

PROTOCOL TITLE:

Double-blind randomized controlled trial comparing Suvorexant 20 mg to placebo for treatment of insomnia in cancer survivors

SPONSOR LOCATION:

Medical University of South Carolina

PRINCIPAL INVESTIGATOR:

*Sarah Tucker Marrison, MD, PhD
Medical University of South Carolina
86 Jonathan Lucas St
Charleston, SC 29425*

*Sponsor: Merck
National clinical Trial Identified Number:*

VERSION HISTORY

Initial version dated 9/11/2023

1.0 Objectives / Specific Aims

1. To evaluate the self-reported efficacy of suvorexant for the treatment of insomnia in breast cancer survivors at least 6 weeks beyond completion of definitive treatment and less than 5 years from time of initial diagnosis.
2. To assess the impact of suvorexant on quality of life in breast cancer survivors.

2.0 Background

Insomnia rates are increased in cancer survivors compared with the general population resulting in unfavorable clinical outcomes for a condition with limited therapeutic options (1). Cancer survivors have up to a two to three-fold increased rates of sleep disturbance with an incidence of up to 50% (2-4). Sleep disturbance is associated with poorer survivorship outcomes in the domains of physical distress, emotional distress, economic distress, and fear of reoccurrence (4). Beyond these domains, insomnia in cancer survivors is associated with increased cancer related fatigue, decreased quality of life, increased all-cause mortality, and increased rates of cancer reoccurrence. Furthermore, insomnia has previously been demonstrated to impact the functional capacity of the immune system, which has been shown to increase the risk of infection in cancer survivors (5). The prevalence of increased rates of sleep disturbance begins to decline approximately five years following diagnosis with cancer (4). Given the increased prevalence of insomnia especially in the early survivorship period and the clinical implications for both all-cause mortality and cancer associated outcomes, management of insomnia is a critical aspect of cancer survivorship care.

Pharmacotherapy options for the treatment of insomnia in cancer survivors have had limited evaluation, have been associated with significant side effects, and have been associated in some cases with unfavorable cancer outcomes. Melatonin has had limited study in cancer survivors with mixed results on sleep quality (6). Additional treatment options include z drugs such as zolpidem and benzodiazepines. Zolpidem and benzodiazepines have been associated with an increased risk of cancer development (7). Zolpidem has been associated with increased cancer mortality in some cancers (8). Side effects of these medications include cognitive impairment, development of tolerance, rebound insomnia, and dependence (9). Other medications have been proposed for sleep onset and latency however many have limited data in insomnia (10).

Cancer survivors have an incidence of sleep disturbance and insomnia higher than the general population, with significant potential implications on health outcomes including in survivorship domains and mortality outcomes. Available pharmacologic options for management of sleep disturbance are limited in efficacy and in their side effects. We propose a double-blind placebo-controlled trial evaluating the use of the use of suvorexant in breast cancer survivors on selective estrogen receptor modulators or aromatase inhibitors with sleep disturbance to assess the impact on insomnia symptoms and quality of life. Evaluation of breast cancer survivors on endocrine therapy uses a study population with high 5-year survival rate while retaining the capacity for recruitment and creating an opportunity to explore potential effects on vasomotor symptoms. suvorexant is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. It has been FDA approved since 2014. Suvorexant has the potential to have a significant impact in cancer survivors not only on sleep related outcomes but also on cancer survivorship outcomes.

3.0 Intervention to be studied

Participants will be randomized to treatment with FDA approved suvorexant vs. Placebo. Initial suvorexant dosing will be 10 mg with a dose increase to 20 mg after 7 days per dosing recommendations for treatment of insomnia. The placebo will be identical and will be dispensed to the control arm in both a 10 mg dose and 20 mg dose. Study drug will be started after enrollment and registration and continue for up to 28 days. All participants will complete several research related questionnaires per the study calendar. All participants will receive information on sleep hygiene.

4.0 Study Endpoints

- Primary study outcome is sleep disturbance as evaluated by the insomnia severity index (ISI).
- Secondary outcomes of pain (brief pain inventory), vasomotor symptoms (hot flash related daily interference scale), medication adherence (SMAQ), and quality of life (SF-36, CPIL) will be evaluated.

5.0 Inclusion and Exclusion Criteria/ Study Population

Subjects must have the following inclusion criteria:

1. Diagnosis of breast cancer and no more than 10 years from initial diagnosis.
2. At least 6 weeks beyond completion of definitive treatment.
3. Female
4. Greater or equal to 18 years old.
5. Currently taking selective estrogen modulator or aromatase inhibitor use without a planned stop during the 28-day study intervention.
6. Participants cannot be on maintenance therapy except endocrine therapy as stated above.
7. Participants should have no residual disease based on recent clinical assessment from the oncologist.
8. *Insomnia Severity Index Score (ISI)* assessed during screening is greater than or equal to 15.
9. Has provided study informed consent.
10. Currently menopausal (participant has not had a menstrual period within 12 months)

Subjects cannot have any of the following exclusion criteria:

1. Male. Due to limited sample size, we will limit participation to women with a diagnosis of breast cancer.
2. Less than 6-month life expectancy
3. Current receipt of hospice care
4. Known severe depression or anxiety. Individuals with a *Patient Health Questionnaire-9* score of greater than 20 or *General Anxiety Disorder-7* score greater than 15 will be excluded from participation.
5. Pregnant
6. Medical history of severe mental illness
7. Known Hepatic impairment with elevation of AST, ALT, or Bilirubin over twice the normal limit
8. Diagnosis of severe obstructive sleep apnea or untreated moderate sleep apnea
9. Medical history of narcolepsy or other sleep related illness other than insomnia
10. Concurrent use of moderate or strong CYP3A inhibitors (See Appendix 1)
11. Current steroid use (see Appendix 2)
12. Current use of greater than 40 morphine milligram equivalents daily. Participants taking less than 40 morphine equivalents daily should be on a stable medication regimen for two weeks prior to enrollment.
13. Treatment with alternate pharmacotherapy for insomnia. Participants may be enrolled if they have discontinued any of these medications 2 weeks prior to trial initiation. Eligible patients on these medications interested in trial participation can discuss appropriate medication tapering under physician supervision with the current prescribing physician. See Appendix 2 for excluded medications.
14. Individuals with previous intolerance or allergy to suvorexant.
15. Individuals with a disability that precludes completion of study activities (e.g. severe cognitive impairment per patient report or as documented in the medical record) will be limited from participating.

6.0 Number of Subjects

A total of 44 participants will be recruited for participation at a 1:1 randomization to treatment and placebo groups.

7.0 Setting

Study Sites

Research will be conducted within the Department of Family Medicine. Participants can meet with study staff at the 135 Cannon Street 4th Floor. Visits will primarily be conducted virtually, however, if in-person visits are preferred, visits will be conducted in the Department of Family Medicine Research Space. There is private meeting space available where participant interactions and visits can occur. Study medication will be stored and dispensed through the MUSC investigational drug pharmacy.

8.0 Recruitment Methods

- Cold Contact: There will be a BMIC data warehouse request of patients with a past history of breast cancer on aromatase inhibitors or selective estrogen modulation therapy who have

not opted out of research. These individuals will be contacted initially by MyChart message to offer the opportunity to participate. Individuals potentially meeting inclusion criteria will be contacted in groups of 25 stratified by age and race with subsequent outreach based on response rate and recruitment.

- **Direct Referral:** Information on the study will be provided to the breast cancer medical oncology group, family medicine providers, and fliers posted in Hollings cancer center. Study personnel can screen referrals based on medication list and medical history for eligibility and formal screening by the insomnia severity index, evaluation of anxiety, depression. Eligible individuals will be identified from oncology and primary care clinics, MUSC's cancer registry, and through social media outreach including viva engage following IRB approval. These individuals will be contacted and given the option to opt out of an initial screening for study participation.

9.0 Consent Process

Teleconsent will be obtained for the study with an in-person option available if needed or preferred by the participant. Teleconsent will be obtained using redcap e-consent using a video call with doxy.me. If an in-person visit is preferred it will occur in the dedicated research space in 135 cannon Street Suite 405. Within the dedicated research space, there is a private area for which consent and surveys can be completed.

Individuals identified as potentially eligible participation after informed consent will be screened to ensure eligibility. Eligibility screening will include a review of medical history, current medications, ISI score, Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7). Screening will be reviewed by the principal investigator or IRB approved study team member prior to randomization.

10.0 Study Design / Methods

Screening and Baseline Assessments: Informed Consent will be obtained in potentially eligible individuals prior to eligibility screening. Eligibility screening will include an Insomnia Severity Index (ISI), the PHQ-9, GAD-7 assessments and the evaluation of current medications and medical history to assess for potential medication interactions. Informed written consent will be provided prior to participation.

At Baseline (T=0), initial evaluation will include review of demographic information, the Brief Pain Inventory (BPI), , 36-Item Short for Survey (SF-36), Simplified Medication Adherence Questionnaire (SMAQ), Hot flash related daily interference scale, and Cancer Problems in Living (CPIL) scale (11-17). The BPI assesses pain level, pain interference in daily activities including impact of pain on sleep. Assessment of vasomotor symptoms has been included based on the recent study by Rahman et al. demonstrating the potential benefit of orexin antagonists on vasomotor symptoms and the frequency of these symptoms in breast cancer survivors on endocrine therapy (17). All patients will be provided with sleep hygiene and suvorexant patient education information at study initiation including information regarding lack of strong feeling of sedation after administration. Subjects will then be randomized to treatment with placebo or suvorexant for 4 weeks.

Randomization: Following baseline screening, individuals will be randomized using permuted block randomization with random block sizes of 2, 4 and 6. All study personnel who may have contact with participants will be blinded to treatment allocation. Randomization will be managed within REDCap. All data including study IDs and treatment assignment will be stored in a password protected HIPAA compliant MUSC database separate from primary study documents.

Blinding protocol: All study staff including the PI interacting with participants or conducting primary data analysis will remain blinded to the study arm of assigned. Participants will be screened, eligibility evaluated, and consented by Department of Family Medicine study team members. The Clinical Trial Office SIS unit designated individual (s) will then communicate with the Investigational Drug Pharmacy for randomization and dispensation of appropriate suvorexant or placebo. This packaging will not identify assigned study arm to the study staff or participant. It will be picked up by the Department of Family Medicine study staff who will then coordinate delivery with patients. All databases will be constructed so that unblinded individuals will not view the assigned study arm. Unblinded individuals include the Investigational drug pharmacy and Kent Armeson as the statistician designate to remain unblinded for preparation of any unblinded tables for review by the data safety monitoring committee. Dr. Elizabeth Hill and Evan Bagley as primary study statisticians will remain blinded to study arm throughout the trial duration.

The Data Safety Monitoring committee will have access to blinded and unblinded data tables available at request for review meetings. This table preparation will be conducted by Kent Armeson and unblinded tables will not be viewed by blinded study team members. If for patient safety unblinding a patient is required, the PI can contact IDS for individual unblinding. This will be reported to the IRB and data safety monitoring committee per protocol.

Study Treatment: After randomization, participant will pick up the study drug from study staff provided by the MUSC Investigational Drug Services. Suvorexant treatment vs. placebo will be initiated at 10 mg for 7 days. Placebo dosages will be administered on the same schedule. Participants will be instructed to take study drug once nightly within 30 minutes of going to bed and with at least 7 hours remaining before the planned time of awakening. Sleep hygiene information will be provided to both trial arms. Participants will be instructed to complete the medication log and record or notify the study team of any side effects. A study team member will contact study participants approximately 7 days after study drug initiation to verify medication compliance.

At day 8, the participant will increase the dosage to 20 mg and will continue to take the study drug up to day 28. Adherence to study medication will be recorded by the patient within the medication adherence form provided as part of the study. If side effects are reported by the participant at any time, a dose reduction to 10 mg will occur for CTCAE grade 3-5 side effects or at the discretion of the principal investigator. Participants can self-report side effects at any time through a REDCap reporting form or direct contacting of the study team or the midpoint evaluation at 14 days. The redcap questionnaire at this time will include medication specific side effect questions. Additional study surveys will be administered per the study calendar.

Assessment of insomnia symptoms and secondary outcomes will be assessed using an online survey delivered via the REDcap platform at Visit T=14 days and Visit T=28 days with a pill count occurring at completion of treatment (28 days). Assessment for insomnia specific quality measures will include assessment of sedation on waking, headache, nausea and other gastrointestinal side effects, nightmares, complex-sleep related behaviors, cognitive side effects, and psychomotor effects will be conducted (18). The study team will be available to be contacted for any potential side effects.

Recruitment will continue until at least 22 patients have been randomized to each arm and are evaluable for the primary endpoint (those who have complete baseline and 28 day-ISI scores) (minimum total sample size = 44), up to a maximum of 52 total patients accrued. Patients evaluable for the primary endpoint must have taken study drug and completed the baseline ISI survey. If, after 52 accruals, there are fewer than 22 evaluable patients in each arm, the study team and DSMB will meet to determine whether to close the trial to accrual or amend the protocol to allow for additional patient accruals. The primary endpoint for the study will be treatment efficacy as assessed by change in the ISI.

Follow up: Participants will be followed for the 4-week duration of the study while on treatment with evaluation at baseline, 2 weeks and 4 weeks. If patients opt to terminate their participation at any time, they will be asked to complete an early termination interview inquiring about reasons for termination and their experiences in the study to date. Compensation will be provided in the form of gift cards at each of the three survey periods for survey completion.

Safety follow up and monitoring: Informed consent will be obtained by teleconsent prior to participation for all participants. Potential risks of participation include diarrhea, drowsiness, dizziness, and headaches. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

The study will remain blinded until data collection is completed. In the event of potential suspected serious adverse reaction, unblinding will be undertaken in coordination with the treating physician to facilitate appropriate patient care. The PI will be kept informed of all instances of unblinding.

Reporting of all serious adverse events will occur to the IRB, Data and Safety Monitoring Board (DSMB) for the study within 72 hours of the study's knowledge of the adverse event. Reporting of all other events will occur quarterly. The Principal Investigator will be responsible for ensuring patient safety. The Hollings Cancer Center Independent Data Safety Monitoring Board will be utilized in this study.

The total study duration is expected to be 2 years during which time 44 participants will complete 4 weeks of treatment.

Study Calendar

Time¹	Appointment type and projected duration	Content
Pre-study	- Video (in-person option) - 30 minutes	Informed Consent Review of Medical History Review of Concomitant Medications Patient Health Questionnaire-9 General Anxiety Disorder-7 Insomnia Severity Index (ISI) Evaluation for study eligibility Study registration and randomization
T=0	- Questionnaires may be done in-person or remotely by patient within RedCap. - 30 minutes - In-Person Pick-up Medication from study personnel following dispensation by the Investigational Drug Pharmacy	Demographic Information Receipt of information on sleep hygiene <i>To be completed prior to first dose of study drug:</i> - Quality of life Surveys (SF-36, CPIL) - Hot flash related daily interference scale - Brief pain inventory
T=7 days	- Phone Call	Study team contact to review study medication compliance
T=14 days	- Questionnaires may be done in-person or remotely by patient within RedCap. - 15 minutes	ISI Hot flash related daily interference scale Brief pain inventory Simplified Medication Adherence Questionnaire (SMAQ)
T=28 days	- Questionnaires may be done in-person or remotely by patient within RedCap. - 30 minutes	ISI Quality of life (SF-36, CPIL) Hot flash related daily interference scale Brief pain inventory Simplified Medication Adherence Questionnaire (SMAQ, pill count)

¹ Study visits may occur +/- 4 days.

11.0 Specimen Collection and Banking (if applicable)

- No specimens will be collected during the study

12.0 Data Management

Power/Sample Size justification:

The primary endpoint is the change in the ISI score. Specifically, let Δ_S = ISI D28 – ISI D0 for the suvorexant arm, and let Δ_P = ISI D28 – ISI D0 for the placebo arm. A sample size of 44 is planned with a 1:1 allocation to the suvorexant and placebo arms. We expect the average change in ISI for the treatment group to be $\Delta_S = -4$ and the average change in the placebo group to be $\Delta_P = 0$. We assume the standard deviation of ISI scores at a single time point is $\sigma = 3.2$ (17, 20, 21) and, based on this assumption, estimate the standard deviation of the trial arm change scores (Δ_S and Δ_P) (the SD of interest since the effect size is based on $\Delta_S - \Delta_P$). Assuming $SD(\Delta_S) = SD(\Delta_P)$, we need only estimate $SD(\text{ISI D28} - \text{ISI D0}) = 2\sigma^2(1 - \rho)$, where $\rho = \text{Corr}(\text{ISI D28}, \text{ISI D0})$. We consider values of ρ ranging from 0.1 to 0.9 to generate plausible SDs for change scores ranging from 1.4 to 4.3. Figure 1 shows power for an effect size of $\Delta_S - \Delta_P = -4$ across the specified range of plausible change score SDs based on a two-sample t-test with two-sided $\alpha = 0.05$. Thus, we expect power of at least 80% to detect an effect size of -4, which is a clinically significant difference. Power analysis and sample size determination was conducted using PASS 2022 version 22.0.4.

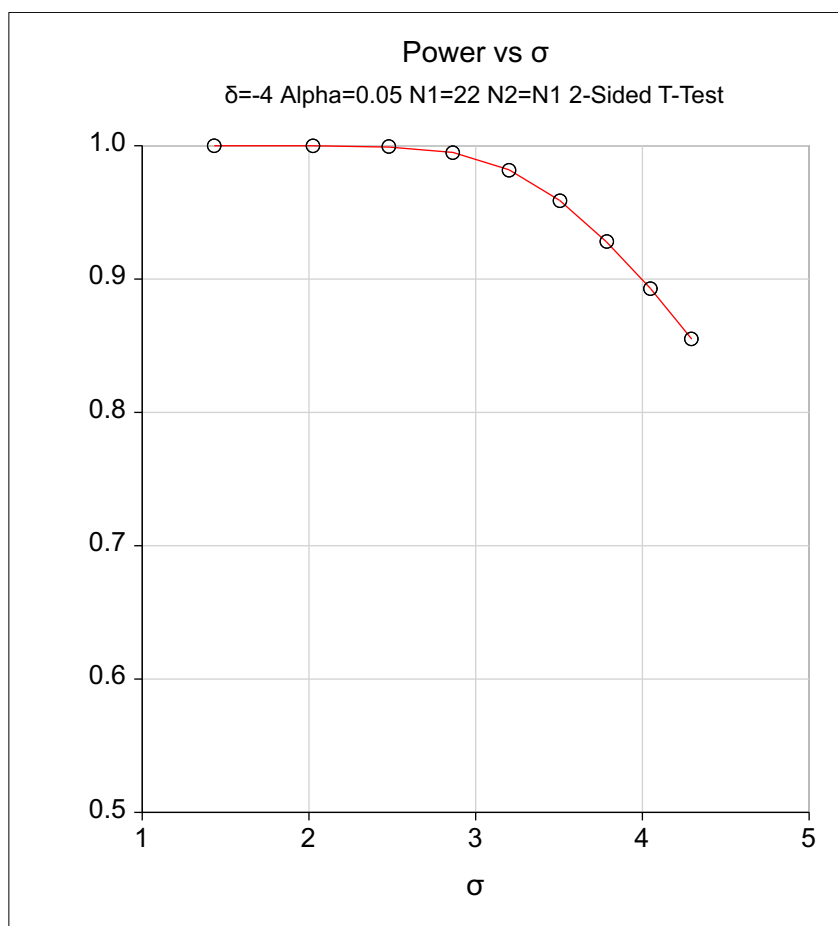


Figure 1: Power curve for various standard deviation values

All patient history and survey results will be kept confidential. Collected data will be stored and managed via MUSC approved HIPAA compliant password protected servers. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). The master list of the codes will be kept separately (physically/electronically) from the collected data on MUSC servers protected by 2 factor authentication. Results will be reported in aggregate and not linked to individual participant responses. All coded confidential project data will be destroyed 10 years after project completion. The principal investigator will randomly review all regulatory documents for a minimum on one participant quarterly during study recruitment to ensure adherence to study guidelines.

Populations for Analyses

The **Safety Analysis Set (SAS)** comprises all patients who take any study drug. Patients will be analyzed as treated regardless of randomization assignment.

The **Full Analysis Set (FAS)** comprises all randomized patients who are evaluable for the primary endpoint. Patients will be evaluable for the primary endpoint if they take any study drug and complete both the baseline ISI survey and the 28-day follow-up ISI survey (modified intent to treat).

Data analysis:

Data analysis will be conducted by the study statistician. Double blinding will be maintained during study protocol with participants identified using assigned study ID numbers. Data will be unblinded following completion of data collection and analysis.

Variables/Time Points of Interest

Demographic variables, including age, race, ethnicity, education, employment status, financial strain, and insurance status will be obtained at the time of study enrollment. Categorical variables will be reported as frequencies and percentages and continuous variables will be reported as means and standard deviations.

Analysis of the primary endpoint

The primary outcome is change in insomnia symptoms evaluated using the Insomnia Severity Index (ISI), a previously validated questionnaire with a series of 7 Likert style questions. Suvorexant has previously demonstrated improvement in symptoms of insomnia using the ISI in individuals in the general population meeting criteria for primary insomnia and otherwise in good physical and mental health (19). We will conduct the analysis using an analysis of covariance (ANCOVA) where final ISI score is the dependent variable, trial arms as factors, and baseline ISI scores as covariates. Timepoints for evaluation are shown in study calendar and may include 0, 2, and 4 weeks depending on the variable. The primary outcome will be assessed at baseline, 2 weeks and 4 weeks. The primary endpoint will be analyzed based on the FAS. Participants who complete the 28-day ISI outside of the +/- 4-day allowed window will be included in the FAS and considered evaluable for the primary analysis. However, a sensitivity analysis excluding these participants will be conducted to assess the impact of deviations from the study calendar.

Analyses of secondary endpoints

Secondary outcomes of BPI, Hot Flash Related Daily Interference Scale, SMAQ, and quality of life (SF-36, CPIL) will be modeled in a similar manner to the primary endpoint so that relevant changes can also be adjusted for the baseline scores. The secondary endpoints will be conducted for the FAS. Subgroup analysis stratified by demographic variables characterized as dichotomously (race: white/non-white, age: <45 years/>45 using, financial strain: high/low) will be conducted to evaluate them as effect modifiers for the primary outcome. Although the exclusion criteria will limit inclusion of participants with severe pain, BPI will also be evaluated as a possible effect modifier, classified dichotomously as high/low based on the median for this variable.

Safety Analyses: All patients in the safety analysis set will be evaluated for safety and toxicity. AEs and SAEs will be presented by System Organ Class (SOC) and by decreasing frequency of Preferred term within SOC. Safety analyses will include the following summaries:

- AEs, including severity and possible relationship to the study drug
- SAEs, including severity and possible relationship to the study drug
- Dose reductions due to study drug side effects
- Discontinuations from study treatment due to AEs or death
- Treatment-emergent abnormal changes in laboratory values
- Treatment-emergent abnormal changes in vital signs and ECGs

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The Principal Investigator will be responsible for ensuring patient safety. Data Safety Monitoring will additionally occur through the Hollings Cancer Center Independent Data Safety Monitoring Board.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate personnel will have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Data capture will occur starting from

the time after first medication administration. Adverse events related to the participant's cancer, treatment or comorbidities will not be captured and reported for this study. Any reportable AEs (as per the definition above) will be recorded on the Adverse Event Reporting form which will be available in the REDCap platform. Adverse events will be reviewed by the investigative team and the Data Safety Monitoring Board.

The proposed study endpoints have a primary endpoint of insomnia with secondary endpoint of evaluation of vasomotor symptoms and patient reported quality of life. Suvorexant is FDA approved for insomnia in 2014 at the current recommended dosing however not specifically evaluated in the population. Exclusion criteria and dose reduction strategies have been selected to reduce potential side effects and for adverse events. Additional monitoring or changes in safety plan will be at the recommendation of the data safety monitoring board who will review all data and adverse events.

14.0 Withdrawal of Subjects (if applicable)

Participants may request withdrawal at any time. If a participant requests to withdraw, an exit interview will be requested. Withdrawal can be considered at the principal investigator's discretion for adverse events grade 3-5 attributed to study participation. In the event of principle investigator initiated withdrawal in setting of adverse events, participants will be notified by phone and mail. Full compensation for study participation will be provided if all appropriate surveys relevant to time in study have been completed with allowance within 5 days of expected completion date.

15.0 Risks to Subjects

Potential risks to participants include loss of confidentiality of health information. Potential side effects of the study medication suvorexant include sedation, complex sleep behaviors, gastrointestinal symptoms, tachycardia, dizziness, lower extremity weakness, worsening depression. Exclusion criteria have been selected to limit participation of those at greatest risk of side effects and to limit use to appropriate current use per FDA approval. These side effects are rated. The frequency of type of potential side effect is outlines in the consent form.

16.0 Potential Benefits to Subjects or Others

Potential benefits to subjects are the improvement in sleep disturbance through education of sleep hygiene and potentially receipt of treatment. Risks are reasonable in the setting of previously approved FDA approved medication for insomnia now evaluated in a specific population without anticipated additional risks. In individuals randomized to placebo control, information will be provided on sleep hygiene and conservative measure. Duration of treatment is limited to 4 weeks.

17.0 Sharing of Results with Subjects

A summary of the study results will be available at study completion to participants at the request of participants.

18.0 Drugs or Devices

Merck is providing the 10 mg and 20 mg oral tablets and the 10mg and 20 mg placebo tablets.

- Suvorexant (Belsomra)
- Placebo Control

References:

1. Shi T, Min M, Sun C, Zhang Y, Liang M, Sun Y. Does insomnia predict a high risk of cancer? A systematic review and meta-analysis of cohort studies. *J Sleep Res.* 2020;29(1):e12876.
2. Zachariae R, Amidi A, Damholdt MF, Clausen CDR, Dahlgaard J, Lord H, et al. Internet-Delivered Cognitive-Behavioral Therapy for Insomnia in Breast Cancer Survivors: A Randomized Controlled Trial. *J Natl Cancer Inst.* 2018;110(8):880-7.
3. Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev.* 2016;30:1-10.
4. Strollo SE, Fallon EA, Gapstur SM, Smith TG. Cancer-related problems, sleep quality, and sleep disturbance among long-term cancer survivors at 9-years post diagnosis. *Sleep Med.* 2020;65:177-85.
5. Ruel S, Ivers H, Savard MH, Gouin JP, Lemieux J, Provencher L, et al. Insomnia, immunity, and infections in cancer patients: Results from a longitudinal study. *Health Psychol.* 2020;39(5):358-69.
6. Jafari-Koulaee A, Bagheri-Nesami M. The effect of melatonin on sleep quality and insomnia in patients with cancer: a systematic review study. *Sleep Med.* 2021;82:96-103.
7. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc.* 2012;87(5):430-6.
8. Hwang S, Son H, Kim M, Lee SK, Jung KY. Association of Zolpidem With Increased Mortality in Patients With Brain Cancer: A Retrospective Cohort Study Based on the National Health Insurance Service Database. *J Clin Neurol.* 2022;18(1):65-70.
9. Sean B.O'Donnell MKN, Jason W.Boland. The Association Between Benzodiazepines and Survival in Patients With Cancer: A Systematic Review. *Journal of Pain and Symptom Management.* 2019;57(5).
10. De Crescenzo F, D'Alo GL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. *Lancet.* 2022;400(10347):170-84.
11. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-13.
12. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092-7.
13. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-83.
14. Zhao L, Portier K, Stein K, Baker F, Smith T. Exploratory factor analysis of the Cancer Problems in Living Scale: a report from the American Cancer Society's Studies of Cancer Survivors. *J Pain Symptom Manage.* 2009;37(4):676-86.
15. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med.* 2015;5(4):470-82.
16. Chen CX, Kroenke K, Stump TE, Kean J, Carpenter JS, Krebs EE, et al. Estimating minimally important differences for the PROMIS pain interference scales: results from 3 randomized clinical trials. *Pain.* 2018;159(4):775-82.
17. Rahman SA, Nathan MD, Wiley A, Crawford S, Cohn AY, Harder JA, et al. A double-blind, randomized, placebo-controlled trial of suvorexant for the treatment of vasomotor symptom-associated insomnia disorder in midlife women. *Sleep.* 2022;45(3).
18. Edinger JD, Buysse DJ, Deriy L, Germain A, Lewin DS, Ong JC, et al. Quality measures for the care of patients with insomnia. *J Clin Sleep Med.* 2015;11(3):311-34.
19. Herring WJ, Connor KM, Snyder E, Snively DB, Morin CM, Lines C, et al. Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data. *Sleep Med.* 2019;56:219-23.
20. Colagiuri B, Sharpe L, Ambarchi Z, Glozier N, Bartlett D, Costa DSJ, et al. Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial. *BMJ Open.* 2021;11(2):e044045.
21. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr Med Res Opin.* 2009;25(10):2487-94.

Appendix 1. Prohibited Strong Cytochrome P450 3A inhibitors and inducers

- Amiodarone
- Aprenavir
- Aprepitant
- Atazanavir
- Berotralstat
- Carbamezepime
- Cimetidine
- Ciprofloxacin
- Clarithromycin
- Cobicistat and cobicistat-containing coformulations
- Conivaptan
- Cyclosporine
- Darunavir
- Diltiazem
- Delavirdine
- Dronedarone
- Erythromycin
- Fosamprevir
- Fluconazole
- Indinavir
- Itraconazole
- Ketoconazole
- Letormovir
- Levoketoconazole
- Lonafarnib
- Lopinavir
- Miconazole
- Mifepristone
- Nefazodone
- Nelfinavir
- Neupitant
- Nirmatrelvir-ritonavir
- Ombitasvir-paritaprevir-ritonavir
- Ombitasvir-paritaprevir-ritonavir plus dasabuvir
- Phenobarbital
- Phenytoin
- Posaconazole
- Rifampin
- Ritonavir and ritonavir-containing coformulations
- Saquinavir
- Verapamil
- Voriconazole

Appendix 2. Additional medications prohibited for concurrent use during study

Insomnia

- clonazepam
- chlordiazepoxide
- daridorexant
- diazepam
- doxepin
- eszopiclone
- lemborexant
- lorazepam
- melatonin
- oxazepam
- ramelteon
- zaleplon
- temazepam
- trazodone
- valium
- zolpidem
- Any additional benzodiazepine medications

Steroid Medications (oral formulations only)

- prednisone
- dexamethasone
- prednisolone
- betamethasone
- hydrocortisone
- methylprednisolone