PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Effect of Suvorexant on Sleep Disturbance in Patients with Chronic Insomnia and Suboptimally Controlled Type 2 Diabetes: A Randomized 3-month Clinical Trial Using a Sequential Parallel Comparison Design

I. BACKGROUND AND SIGNIFICANCE

Type 2 diabetes results from a progressive insulin secretory defect on the background of insulin resistance and is a growing pandemic and a leading cause of morbidity and mortality. Sleep disturbance is one of the underappreciated and important features of Type 2 diabetes. A recent large study of patients with type 2 diabetes found that over three-quarters regularly have difficulty falling and staying asleep[1]. Patients with Type 2 diabetes have many disease-related etiologies for nocturnal awakenings from, and difficulty returning to, sleep (e.g. nocturia, pain, blood sugar assessments, anxiety, sleep apnea), producing sleep-maintenance insomnia and reduced total sleep duration.

Sleep disturbance may contribute to the development of Type 2 diabetes. A recent meta-analysis of epidemiological studies confirmed the risk of both self-reported difficulty initiating sleep (1.57, 95% CI 1.25-1.97) and maintaining sleep (1.84, 95% CI 1.39-2.43)[2] for incident Type 2 diabetes. Our recent analysis[3] of 10-year longitudinal data from the Nurses' Health Study confirmed these previous studies. After adjustment for lifestyle factors at baseline, compared to women without sleeping difficulty, those having difficulty falling or staying asleep "all of the time" or "most of the time" had a multivariate-adjusted HR for incident type 2 diabetes of 1.22 (95% CI 1.12-1.34) even after adjustment for hypertension, depression, and BMI.

In those with established Type 2 diabetes, there is emerging evidence from cross-sectional studies that sleep disturbance affects glycemic control. This issue is of particular importance, as rates of sleep disturbance and shortened sleep duration are high in this disorder[4-10]. A meta-analysis of patients with type 2 diabetes showed that self-reported poor sleep quality (assessed by the Pittsburgh Sleep Quality Index) and short sleep duration (<6 h/night) were both associated with increased HbA1c[11]. In an important examination of the relationship of insomnia and Type 2 diabetes, the Coronary Artery Risk Development in Young Adults (CARDIA) study found that both actigraphic-determined sleep fragmentation and a combined measure of insomnia from actigraphy and self-reported sleep disturbance were substantially associated with abnormalities in fasting glucose, insulin, and homeostatic model assessment (HOMA) index (an estimate of insulin resistance) in those with established diabetes[12]. However, in those without diabetes these associations were not apparent. Finally, in a recent study[13] in hospitalized patients, a 10% increase in actigraphic-measured sleep efficiency was associated with an 18% lower proportional odds of a higher morning glucose category (hyperglycemia vs. elevated, and elevated vs. normal), even after controlling for multiple potential confounding factors. This finding was present in those patients both with and without diabetes.

Hyperglycemia defines diabetes, and glycemic control is fundamental to the management of diabetes. The Diabetes Control and Complications Trial[14] showed definitively that improved glycemic control in Type 1 diabetes is associated with significantly decreased rates of microvascular (retinopathy and nephropathy) and neuropathic complications. The UK Prospective Diabetes Study (UKPDS)[15,16] confirmed that intensive glycemic control was associated with significantly decreased rates of microvascular and neuropathic complications in patients with type 2 diabetes. Long-term follow-up of the UKPDS cohorts

showed persistence of the effect of glycemic control on most microvascular complications[17], and subsequent trials confirmed a benefit on cardiovascular outcomes. For these reasons, a consensus among clinical guidelines has emerged that normalizing glycemic control prevents diabetes mellitus complications.

Although cross-sectional studies suggest a relationship between sleep disturbance and glycemic control in Type 2 diabetes, causality is best investigated by interventional studies. To our knowledge, only one study has examined the effects of insomnia treatment in patients with Type 2 diabetes[18]. In that study, 36 middle-aged patients with suboptimally controlled Type 2 diabetes (mean HbA1c=9.1%) and insomnia were randomized in a crossover design to 3 weeks of either prolonged-release melatonin or placebo. No differences between groups were observed in any measure of glycemic control even though actigraphically-recorded sleep efficiency, wake after sleep onset (WASO) and number of awakenings improved with melatonin compared to placebo. In a 5-month open-label extension using chronic prolonged-release melatonin, improvements in HbA1c were observed compared to baseline values (9.13% ± 1.55% at baseline versus 8.47% ±1.67% after 5 months on treatment, p=0.005).

Recently published data from our group[19] suggests that hypnotic-related sleep improvement is associated with improvements in glycemic control in insomnia patients without diabetes. In a 2-month randomized placebo-controlled study of eszopiclone in the treatment of primary insomnia, significant changes in the treatment vs. placebo groups were not observed (in glycemic control or insomnia). However, we found a strong correlation between improvement in diary-reported total sleep time and improvement in HbA1c in the eszopiclone group (r=0.66, p=0.0360). Similarly, changes in PSG-measured WASO were positively correlated with changes in IVGTT-derived glucose effectiveness (r=-0.48, p=0.0391). These data suggest that changes in sleep may modify glycemic control even in those with normal baseline measures when the appropriate measures are investigated. It is our belief that abnormal glucose regulation, as seen in Type 2 diabetes, will be even more responsive to improvements in sleep disruption and duration with suvorexant. The lack of therapeutic benefit of eszopiclone in this study is most likely a result of the small sample size as well as the characteristics of the enrolled primary insomniacs who were willing to tolerate the repeated instrumentation (two home sleep studies, MRIs, and IVGTTs) required by the protocol.

The most popular on-label and off-label agents for insomnia (benzodiazepine-receptor agonists, antidepressants and antipsychotic agents) have not been investigated for treatment of insomnia in the context of Type 2 diabetics. Many of these agents may have side effects (weight gain, exacerbation of OSA, risk of cognitive dysfunction, and glucose and lipid abnormalities) that are of particular concern in that population[20]. Suvorexant provides an important therapeutic option to treat insomnia in the context of Type 2 diabetes[21]. It has demonstrated long-term efficacy, particularly in shortening the duration of nocturnal awakenings and increasing total sleep time[22]. Similarly, it has a comparatively benign side effect profile compared to many of the agents described above.

There are also hypothetical reasons that an orexin antagonist may have particular efficacy on glucose regulatory effects in patients with Type 2 diabetes and insomnia. Administration of suvorexant for 2-4 weeks during the resting phase in diabetic *db/db* mice was associated with both reduced wake time/increased total sleep time as well as glucose metabolism[23]. The authors concluded that this effect was mediated through CNS suppression of sympathetic influences on hepatic gluconeogenesis. As hyperglycemia in Type 2 diabetics is related to excessive hepatic gluconeogenesis, nocturnal administration of suvorexant may improve glycemic control by both improving sleep and by stabilizing the orexin system.

II. SPECIFIC AIMS

Primary Aim:

- To determine the effect of suvorexant on subjective total sleep time (TST) in suboptimally controlled Type 2 diabetics with chronic insomnia in a randomized placebo-controlled trial for 3 months.

Secondary Aims:

- To determine the effect of suvorexant on subjective wake after sleep onset and ISI.
- To assess correlations of subjective total sleep time (TST) with changes in HbA1c levels, other subjective sleep endpoints, ISI, PSQI, inflammatory markers, mood, and diabetes-related quality of life measures.

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 25–75 years
6) Diagnosis of Type 2 diabetes with suboptimally controlled blood sugar determined by HbA1c > 6.5% (and < 10.0%) at both the screening and randomization visits[24]
7) No changes in diabetes medication in the previous month
8) DSM-5 criteria for Insomnia Disorder
9) Score on the Insomnia Severity Index (ISI) measure > 10, indicating at least a moderate level of insomnia symptoms[25]
10) Report a total sleep time ≤ 6.5 hours and a combined sleep onset latency (SOL) and wake after sleep onset (WASO) > 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. Combined SOL and WASO does not decrease by more than 50% on the 2-week sleep diary obtained between the screening visit and the randomization visit.

Exclusion Criteria:

1) Sleep and medical factors:
    a. Diagnosis of severe obstructive sleep apnea not using CPAP (can be included if CPAP adherent), or other untreated primary sleep disorders (e.g. narcolepsy, moderate to severe restless legs syndrome)

b. Shift workers
c. Use of hypnotic medications more than twice per week in the past month
d. Unwillingness to not use sedative-hypnotics (other than suvorexant) during the study period
e. Unwillingness to maintain stable diabetes medication during the study unless medically indicated
f. Positive urine toxic screen for any drugs of abuse other than marijuana at Screening Visit
g. HbA1c ≥ 10.0% at either the screening or randomization visit

2) Psychiatric factors:
   a. Current major depressive episode, by report and as indicated by the Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR).
   b. Subjects with active or unstable major psychiatric disorder, who, in the investigator's judgement, require further treatment.
   c. Current alcohol/substance use disorder
3) Medical factors:
   a. Renal or hepatic disease judged to interfere with drug metabolism and excretion
   b. Pregnant or breastfeeding
   c. Malignancy within past 2 years
   d. Surgery within past 3 months
   e. 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
   f. Medical instability considered to interfere with study procedures
   g. Concomitant medications with drug interaction or co-administration concerns
   h. Contraindications or allergic responses to suvorexant
   i. 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

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 this study is N = 120 men and women with insomnia and suboptimally controlled Type 2 diabetes. Potential subjects will be informed of the study in one of six ways: 1) through advertisements on the Partners Clinical Trials webpage and flyers in local diabetes clinics, 2) through advertisements on Facebook (targeted at individuals aged 25-75 in the Boston area), Craigslist, and Google, 3) through a research coordinator stationed at local diabetes clinics to recruit subjects, 4) through referral by a providing clinician, 5) through RPDR and the MGH Diabetes Research Center Patient Registry, or 6) through the RSVP for Health.

Prospective subjects may be identified via registry searches using the MGH Diabetes Research Center Patient Registry. Study staff will conduct a preliminary pre-screening for basic inclusion and exclusion criteria using the medical records (via EPIC) of the potential subjects identified in the registry. If these potential subjects have indicated that they can be contacted directly, an opt-out letter from the principal investigator will be sent to them describing the study and opt-out procedures if they are not interested. If these potential subjects have not indicated that they can be contacted directly, we will use the two-letter approach, where a treating clinician gives permission to contact the patient. Provider permission will be secured by generating a list of potential participants and sending them in a format, with eligibility criteria, where the provider can document yes or no for each patient that may be suitable or unsuitable for the project. After securing provider permission, the potential subject will then be sent a packet including two letters, one non-endorsing, informative letter signed by the clinician stating that they allowed the study team to contact them, and an opt-out letter from the principal investigator describing the study and opt-out procedures if they are not interested. After the opt-out period has ended, a member of study staff will contact all subjects who have not opted out regarding study procedures.

The enrollment requirement for poorly-controlled Type 2 diabetes will be addressed by specifically targeting the primary care and diabetes clinics at Massachusetts General Hospital, Brigham and Women's Hospital, and Newton-Wellesley Hospital, as well as the HMS-affiliated Joslin Diabetes Clinic. The principal investigator has close ties to many clinicians in these clinics (one of whom is a consultant to this study), and they have conveyed their interest in recruiting for this study given the high prevalence of insomnia in this population and the recognition that it influences glycemic control.

At Brigham and Women’s Hospital, study staff will conduct a preliminary pre-screening for basic inclusion and exclusion criteria using the medical records (via EPIC) of the potential subjects. Once potential subjects are identified, the research coordinator will notify treating clinicians, who will ask the patients if they are interested in learning more about the study. If patients express interest in the study, they will meet with the research coordinator, who will obtain informed verbal consent and screen the subjects using the approved screening script.

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 effect of suvorexant on sleep disturbance in people with insomnia and Type 2 diabetes. 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) regardless of whether the visit is in-person or remote. 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 parallel, two-arm, double-blind, randomized placebo-controlled 3-month trial using the sequential parallel comparison design (SPCD), investigating the effects of suvorexant 10–20 mg on subjective total sleep time in patients with suboptimally controlled Type 2 diabetes. The SPCD[26] consists of two stages, with data being pooled from both stages. The first phase involves an unbalanced randomization between placebo and active treatment with more patients randomized to placebo. In the second phase, non-responders treated with placebo are re-randomized to either active treatment or placebo. The first stage is a standard parallel comparison design. However, this first stage generates a cohort of placebo non-responders who then enter the second stage where placebo responses will be lower. This design enriches the primary analysis population, reducing the impact of placebo response rates, and allowing trials to be conducted with reduced study sample size without corresponding decreases in statistical power.

All study procedures will be conducted at Massachusetts General Hospital. We expect to consent and evaluate for eligibility up to 120 Type 2 diabetics in order to achieve our projected randomized sample size of 72 patients with Type 2 diabetes. Subjects will be randomized in a 1:2 ratio to suvorexant 10–20 mg or equivalent placebo for six weeks followed by re-randomization of placebo non-responders to either suvorexant or placebo in a 1:1 design; this will allow 62 Type 2 diabetics to complete the trial at 3 months, after allowing for post-randomization drop-outs.

Eligible patients will be randomized to 6 weeks of suvorexant or placebo after an initial 2-week screening period and a two-week screening run-in period to ensure the stability of sleep disturbance. Participants will complete 4 study visits (consent/screening visit, randomization visit, a 6-week visit, and a 3-months-on-treatment visit). In addition, an initial telephone-based screening assessment and 2 interim phone visits (at 1 week and 7 weeks on treatment) will occur. Suvorexant will be started at 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 visits (at 1 week and 7 weeks of treatment for those originally randomized to suvorexant and placebo, respectively), the dose can be increased to 20 mg.

All of the participants in this trial are diagnosed with type 2 diabetes, a condition which is associated with COVID-19-related complications. Many of the participants also 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, participants will have the choice of completing any of the visits remotely. However, if a reversion to more restrictions is mandated, all visits will be performed remotely. If such a situation occurs, enrolled participants who had been completing in-person visits will be informed about the switch to mandatory remote visits via phone call.

For the remote visits, research staff will follow the MGB requirements for using the appropriate virtual tools: visits will occur via Zoom. In exceptional cases where subjects are unable to use this program, visits may occur by telephone. These remote visits will include all assessments and questionnaires typically performed at in-person visits (the study clinician and research coordinator will perform the tasks that they normally perform in-person), with two exceptions: recording vital signs, and the physical exam at the Screening Visit. The study physician will remain on call during all points of these remote visits in case there any emergent medical or psychiatric issues.

After the video or phone call visit, subjects will be required to visit an affiliated site or a satellite clinic to have labs performed; the study physician will order these tests. After the Randomization and 6-Week Visits, study medication will be mailed to study participants; these mailings will follow the same protocol already used for shipping study medication at other points in the study.

V. OVERVIEW OF STUDY PROCEDURES

TELEPHONE SCREEN:

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
2) the QIDS-SR to screen for depression
3) the PSQI to assess sleep quality
4) the STOP-BANG questionnaire to screen for sleep apnea
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 an in-person Screening Visit.

SCREENING VISIT:

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. At in-person visits, vital signs will be obtained, urine screens collected for pregnancy and disallowed substances, and blood will be drawn for HbA1c and C-Reactive Protein. When the Screening Visit is virtual, the subject will have the pregnancy, drug, HbA1c, and C-Reactive Protein tests performed at an affiliated site or a satellite clinic; the study physician will order these tests. The drug screen will only be performed at the Screening Visit.

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.

RANDOMIZATION VISIT AND TREATMENT PERIOD:

At the Randomization Visit, the 2-week sleep diary and laboratory results will be reviewed for definitive eligibility before the participant is randomized to treatment. Baseline subjective sleep measures will be determined from this 2-week period. Baseline questionnaires will be determined at the Randomization Visit; these questionnaires will be determined again at both the 6-week and 12-week visits. HbA1c and C-Reactive Protein tests will only be performed at the Randomization Visit if more than 4 weeks have elapsed between this visit and the Screening Visit. Baseline pre-treatment symptom measures will be determined at the Randomization Visit. Eligible participants will be randomized in a 2:1 ratio to 6 weeks of placebo or suvorexant. At their 6-week visit, placebo non-responders will be re-randomized to either suvorexant or placebo in a 1:1 ratio. The placebo non-responders will be determined by the unblinded research coordinator, who will review the 2 weeks of sleep diaries completed before the 6-week visit.

Compensation:

Subjects will be compensated for each study visit ($75 for the Screening Visit and Randomization Visit, and $125 for Visit 3) and for the 1-week and 7-week phone calls ($25 each). Subjects will receive a completion bonus when they have completed the study in its entirety ($200 for the Final Visit).

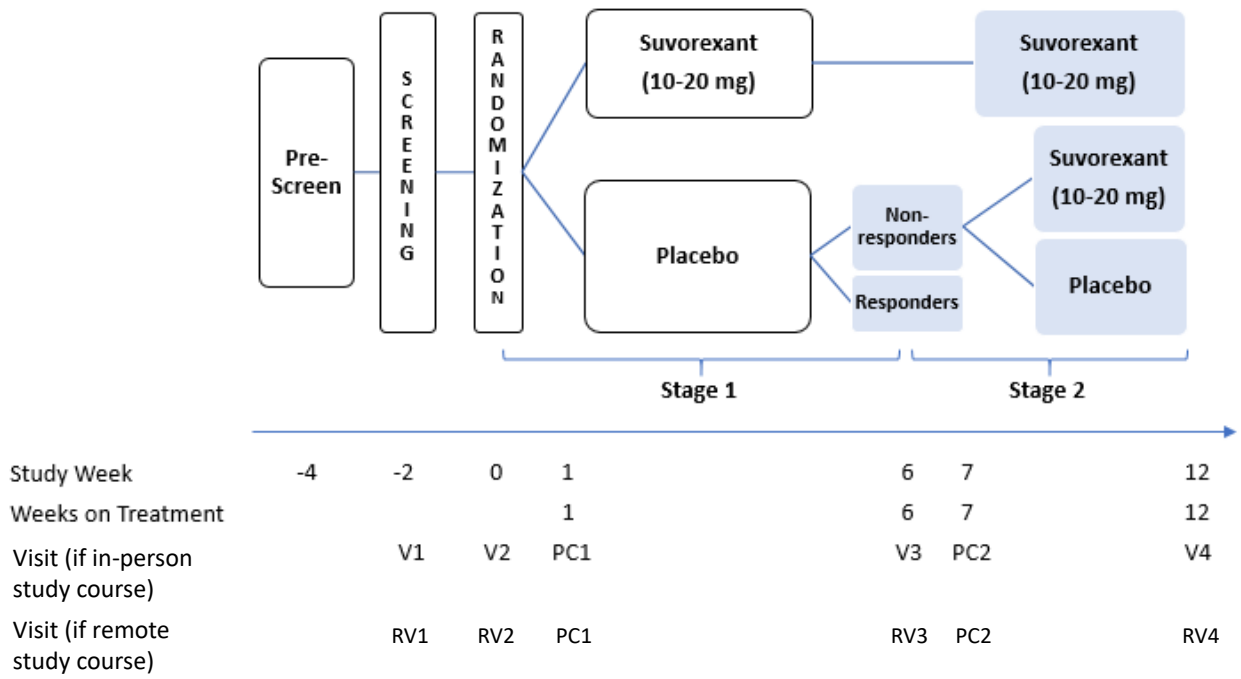
See below for the **Study Flowchart** and **Table of Procedures**.

Table of Procedures:

		Screening Period			Treatment Period			
Visit		**Pre-V1**	**V1/ Screening**	**V2/ Randomization**	**Phone contact 1**	**V3/ Placebo non-responder re-randomization**	**Phone contact 2**	**V4/ Treatment End**
Study Week		**-4**	**-2**	**0**	**1**	**6**	**7**	**12**
Visit Location		**Phone**	**Office/ Phone**	**Office/ Phone**	**Phone**	**Office/Phone**	**Phone**	**Office/ Phone**
General/ Screening Assessment	Sleep/medical/mental health phone screening and verbal consent	x						
	Written Informed Consent		x					
	Eligibility Criteria		x	x				
	Medical History & Physical Exam		x[a]					
	Urine hCG		x			x		
	Drug Panel Urinalysis		x					
	Concomitant Medication		x	x	x	x	x	x
	ISI	x		x		x		x
	PGI-I					x		x
	BDI			x		x		x
	DQOL			x		x		x
	Diabetes Distress Scale			x		x		x
Vitals	Height/Weight/Heart Rate/Blood Pressure		x[a]	x[a]		x[a]		x[a]
Lab Tests	HbA1c		x	x[b]		x		x
	CRP		x	x[b]		x		x
Sleep Assessment	Sleep Diaries (administer/review)	x[c]	x[c]			x[d]		x[d]
	PSQI			x		x		x
Medication Dispensing *by mail				x	x*	x	x*	
Safety Assessment/ Adverse Event Reporting					x	x	x	x
Medication Adherence						x		x

Conditional study procedure: a = only performed at in-person visit
b = only performed if four weeks have passed between Screening and Randomization Visits
Study procedures completed between study visits: c = daily for 2 wks following visit, d = daily for 2 wks prior to visit

Study Flowchart:



Study Week	-4	-2	0	1	6	7	12
Weeks on Treatment				1	6	7	12
Visit (if in-person study course)		V1	V2	PC1	V3	PC2	V4
Visit (if remote study course)		RV1	RV2	PC1	RV3	PC2	RV4

VI. STUDY MEDICATION AND SUPPLIES

Study Treatments:

The study medication will consist of 10 mg or 20 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 Topiramate / Placebo Dosing

Week	Study Medication Treatment	Placebo	Placebo Non-Responders
1	10 mg capsule	10 mg capsule	
2 - 5	10 or 20 mg capsule	10 or 20 mg capsule	
6	10 or 20 mg capsule	10 or 20 mg capsule	10 mg capsule
7-12	10 or 20 mg capsule	10 or 20 mg capsule	10 or 20 mg capsule

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. This will be repeated at the 6-week visit for placebo non-responders.

Subjects will taper off their study medication by taking 10 mg for 3 days after the Final Visit, if 20 mg was taken during the study.

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, then enough for weeks 2-5. After the 6-week visit, a 14-day supply will again be dispensed, following a supply sufficient for weeks 7-12. Bottles will be labeled with the patient name and ID and the dosing information. Bottles will be clearly labeled as containing either 10 mg or 20 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 return all unused medication and packaging (including empty bottles) at the next study visit in order to assess compliance. In the case of virtual study visits, participants will be required to show the study team over video how much medication is remaining. Returned study medication bottles may be re-dispensed to the same subject if appropriate. 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. An unblinded research coordinator will be responsible for all re-randomization determinations and communicating with the pharmacy in that regard.

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 and unblinded research coordinator will provide and maintain randomization and blinding. Subjects will be randomized to receive either suvorexant or placebo in a 1:2 ratio, and placebo non-responders will be re-randomized to suvorexant or placebo in a 1:1 ratio at the 6-week visit. The re-randomization will be balanced by using permuted blocks of 4. 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. CONCOMITANT MEDICATIONS

Concomitant medications will be assessed and recorded at each contact with study subjects (in-person and over the phone).

Rescue medications for the acute treatment or ongoing management of hyperglycemia will be based on the judgment of the participants' health care providers. Modification in the antidiabetic medication will be considered relevant if there is a 2-fold change in dosage for a hypoglycemic drug, a change of more than 10% in the dosage of insulin, or the addition or subtraction of an oral hypoglycemic agent or insulin. Relevant modifications will be recorded.

The following medications are considered exclusionary for this study, in addition to any medications not listed here but decided to be exclusionary by the Study Physician:

Exclusionary Medications

- Strong inhibitors of CYP3A
    - 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
    - Amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil

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).

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. STATISTICAL ANALYSIS

Analysis of all study data will be conducted by Dr. Winkelman and Dr. Bettina Hoeppner, a statistician at Massachusetts General Hospital. All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the unblinded research coordinator, who will assess treatment response at 6-weeks, and 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.

The sequential parallel comparison design was developed at Massachusetts General Hospital and has been used extensively in clinical trials funded by both industry and NIH. Experts at MGH in SPCD will be consultants in the statistical analyses of our data.

Overview of analytic plan:

The primary hypothesis for this trial is that suvorexant is superior to placebo in reducing subjective total sleep time at 3 months of treatment in patients with insomnia and suboptimally controlled Type 2 diabetes. The primary endpoint is the change in total sleep time as determined by subjective reporting measures (sleep diaries) from baseline to the 6-week and 3-month follow-ups, adjusted for subjective total sleep time at baseline, consistent with the SPCD statistical approach. Key secondary endpoints include subjective wake after sleep onset and ISI. Exploratory analyses will examine the effect of suvorexant relative to placebo on other sleep continuity parameters (sleep efficiency, sleep quality, sleep latency), HbA1c levels, inflammatory markers, mood, and diabetes-related quality of life, as well as the correlation between the change in the subjective total sleep time and each exploratory endpoint.

Study endpoints:

The primary outcome (subjective 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 final total sleep time evaluated after 6 weeks and 3 months of treatment, consistent with SPCD statistical analyses. The key secondary variables are the difference from baseline to either the 6-week visit or the 3-month (Final Treatment) visit (based on SPCD analyses) in: 1) subjective wake after sleep onset and ISI.

Exploratory analyses will similarly focus on the differences from the baseline value to the final observed value of each outcome evaluated after either 6 weeks or 3 months of treatment (based on SPCD analyses). As these are exploratory analyses, no p-values will be determined other than as described below in the hierarchical testing. These endpoints include:

1. PSQI
2. Subjective SOL, sleep efficiency and sleep quality
3. Depressive symptoms (BDI Score) and quality of life measures (DQOL, Diabetes distress scale)
4. HbA1c
5. Inflammation markers (e.g., C-Reactive Protein)

STATISTICAL METHODS

Primary analysis:

The primary analysis will be based on a weighted average of effects of the change in subjective total sleep time as a function of randomization assignment. 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.

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 two weeks of sleep diaries following randomization. In addition to the primary and key secondary end points, other secondary end points will be tested in sequential order to control for multiplicity, with an overall type 1 error rate of 5%. Following the primary and key secondary outcomes, the order will be: HbA1c, then CRP. No adjustments for multiple comparisons will be made for additional secondary end points, and thus, statistical probability will not be tested for these variables.

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 6-week and 3-month visits. Variables related to subjective total sleep time will be determined by Pearson correlation and simple regression analysis using weighted least squares. Those significant contributors will then be input into a stepwise multiple linear regression analysis to identify independent determinants of the change in total sleep time. A two-sided P value <0.05 will be considered significant.

Key secondary and exploratory analyses:

Analyses of the key secondary and exploratory endpoints will be conducted using a weighted average of effects from the two 6-week periods, based on randomization assignment. Exploratory correlational analyses will be performed using simple Pearson or Spearman correlations between the change in the subjective total sleep time and secondary and exploratory endpoints.

Power/Sample Size:

In total, we expect to randomize 72 participants to treatment with 62 completed subjects (31 per treatment group). Using the SPCD calculator, to achieve 80% power to detect an effect size of .40, at a statistical significance level of 0.05, 70 randomized subjects are required.

The intervention effect is based on data from trials of eszopiclone for rheumatoid arthritis[27] and low back pain[28] which, like diabetes mellitus, are chronic medical conditions associated with high rates of insomnia. We believe that these populations are more appropriate for statistical modeling than the primary insomnia population used in previous suvorexant clinical trials. Similarly, our inclusion criterion of wake after sleep time of 45 minutes is more stringent than that used in the suvorexant trials[27] and the same as that in the rheumatoid arthritis clinical trial. Effect sizes for change in total sleep time in the rheumatoid arthritis and low back pain trials with eszopiclone were .36 and .67, and we have thus used a conservative intermediate effect size of .40 for our sample size calculation.

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