MASS GENERAL BRIGHAM HUMAN RESEARCH COMMITTEE (FORMERLY CALLED PARTNERS HUMAN RESEARCH COMMITTEE (PHRC))
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I. BACKGROUND AND SIGNIFICANCE

Insomnia is highly prevalent in women during midlife, particularly during the menopause transition, when epidemiologic studies show that *one-quarter of women meet criteria for chronic insomnia*.[1] Nocturnal hot flashes are the primary predictor of subjective sleep disturbance[2,3] and of a chronic insomnia syndrome in midlife women.[1] Hot flashes are the most common symptom of the menopause transition, occurring in up to three-quarters of women during this reproductive transition.[4] While present both during the day and night, nocturnal hot flashes (or night sweats) can be especially distressing when they disrupt sleep,[5] leading many women to seek medical treatment. By repeatedly awakening women, hot flashes are responsible for a sleep maintenance condition, which is the most common pattern of sleep disruption reported by midlife women.[6] We have shown that nocturnal hot flashes fragment sleep and increase the amount of time spent awake after sleep onset (WASO) on subjective (sleep diary) measures,[7] polysomnography,[7] and actigraphy (see Preliminary Data section). In contrast, hot flashes do not increase sleep-onset latency (SOL).[2,3,7] Hence, a large proportion of midlife women are susceptible to developing an insomnia syndrome that manifests predominantly with a sleep maintenance problem when they experience nocturnal hot flashes. Moreover, insomnia related to hot flashes can persist for a long period of time as the mean duration of hot flashes is 7.4 years.[8] This protracted exposure to hot flashes and sleep disturbance can have important implications for quality of life and work productivity.[9] Poor sleep and hot flashes are the primary reason midlife women seek medical attention.

Treatment options for menopause and hot flash-related insomnia have received little attention to date.[10] Cognitive behavioral therapy for insomnia (CBTi) has recently been shown to be an effective treatment for insomnia in women with insomnia symptoms and hot flashes.[11] For women with hot flashes, nonbenzodiazepine GABA-A receptor modulators have been demonstrated to treat insomnia.[12–14] whereas estrogen therapy improves sleep quality, but its efficacy is less clear in women with chronic insomnia.[10] However, use of these agents is limited by their side effects and risks, particularly breast cancer, cardiovascular, and cognitive risks that emerge with long-term use.

Given the prevalence of insomnia characterized by hot flashes and sleep maintenance problems, the particular efficacy of suvorexant for middle-of-the night sleep disturbance makes it an optimal agent for this population. Its safety profile and long-term tolerability make it an ideal strategy for use in midlife women.[15] An additional rationale for using a dual orexin receptor antagonist in the treatment of hot flash-related insomnia is the specific mechanistic suppression of arousal pathways that are activated in insomniacs.[16] Our preliminary data similarly show that, for women whose sleep disturbance is related to hot flashes, arousal is heightened in relation to the amount of WASO reported (see Preliminary Data section). Finally, orexin becomes hyperactive during the menopause transition, when estrogen levels fall.[17] Animal data show that administration of suvorexant to ovariectomized hypo-estrogenic rats mimics the stabilizing effect of estrogen therapy on thermoregulation,[18] suggesting that suvorexant may have a specific therapeutic effect on menopause-related sleep disturbance as well as a secondary beneficial effect on hot flashes. Taken together, these data potentially implicate orexin in the mechanism underlying the

emergence of hot flashes and related sleep disturbance and provide a specific justification for testing the efficacy of orexin receptor antagonists in the treatment of hot flash-related insomnia.

Preliminary Data

Preliminary data relevant for the current proposal derive from our Merck-funded hot flash-related insomnia study of psychological and physiological arousal in midlife women, all of whom have hot flashes but only some of whom meet criteria for a concurrent insomnia syndrome. Eligibility criteria for women meeting criteria for an insomnia syndrome included a minimum of 20 minutes of time for subjective WASO (sWASO) plus subjective sleep-onset latency (sSOL) together, but there was no requirement for a maximum total sleep time (sTST) or minimum Insomnia Severity Index (ISI) score. At the time when this current protocol was developed, we had enrolled 73% of our total accrual goal of 40 participants. Of 29 women who had consented, data were available on 23 who had already completed study procedures. Of those who met criteria for an insomnia syndrome (n=17), 6 (35%) had an ISI score ≥15, consistent with eligibility criteria for the proposed trial. As such, we report interim findings for this subgroup based on sleep parameter data obtained using a 7-day sleep diary and actigraphic assessment. This subgroup showed a mean ISI score of 18.8 ± 1.7 and a mean sleep efficiency of 66.8% ± 31.8% on the diary and 81.9% ± 8.9% on actigraphy.

Sleep maintenance problems characterize hot flash-related insomnia: Those who would be eligible for the proposed trial report experiencing 128.7 ± 67.9 minutes of sWASO and 34.7 ± 15.4 minutes of sSOL on their diary. sWASO time comprises 78.8% of the total wake time (sWASO+sSOL). All of these women would meet our proposed eligibility criterion of sWASO≥30 minutes). This observed predominance of sleep maintenance problems is consistent with our prior experience[7,19,20] and with extensive epidemiologic data[3,21] on hot flash-related sleep disruption. Data using actigraphy to quantify WASO and SOL similarly indicate that aWASO time accounts for the vast majority (78.7%) of wakefulness (aWASO+aSOL). Consistent with extensive data from other insomniac populations,[22] the total number of minutes of aWASO and aSOL on actigraphy is reduced relative to that reported on the diary. However, the actigraphic aWASO is consistent with our planned 30 minute average of WASO, with 100% of these women having at least 30 minute average of WASO over a week.

Total sleep time is reduced in women with hot flash-related insomnia: Despite an absence of TST eligibility criteria, 100% of women in our physiologic study who would meet criteria for the proposed trial also meet our similar criterion to have subjective TST (sTST) <7 hours both on sleep diary and on actigraphy during at least 4 nights per week.

Distribution of WASO time across the night in hot flash-related insomnia: Further analyses of actigraphic data in this subgroup of women who would be eligible for the proposed trial show that 36.9% of their aWASO time occurs within the terminal one-third of the night.

Within-person night-to-night variability in sleep parameters: It is increasingly recognized that sleep patterns vary night-to-night in insomniacs, on both sleep diary[23] and at-home polysomnography (PSG)[24] measures. We explored this within-person variability across the 7 consecutive days of sleep diary and actigraphic monitoring in the subgroup of women who would be eligible for our proposed study. The coefficients of variation (CV) show that there is limited within-person night-to-night variability in SOL or WASO as a proportion of the respective mean value for each person, regardless of whether they were measured using the sleep diary (sSOL, sWASO) or actigraphy (aSOL, aWASO). For the group as a whole, the mean CV for each sleep parameter was less than or close to one, indicating limited variation.

Hot flash-related insomnia and psychological indicators of hyperarousal: In our investigation examining the association between hyperarousal and insomnia in women with hot flashes, we have observed a pattern of greater psychological arousal among women with hot flashes that is proportionate to the amount of sleep interruption. As one indicator of psychological activation in the sample overall (n=23), those who had more anticipatory anxiety also had more sWASO (r_s=0.48, p=0.02)..

Summary of preliminary data: Taken together these preliminary data highlight that for women with hot flash-related insomnia syndromes who would be eligible for our proposed trial: 1) the extent of their sleep disturbance is high, 2) sleep maintenance problems dominate the time spent awake, and 3) WASO time persists into the final third of the night. In addition, within-person night-to-night variability of SOL and WASO is low on both subjective and actigraphic measures. In addition, psychological indicators of hyperarousal correlate with the degree of sleep disruption among women with hot flashes. *In summary, women with a hot flash-related insomnia syndrome have substantial sleep continuity problems that are composed of a distinctive profile of sleep disruption dominated by reduced TST and large amounts of WASO, which persists throughout the night. These characteristics of hot flash-related insomnia make this population an ideal one in whom to investigate the efficacy of suvorexant.*

II. SPECIFIC AIMS

PRIMARY AIM: To determine the effect of suvorexant on insomnia symptoms in peri- and postmenopausal women with a chronic insomnia syndrome related to nighttime hot flashes using a randomized placebo-controlled trial.

HYPOTHESIS: Women randomized to suvorexant will show greater improvement in insomnia symptoms compared with women randomized to placebo.

SECONDARY EXPLORATORY HYPOTHESES

1. Relative to those assigned to placebo, women randomized to suvorexant will show:
    a. Greater reduction in wake-time after sleep-onset.
    b. Greater improvement in mood, anxiety, and quality of life.
    c. Greater reduction in hot flash frequency.
2. Improvement in insomnia symptoms will be positively correlated with improvement in mood, anxiety, hot flashes, and quality of life.

III. SUBJECT SELECTION

Inclusion/Exclusion Criteria

We plan to enroll up to 90 women who meet the following criteria in order to have 72 women randomized in a 1-to-1 ratio to suvorexant 10-20 mg or equivalent placebo in order to have 60 women (30 per arm) complete the trial.

Inclusion criteria:

1. Age 40–65 years
2. Peri- or postmenopausal women, with menopause status determined by menstrual marker. Women who underwent bilateral oophorectomy will be enrolled if 6+ months from surgery. Those who underwent hysterectomy with ovarian preservation, or who have amenorrhea from progesterone-secreting IUD, or endometrial ablation may be enrolled based on clinical assessment and judgment.
3. DSM-5 criteria for Insomnia Disorder.

4. Score on the Insomnia Severity Index (ISI) measure ≥15, indicating at least a moderate level of insomnia symptoms
5. Subjective sleep disruption reported retrospectively over the past month and confirmed prospectively on a 7-day sleep diary shows:
    a. <9 hours average for subjectively reported total sleep time (TST).
    b. 30+ minute average for subjectively reported wake after sleep onset (sWASO).
    c. Sleep parameter in inclusion criteria 5a does not decrease by more than 50% on a 2nd week of sleep diary monitoring obtained after the screening visit.
    d. Sleep parameter in inclusion criteria 5b does not both decrease by more than 50% and fall below 30 minutes on average on a 2nd week of sleep diary monitoring obtained after the screening visit.
6. Average of 2 or more hot flashes per 24 hours, at least some of which occur each night, reported retrospectively to have occurred over the past month and confirmed prospectively on one 7-day hot flash diary
7. Subjective report that at least some awakenings co-occur with night time hot flashes.

Exclusion criteria:

1. Sleep factors:
    a. Diagnosis, or strong clinical suspicion, of other primary sleep disorders: obstructive sleep apnea, periodic limb movement disorder, narcolepsy, or RLS
    b. Shift workers
    c. Use of hypnotic medications more than twice per week in the past month
    d. Willingness to not use other sedative-hypnotics during the study period
2. Psychiatric factors:
    a. Current major depressive episode, by report and as indicated by the Patient Health Questionnaire (PHQ-9)
    b. Current suicidal ideation
    c. Lifetime history of bipolar disorder, psychosis, or other serious mental health problem
    d. Current alcohol/substance use disorder
3. Medical factors:
    a. Abnormal vital signs at screening visit
    b. BMI ≥ 40 kg/m^2
    c. Renal or hepatic disease judged to interfere with drug metabolism and excretion
    d. Pregnancy or breastfeeding
    e. Malignancy within past 2 years
    f. Major surgery within past 3 months
    g. 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
    h. Medical instability considered to interfere with study procedures
    i. Concomitant medications with drug interaction or co-administration concerns
    j. Contraindications or allergic responses to suvorexant
4. Lifestyle and other factors:
    a. Travel across time zone in 2 weeks prior to enrollment or planned during study
    b. Greater than 6 cups of coffee per day
    c. Greater than 15 cigarettes per day
    d. Unwilling to limit alcohol, nicotine, and caffeine consumption during study
5. Adherence factors:
    a. Ability to adhere to study procedures completed between screening and randomization visits

Off-Study Criteria:

Subjects will be dropped from the study if any of the following:

1. Meeting criteria for a current episode of major depression on the Patient Health Questionnaire 9 (PHQ-9) or depressive symptoms that are deemed by the psychiatrist investigator to be too severe to continue with study procedures
2. Emergence of suicidal ideation; homicidal ideation, or psychotic symptoms
3. Initiation of stimulants, medications for sleep, hormonal medications, or other contraindicated medications
4. Evidence of abuse or misuse of study medications
5. Development of any significant medical problem
6. Pregnancy
7. Enrollment in another clinical trial involving study procedures or medications that might put subject at risk for drug interactions or interfere with study procedures.
8. Significant deviation from study protocol or protocol violation
9. Serious side effect from study medication
10. Inability to tolerate a minimum dose of 10-mg/day of suvorexant

Participants who are dropped from the study will be asked to complete final questionnaires remotely. In this case, vitals will not be collected, and adverse event monitoring will be completed over the phone.

Source of Subjects & Recruitment Methods

Co-investigators and staff will be responsible for recruiting study participants. Subjects will be recruited from the general population, from BWH and affiliated outpatient and community clinics around Boston, using posted signs, Craigslist, the Partners All-User and RSVP for Health (Research Study Volunteer Program), as well as paid advertising (e.g., Metro, PostcardMania, Facebook). ResearchMatch.org will be utilized as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. Insomniacs will also be recruited through the BWH sleep clinics (pulmonary and neurology) in Boston and Chestnut Hill. We will post IRB-approved flyers in these clinics, as well as provide them to other sleep clinicians, and these sleep physicians can decide to distribute to their own patients as they see fit. Subjects answering posted or printed ads will be directed to a pre-screen survey on REDCap. If initial eligibility requirements are met, the research coordinator will assess further eligibility using an IRB-approved telephone screen and diaries completed at home.

IV. SUBJECT ENROLLMENT

Methods of Enrollment & Consenting Procedures

Pre-Screening

In response to local recruitment efforts and after passing initial eligibility on the REDCap pre-screen survey, women will speak with a study coordinator. During the phone screen the preliminary eligibility criteria and study protocol will be discussed with each woman.

Consent to complete the telephone screen will be obtained orally at the start of the phone call. Before the research coordinator asks any of the screening questions, she will inform the potential participant that the purpose of the call is to begin the process of pre-screening for eligibility and that all responses are confidential and completely voluntary. Continuation of the phone call and responding to questions implies consent to the phone call screening. Women who prefer not to

answer questions will be thanked for their time and the phone call will end. Women may ask to stop the screening phone call at any time. The pre-screen questionnaires will be administered to assess insomnia status. The full written ISI will be administered at Visit 3 and Visit 4. The ISI may be administered again over the phone before Visit 1 or Visit 2, if one of these visits has been delayed, and insomnia status must be reassessed. Preliminary screening determination will include questions modified from the Berlin Questionnaire to exclude women at high risk for obstructive sleep apnea. We will also ask some questions drawn from the PHQ-9 which will be completed at the first visit. The PHQ-2 asks specifically about frequency of anhedonia and depression in the past two weeks. We will exclude participants who do not qualify initially on the phone screen. Anyone identified as being at risk for depression will be instructed to assess their symptoms with their physician and be offered resources for where they can seek additional help. The full PHQ-9 will be administered at Visit 1, Visit 3, and Visit 4.

Following the screening phone call, women who are interested and preliminarily eligible to complete the screening process will be mailed or emailed the pre-screening materials, a copy of the informed consent and a cover letter describing the pre-screening procedures. The pre-screening materials include hot flash and sleep diaries to be completed at home for 1 week. BWH study staff will call potential participants to determine whether they received these materials and review how to complete them. Women who are currently taking medications to help them sleep will be asked if they are willing to refrain from taking sleep medications for the duration of the study (approx. 6 weeks) beginning with the tracking period. Women who agree to complete the pre-screening diaries will be contacted by phone after ample time has elapsed. During this call, the BWH study staff member will review the diary entries to determine eligibility for the screening visit. The pre-screening diaries are used to reduce subject burden by only scheduling subjects eligible for the screening visit.

Women whose pre-screening diaries indicate that they are eligible to proceed with the study will be scheduled for an initial visit at Brigham and Women's Hospital. If the participant does not have a medical record number, she will be asked to call patient registration and register as a patient before her initial visit can be scheduled. A reminder will be sent one day before the visit is to occur.

Obtaining Informed Consent

No subject will undergo any study procedures until it is clear that she understands the risks and benefits and consents to participate. At the screening visit, the PI or one of her co-investigator designates will carefully review the consent form in its entirety with prospective subjects. The consent form will include information about the risks and benefits of study participation. Women enrolling must be capable of understanding the nature of the study as well as the discomforts and potential benefits. Any questions or areas of concern regarding the protocol will be addressed by the PI or a co-investigator designate. If a woman feels comfortable with the study procedures, she will sign the consent form along with the PI or a co-investigator designate. During the screening visit, study staff will explain the purpose of the study, the procedures used, the requirements of participation, risks and benefits, and the right to withdraw at any time, and answer any questions. Signed consent forms will be placed in the participant's administrative research file and a copy will be given to the participant.

All subjects will be given contact information for the investigator, research assistant and IRB office, in the event that they have any questions or concerns, before any study procedures are completed. If subjects have reservations about study participation at the first visit, they have the option to take the consent form home to review the decision to participate in the study with their family and health-care providers, and then return at a later date to discuss the study again with

research physicians before signing the consent form and initiating study procedures. Subjects will be informed that they may choose to decline to participate or withdraw from the study. She will be informed that the decision whether or not to participate will not affect her care at Brigham and Women's Hospital and she is free to withdraw at any time.

After the informed consent process is complete, study staff will continue with screening procedures.

Final eligibility determination

Final eligibility criteria will be assessed after the informed consent process is complete, including a clinical interview conducted by a study clinician to diagnose a chronic insomnia disorder and to ensure that women with contraindicated sleep, medical, and psychiatric problems and medications are excluded. Vital signs will be obtained, and blood will be drawn (15mL) for screening safety labs, a toxicology screen, and female reproductive hormones. All women who sign the consent form will be assigned a study identification number regardless of eligibility status. Eligible participants will be sent home with a 7-day sleep and hot flash diary to complete during the screening run-in period. They will also be given the Actiwatch actigraphic monitor and Biolog skin conductance hot flash monitor, which will be worn continuously for one week (Actiwatch) or one 24-hr period (Biolog) to quantify sleep patterns (Actiwatch) and the number of objectively measured nighttime and daytime hot flashes (Biolog). No medication will be provided. They will be asked to bring their diaries, Actiwatch, and Biolog monitors back for review at the Randomization Visit, at which point final review of the sleep diary, and laboratory results for definitive eligibility will be conducted before the participant is randomized to treatment.

Treatment Assignment and Randomization

Women who are deemed eligible after screening procedures have been completed will then complete a Randomization Visit, at which eligible women will be randomized to 4 weeks of suvorexant or placebo. Suvorexant and identical placebo will be obtained from Merck and stored in the Brigham and Women's Hospital Research Pharmacy. The Research Pharmacist will generate a confidential randomization schema using a block size of 4 to balance the one-to-one treatment assignment between the two study arms. Study participants and all study personnel, including those entering data, will be blinded to the assignment. Only the Research Pharmacist will be unblinded to treatment assignment.

At the Randomization Visit, a one-week supply of suvorexant 10-mg pills or identical placebo will be given to each participant. Participants will be instructed to start taking 10-mg nightly for the first 7 days. At the Interim Treatment Visit conducted after one-week on treatment, the dose will be increased up to 20-mg nightly unless there are dose-limiting side effects. After the Interim Treatment Visit, women unable to tolerate a 20-mg dose will be given the option to reduce to a 10-mg dose. Consistent with FDA-approved directions, suvorexant will be started at 10-mg to first establish tolerability and then expected treatment efficacy will be optimized by increasing to the target 20-mg dose 7 days later. Women who are unable to tolerate the 10-mg dose will be dropped from the study. Any unused medication will be returned at the Final Treatment Visit, and unused pills will be counted as an indicator of adherence. Participants will not be informed of their treatment assignment at the Final Treatment Visit to maintain the blinding for study personnel. Participants who choose to stop participating in the study will be asked to complete remaining study questionnaires remotely. In this case, participants will return unused medication by mail.

V. STUDY PROCEDURES

Study Procedures and Outcome Measures

This study is a parallel-arm randomized trial involving 4 in-person study assessments conducted over approximately 6 weeks, during which participants will be randomized to receive double-blinded suvorexant 10–20 mg/day or placebo for the final 4 weeks of the study. See attached Table of Procedures for all study procedures. Details describing individual study procedures and surveys are provided below:

Screening period: There are 3 phases to our screening procedures: 1) an initial screening conducted via REDCap and over the phone, 2) prospective sleep and hot flash diary screening process completed over 14 days, and 3) final screening conducted at and after the in-person Screening Visit. We have found this phased screening approach to be highly efficient and readily approved by our Institutional Review Board. Consent to screen will be obtained orally on the phone for the initial screening procedures and diaries, and written informed consent will be obtained at the Screening Visit for the remaining screening procedures and all treatment-related procedures. Risks and benefits associated with use of suvorexant will be described.

Women interested in participating in this trial will be screened by phone to assess preliminary eligibility after oral consent for screening is obtained. Some questions from the Berlin Questionnaire will be administered to screen for sleep apnea, and the ISI will help assess eligibility. Those who are interested and appear eligible will be sent a 7-day sleep and hot flash diary. Subjects who are taking any medications to help them sleep will be asked if they are willing to suspend taking those medications for the duration of the study, beginning with the tracking period, in order to attain an accurate assessment of their current sleep difficulties. Upon receiving these completed diaries, those who meet further eligibility criteria determined by the diaries (see Inclusion and Exclusion Criteria above) will be scheduled for an in-person Screening Visit.

At the Screening Visit, written informed consent will be obtained and final eligibility criteria will be assessed, including a clinical interview conducted by a study clinician to diagnosis a chronic insomnia disorder and to ensure that women with contraindicated sleep, medical, and psychiatric problems and medications are excluded. Vital signs will be obtained and blood will be drawn (15mL) for screening safety labs, a toxicology screen, and female reproductive hormones. The PHQ-9 will be administered in person. All women who sign the consent form will be assigned a study identification number regardless of eligibility status. Eligible participants will be sent home with a 7-day sleep and hot flash diary to complete during the screening run-in period. They will also be given the Actiwatch actigraphic monitor and Biolog skin conductance hot flash monitor, which will be worn continuously for one week (Actiwatch) or one 24-hour period (Biolog) to quantify sleep patterns (Actiwatch) and the number of objectively measured nighttime and daytime hot flashes (Biolog). No medication will be provided. They will be asked to bring their diaries, Actiwatch, and Biolog monitors back for review at the Randomization Visit, at which point final review of the sleep diary and laboratory results for definitive eligibility will be conducted before the participant is randomized to treatment.

Treatment period: At the Randomization Visit, eligible women will be randomized to 4 weeks of suvorexant or placebo. Pre-treatment symptom measures will be assessed at the Randomization Visit and interim and final on-treatment symptom measures will be assessed at the Interim Treatment Visit and Final Treatment Visit, respectively. The primary endpoint measures will be obtained at the Final Treatment Visit, conducted after 4 weeks on treatment. Participants will complete sleep and hot flash diaries for the 4 weeks they are on treatment and will be sent an Actiwatch and Biolog monitor to wear for one week (Actiwatch) and for one 24-hr period (Biolog) before returning them at the Final Treatment Visit. Participants will also be asked to provide saliva samples for two consecutive days in between Visits 1 and 2 and Visits 3 and 4. These samples will be used to measure cortisol. We have implemented these procedures in prior clinical trials

with efficiency and high levels of adherence. Adverse events will be assessed at each study visit using spontaneous-reporting adverse event procedures employed in our other clinical trials.

Intervention design: Suvorexant and identical placebo will be obtained from Merck and stored in the Brigham and Women's Hospital Research Pharmacy. The Research Pharmacist will generate a confidential randomization schema using a block size of 4 to balance the one-to-one treatment assignment between the two study arms. Study participants and all study personnel, including those entering data, will be blinded to the assignment. Only the Research Pharmacist will be unblinded to treatment assignment.

At the Randomization Visit, a one-week supply of suvorexant 10-mg pills or identical placebo will be given to each participant. Participants will be instructed to start taking 10-mg nightly for the first 7 days. At the Interim Treatment Visit conducted after one-week on treatment, participants who do not have treatment-limiting side effects will be instructed to increase the dose to 20-mg nightly. After the Interim Treatment Visit, women unable to tolerate a 20-mg dose will be given the option to reduce to a 10-mg dose. Consistent with FDA-approved directions, suvorexant will be started at 10-mg to first establish tolerability and then expected treatment efficacy will be optimized by increasing to the target 20-mg dose 7 days later. Any unused medication will be returned at the Final Treatment Visit, and unused pills will be counted as an indicator of adherence. If participants are unable to attend the Final Treatment Visit in person, subjects will complete remaining study procedures remotely, and will mail back any unused medication for a measure of adherence. Participants will also return the Actiwatch, Biolog monitor, and saliva samples by mail if a remote Final Treatment Visit is performed. In addition to answering questionnaires remotely, a study clinician will call the participant for safety monitoring. Study staff will review responses to the PHQ9 before ending study visits, and a study clinician will query participants directly about suicidal ideation and other adverse events at study visits while participants are on medication. Participants will not be informed of their treatment assignment at the Final Treatment Visit to maintain the blinding for study personnel.

Protocol Schema

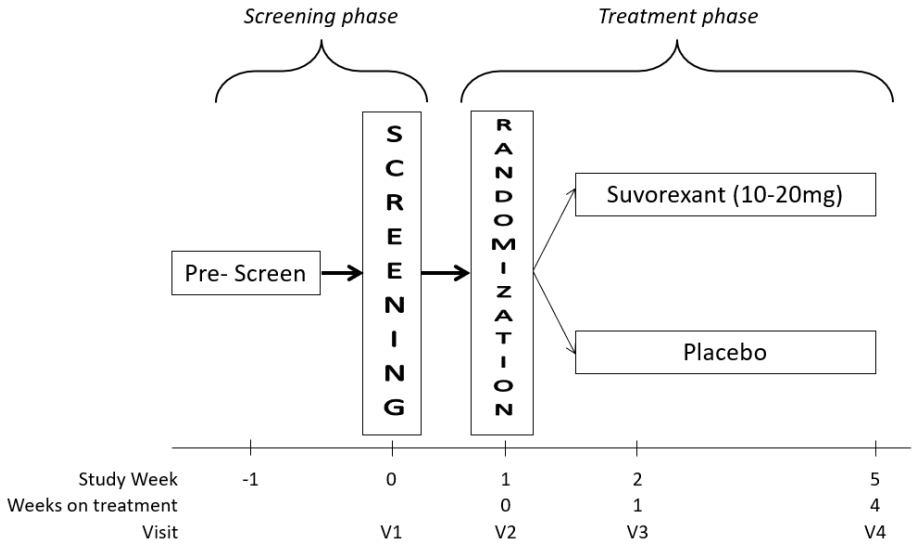

Table of Procedures

		Screening		Intervention		
	Visit Type	**Pre-V1**	**V1**	**V2 Random-ization**	**V3**	**V4**
	Study Week	-1	0	1	2	5
	Weeks on Medication			0	1	4
	Visit Location	Phone + Mail	Office	Office	Office	Office
General/ Screening Assessment	Screening Consent	X				
	Written Informed Consent		X			
	Health and Personal History Questionnaire		X			
	Insomnia Diagnostic Assessment		X			
	Medical History		X			
	Concomitant Medications	X	X	X	X	X
	Screening Assays (hepatic, renal, HCG, tox)		X			
	Hormone Assays (FSH, estradiol, progesterone)		X			
	Berlin Questionnaire	X				
	Neck circumference		X			
	PHQ-2	X				
Vitals	Height/Weight/Heart rate/Blood Pressure		X	X	X	X
	Waist to Hip Ratio		X			
Medication Dispensing & Instructions				X	X	
AE Reporting			X	X	X	X
Sleep Assessment	Sleep Diary[b]	→	→	→	→	→
	Actigraphy Watch[c]		→			→
	ISI	X		X	X	X
	PSQI			X		X
	DBAS			X		X
	Sleep Locus of Control Scale			X		X
Hot Flash Assessment	Hot Flash Diary[b]	→	→	→	→	→
	Hot Flash Monitor[a]		→			→
	HFRDIS			X		X
Hyperarousal	Salivary Cortisol		→			→
	Hyperarousal Scale			X		X
	PSAS			X		X
Exploratory Measures	PHQ-9		X		X	X
	CES-D			X	X	X
	ASI-3			X	X	X
	GAD-7			X	X	X
	MENQOL			X		X
	PGI (Severity & Improvement)		X		X	X

Study procedures completed between study visits: a = for 24 hours; b = daily for 6 weeks; c = daily for 1 week DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, HCG = Human Chorionic Gonadotropin, FSH = Follicle Stimulating Hormone, ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, PSAS = Pre-Sleep Arousal Scale, DBAS = Dysfunctional Beliefs and Attitudes about Sleep Scale, HFRDIS = Hot Flash Related Daily Interference Scale, PHQ-8 = Patient Health Questionnaire Depression Scale, CES-D, Center for Epidemiological Studies Depression Scale, ASI-3 = Anxiety Sensitivity Index, GAD-7= General Anxiety Disorder Questionnaire MENQOL = Menopause-Specific Quality of Life Questionnaire, PGI-Patient= Clinical Global Impression Scale – Patient

Study assessments and procedures include the following:

1. *Insomnia and sleep quality symptoms* will be measured using:
    1. *DSM 5 diagnostic interview for chronic insomnia*. A clinical diagnosis of chronic insomnia will be made using the DSM-V diagnostic interview, allowing for associated hot flashes (see Inclusion Criteria).
    2. *Sleep diary*. Consistent with research consensus guidelines of insomnia,[25] a standard daily sleep diary will be completed to quantify perceived total sleep time, sleep latency, wake time after sleep onset, number of awakenings, sleep efficiency, and sleep quality.
    3. The *Actiwatch actigraphic watch* (Philips Respironics, Murrysville, Pennsylvania) will be worn on the non-dominant wrist to quantify sleep patterns based on acceleration and movement and the data output will be analyzed using standard actigraphic analysis algorithms.
    4. The *Insomnia Severity Index (ISI)*, a 7-item self-rated questionnaire (range 0–28) used to assess the severity of insomnia symptoms over the past 2 weeks.[26]
    5. The *Pittsburgh Sleep Quality Index (PSQI)*, a 19-item self-rated measure of global sleep quality (range 0–21) occurring during the past one-month.[27]
    6. *Pre-Sleep Arousal Scale (PSAS)*, a 16-item self-rated scale that generally assesses physiological and cognitive arousal prior to sleep.[28]
    7. *Dysfunctional Beliefs and Attitudes about Sleep (DBAS)*, a 30-item self-rated scale about cognitions related to sleep (e.g., expectations, consequences).[29]
    8. *Sleep Locus of Control Scale*, an 8-item self-rated scale that measures perception of control of sleep as being internal or by chance.[30]
    9. *Hyperarousal Scale*, a 26-item self-rated scale of alertness during wake that is widely used to measure trait arousal.[31]
2. *Sleep apnea* will be screened out using a combination of self-reported prior diagnosis and the following study procedure to exclude women likely to have apnea:
    1. The *Berlin Questionnaire*, a validated 10-item questionnaire to assess risk of obstructive sleep apnea.[32,33]
3. *Mood, anxiety, and quality of life symptoms* will be measured using the:
    1. *Patient Health Questionnaire 9-item (PHQ-9)*, an 9-item self rated measure of depression based on DSM criteria that assesses the core psychological and neuro-vegetative symptoms of depression occurring over the past 2 weeks.[34]
    2. *Center for Epidemiological Studies Depression Scale (CES-D)*, a 20-item self-rated scale (range 0–60) that measures the severity of predominantly psychological symptoms of depression experienced over the past week.[35]
    3. *Anxiety Sensitivity Index (ASI-3)*, an 18-item self report questionnaire (range 0–72) assessing sensitivity to the experience of anxiety as an indicator of anxiety and psychological hyperarousal.[36]
    4. *Generalized Anxiety Disorder Questionnaire (GAD-7)*: The GAD-7 is a 7-item self-report measure frequently used in clinical and research settings to identify four of the most common anxiety disorders in primary care: generalized anxiety, panic, social anxiety, and posttraumatic stress disorder.[37]
    5. *Menopause-Specific Quality-of-Life Questionnaire (MENQOL)*, a widely used 33-item self-rated questionnaire about quality-of-life specifically in menopausal women.[38]
    6. The *Clinical Global Impression (CGI) and Patient Global Impression (PGI)*, which are widely used 2-item clinician-rated and patient-rated measures, respectively, which are used to assess global severity of illness and change in a patient over time. They are widely used in clinical trials for depression, fatigue, and other neuropsychological endpoints.

4. *Hot flashes* will be measured using:
    1. *Hot flash diaries* will be completed twice daily (morning and night) to capture the number of hot flashes, their severity, and how bothersome they are.[39]
    2. The *Biolog skin conductance hot flash monitor* (UFI, Morro Bay, CA) is a widely used and validated ambulatory monitor that will be worn to quantify the number of objectively measured hot flash events by detecting changes in skin conductance on the sternum. This approach measures physiologic hot flashes independent of recall for the events, thereby eliminating potential recall bias for nighttime events.
    3. The *Hot Flash Related Daily Interference Scale (HFRDIS)* is a 10-item self-rated scale (range 0–100) that measures the degree to which hot flashes interfere with daily activities and quality-of-life during the prior week.[40]

Drugs to be used
This study will compare the effect of suvorexant 10–20 mg to placebo on insomnia symptoms in peri- and postmenopausal women who have an insomnia syndrome related to nighttime hot flashes. Up to seventy-two women will be randomized in a 1-to-1 ratio to suvorexant 10–20 mg or equivalent placebo (see Schema) in order to have 60 women (30 per arm) complete the trial, after allowing for post-randomization drop-outs.

Eligible women will be randomized to 4 weeks of suvorexant or placebo after a 1-week screening period and a one-week screening run-in period. Participants will complete 4 in-person study visits (consent / screening visit, randomization visit, one-week on-treatment visit, and a final week-4 on-treatment visit) and one telephone-based initial screening assessment. Suvorexant will be started at 10-mg nightly for the first 7 days. After one-week of treatment, the dose will be increased to 20-mg nightly unless there are dose-limiting side effects. Women unable to tolerate a 20-mg dose will be given the option to reduce to a 10-mg dose.

Known toxicities of suvorexant include daytime somnolence, nighttime “sleep driving”, worsening of depression or suicidal thinking, compromised respiratory function, sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms.

Devices to be used
Actiwatch actigraphic Watch: This is an actigraphic watch (Philips Respironics, Murrysville, Pennsylvania) that will be worn on the non-dominant wrist to quantify sleep patterns based on acceleration and movement data. The data output will be analyzed using standard actigraphic analysis algorithms.

Biolog skin conductance hot flash monitor: This is a widely used and validated ambulatory skin conductance monitor (UFI, Morro Bay, CA) that will be worn to quantify the number of objectively measured hot flash events by detecting changes in skin conductance on the sternum. This approach measures physiologic hot flashes independent of recall for the events, thereby eliminating potential recall bias for nighttime events.

Surgical Interventions
No surgical interventions will be used in this study.

VI. BIOSTATISTICAL ANALYSIS

Overview of analytic plan: The primary hypothesis for this trial is that suvorexant is superior to placebo in treating insomnia symptoms. The primary endpoint is the change in the ISI score from

baseline to 4-week follow-up. Exploratory analyses will examine the effect of suvorexant relative to placebo on secondary endpoints of sleep continuity parameters and diary-reported hot flashes, and exploratory endpoints including mood, anxiety, hot flashes (skin-conductance monitor), physiological stress (salivary cortisol), and quality of life.

Study endpoints:

Primary endpoint:

1. The primary endpoint is the change in the ISI score from baseline to 4-week follow-up.

Secondary endpoints:

1. Diary-reported WASO, SOL, TST, and sleep efficiency
2. Number of hot flashes reported on the diary separately during the day and night

Exploratory endpoints:

1. Actigraphy-measured WASO, SOL, TST, and sleep efficiency
2. Depressive symptoms
3. Anxiety symptoms
4. Quality of life
5. Number of hot flashes measured on the skin-conductance monitor
6. Physiological Stress (measured by salivary cortisol)

Primary analysis: The primary analysis will compare the within-person change in outcomes at Week 4 relative to baseline using general linear models, adjusting for baseline values and relevant covariates showing group differences at baseline. Diagnostic methods will be used for all models to assess their distributional assumptions, model adequacy, and to examine potential outlying or influential data points. An additional exploratory ISI responder analysis will be conducted using logistic regression to determine whether there is a group difference in the proportion of women that had a 8-point reduction in the ISI score from baseline.[41]

Missing data: Every effort will be made to avoid missing data and to include all randomized subjects in the analysis. The effects of missing information on statistical power have been addressed to the degree feasible in the sample size calculations. Missing data will be imputed as last observation carry forward.

Power and sample size: In total, up to 90 women will be enrolled in this study. Treatment will be randomly assigned in a 1:1 ratio. Allowing for 10% to be lost to follow up after consent (n=8) and 15% to be lost after randomization (n=12), we expect to randomize up to 72 participants to treatment and complete 60 subjects (30 per treatment group). This sample size provides enough subjects to have 80% power for the primary hypothesis, assuming that there is a between-group difference in the change from baseline to study-end in the ISI score of 4 points with a standard deviation of 4.86 (two-sided alpha = 0.05). Previous clinical trials have found between-group differences in ISI change scores of 5.2 points[11] when women with hot flash-related insomnia were randomized to CBTi vs. behavioral control and between-group differences in ISI change scores of 2–3 points[43] when women with hot flashes and sleep disturbance were randomized to the SSRI citalopram vs. placebo. The standard deviation in the change in ISI for these interventions and controls arms was selected because it is in the midpoint of standard deviations from previous studies, which ranged from 4 to 6.[11,43] Data from the Phase 3 suvorexant trials were not used to support our sample size calculations because of differences in the sleep profile between our hot flash-related insomnia population (see Preliminary Data) and the general insomnia population

enrolled in suvorexant trials for which there was no minimum ISI score required for eligibility (mean ISI ~14).[44]

VII. RISKS AND DISCOMFORTS

Potential risks of study procedures:
Potential risk to study subjects is minimized by the frequent visits and tests required by the study design. Careful screening procedures, including medical history and evaluation, laboratory tests, and psychological interviews, will facilitate the identification of any medical problems and potential adverse events so that subjects can be treated appropriately. At each visit, spontaneously reported adverse events will be noted by research staff. Any serious or non-serious adverse event will be recorded in the participant's study binder at each examination. Serious and non-serious adverse events will be reported to the Partners Human Research Committee in accordance with Human Research Committee reporting guidelines, following the timeframes specified by the Partners Investigator's Guidelines. In case of a serious adverse event, study medication will be unblinded and discontinued, and appropriate diagnostic and therapeutic measures will be taken, as determined by the investigator. All adverse event reports will be reviewed by the study physician.

The risks of the study are mainly from drug side effects, phlebotomy, and psychosocial risks.

Common side effects of suvorexant:
The most common side effects that were reported in previous studies with suvorexant included:

- Headache (7 out of 100 people reported this side effect)
- Next-day drowsiness (7 out of 100 people reported this side effect)
- Dizziness (3 out of 100 people reported this side effect)
- Abnormal dreams (2 out of 100 people reported this side effect)
- Cough (2 out of 100 people reported this side effect)
- Diarrhea (2 out of 100 people reported this side effect)
- Dry mouth (2 out of 100 people reported this side effect)
- Upper respiratory tract infection (2 out of 100 people reported this side effect)

Suvorexant may cause serious side effects that participants may not know are happening. These side effects include:

- Sleepiness during the day
- Not thinking clearly
- Acting strangely, confused or upset
- "Sleep-walking" or doing other activities when you are asleep like eating, talking, having sex, or driving a car.

Suvorexant can cause next-day mental impairment, and this risk is increased with higher doses if instructions are not carefully followed. Subjects in their second, third, or fourth week of study drug dosing should avoid driving and other activities requiring full mental alertness in the morning. Subjects in their first week of study drug dosing should also be careful about driving in the morning, because there is individual variation in people's sensitivity to suvorexant. Before taking the study drug subjects will be advised to read the FDA-approved Medication Guide.

The participant will be informed that the study medication suvorexant must only be taken by the subject alone, the person for whom it was intended. In addition, the study medication must be kept out of the reach of children or persons with limited ability to read and understand.

Reproductive Risks
There are no adequate and well-controlled studies of either suvorexant in pregnant women. The study drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of the study drug on infants or unborn children is not known, and, as with any new drug, there is the potential for very serious harmful effects. In order to prevent any possible damage to an unborn child, subjects must not become pregnant while participating in this research study and for 30 days after finishing the study. Contraceptive methods must be used during and immediately after this study by women who are sexually active and have reproductive potential. Women using hormones will be excluded from study participation. Study participants will be required to use barrier methods of contraception if they are of reproductive potential. The following is a list of acceptable birth control methods: female sterilization, intrauterine device (IUD), diaphragm with spermicide, male condom, female condom, cervical cap, etc.

Women who are pregnant or breastfeeding will be excluded from the study. A pregnancy test will be conducted at screening for all subjects. If a subject thinks she might be pregnant at any time during this study, she will be advised to contact the study physician or research assistant immediately. In addition, participants will be informed that they cannot use hormonal contraception as a primary form of birth control until after medication discontinuation. At each visit these precautions will be discussed thoroughly with the subject.

Psychological Risks
Answering questions on the research instruments and questionnaires used to evaluate psychological symptoms can be upsetting to some subjects.

Blood Sampling
The risks associated with phlebotomy are minimal and include hematoma, pain, infection, and fainting spells. The amount of blood drawn for this study is approximately 15 mL (3 teaspoons) and is not enough to cause harm to the subjects. All blood draws will be performed by trained personnel who use standard sterile techniques.

Objective hot flash monitor
There are no significant risks associated with skin-conductance methodologies. The Biolog ambulatory recorder is an 8-ounce, 9V battery-powered device measuring 1.3 x 2.8 x 5 inches that is worn in a pouch and suspended by a shoulder strap, similar to a Holter monitor. It is a portable and ambulatory device. There is a minor risk of skin irritation and reddening from the adhesive gel required to attach the electrodes to the sternum. This irritation is typically mild and resolves within a few days.

Actigraphy watch
There are no significant risks associated with the actigraphy watch. The actigraphic watch is a light-weight sports watch that can be worn continuously and can get wet.

Procedures to Minimize Risks
All study procedures will be approved by the Partners (renamed Mass General Brigham) IRB before being initiated. To avoid serious adverse effects from medications, the following precautions will be taken:

A urine HCG test will be performed on all subjects at the screening visit to confirm that subjects are not pregnant. This procedure for confirming the absence of pregnancy will be followed regardless of whether or not the subject informs us that she is sexually active and regardless of the specific type of contraception that is being used. All subjects who are of reproductive potential will be advised to use a barrier method of contraception for the duration of the study and after study completion until menses resume. Adverse events will be monitored at each study visit.

The dose of study medication will be reduced to 10-mg/day if a participant is unable to tolerate the target dose of 20-mg/day.

Participants with conditions which are contraindications to suvorexant use will be excluded.

In order to minimize risks to participants, all research records will be kept with maximum possible confidentiality. Results will be de-identified and subject binders will be maintained in a locked closet. No names will be used in the presentation of any data. Source documents will be reviewed only by study personnel. All HIPAA regulations will be followed.

Participants will be informed that they are free to withdraw from the study at any time and that withdrawing will not have any adverse effects on their medical care within Partners/Mass General Brigham.

Adverse events requiring medical attention are expected to be rare in this proposal. The investigators have substantial experience conducting the proposed study procedures and managing adverse events that may result from the implementation of these procedures. Emergency facilities for managing any serious adverse event that requires urgent evaluation and treatment are available to the investigators.

In order to minimize potential psychological risks, those who self report on the phone screen and in the screening questionnaires and are judged by the PI to meet criteria for a current depressive episode will be encouraged to follow up with their primary care physician and provided referrals to mental health services. They will not be eligible for enrollment. Treatment decisions (including type of and when to initiate) will not be influenced by study participation. Additionally, as answering questions on the research instruments and questionnaires used to evaluate psychological symptoms can be upsetting to some, subjects will be told that they can skip questions that make them feel uncomfortable. The informed consent process will include an explicit discussion that the study is not guaranteed to provide treatment for symptoms.

As stated above, the amount of blood drawn for this study is approximately 15 mL (3 teaspoons) and is not enough to cause harm to the subjects. All blood draws will be performed by trained personnel that use standard sterile techniques. These procedures will be included in the patient informed consent document.

VIII. POTENTIAL BENEFITS

A potential benefit of participating in this study is to improve the subject's overall quality of life and decrease insomnia symptoms. Participants may benefit from the close monitoring of their vasomotor symptoms (VMS), sleep patterns, and psychological symptoms. If a significant abnormality is detected on any of the study measures, including hormone assays, participants will be informed and encouraged to follow up with their health care providers.

Information from this study will benefit others because the medical community will gain more knowledge on the efficacy of suvorexant for hot flash associated insomnia.

As a way of thanking participants for their time, subjects will be compensated up to $275.

IX. MONITORING AND QUALITY ASSURANCE

Independent Monitoring of Source Data
Confidentiality will be maintained by storing data with a subject identification number only. Only the PI, co-investigators, and study staff will have access to the database and the study binders. Data will be entered into a secure, HIPAA-compliant Research Electronic Data Capture (REDCap) database hosted by Partners HealthCare and analyzed using STATA 14.0 (College Station, Texas). All exported data will be de-identified using only the subject's identification number. Analysis of all study data will be conducted by Dr. Joffe, other co-Investigators on the study, and a master's level statistician in her lab in consultation with [redacted], the statistical consultant on this project. All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the BWH Research Pharmacist who generates the randomization code will be unblinded to treatment assignment.

Medical Monitoring Plan
[redacted] a clinical psychiatrist and co-Investigator on this protocol, has been appointed the Medical Monitor for this protocol by the Principal Investigator. An SOP for the medical monitor has been developed and includes the following:

- Reviews all safety data from all study visits within 2 business days. Serious adverse events will be reviewed and reported to the IRB within 24 hours, per PHRC guidance. Additional procedures regarding assessment of suicidal ideation are described below.
- Meets with the Research Coordinator weekly to review status of all active participants
- If a safety concern is identified, confers with consenting MD, PI, and/or Independent Safety Monitor to create an action plan.

A Medical Monitoring Checklist has been developed to be included with each participant's binder, which triggers the Medical Monitor to double-check lab results, vital signs, concomitant medications, adverse events, and the scores on the Patient Health Questionnaire-9 (PHQ-9) at all visits.

Additional measures for assessing suicidal ideation
Several measures are in place to assess for suicidal ideation in participants throughout the study.

1. The Informed Consent form includes a statement informing participants to let study staff know if at any time they experience thoughts of self-harm or suicidal ideation during the study. The consenting clinician verbally confirms this statement prior to the participant signing the form.
2. Participants are screened by a study clinician for current Major Depressive Disorder and/or suicidal ideation at the Screening Visit after consent. Both are exclusion criteria for continued participation in the study. If excluded for depression or suicidal ideation, participants would be assessed by a study clinician for need for urgent care and referred to mental health services for treatment.
3. Participants complete the PHQ-9 at study visits while on medication. The PHQ-9 is completed on an iPAD during the study visit. If a participant indicates thoughts of self-harm or suicidal ideation on the PHQ9, an alert is set to immediately send an email to the Principal Investigator, the Medical Monitor, the Sr. Project Manager, and the Research Coordinator.

4. Study staff review the responses to the PHQ9 before ending the study visit.
5. A study clinician will query participants directly about suicidal ideation and will inquire about adverse events at study visits while participants is on medication.
6. Any participant indicating emergence of suicidal ideation as determined by a study clinician will be taken off-study and referred to mental health services for further treatment.

Independent Safety Monitor

[redacted], will serve as the Independent Safety Monitor (ISM) for the remainder of this trial. The plan for Independent Safety Monitoring is as follows:

- In the case of a Serious Adverse Event (SAE), the study team will notify the ISM within 24 hours of becoming aware of the SAE. The ISM will review the case and, if appropriate, will examine the participant. The ISM will produce a short report on the SAE.
- Every month, the ISM will review all Adverse Events. This review and any recommended actions will be documented in the Regulatory Binder.
- Upon completion of data collection, the final database will not be unblinded until the ISM has completed all reviews, protocol violators have been identified, and all study data are complete.

Adverse Event Reporting

Subjects will be closely monitored for adverse events at every visit. Research staff will record adverse events using standard spontaneous IRB-approved reporting procedures. Participants will be told during the consent process that they should report any changes in mood or thoughts of self harm immediately to the study team, using the contact information provided on the form. Participants will be informed that they can contact the investigator between visits if they have concerns about potential side effects. Routine adverse events and serious adverse events will be reported consistent with local IRB requirements and per Merck guidelines for reporting to the sponsor. In addition, the Medical Monitor and Independent Safety Monitor will review all adverse events and investigate those considered serious and unexpected consistent with standard ISM procedures.

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