMD, other circadian rhythm sleep disorders, narcolepsy, or RLS determined by a previous sleep-lab diagnosis or during the home sleep test.
13. History of excessive caffeine use or anticipated excessive use (>600mg/day) during the study.
14. Use of any OTC or prescription medications that could affect the evaluation of EDS within a time period prior to the Baseline visit corresponding to at least 5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the treatment period. Examples of excluded medications include OTC sleep aids, stimulants (e.g. methylphenidate, amphetamines, modafinil, and armodafinil), sodium oxybate, pemoline, pitolisant, bupropion, trazodone, vortioxetine, duloxetine, tricyclic antidepressants, hypnotics, benzodiazepines, barbiturates, and opioids.

15. Received an investigational drug in the past 30 days or 5 half-lives (whichever is longer) prior to the Baseline visit or plans to use an investigational drug (other than the study drug) during the study.
16. History or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
17. Current or recent (within the past 2 years) diagnosis of a moderate or severe substance use disorder (excluding caffeine) according to DSM-5 criteria. Nicotine use disorder is exclusionary only if it has an effect on sleep (i.e., a participant who routinely awakens at night to smoke) or will interfere with study compliance.
18. Current, recent (within the past 2 years), or seeking treatment for a substance-related disorder.
19. Positive urine drug screen (UDS) for opiates, phencyclidine (PCP), cocaine, cannabinoid (THC), or amphetamines at Screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at Screening.
20. History of regular heavy use of tetrahydrocannabinol containing products. Recreational users of cannabis may be repeat UDS tested once during the Screening period. If this is negative, the participant may be allowed to enter the study.
21. Positive alcohol test at Screening. Binge drinking (5 or more drinks per day for men, 4 or more drinks per day for women) within the past month.
22. History of PKU or history of hypersensitivity to phenylalanine-derived products.
23. Previous exposure to solriamfetol (JZP-110, ADX-N05, R228060, or YKP-10A).

Inclusion of racial/ethnic minorities. Our recruitment procedures will provide all applicants with an equal opportunity to participate in our studies regardless of race, ethnicity, or national origin.

Sex. We will attempt to include equal numbers of women and men in the proposed study.

Source of participants and recruitment methods:
We will recruit early-morning shift workers who work a fixed work schedule, where work times start between 3 AM-7 AM at least 3 days per week. We may use a participant recruitment company to pre-screen individuals for eligibility to the study. We will recruit participants through internet, radio, and newspaper advertising, RSVP, Rally, and social media notices. We will also use snowball sampling where participants may notify their coworkers. We will recruit among all occupations, and include participants within approximately a 1-2 hours distance from BWH.

We plan to screen up to 500 people, randomize 110 people in order to obtain 100 who meet all criteria and complete the study.

Screening questionnaires
The following questionnaires/instruments will be administered during the screening process in order to collect information necessary for determining inclusion/exclusion criteria or to meet regulatory requirements [see Appendix I for copies of each questionnaire]:

At phone/ online (REDCap) screening:
Shiftwork Disorder screening instrument, a 4 item questionnaire
Modified Epworth Sleepiness Scale, an 8-item questionnaire that rates the probability of falling asleep in different situations [scores <11 will be exclusionary]

At Screening Visit:
1. Subject Information questionnaire [used to collect medical, sleep-wake, and work history]
2. Personal Data (race/ethnicity) form
3. BDI II [scores >19 indicating moderate or severe levels of depression will be exclusionary]
4. BAI [scores >35 indicating high anxiety levels will be exclusionary]
5. C-SSRS [any endorsement of suicidal ideation or behaviour will be exclusionary]
6. Pittsburgh Sleep Quality Index [PSQI, not used for inclusion/exclusion]

At Baseline Visit:

1. Chronotype questionnaire for Shift-Workers [not used for inclusion/exclusion]

Treatment assignment and randomization.
We will use a double-blind, randomized placebo-controlled control trial design. The Investigational Drug Service (IDS) at BWH will encapsulate the drug and prepare the matching placebo capsules to ensure double-blinding. The IDS will randomly assign participants to the treatment or placebo group. The randomization will not be broken or released until all study data have been collected and are ready for analysis, except in the event of emergency unblinding for a serious adverse event (SAE). In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. In the event of a SAE, the participant's treatment assignment may also be unblinded. If a participant's intervention assignment is unblinded, the date and reason that the blind was broken will be recorded in the source documentation. Notification of the treatment assignment will only be made known to those who require it for safety reporting and submission processes. When possible, all other individuals involved in the study will remain blinded to treatment assignment. Participants for whom the blind is broken for this reason will not be automatically withdrawn from the study.

IV. PARTICIPANT ENROLMENT

Methods of enrollment, procedures randomization.
Study staff or the recruitment company/ call center may pre-screen potential participants by phone to explain the study requirements and determine whether they meet basic inclusion/exclusion criteria [currently employed 20 or more hours per week; early morning shifts starting between 3-7 AM at least 3 days per week]. Next, eligible participants will receive a phone pre-screening by study staff designed to select individuals with shift work disorder and excessive daytime sleepiness when working early morning shifts. Alternatively, potential participants may fill out an online screening (REDCap) questionnaire linked from advertisements which will help assess their eligibility. After the phone/ online (REDCap) pre-screening, a virtual e-consent visit will take place and once completed participants will be invited to the first screening visit (see procedures below). Alternatively, the consent may be scheduled to occur at the start of the Screening Visit if circumstances permit.

Participants who have completed the informed consent process will have the option to consent to being contacted by text message for study visit reminders, study check in visits, and reminders to complete other study procedures. The MGB recommended consent text disclosing security risks of text messaging is shown to participants at the end of the consent, and participants have the option to opt in to receive text reminders. Text reminders are not used after completion of the research study. Text messaging will be carried out using Twilio, a secure texting platform integrated with REDCap through the REDCap + Twilio Module.

Procedures for obtaining informed consent
Prior to beginning the Screening Visit, eligible participants will provide written informed consent in person or remotely by secured video conference or phone. When done remotely, participants will sign the informed consent form using a REDCap informed consent module. This virtual e-consent visit will take place before Screening Visit 1 (see below), or if carried out in person it will take place at the start of Screening Visit 1. An Investigator or a Post-Doctoral Research Fellow will obtain consent from each participant.

V. STUDY PROCEDURES

This will be a prospective, randomized, parallel arm, double-blind, placebo-controlled outpatient study conducted at BWH, in compliance with Partners HealthCare / Mass General Brigham Human Research Committee policies.

Study visits and parameters to be measured
- An initial IRB-approved phone/ online (REDCap) **pre-screening**: designed to select early morning start shift workers with shift work disorder, using the validated 4-item Screening Questionnaire for Shift Work Disorder (Barger et al., 2012) and excessive daytime sleepiness when working early morning shifts using a modified ESS (Johns, 1991). The study will be explained and the participant's questions answered. This is expected to take 20-30 minutes.

- **Virtual e-Consent Visit:** An Investigator or Post-Doctoral Research Fellow will explain details of the study procedures including the randomization process, study duration, visits, data collection process, and then obtain consent from each participant using a REDCap informed consent module. This is expected to take 1-1.5 hours.
- **Screening Visit 1**: Screening including medical history, physical exam (PE), vital signs, urinalysis (UA), electrocardiogram (EKG), comprehensive metabolic panel, thyroid stimulating hormone (TSH), complete blood count (CBC), pregnancy test (if female), and urine drug screen (UDS). In addition, standardized psychological questionnaires [C-SSRS (Posner et al., 2011), BDI and BAI (Beck et al. 1988, 1996)], and the PSQI [Buysse et al., 1989] will be administered. If no exclusion criteria are identified, the potential participant is sent home with home sleep test (HST) equipment to carry out the HST that night or the following night. Upon review of the blood, urine, and HST results a physician or other qualified study staff member will make a determination whether to exclude the participant or to proceed. This visit is expected to take 3-4 hours.
- **Baseline Visit 2**: Maintenance of Wakefulness Test (MWT; Littner et al., 2005). The potential participant will report to the Center for Clinical Investigation (CCI) at BWH approximately one hour after their usual wake time (UW) on early morning start days. The participant will have their vitals taken and then be instrumented for polysomnography (PSG) and a 40-min MWT will be carried out at UW+ ~2, 4, 6, and 8 hours. Five minutes prior to each nap, a KSS will be administered. In between MWTs, the participant will complete baseline questionnaires [Chronotype questionnaire for Shift-Workers (MCTQ ^{shift}, Juda et al., 2013), WPAI-SHP, FOSQ-10, SDS, modified ESS]. A physician will evaluate the participant on the CGI Severity of Illness scale and the participant will self-report on Patient's GI Severity of Illness scale. A breakfast and lunch will be served between MWTs, shortly after the end of a nap. If daytime sleepiness is confirmed (average sleep latency of <20 min on the four MWT naps), the participant is considered to meet the inclusion criteria and the study can start. The participant will take home a wrist activity monitor to wear 24/7, and will be instructed to complete an electronic daily diary containing questions related to wake and sleep patterns. This visit is expected to take 10 hours.
- **Baseline Segment**: Two weeks of activity monitoring and daily completion of a sleep and work diary. Daily sleep surveys will be administered prior to starting work and daily work diaries will be administered after work at participant-selected times and will be sent to participants via email or via text message using Twilio, or provided in a hard-copy binder.
- **Randomization Visit 3:** The participant will have their wrist activity monitor downloaded and re-initialized, vital signs will be recorded, they will be asked about their symptoms and about any adverse events, and have the C-SSRS-since-last-visit reviewed with them, and female participants will have a urine pregnancy test**.** If no exclusionary criteria are identified, the participant will be randomized and given their first 2 weeks of study medication**.**
- **Treatment Segment I:** Two weeks of activity monitoring and daily sleep and work diaries. Treatment day 1 will be a day with an early morning work shift. Participants will start treatment at 75mg solriamfetol or placebo the first 3 consecutive days (treatment days 1-3) regardless of whether they are working or have a day off, which will be taken at home shortly after awakening (<30 minutes after waking). On all subsequent work days, they will either continue to receive placebo, or will receive 150mg solriamfetol. After one week, a remote visit by phone will be carried out. During this visit they will be contacted by a study staff member to check their symptoms and adverse events (AE), and a C-SSRS-since-last-visit will be administered.
- **Visit 4**: At the end of the second week of treatment, an in-person visit will be scheduled. During this visit, the participant will have their wrist activity monitor downloaded and restarted, vital signs will be recorded, they will be asked about their symptoms and about any adverse events, and the CSSRS-since-last-visit will be administered. If no problems are identified, the participant will be given their next 2 weeks of study medication.
- **Treatment Segment II**: Two weeks of activity monitoring and daily sleep and work diaries. Participants will continue to receive placebo or 150mg solriamfetol as in Treatment Segment I. After one week, a remote visit by phone will be carried out. During this visit they will be contacted by a study staff member to check their symptoms and adverse events (AE), and a C-SSRS-since-last-visit will be administered.
- **End of Treatment Visit 5**: This visit will occur at the end of the second 2-week treatment segment. The participant will take their scheduled dose of study medication after awakening at home and then travel to

the CCI where MWT and KSS will be carried out as at Visit 2. Thus, the first MWT will start approximately 2 hours after taking the study medication. In between MWTs, the participant will complete post-treatment questionnaires [WPAI-SHP, FOSQ-10, SDS, modified ESS]. After the MWT is complete, a PE including vital signs and an EKG will be carried out, and a symptom check and AE review will be done along with a C-SSRS-since-last-visit. A urine sample will be collected for UA and blood will be collected for a CBC and metabolic panel. A physician will evaluate the participant on the CGI-Change to assess changes from baseline in symptom severity and efficacy, and the participant will self-report on Patient's Global Impression of Change.

- **Final Safety Visit 6:** Approximately one week after Visit 5, a final Safety Visit is scheduled including a PE, vital signs, symptoms, AEs, and C-SSRS-since-last-visit.

If a participant drops out after at least 1 week on treatment, they will be encouraged to come in for an MWT (Visit 5).

Drugs to be used.

The administered drug is SUNOSI (solriamfetol) tablets for oral use. Initial U.S. Approval: 2019.

Participants will start at 75 mg and take that dose for 3 consecutive days. Participants will take their first 75mg dose on an early morning work day and take the next two 75 mg doses upon awakening regardless of their work schedule.

They will then move to 150mg on the next early morning work day and for all subsequent early morning shift work days. The drug/placebo will be taken orally within 30 minutes after awakening, before the start of each early morning shift. Prior to the end of study of visit (Visit 5), drug will be taken at home within 30 minutes of awakening.

Devices to be used

No experimental/investigational devices will be used in the study. Several devices will be used to collect screening or research data in the study:

- During screening, an Embletta or equivalent home sleep monitor (battery-operated) will be used to record breathing/leg movements for the overnight HST.
- Throughout the Baseline Segment and the Treatment Segments, a battery-operated wrist activity monitor (MotionWatch 8) will be used to record activity data.
- During the MWT tests carried out at the CCI, a Vitaport 3 sleep recorder will be used to record PSG data.

All these devices are battery-operated, non-invasive, and are currently used in multiple research studies at BWH.

Data to be collected

For 6 weeks, during the Baseline and Treatment I & II segments:

- Daily diaries about sleep timing and quality, work hours, medication use.
- 24-h actigraphy to assess sleep duration and sleep quality

At Baseline and End of Treatment Visits (Visit 2 & 5):

- Objective sleepiness (MWT)
- Subjective sleepiness (KSS, modified ESS)
- Clinical global impression (severity and change) (CGI, CGI-S, CGI-C)
- Patient global impression (severity and change) (PGI, PGI-S, PGI-C)
- Work function and daily activity (WPAI-SHP)
- Subjective global functioning (FOSQ-10, SDS)

V.a. DETAILS OF METHODS

Actigraphy data. Actigraphy data will be collected in 60 s epochs and sleep–wakefulness will be scored in each sleep episode per epoch by MotionWare (CamNTech, Cambridge, UK) using the high-sensitivity setting. Bed and wake times will be determined from sleep diaries and input into the software for sleep–wakefulness analysis.

Total sleep time (TST) will be calculated as minutes of sleep in each sleep episode. Naps will be scored separately from nighttime sleep.

Fragmentation Index (FI) will be calculated as the sum of the “Mobile time” (percent of presumed sleep episode categorized as mobile) and the “Immobile bouts” <=1min (%)” (percentage of the total number of immobile bouts that are less than or equal to one minute).

Daily diaries. During the 2-week Baseline Segment and the 4-week Treatment Segment, the participant will complete daily sleep and work diaries. These will consist of questions about work timing, subjective work performance and sleepiness, caffeine use, napping (included in work diary and completed after work), prior night’s bedtime and waketime, subjective sleep latency, number of awakenings, and soundness, reason for waketime, sleep aid use (included in sleep diary and completed after waking and before beginning work). During the Treatment Segment, we will also ask them about whether they used the study medication that day.

CCI unit environment and conditions. During the MWT assessment days, participants will stay in specially-designed research room at the BWH Center for Clinical Investigation. Some of the rooms are regular patient rooms that have blackout shades, while others were designed without windows. We will attempt to study the participant in the same type of room at each of their MWT visits. While at the CCI, the participant will be asked to remain within their study room at all times. The experimental rooms are equipped with hand-held terminals for on-line event recording, and a closed-circuit camera and a voice-activated microphone for participant monitoring. Technicians and/or nurses are present 24 hours a day to conduct the protocol, monitor data acquisition, collect biologic specimens, and carry out polysomnographic recordings of sleep or wake. CCI nurses are present 24 hours a day to ensure participant health and safety. An extensive series of written protocols and checklists insures uniformity in execution of standard procedures and to foster intra-staff communications (e.g., at shift change).

The participant will be asked to arrive within ~one hour after their usual wake time on their early morning work days. They will enter their study room and have a quick orientation. PSG electrodes will be placed (see below) for the MWT recordings. During wake between MWTs, the participants will be free to move about their study room as desired, except that they will be instructed not to lie down or nap. The participant's activity will be monitored for compliance by means of closed-circuit cameras. Two meals will be served to the participant, in each case shortly after a nap ends so as to not interfere with the subsequent nap.

Karolinska Sleepiness Scale. Participants will complete computer-administered or pencil-and-paper KSS approximately 5 minutes before each MWT nap. The KSS requires the participant to select a number on a scale from 1 to 9 spanning the range from very sleepy to very alert, and takes less than a minute to complete.

MWTs. Four naps will be carried out during each MWT day (Littner et al., 2005). The first will occur approximately two hours after usual wake time, and the rest every two hours after. Shortly before each nap, the participant will be asked to use the toilet, turn off all electronic devices, and get into bed. They will take the KSS. The recording electrodes will be checked and replaced if necessary and a series of bio-calibrations will take place. At the start of the nap, the participant will be instructed to try to remain awake as long as possible, then the overhead room lights will be turned off (a small night light will remain on) and staff members will leave the room. The PSG recording will be monitored and if the participant falls asleep the nap will be terminated. If the participant does not fall asleep, the nap will be terminated after 40 minutes. At the end of the nap, the overhead lights will be turned back on and the participant will get out of bed.

MWT Polysomnographic recordings. The MWT PSG will include central (C3, C4) and occipital (O1, O2) electroencephalogram (EEG) with contralateral references; left and right electrooculograms (EOGs); mental/submental electromyogram (EMG); and electrocardiogram (EKG). Gold cup or equivalent electrodes will be applied to each location, using the standard 10-20 system of electrode placement. After application and just before the start of each nap, impedances will be checked and electrodes reapplied if necessary. Data will be collected using a Vitaport 3 digital sleep recorder or equivalent. PSG data will be monitored from a control area outside the participant’s room by a trained technologist. Sleep onset will be defined as the first epoch of >15

seconds of cumulative sleep in a 30-second recording epoch. Unequivocal sleep for nap termination is defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep (Littner et al., 2005).

Study questionnaires and evaluations. At the Baseline MWT and the End of Treatment MWT visits, the participant will complete questionnaires to evaluate their quality of life, daytime sleepiness, and work productivity. These include: the WPAI-SHP, the FOSQ-10, the SDS, and a modified ESS.

WPAI-SHP: This questionnaire assesses to what extent the participant's work productivity and daily activities have been impaired by a specific health problem (in this study, daytime sleepiness/fatigue).

FOSQ-10: The purpose of this questionnaire is to find out if the participant has difficulty carrying out daily activities because they are too sleepy.

SDS: This questionnaire was developed to assess functional impairment in three inter-related domains: work/school, social, and family life.

Modified ESS: This questionnaire rates the chances of the participant dozing off or falling asleep while taking part in eight different activities. The standard questionnaire refers to "in recent times". We will modify the questionnaire to ask about the past week while working early morning shifts and we will modify questions so they are related to work situations.

In addition to completing the study questionnaires, a physician will complete a Clinical Global Impression of the patient in which they are asked to rate the patient relative to their past experience with other patients with the same diagnosis (Shift Work Disorder, Excessive Daytime Sleepiness), with or without collateral information. The **CGI** is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). Illness severity (CGI-S) will be rated at the Baseline MWT Visit to establish a baseline for each patient and change or improvement (CGI-C) will be rated at the End of Treatment MWT to measure the patient's change (improvement or worsening) compared to baseline. The participant will self-report at the same two time points on the Patient's Severity of Illness scale (PGI-S, baseline) and change (PGI-C).

Data management and privacy. All data (PSG data, KSS data, actigraphy data, responses to questionnaires) will be collected and recorded using a study code rather than individually-identifying information. This is a routine practice in our laboratory, and we therefore have systems in place to assign a study code upon enrollment into the protocol and to use study codes on data collection systems. Study questionnaires will be collected in REDCap. All data from the study will be stored on a Partners shared file area where access will be limited to study personnel.

V.b. BIOSTATISTICAL ANALYSIS

Variables

- Daily diary about work timing, subjective work performance and sleepiness, study medication use and timing, caffeine use, napping, prior night's bedtime and waketime, subjective sleep latency, number of awakenings, and soundness, reason for waketime, sleep aid use.
- 24-h actigraphy to assess sleep duration and sleep quality

At baseline and End of Treatment visits (visit 1 & 5):

- Objective sleepiness (MWT)
- Subjective sleepiness (KSS, ESS)
- Clinical global impression (CGI, CGI-S, CGI-C)
- Patient global impression (PGI, PGI-S, PGI-C)
- Work function and daily activity (WPAI-SHP)
- Subjective global functioning (FOSQ-10, SDS)

Analysis of objective sleepiness.
The **Primary Endpoint** of this study is the change in objective sleepiness between the Baseline MWT and the End of Treatment (EOT) MWT [average sleep latency on first 4 scheduled naps]. To test the primary hypothesis, the primary endpoint of the change in MWT from Baseline to EOT between the solriamfetol group and the placebo group will be analyzed using a mixed model repeated measures analysis that will include Baseline MWT, treatment (solriamfetol, placebo), time (as a discrete factor), and treatment by time interaction as fixed effects and participant as a random effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The degrees of freedom will be estimated by the Kenward-Roger approximation method. A 2-sided 95% confidence interval (CI) of the mean difference in MWT from Baseline to EOT between solriamfetol and placebo will be constructed.

Analysis of subjective sleepiness and clinical condition.

The **Secondary Endpoints** are:

a) the change in subjective sleepiness between the Baseline KSS and the EOT KSS [average of the KSS given before the first 4 scheduled naps]
b) the change in clinical condition between Baseline and EOT as assessed by a physician using the CGI-C.
c) the change in the patient's subjective report between Baseline and EOT visit as assessed by PGI-C.

To test the secondary objectives, the secondary endpoint of the change in KSS from Baseline to EOT between the solriamfetol group and the placebo group will be analyzed using a mixed model repeated measures analysis that will include Baseline KSS, treatment (solriamfetol, placebo), time (as a discrete factor), and treatment by time interaction as fixed effects and participant as a random effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The degrees of freedom will be estimated by the Kenward-Roger approximation method. A 2-sided 95% CI of the mean difference in KSS from Baseline to EOT between solriamfetol and placebo will be constructed.

For the secondary endpoints of CGI and PGI, change between the treatment group and the placebo group will be analyzed using a chi-square test.

To address the multiplicity issue due to the hypothesis testing on the primary and secondary endpoints, a fixed hierarchical testing sequence will be employed. The familywise type I error rate will be controlled at the 2-sided significance level of 0.05. The testing procedure will be stopped when the p-value of a specific endpoint exceeds the significance level of 0.05. Statistical hypotheses will be tested in the following sequential order:

1. the change in objective sleepiness between the Baseline MWT and the End of Treatment (EOT) MWT
2. the change in subjective sleepiness between the Baseline KSS and the EOT KSS
3. the change in clinical condition between Baseline and EOT as assessed by a physician using the CGI-C
4. the change in the patient's subjective report between Baseline and EOT visit as assessed by PGI-C.

The **Exploratory Endpoints** are:

a) the change in subjective sleepiness between Baseline and EOT visit as assessed by modified ESS.
b) the change in work function and daily activity between Baseline and EOT visit as assessed by WPAI-SHP.
c) the change in subjective global functioning between Baseline and EOT visit as assessed with FOSQ-10 and SDS.
d) no change in objective sleep duration or sleep quality assessed by actigraphy-estimated TST and actigraphy-estimated FI, averaged across the 2 Baseline weeks compared to weeks 3+4 of Treatment.

To test the exploratory objectives, we will analyze the change from Baseline to EOT between the solriamfetol group and the placebo group by descriptive statistics, and to analyze the continuous variables using a mixed model with repeated measures analysis that will include baseline measure, treatment (solriamfetol, placebo), time (Baseline, EOT), and treatment by time interaction as fixed effects and participant as a random effect, and to analyze discrete variables using a chi-square test.

All significance tests will be 2-tailed and at $p < 0.05$ level.

Sample Size Justification
The sample size estimate for the primary endpoint is based on the results of the study of solriamfetol in patients with OSA (Schweitzer, 2019). With 50 participants per group, we can detect a difference of 5.7 minutes or greater on the MWT with power of 97% (α=0.05, assumed σ=7.2). Sample size estimates for the secondary endpoints are based on the results of the study of modafinil in patients with SWD (Czeisler, 2005). With 50 participants per group, we can detect a difference as small as 0.6 points on the KSS with power of 84% (α=0.05, assumed σ=1), and a difference of 27% or greater in the proportion of patients reporting at least minimal improvement on the CGI-C with 80% power (α=0.05, assumed a placebo proportion at 49%).

The study will randomize 110 individuals and allow for a 10% dropout rate. If a participant drops out after at least 1 week on treatment, they will be encouraged to come in for an MWT visit.

VI. RISKS & DISCOMFORTS

Contraindications
Solriamfetol is contraindicated in patients receiving concomitant treatment with MAOI, or within 14 days following discontinuation of MAOI, because of the risk of hypertensive reaction.

Drug side effects and toxicities
Solriamfetol is an FDA-approved (for excessive daytime sleepiness associated with OSA and narcolepsy) medication with a robust clinical safety database comprised of healthy participants and participants with OSA, narcolepsy, Parkinson's disease, and MDD with a consistent safety profile across conditions. The robust efficacy of solriamfetol has been demonstrated among participants with OSA and narcolepsy including examination of post-hoc analysis of the subgroup of participants on concomitant antidepressants. The risks to participants in this study are expected to be similar to those seen in prior clinical studies that evaluated the effects of 75 mg and 150 mg solriamfetol in OSA and narcolepsy patients, including those on concomitant antidepressants. Current information on the efficacy, pharmacokinetic(s), and safety of solriamfetol is provided in the solriamfetol Investigator's Brochure (IB), the United States Package Insert (USPI) and the Summary of Product Characteristics (SmPC).

Underlying psychiatric comorbidities (ie, affective disorders and suicidal ideation) could be exacerbated by the use of a stimulant or wake-promoting agent. In the solriamfetol clinical development program, serious psychiatric events occurred more commonly in the narcolepsy population than the OSA population. Further, although solriamfetol blocks dopamine and norepinephrine reuptake, nonclinical and clinical data show that the potential for abuse for solriamfetol is low.

Dose-dependent increases in blood pressure (BP) and heart rate (HR) have been seen in clinical studies of solriamfetol in patients with narcolepsy and OSA. This population may be at risk for cardiovascular events due to certain intrinsic factors, such as increasing age, obesity, concurrent diabetes mellitus or cardiovascular disease, hyperlipidemia, and hypertension. In addition, shiftwork may predispose patients to cardiovascular disease. Based on the cardiovascular co-morbidities in this population and depending on the cardiovascular risk profile these events are anticipated to occur in this population.

In previous studies, the most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of solriamfetol than placebo were headache, nausea, decreased appetite, anxiety, and insomnia

Other risks.
<u>Common</u>

- There may be some discomfort or bruising on collection of the blood samples during the screening and EOT visits. The amount of blood drawn for biochemical screening tests of blood and urine should not significantly alter blood volume.
- The tape and special paste used to attach the EEG electrodes for the MWTs may cause some minor discomfort or skin irritation, and the glue (collodion) used to hold electrodes to the scalp may leave a flaky residue in the hair for several days.
- The adhesive EKG and EMG pads may cause some skin irritation when they are removed.

Uncommon
- There is the possibility that the participant may faint during or after the blood draw procedure.

Device complications/malfunctions
The battery-operated monitoring devices are electrically safe and involve minimal risk. The devices used to monitor brain electrical activity (EEG) in the laboratory are battery-operated.

Psychosocial (non-medical risks)
- The daily diaries pose no risks, although they will be repeated many times over the course of the study.
- During the MWT days, the participant will be asked to lie in bed in the dark trying to remain awake for up to 40 minutes on 4 separate occasions (every ~2 hours). This may be difficult if they are feeling sleepy. If they fall asleep, they will be awakened and asked to get out of bed. They will not be allowed to lie on the bed or nap in between these scheduled study "naps".
- The participant may become bored or frustrated during the stay at the CCI for the MWT.
- No exercise will be permitted during the MWT days at the CCI.
- The participant will not be able to have visitors during their stay at the CCI.
- The participant will be asked to turn off their mobile phone and it will be removed from their study room during each of the scheduled naps.

Radiation risks
None.

Risks of receiving study visit reminders by text message
Text messages are not encrypted, and thus there is a risk of a loss of privacy. To minimize this risk, we will adhere to the principles of minimum necessary; thus, study-initiated text messages will not contain participant names or other identifiers, sensitive information that could expose financial risk to individuals (social security numbers, driver license numbers, credit card numbers, etc), results of any clinical tests conducted for the purpose of research, or potentially sensitive information about the study visit. Additionally, participants who consent to receiving text messages will first be sent a welcome message by text that requests the participant to respond "yes" to indicate their preference to continue to receive research texts.

VII. POTENTIAL BENEFITS

Benefits to participating individuals
It is possible that treatment with solriamfetol may improve the participant's EDS, and thereby improve their overall functioning.

There is a chance that the pre-study screening will reveal some medical abnormality. This information will be conveyed to the participant, together with a recommendation of a local clinic or physician from whom to seek treatment.

Monetary compensation for participation in the study will be based on the following criteria. $150.00 for completing the screening; $ 420.00 per week for the baseline and treatment weeks (total of 6 weeks; $2,520); $ 350.00 per MWT visit (baseline visit and end of treatment visit); and a $2,630 .00 bonus for completion of the entire study. If all procedures are completed, a participant will receive up to a total of $6,000 by check.

The participants will be given a parking voucher or reimbursed up to $15.00 for parking at 221 Longwood Avenue for visits 1,3,4, and 6. For visits 2 and 5 (the Nap studies) they will be reimbursed for the cost of their transportation up to $50.00 ($25.00/ each way)

Potential benefits to society
Early-morning shift work can result in shortened and disrupted sleep at night, leading to sleepiness that day and an increased risk of accidents both at work and while driving. Due to the growing 24/7 economy, early-morning workers who start around the circadian nadir (between 3-7 AM) have become an increasing segment of the workforce. These are occupations such as fast order/ delivery (e.g., FedEx, Amazon fulfilment center workers), early opening of coffee/breakfast bars, public transport, etc. Previous shift work studies have focused primarily on night shift workers, whereas this early morning group is understudied and more research is needed. This study aims to examine whether solriamfetol during work hours can improve daytime sleepiness. If this study finds that solriamfetol can improve EDS in early-morning shift workers, additional studies could be carried out to examine the generalizability of the results and examine if solriamfetol could be effective in rotating shift workers, night-shift workers or other (patient) groups coping with ES. Alternatively, future studies could also be focused on testing solriamfetol in combination with lifestyle (non-pharmalogical) interventions to personalize treatment to each individual.

VIII. MONITORING AND QUALITY ASSURANCE

Many shift workers work in safety-sensitive occupations, such as healthcare and transportation. Although participants in the study are not expected to be at greater risk for errors, injuries, or crashes by being in the study, by nature of their shiftwork schedule they may be at greater risk than the general population. Therefore, excessive sleepiness and risk for errors, injuries, or crashes due to insufficient sleep and shift work will be discussed with participants, and any errors and accidents will be recorded as part of the weekly AE and symptom query during the study. Transportation to and from the Baseline and EOT will be provided.

Independent monitoring of source data.
Data quality will be monitored by the PI and the study personnel. All data will be collected and recorded using a study code rather than individually-identifying information. The questionnaires will be collected using REDCap.

Safety monitoring.
Data and safety will be monitored by the PI, co-investigators, and study personnel. During the MWT visits (Visits 2 and 5) conducted at the BWH CCI, participants will be monitored by CCI nursing staff and technical laboratory personnel.

The PI will be responsible for ensuring all Human Subjects regulations and policies are followed, and for reporting to the Human Subjects Committee, as required.

Aggregate data reviews will be conducted at a minimum annually, for the annual reviews required for the IRB.

BWH IDS will fill out a drug order form from Axsome Therapeutics to receive deliveries of the study drug solriamfetol. The study doctor will go through the IDS to dispense the study drug to participants.

All study personnel involved in the participant recruitment, study execution, data collection and analysis have completed Human Subjects training as well as training in the procedures required by HIPAA.

Specific procedures that will be used to minimize potential risks include the following:

Screening blood and urine samples will be taken at Visit 1 and safety blood samples will be taken at Visit 5.

Participants will undergo an EKG and have vital signs taken at Screening Visit 1 and those with evidence of uncontrolled hypertension, clinically significant arrhythmia, or other clinically significant abnormalities on the EKG will be excluded. Vitals will be re-checked at each visit (2-week intervals).

The participant's vital signs will be checked at each visit. This will include pulse rate, respiratory rate, systolic and diastolic BP.

Female participants who are pregnant, planning to become pregnant, or breast feeding will not be enrolled. Women of reproductive capacity will be required to use birth control throughout their participation.

Participants will take the BAI and those with a score indicating high levels of anxiety [scores >35] will be excluded].

Participants will take the BDI and those who indicate suicidal thoughts (score of 1 or greater on question 9) and/or indicate moderate or severe depression (total score of 19 or greater) will be excluded. Responses to the BDI will be reviewed before the participant leaves the Screening Visit. Those who have indicated suicidal thoughts will be immediately referred to a clinical psychologist, a psychiatrist, or other clinician for appropriate assessment and triage. All other participants and their responses to the BDI will be evaluated by a licensed physician to exclude those with a history of suicidal thoughts or substance abuse disorder.

Current suicide risk will be assessed via the C-SSRS. "Baseline/Screening" version of the C-SSRS will be used at Visit 1. "Since Last Visit" version of the C-SSRS will be used at visits 3, 4, 5, and 6. Responses to the C-SSRS will be reviewed before the participant completes the visit. Participants who indicate a positive response to item number 4 and/or number 5 on the C-SSRS will be immediately referred to a clinical psychologist, a psychiatrist, or other clinician for appropriate assessment and triage. They will be excluded from further participation in the study. In addition, any spontaneous expression of suicidality will be immediately referred to a clinician for appropriate assessment and triage.

Safety and tolerability assessments throughout the study will include weekly queries for adverse events. After two weeks of treatment, an in-person visit to evaluate vital signs and AEs will be conducted. After four weeks of treatment, a PE including vital signs, EKG, UA, CBC, and a metabolic panel will be conducted. Approximately one week after completion of the study, a final safety visit is scheduled. This will include a PE, vital signs, symptoms, AEs, and C-SSRS change.

In order to minimize the safety risks associated with inadequate sleep, the participant will not be allowed to drive to and from the MWT visits.

All participants who withdraw from the study will be asked to come in for a final Safety Visit. If participants withdraw after more than one week in the treatment phase of the study, they will be asked to come in for a MWT visit.

Population pharmacokinetic analysis indicated that age, gender, and race do not have clinically relevant effects on the pharmacokinetics of solriamfetol.

Outcomes monitoring
Ongoing study progress, including enrollment, data quality/integrity, completeness, and safety issues, will be reviewed weekly by the study team.

While they are enrolled in the study, a study team member will be available to the participant at all times via telephone or text/email to answer questions, and to take reports of any accidents, injuries, or AEs. The daily diary entries will be monitored regularly to ensure the participant is completing them and to follow-up in cases where there are missing or potentially incorrect entries.

Adverse event reporting guidelines
The PI will be ultimately responsible for reviewing and reporting all adverse events to the IRB as outlined in the

policy “Reporting Unanticipated Problems including Adverse Events”. As outlined in that policy, SAEs will be reported to the IRB within 5 business days or 7 calendar days of the Investigator becoming aware of the incident. The PI will also be responsible for reporting all serious and unexpected adverse events to the FDA per 21CFR312.32. As outlined there, an IND safety report will be submitted as soon as possible, but in no case later than 15 calendar days in the case of all serious and unexpected suspected adverse reactions; unexpected fatal or life-threatening suspected adverse reaction reports will be filed within 7 days. SAEs will be reported to Axsome at safety@axsome.com as soon as possible after the Investigator becomes aware of the incident, but no later than the time the IRB is notified. Adverse events will also be reported to Axsome at safety@axsome.com at the end of the study or upon request.

Study clinicians involved in physical examinations and review of data will be involved in assessing Adverse Events. A qualified physician co-investigator will make the final determination on the severity of the event, nature of the event, seriousness of the event, and relationship of the event to study drug/procedures for reporting purposes.

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APPENDIX I

Questionnaires to be Used in the Study

At phone/ online (REDCap) screening:
Shiftwork Disorder screening instrument
Modified Epworth Sleepiness Scale

At Screening Visit:
Subject Information questionnaire
Personal Data (race/ethnicity) form
Beck Depression Inventory II
Beck Anxiety Inventory
Pittsburgh Sleep Quality Index

At Baseline Visit:
Chronotype questionnaire for Shift-Workers
Work Productivity and Activity Impairment scale-Specific Health Problem version
Functional Outcomes of Sleep Questionnaire-10 item version
Sheehan Disability Scale
Epworth Sleepiness Scale-modified version
Patient Global Impairment scale

During Baseline Segment and Treatment Segments:
Daily sleep and work diary.

At End of Treatment Visit:
Work Productivity and Activity Impairment scale-Specific Health Problem version
Functional Outcomes of Sleep Questionnaire-10 item version
Sheehan Disability Scale
Epworth Sleepiness Scale-modified version
Patient Global Change scale

APPENDIX II - Screening Laboratory Test Acceptable Ranges

	Description	Normal Values	Acceptable Values	Comments
Comprehensive Metabolic Panel				**SST, 8.5mL**
Glucose (Random)	Serum Glucose	54-118mg/dl	54-150mg/dl	Non-fasting. If >150mg/dl then repeat fasting
Glucose (Fasting)	Serum Glucose	54-118mg/dl	54-125mg/dl	
Urea	BUN	9-25 mg/dl	6-50 mg/dl	
Creatinine	Serum Creatinine	0.7-1.3 mg/dl	0.4-1.4mg/dl	
Sodium	Serum Sodium	136-142 mmol/L	133-146 mmol/L	
Potassium	Serum Potassium	3.5-5.0 mmol/L	3.5-5.0 mmol/L	
Chloride	Serum Chloride	98-108 mmol/L	94-114 mmol/L	
Total CO2	Serum Total CO2	23-32 mmol/L	22-36 mmol/L	
Anion Gap		3-15 mmol/L	2-16 mmol/L	
ALT/GPT	Liver Enzyme	7-52 U/L	5-60 U/L	
AST/GOT	Liver Enzyme	9-30 U/L	5-40 U/L	
Alk Phos	Liver Enzyme	36-118 U/L	20-135 U/L	
Total Bili	Liver Function	0.2-1.2 mg/dl	0.0-1.9 mg/dl	1.3-1.9mg/dl acceptable as long as other LFTs are WNL
Total Protein	Serum Protein	6.0-8.0 g/dl	5-8.5 g/dl	
Albumnin	Serum Protein	3.7-5.4 g/dl	3.5-5.9 g/dl	
Globulin	Serum Protein	2.0-4.0 g/dl	1.6-4.2 g/dl	
Calcium	Serum Calcium	8.8-10.5mg/dl	8.7-10.5mg/dl	
Complete Blood Count with Differential				**EDTA, 3mL**
WBC	White Blood Cells	4-10 KI/uL	3-10.5 K/uL	
RBC	Red Blood Cells	3.9-6.0M/ul	3.0-7.0M/ul	
HCT (women)	Hematocrit	36-48 g/dl	34-48 g/dl	
HCT (men)	Hematocrit	38-49 g/dl	36.5-49 g/dl	
HGB (women)	Hemoglobin	11.5-16.4 g/dl	11.0-16.4 g/dl	
HGB (men)	Hemoglobin	12.5-16.6g/dl	12.0-16.6g/dl	
MCV	Blood MC volume	80-95 um3	76-100 um3	
MCH	Blood MCH	27-32 uug	24-36 uug	
MCHC	Blood index	32-36 g/dl	30-38 g/dl	
RDW	Blood index	10-14.5	9-15.5	
PLT	Platelets	150-450 K/ul	140-500 K/ul	
Lymph %	Lymphocyte %	18-41	10-60%	
Mono %	Monocyte %	2.5-8.5	1.8-14%	
Neut %	Neutrocyte %	48-76	32-84%	
EOS %	Eosinophil %	0-5	0-9%	
Baso %	Basophil %	0-2.5	0-9%	
Lymph #	Lymphocyte Absolute	0.8-4.1 K/ul	0.4-5.8 K/ul	
Mono #	Monocyte Absolute	0.10-0.80 K/ul	0.02-1.4 K/ul	
Neut #	Neutrocyte Absolute	3.9-7.6 K/ul	2.9-9.0 K/ul	
Eos #	Eosinophil Absolute	0.0-0.5 K/ul	0.0-0.6 K/ul	
Baso #	Basophil Absolute	0.0-0.15 K/ul	0.0-0.3 K/ul	
TSH	Thyroid Stim Hormone	0.5-5.0	0.5-5.0	**SST, 3.5mL**
Urinalysis				
COLOR		clear/yellow	clear/yellow/amber/cloudy	
SP GR	Specific Gravity	1.003-1.035	1.003-1.045	
PH	pH	4.5-8.0	4.3-8.5	
PRO	Protein	Negative	1+	
KET	Ketone	Negative	1+	
BILI	Bilirubin	Negative	trace	
BLOOD	Blood	Negative	negative (Males) 1+ (females)	
LEUK	Leukocyte	Negative	No more than one	
ES	Esterase	Negative	of these may be	
NIT	Nitrates	Negative	positive	
URO	urobilinogen	0.2-1.0	0.2-1.2	
WBC	white blood cells	0-4/hpf	<10	
RBC	red blood cells	0-2/hpf	0-2 (males) <10 (females)	
BACT	bacteria	negative	1+ (unless sq epitherial cells present)	
SQ EPI	squamous epithelial cel	variable	variable	
Drug screen				
Comprehensive Drug Analysis (urine)		Negative	Negative	If positive for THC, test may be repeated once

Test results that fall outside the "Acceptable" range can be repeated once to confirm findings

APPENDIX III

Abbreviations

AE	adverse event
AICD	automatic implantable cardioverter defibrillator
BDI	Beck depression inventory
BMI	body mass index
BP	blood pressure
BWH	Brigham and Women's Hospital
CBC	complete blood count
CCI	Center for Clinical Investigation
CGI-C	clinical global impression (of change)
CGI-EI	clinical global impression (efficacy index)
CI	confidence interval
EEG	electroencephalogram
EKG	electrocardiogram
EMG	electromyogram
EOG	electrooculogram
EOT	end of treatment
ES	excessive sleepiness
ESS	Epworth sleepiness scale
FDA	Food and Drug Administration
FI	fragmentation index
FOSQ	Functional Outcomes of Sleep Questionnaire
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HST	home sleep test
IB	Investigator's Brochure
IDS	Investigational Drug Service
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
KSS	Karolinska Sleepiness Scale
LFT	liver function tests
MAOI	monoamine oxidase inhibitor
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
OSA	obstructive sleep apnea
OTC	over-the-counter
PE	physical examination
PI	principal investigator
PKU	phenylketonuria
PLMD	Periodic Limb Movement Disorder
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
REM	rapid eye movement
RLS	restless legs syndrome
SAE	severe adverse event
SDS	Sheehan Disability Scale
SE%	sleep efficiency
SL	sleep latency
SmPC	Summary of Product Characteristics
SWD	shift work disorder
TSH	thyroid stimulating hormone
TST	total sleep time

UA	urinalysis
UDS	urine drug screen
USPI	United States Package Insert
UW	usual wake time
WASO	wake after sleep onset
WOCBP	women of childbearing potential WPAI-SHP Work Productivity and Activity Impairment-Specific Health Problem