**PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL**

Efficacy of Suvorexant in Patients with Effectively Treated Restless Legs Syndrome and Persistent Chronic Insomnia: A Randomized Placebo-Controlled Crossover Trial

## I. BACKGROUND AND SIGNIFICANCE

Restless Legs Syndrome (RLS) is a sensory-motor neurological disorder characterized by an irresistible urge to move the legs that is often paired with leg discomfort. Symptoms are provoked by rest, relieved with movement, and worst in the evening or at night.[1] Clinically significant RLS that occurs at least two times per week, and is associated with moderate to severe distress, is present in roughly 3% of the general population.[2] Such sufferers describe these leg sensations on a spectrum from annoying to unbearable and the physical distress and lack of sleep associated with RLS contribute to high levels of morbidity and poor quality of life.[3-5]

Sleep disturbance is present in over 75% of individuals with RLS, producing most of the morbidity of moderate to severe RLS,[6] and is the primary complaint which drives individuals with RLS to seek medical attention.[2] RLS is associated with difficulty falling asleep, repeated awakenings, and total sleep times averaging less than 5.5 hours.[7] Both the sensory discomfort as well as the periodic limb movements of sleep (PLMS) are thought to contribute to RLS sleep disturbance.

Dopamine agonists (DAs) have been the mainstay of medical treatment for 20 years and remain first-line therapy for many patients. Most patients with RLS initially experience prompt suppression of the sensory symptoms upon treatment with a DA.[8] Alpha-2-delta agents such as gabapentin and pregabalin are also used in RLS treatment with substantial benefit for the sensory symptoms.[9]

Unfortunately, persistent difficulties with all phases of sleep are common in patients whose RLS symptoms are resolved with treatment. Meta-analyses of DA clinical trials in RLS demonstrate that the absolute effect size (as change from baseline) is only .4 when compared to placebo.[10] These small to moderate effects of DAs leave the average treated RLS patient with sleep durations of just over 6 hours.[11,12] Alpha-2-deltas also leave effectively treated RLS patients with persistent insomnia,[13,14] with average sleep latencies over 30 minutes, WASO of 60-90 minutes, and sleep efficiencies of 75-85%. Similarly, iron treatments, which often produce substantial benefits for RLS symptoms, do not produce any improvement for sleep in clinical trials.[13] In community surveys of treated RLS patients, 53% report sleep disruption four or more nights per week.[15]

Multiple potential causes for treatment-refractory sleep disturbance exist, including activating effects of DAs, conditioned insomnia and poor sleep habits as a result of chronic RLS-related sleep disturbance, and comorbid medical and psychiatric illness. Another potential explanation is the suggestion from emerging data that RLS and insomnia share genetic underpinnings and thus may be comorbid independent of any prior sensory symptoms.[16]

In the absence of any clinical trials addressing the issue, the persistent insomnia in patients with effectively treated RLS is currently addressed empirically with FDA-approved (benzodiazepine receptor agonists) and non-approved (trazodone) agents, with varying success. Use of the former category risks the emergence of complex sleep-related behaviors, which occur at higher rates in RLS,[17,18] whereas the latter risks worsening the underlying RLS.[19] Gabapentin is sometimes attempted as a hypnotic in such patients though its side-effect profile may worsen underlying gait instability in older patients. Cognitive-behavioral treatment of insomnia (CBT-I) is generally efficacious for chronic insomnia and is first-line treatment for this disorder. However, as the sleep deprivation initially produced by CBT-I is known to exacerbate RLS severity,[20] this approach is generally not used in RLS.

Suvorexant provides an important therapeutic option to treat insomnia in the context of RLS. It has demonstrated long-term efficacy, particularly in shortening the duration of nocturnal awakenings and increasing total sleep time.[21] Similarly, it has a comparatively benign side effect profile compared to many of the agents described above.

Orexin is thought to play a key role in the central regulation of arousal which accounts for its benefits in insomnia. RLS, like insomnia, has been associated with hyperarousal. Whether orexin plays a specific role in RLS-related sleep disturbance is unclear. Two previous studies have examined orexin levels in RLS patients, with conflicting results.[22,23]

To summarize, the proposed study is not to treat RLS but rather to address the substantial proportion of RLS patients whose core RLS symptoms are effectively managed by medications but are left with persistent insomnia. Clinically significant RLS is present in 3% of adults, roughly one-half of whom have control of core RLS symptoms with treatment. Over half of these patients report persistent insomnia, even with substantial control of their RLS symptoms, due to the limitations of current RLS medications. Thus, roughly 0.5-1% of adults have persistent insomnia with effectively treated RLS. Existing insomnia treatments can either worsen underlying RLS or lead to complex sleep-related behaviors or other side effects in this primarily older population. Suvorexant provides a potentially important option due to its efficacy and tolerability profile.

## II. SPECIFIC AIMS

**Primary Aim:**

- To determine whether suvorexant will have significantly greater effect than placebo in increasing actigraphically-derived total sleep time (TST) in patients with effectively treated restless legs syndrome (RLS) with persistent insomnia.

**Secondary Aims:**

- To determine whether suvorexant will have significantly greater effect than placebo in reducing actigraphically-derived wake after sleep onset (WASO) in patients with effectively treated RLS with persistent insomnia.
- To determine whether suvorexant will have significantly greater effect than placebo in decreasing Insomnia Severity Index (ISI) scores in patients with effectively treated RLS with persistent insomnia.

**Exploratory Aims:**

- To determine whether suvorexant will have significantly greater effect than placebo for self-reported sleep metrics (e.g., quality, disturbance, sleep latency and duration) in patients with effectively treated RLS with persistent insomnia.
- To determine whether suvorexant will have an effect on RLS severity in patients with effectively treated RLS with persistent insomnia.

## III. SUBJECT SELECTION

The following lists the inclusion/exclusion criteria for prospective participants.

**Inclusion Criteria:**

1. Men or women of any ethnic origin
2. Written informed consent is obtained
3. Speaks and writes in English
4. A willingness and ability to comply with study procedures.
5. Age 18 years or older
6. Diagnosis of RLS via Cambridge-Hopkins RLS questionnaire[24]
7. International Restless Legs Syndrome Study Group scale score (IRLS)<15[25]
8. RLS treatment with a dopaminergic agonist, an alpha-2-delta agent, iron, cannabinoids, or an opioid*
9. No changes in RLS medication in the previous month
10. DSM-5 criteria for Insomnia Disorder
11. Report a total sleep time ≤ 7 hours and wake after sleep onset > 45 minutes on 7 or more of the 14 nightly sleep logs during both the initial 2-week screening period and the two-week screening run-in period. WASO does not decrease by more than 50% on the 2-week sleep diary obtained between the screening visit and the randomization visit.

*If patient is using an opioid to treat their RLS, the following additional exclusion criteria will apply:

1. Individuals taking opioids at an MME > 40 MME daily (e.g., oxycodone > 26 mg, methadone > 10 mg)
2. Individuals taking opioids who have comorbid conditions accompanied by significant hypoxia, hypercapnia, or decreased respiratory reserve such as: severe asthma, chronic obstructive pulmonary disease, or severe obesity

3. Individuals taking opioids at any dose with concurrent gabapentin, pregabalin or gabapentin enacarbil
4. Individuals who have changed their opioid dose within the past 6 weeks

**Exclusion Criteria:**

1. Sleep and medical factors:
   a. Diagnosis of moderate/severe obstructive sleep apnea (AHI>30) not using CPAP (can be included if CPAP adherent), or other untreated primary sleep disorders (e.g. narcolepsy)
   b. Shift workers
   c. Unwillingness to not use sedative-hypnotics (other than suvorexant) during the study period
   d. Unwillingness to maintain stable RLS medication during the study unless medically indicated
   e. Current use of an opiate medication.
   f. Unwillingness to not take stimulants (e.g. caffeine) after 4:00 pm during the study.

2. Psychiatric factors:
   a. Current major depressive episode, by report and as indicated by the Patient Health Questionnaire (PHQ-9)[26]
   b. Lifetime history of bipolar disorder, psychosis, or other serious psychiatric illness
   c. Current alcohol/substance use disorder

3. Medical factors:
   a. BMI $\geq$ 40 kg/m$^2$
   b. Renal or hepatic disease judged to interfere with drug metabolism and excretion
   c. Pregnancy or breastfeeding
   d. Malignancy within past 2 years
   e. Surgery within past 3 months
   f. Neurological disorder or cardiovascular disease raising safety concerns about use of suvorexant and/or judged to interfere with ability to assess efficacy of the treatment
   g. Medical instability considered to interfere with study procedures
   h. Concomitant medications with drug interaction or co-administration concerns
   i. Contraindications or allergic responses to suvorexant
   j. History of being treated with suvorexant

4. Lifestyle and other factors:
   a. Travel across two time-zones during the week prior to enrollment
   b. Greater than 6 cups of coffee per day

**Exclusionary Medications**

The following medications are considered exclusionary:

- Strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, conivaptan)
- *Maximum dose of 10 mg will be considered for subjects taking: moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil)
    - In certain cases, subjects on moderate CYP3A inhibitors may be administered 20 mg of suvorexant if the study doctor determines that side effects at 10 mg do not preclude an increase in dose. In these events, an additional safety phone call will be performed after 1 week at the higher dose (20 mg) in both treatment periods, in which it will be determined whether the subject should stay at 20 mg or decrease back to 10 mg.

## IV. SUBJECT RECRUITMENT AND ENROLLMENT

**Methods of recruitment and procedures for informed consent:**

The target enrollment for the study is N=90 individuals with treated RLS and insomnia. Potential subjects will be informed of the study in one of five ways: 1) through advertisements on the Partners Clinical Trials webpage, 2) through advertisements on Facebook, Google, and Reddit, 3) through referral by a providing clinician, 4) through the RSVP for Health, or 5) through letters/announcements via Patient Gateway. Patients will be identified using RPDR and Epic. We will only send targeted letters and announcements to patients with a diagnosis of RLS.

The enrollment goal for effectively treated RLS with persistent insomnia will be addressed by specifically targeting sleep clinics at Massachusetts General and Brigham and Women's Hospital, as well as the HMS-affiliated Beth Israel Deaconess Hospital, for all of which the PI teaches and supervises Fellows in sleep clinics. The PI has close ties to many clinicians in these clinics, and they have conveyed their interest in recruiting for this study given the high prevalence of insomnia in this population.

Interested patients may contact the study staff using the contact information provided in the advertisements or by the research coordinator/clinician (in the form of a small handout). During initial phone contact with MGH staff, interest in the study will be re-confirmed and verbal informed consent will be obtained, after which a phone screen will be conducted by a member of the study staff.

The potential risk of coercion for study subjects will be managed by ensuring that their treating physician provides only a study handout to potential study participants. Potentially eligible patients may separately contact a research coordinator to further inquire about participation. Once the subject has agreed to participate, the MGH study physician will participate in the consenting

procedures to ensure that any questions regarding the study are answered accurately and to the fullest extent possible.

Interested subjects will provide verbal consent at the time of the initial phone call, at which time they will be informed that their data will be used to study the effect of suvorexant on sleep disturbance in people with treated RLS. Verbally consented subjects will be assigned a unique identifier that will be used to link screening questionnaire data to the subject's record.

Verbally consented subjects will be re-consented during the Screening Visit. Written consent will be obtained by the study physician using a written Informed Consent Form including a summary of HIPAA policies; the signatures on the Informed Consent Form will be obtained electronically (via the REDCap e-consent framework). A signed copy will be given to the subject. Once consent is obtained, patients will be assigned a new unique identifier, which will be used to link all questionnaire data with the patient's record throughout the study. The questionnaire data linked with each unique identifier will be collected and stored on REDCap (Research Electronic Data Capture), which is a secure, HIPAA compliant web-based application and database hosted by Partners HealthCare. A separate database at the Sleep Disorders Clinical Research Program at Massachusetts General Hospital will contain personal identification data.

If subjects have questions concerning their rights as a research subject, they may call the Human Subjects Committee office at MGH, or speak with study clinicians. All study documents will be stored electronically in REDCap as well as encrypted laboratory computers, and access to this information will only be given to the research personnel.

**Study Design and projected enrollment:**

This is a two-arm, double-blind, randomized placebo-controlled crossover 2.5-month trial, investigating the effects of suvorexant 10–20 mg on actigraphically-derived total sleep time in patients with persistent insomnia and effectively treated RLS.

All study procedures will be conducted at Massachusetts General Hospital. Based on experience from our research group in patients with insomnia and RLS, we expect to consent and evaluate for eligibility up to 90 patients in order to achieve our projected randomized sample size of 44 patients with effectively treated RLS, who will be randomized in a 1:1 ratio to suvorexant 10–20 mg or equivalent placebo for four weeks followed by crossover (after a 2 week washout) to the alternate treatment. Our goal is to have 34 patients with effectively treated RLS complete the trial with evaluable data at 2.5 months, after allowing for post-randomization drop-outs.

We expect that many of the participants in this study will have numerous other health conditions which are thought to place them at higher risk of COVID-19-related complications. Thus, considering the safety and mental wellbeing of our subjects, all study visits will occur remotely.

For the remote visits, research staff will follow the MGB requirements for using the appropriate virtual tools. The study physician will remain on call during all points of remote visits in case there any emergent medical or psychiatric issues.

## V. OVERVIEW OF STUDY PROCEDURES

### Visit 1: TELEPHONE SCREEN (WEEK -4)

An initial screen will be conducted over the phone, consisting of a brief clinical and sleep history for inclusion and exclusion criteria. If preliminary eligibility appears adequate and the individual expresses interest, they will be sent links to complete the following questionnaires on REDCap:

1) the Insomnia Severity Index to assess insomnia severity[27]
2) the PHQ-9 to screen for depression
3) the IRLS to assess RLS severity
4) the STOP-BANG questionnaire to screen for sleep apnea[28]
5) an electronic 14-day sleep diary

Upon our review of these completed surveys and diaries, those who meet further eligibility criteria, as determined by the diaries (see Inclusion and Exclusion Criteria above), will be scheduled for a Screening Visit.

### Visit 2: SCREENING VISIT (WEEK -2)

Written informed consent will be obtained by the study doctor at the Screening Visit for the remaining screening procedures and all treatment-related procedures (via the IRB-approved Informed Consent Form via the REDCap e-consent framework). Risks and benefits associated with use of suvorexant will be described. At that time, further eligibility will be assessed with a clinical interview conducted by a sleep medicine-trained psychiatrist to diagnose chronic insomnia disorder and to ensure that contraindicated sleep, medical and psychiatric problems and medications are excluded. Urine screens for pregnancy will be performed at an affiliated site; the study physician will order these tests.

Phillips Actiwatch Spectrum Plus actiwatches will be mailed to participants, and returned by mail to investigators, at the outset and the end, respectively, of the screening run-in. Actigraphy baseline data will be collected during the 14 days of the screening run-in period. Actiwatches will be worn on the non-dominant wrist both day and night at all times except when showering. Standardized operating procedures developed by the Actigraphy Core of the Division of Sleep Medicine at MGH will be followed. Event marker button press will establish “lights out” and “lights on” and will be compared with the daily diary times and adjusted if necessary, using written protocols. Sleep onset

and offset times will be computed using the vendor provided software by a trained technician supervised by the consultant (Dr. Klerman, the Core Chief). The following key standard actigraphy metrics will be generated on each day's data: Sleep onset, sleep offset, time in bed (TIB), total sleep time (TST), sleep latency, wake after sleep onset (WASO), sleep efficiency and naps.

Screening Run-In: They will receive daily email links to an online sleep diary to complete on 14 consecutive days during the screening run-in period.

**Visit 3: BEGIN FIRST TREATMENT (WEEK 0)**

At this Randomization Visit, the 2-week sleep diary will be reviewed for definitive eligibility before the participant is randomized to treatment. Baseline questionnaires will be determined at this visit. Baseline subjective and actigraphic sleep measures will be determined from the last 7 days of this 2-week period. Baseline pre-treatment symptom measures will be determined from the Randomization Visit. If the subject did not wear the actiwatch over 80% of the time during the two weeks before randomization, or if their data is missing (e.g. due to device malfunction), the actigraph will be sent back to the subject and he or she will be asked to repeat the baseline data collection period.

Eligible participants will be randomized in a 1:1 ratio for the first 4-week period of placebo or suvorexant. Subjects will be mailed 14 days of the 10 mg dose of study medication following this visit.

Subjects will also be mailed 42 additional pills of the 10 mg dose for use in weeks 1 to 3. Subjects will also be mailed actiwatches, and will be instructed to wear these during the two weeks leading up to Visit 5.

**Visit 4: INTERIM PHONE CONTACT 1 (WEEK 1)**

The study physician will call the participant to inquire about efficacy and adverse events. If the 10 mg dose is well tolerated but not effective, the dose can be increased to 20 mg. The study physician will instruct the participant to take either one pill (10 mg) or two pills (20 mg) nightly over the next three weeks.

**Visit 5: END FIRST TREATMENT (WEEK 4)**

At this virtual visit, participants will meet with a study physician and the study coordinator. The physician will assess the participant on the Clinical Global Impression-Improvement (CGI-I) scale and will also inquire about any adverse events experienced. Questionnaires will also be determined at this visit. Subjects will be asked to mail actiwatches back to the study team.

At this point, subjects will begin the 2-week washout phase.

## Visit 6: BEGIN SECOND TREATMENT (WEEK 6)

After the 2-week washout phase all participants will be crossed over to the other treatment for the second 4-week treatment phase. Subjects will be mailed 14 days of the 10 mg dose of either suvorexant or placebo following this visit.

Subjects will also be mailed 42 additional pills of the 10 mg dose for use in weeks 7 to 9. Subjects will also be mailed actiwatches, and will be instructed to wear these during the two weeks leading up to Visit 8.

## Visit 7: INTERIM PHONE CONTACT 2 (WEEK 7)

The study physician will call the participant to inquire about efficacy and adverse events. If the 10 mg dose is well tolerated but not effective, the dose can be increased to 20 mg. The study physician will instruct the participant to take either one pill (10 mg) or two pills (20 mg) nightly over the next three weeks.

## Visit 8: END SECOND TREATMENT (WEEK 10)

During this final virtual study visit, participants will meet with a study physician. The physician will assess the participant on the Clinical Global Impression-Improvement (CGI-I) scale and will also inquire about any adverse events experienced. Questionnaires will also be administered at this visit. Subjects will be asked to mail actiwatches back to the study team after the visit.

## Compensation:

Subjects will be compensated $50 for study visit 2 and for virtual visits 3-8 ($25/visit). Subjects will receive a completion bonus when they have completed the study in its entirety ($50). The total possible compensation is $250.

See below for the **Table of Procedures** and **Study Flowchart**.

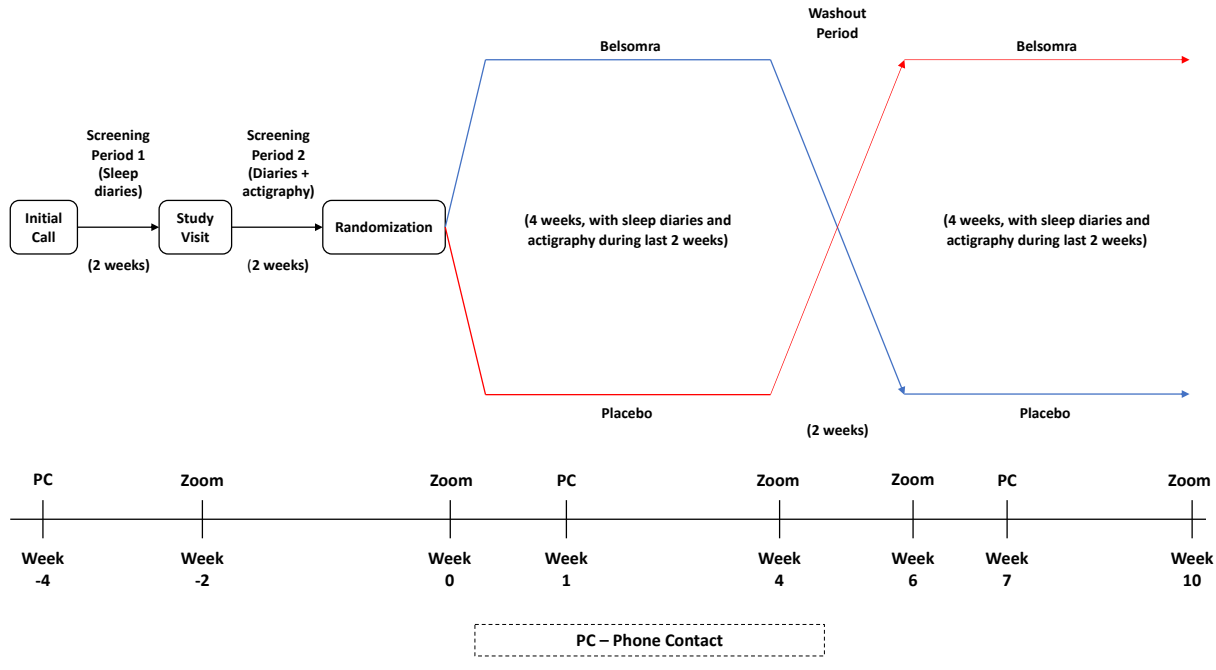
## Table of Procedures:

| Visit | | Screening Period | | Treatment Period 1 | | | Treatment Period 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | V1/ Initial Screening | V2/ Screening | V3/ Randomization | V4/ Interim phone Contact 1 | V5/ End of 1st Treatment | V6/ Begin 2nd Treatment | V7/ Interim phone Contact 1 | V8/ End of 2nd Treatment |
| Study Week | | -4 | -2 | 0 | 1 | 4 | 6 | 7 | 10 |
| Visit Location | | Phone | Zoom | Zoom | Phone | Zoom | Zoom | Phone | zOOM |
| General/ Screening Assessment | Sleep/medical/mental health phone screening and verbal consent | x | | | | | | | |
| | Written Informed Consent | | x | | | | | | |
| | Eligibility Criteria | | x | x | | | | | |
| | Medical History | | x | | | | | | |
| | Urine hCG | | x | | | | | | |
| | Concomitant Medication | | x | x | x | x | x | x | x |
| | ISI | x | | x | | x | | | x |
| | PHQ-9 | x | | | | | | | |
| | STOP-BANG | x | | | | | | | |
| | CH-RLSq | | x | | | | | | |
| | BDI | | | x | | x | | | x |
| | IRLS | x | | x | | x | | | x |
| | CGI-I | | | | | x | | | x |
| | PGI-I | | | | | x | | | x |
| | DBAS | | | x | | | | | |
| Sleep Assessment | Sleep Diaries (administer/review) | x[a] | | x[b] | | x[b] | | | x[b] |
| | Actigraphy (administer/download) | | | x[b] | | x[b] | | | x[b] |
| | PSQI | | | x | | x | | | x |
| Dispensing of Actiwatches in mail | Given to subject | | x | | x | | | x | |
| | Returned by subjects | | | x | | x | | | x |
| Medication Dispensed in Mail | | | | x | x | | x | x | |
| Safety Assessment/ Adverse Event Reporting | | | | | x | x | | x | x |
| Medication Adherence | | | | | x | x | | x | x |

Study procedures completed between study events: a = daily for 2 wks following visit, b = daily for 2 wks prior to visit

*hCG = Human chorionic gonadotropin, ISI = Insomnia Severity Index, PHQ-9 = Patient Health Questionnaire, CH-RLSq = Cambridge-Hopkins RLS questionnaire, BDI = Beck Depression Inventory, IRLS = International Restless Legs Scale, CGI-I = Clinician Global Impression of Improvement, PGI-I = Patient Global Impression of Improvement, DBAS = Dysfunctional Beliefs and Attitudes about Sleep[29], PSQI = Pittsburgh Sleep Quality Index.[30]*

## Study Flowchart:



## VI. STUDY MEDICATION AND SUPPLIES

### Study Treatments:

The study medication will consist of 10 mg suvorexant tablets, or matching placebo, prepared in identically appearing capsules by Merck and distributed by the MGH Clinical Trials Pharmacy. The medication will be titrated and distributed according to the following schedule:

### Dispensing Schedule:

| **Double-Blind Suvorexant / Placebo Dosing** | | |
|---|---|---|
| | **Group:** | |
| | **Treatment →** | **Placebo →** |
| **Week** | **Placebo** | **Treatment** |
| 0 | One 10 mg suvorexant tablet | One 10 mg placebo tablet |
| 1-3 | One or two 10 mg suvorexant tablets | One or two 10 mg placebo tablets |
| 6 | One 10 mg placebo tablet | One 10 mg suvorexant tablet |
| 7-9 | One or two 10 mg placebo tablets | One or two 10 mg suvorexant tablets |

Subjects will be instructed to take the study medication within 30 minutes of going to bed and will be informed during the consent process that they may be receiving drug or placebo at different points during the study. Participants will be instructed to take 10 mg nightly for the first 7 days. If the 10-mg dose is well tolerated but not effective after one week of treatment, as determined by the one-week phone visit, the dose can be increased to 20 mg (i.e. two 10 mg pills). This will be repeated at the 7-week phone call.

### Study Medication Packaging:

Medication will be prepared and packaged by the MGH Clinical Trials Pharmacy. The medication will be dispensed in bottles containing enough for 14 days of medication after the Randomization visit, as well as enough for weeks 1-3. After the 6-week visit, a 14-day supply will again be dispensed, as well as a supply sufficient for weeks 7-9. Bottles will be labeled with the patient

name and ID and the dosing information. Bottles will be clearly labeled as containing 10 mg matching placebo or suvorexant tablets.

Subjects will be dispensed the appropriate number of tablets needed until the next medication dispensing date. Study medication should be stored at room temperature 15-30°C (59-86°F), be protected from moisture, and be maintained in a secure area.

**Study Medication Accountability and Compliance:**

Starting at the Randomization Visit, study medication will be dispensed to each subject with instructions to save all unused study medication in order to assess compliance. Participants will be required to show the study team over video how much medication is remaining. Additional bottles will be dispensed to each subject as needed.

All study medication dispensed by the investigator or designee will be accounted for throughout the study. Information about subject dosing and compliance will be recorded in the subject's study records. Subjects who are noncompliant with medications (according to pill counts and diaries) may be removed from the study at the discretion of the investigators.

The investigator agrees not to allow access to the study medication to any person except those named as sub-investigator(s) or clinical care staff and dispense only to qualified subjects participating in the study.

**Randomization:**

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

At the Screening Visit, subjects will be assigned a 3-digit subject number, in ascending sequential order beginning with 001. The subject number will be retained by the subject for the duration of the study. The MGH Clinical Trials Pharmacy will provide and maintain randomization and blinding. Subjects will be randomized to the two crossover groups in a 1:1 ratio. Subject and investigator will be blinded to treatment assignment. Subjects will be randomized sequentially as they qualify for the study.

**Blinding:**

The randomization code will be maintained by the MGH Clinical Trials Pharmacy and will not be revealed to study subjects, investigators or blinded clinical staff until all subjects have completed and the database has been finalized.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific treatment would be dictated by knowing the treatment status of the subject. Individual code breaks by the investigator will normally result in withdrawal of the subject from the trial. The date, time and reason for the unblinding must be documented in the study files.

## VII. RISKS AND DISCOMFORTS

**Medication Side Effects and Adverse Events:**

The package insert for suvorexant includes warnings and precautions related to the following side effects or adverse events: sleepiness during the day, not thinking clearly; acting strangely, confused, or upset; "sleep-walking" or doing other activities during sleep, such as eating, talking, having sex, or driving a car; temporary weakness in your legs or inability to move or talk, cataplexy; and diarrhea, dry mouth, upper respiratory tract infection, headache, next-day drowsiness, dizziness, abnormal dreams, and cough.

Subjects will be informed of the risks associated with consuming alcohol while taking suvorexant, both at the time of consent and throughout the study. Subjects will be advised not to consume alcohol in combination with suvorexant due to additive psychomotor effects.

Subjects will be assessed for depression and suicidal ideation at each study visit, using the Beck Depression Inventory (BDI).[31]

All adverse events that occur between the first study-related procedure and within 30 days of the last dose of study medication will be reported. Adverse events will be reported to the Partners IRB according to guidelines.

Subjects should report any adverse events voluntarily or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?). For each adverse event reported by the subject, the investigator should obtain all the information required to complete documentation in the subject's research file.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the subject's study documents. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The investigator must document his/her opinion concerning the relationship of the adverse event to the study medication. All measures required for adverse event management must be recorded in the source document.

## VIII. POTENTIAL BENEFITS

Subjects will receive suvorexant, which may help their condition. They may benefit from the sleep diaries, actigraphy, review of symptoms, and regular discussions with the study doctor. Their participation in this study may help other people with RLS and insomnia by adding to the knowledge about this drug, and whether it is a beneficial treatment.

## IX. BIOSTATISTICAL ANALYSIS

Analysis of all study data will be conducted by Dr. Winkelman. All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the hospital Research Pharmacist who generates the randomization code will be unblinded to treatment assignment. The final database will not be unblinded until a medical and scientific review, protocol violators have been identified, and all study data are complete.

### Overview of analytic plan:

The primary hypothesis for this trial is that suvorexant is superior to placebo in reducing actigraphically-derived total sleep time in patients with persistent insomnia in the context of effectively treated restless legs syndrome. The primary endpoint is the change in actigraphically-derived total sleep time from baseline to the end of each 4-week treatment period. Key secondary endpoints include actigraphically-derived wake after sleep onset and self-reported ISI, and exploratory endpoints include subjective total sleep time and wake after sleep onset, and RLS severity.

### Study endpoints:

The primary outcome (actigraphically-derived total sleep time) and all secondary and exploratory measures are continuous variables. Primary analyses will focus on the difference from the baseline total sleep time (in minutes) to the total sleep time evaluated in each of the two treatment periods, within subjects. The key secondary variables are the difference from baseline to the end of each treatment period are actigraphically-derived wake after sleep onset and self-reported ISI.

Exploratory analyses will similarly focus on the differences from the baseline value to the final observed value at the end of each treatment period. As these are exploratory analyses, no p-values will be determined other than as described below in the hierarchical testing. These endpoints include:

a) Diary-derived wake after sleep onset

b) Diary-derived total sleep time

c) Diary-derived SOL, sleep efficiency and sleep quality

d) RLS severity via IRLS

## STATISTICAL METHODS

Efficacy variables will be analyzed using an analysis of variance model with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Least squares (LS) mean treatment difference will be calculated from the model. Diagnostic methods will be used for all variables to assess their distributional assumptions and to examine potential outlying or influential data points. This analytical method will similarly be used to assess secondary outcomes. Within-treatment changes from baseline will also be evaluated using a paired t-test for the primary and secondary efficacy variables of change from baseline in total sleep time, wake after sleep onset, and ISI.

The primary outcome analysis will use the intention-to-treat principle and include all participants who received at least one dose of study medication and completed at least one week of sleep diaries following randomization.

Per-protocol analyses will be repeated on the subgroup of subjects that achieve 85% medication adherence based on the number of pills returned at the end of study. Variables related to subjective total sleep time will be determined by Pearson correlation and simple regression analysis using weighted least squares. A two-sided P value $<0.05$ will be considered significant.

## Power/Sample Size:

Statistical power for the primary endpoint, actigraphically-assessed total sleep time, was estimated from pooled analyses of data from placebo-controlled clinical trials of suvorexant for the treatment of insomnia using polysomnographically-measured total sleep time.[21] The difference between 15/20 mg suvorexant and placebo at 1 month in least squares mean change from baseline was 34.7 minutes (95% CI: 27.8, 41.5), corresponding to an effect size of 0.58. Although actigraphy is not identical to polysomnography, multiple studies (including one by our group and two using the Phillips Spectrum actiwatch) with insomnia patients demonstrate high correlations between these two objective recording methods for total sleep time, wake after sleep onset, and sleep efficiency, particularly when event markers are employed.[32-34]

With an effect size of .58, 34 randomized subjects are required to achieve 90% power to detect a statistical significance level of 0.05. In total, we expect to randomize 44 participants to treatment to have 34 completed subjects with evaluable data.

## XI. REFERENCES

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