PROTOCOL TITLE

Efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older surgical patients: A double-blinded, randomized, placebo-controlled trial

Short Title: REPOSE Study: Reducing Delirium by Enhancing Postoperative Sleep with Suvorexant

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Funding Sponsor:	*Scientific Affairs Neuroscience* *Global Center for Scientific Affairs* *Merck Sharp & Dohme LLC* [redacted]
Study Product:	*Suvorexant (Brand name: Belsomra)*

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List of Abbreviations

Abbreviation	Definition
3D-CAM	3-minute diagnostic interview for confusion assessment method
AE	Adverse Event

EEG	Electroencephalography
CAM-ICU	Confusion Assessment Method for the ICU
CQMP	Clinical Quality Management Plan
CRF	Case Report Form
CT	Cat Scan
CYP2A4	Cytochrome P450 3A4
DUMC	Duke University Medical Center
EC	Ethics Committee
EDTA	Ethylenediaminetetraacetic Acid
FDA	Food and Drug Administration
HIPPA	Health Insurance and Portability and Accountability Act
ICU	Intensive Care Unit
IDS	Investigational Drug Services
IRB	Institutional Review Board
ISI	Insomnia Severity index
MOCA	Montreal Cognitive Assessment
NPO	Nothing by Mouth
OHRP	Office for Human Research Protections
PSQI	Pittsburgh sleep quality inventory
PHI	Private Health Information
PI	Principal Investigator
PVT	Psychomotor Vigilance Task
RASS	Richmond-Agitation Sedation Scale
RCSQ	Richmond-Campbell Sleep Questionnaire
RPM	Revolutions Per Minute
SAE	Serious Adverse Event
SD	Standard Deviation
TST	Total Sleep Time

Study Summary

Title	Efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older surgical patients: A double-blinded, randomized, placebo-controlled trial.
Short Title	REPOSE Study: Reducing Delirium by Enhancing Postoperative Sleep with Suvorexant.
Protocol Version	1.0
Phase	Phase 2
Methodology	Double-blinded, randomized, placebo-controlled trial
Study Duration	30 months
Study Center(s)	Single-center

Objectives	<u>Primary Objective</u>: - To determine the effect of the postoperative administration of oral suvorexant (20 mg) on electrographic total sleep time on the first night after surgery that patient received study drug. <u>Secondary Objectives</u>: - To determine the effect of the nightly administration of postoperative suvorexant or placebo on peak postoperative delirium severity scores up through postoperative day 5 or discharge, whichever occurs first. <u>Exploratory Objectives</u>: Objective sleep measures - To determine the impact of the daily administration of postoperative suvorexant or placebo on 3-night average electrographic total sleep time over nights of postoperative day 0, 1, and 2. Subjective sleep measures: - To determine the effect of the daily administration of postoperative suvorexant or placebo on average postoperative Richards-Campbell subjective sleep quality scores over postoperative day 1, 2,3, 4 and 5. Other endpoints: - Additional study endpoints that will be compared between suvorexant and placebo groups include: 1. postoperative length of stay 2. postoperative pupil diameter fluctuations 3. average response latency on postoperative psychomotor vigilance testing. Potential effect modifiers: - In exploratory analyses, we will determine if the effect of suvorexant on sleep characteristics and peak delirium severity is modified by specific patient baseline characteristics including: 1. Actigraphically measured long vs. short preoperative sleep duration 2. High vs. low resting preoperative pupil diameter fluctuations; and 3. Preoperative average response latency on psychomotor vigilance testing. 4. Insomnia severity index scores ≤7 vs ≥8.

Number of Subjects	130
Diagnosis and Main Inclusion Criteria	Patients ages 65 years old or older undergoing non-cardiac, non-neurologic surgery who are scheduled to stay overnight in the hospital postoperatively
Study Product, Dose, Route, Regimen	Suvorexant (Belsomra®) 20 mg, administered as two 10 mg tablets by mouth nightly
Duration of administration	3 days or until hospital discharge, whichever occurs first.
Reference therapy	Placebo

Statistical Methodology	Total sleep time on the first postoperative night that study drug is received will be compared between treatment groups (placebo vs. suvorexant) using a two-sample t-test. Total sleep time on the night of postoperative day 1 will be compared between treatment groups (placebo vs. suvorexant) using a two-sample t-test. Peak postoperative delirium severity scores between treatment groups will be compared using a two-sample t-test. A two-sided alpha level of 0.05 will be required for statistical significance.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Sleep deprivation is associated with immune dysfunction,[1] disturbed metabolism,[2] cardiovascular disease,[3] earlier onset of dementia,[4] and increased mortality.[5] Thus, there is increasing focus on improving sleep in vulnerable patient populations such as older surgical patients, because they are at increased risk for postoperative complications and prone to sleeping problems before and after surgery.[6] Preoperative sleep problems are further exacerbated postoperatively in hospital settings due to frequent nursing assessments, noisy environments, postoperative pain, and administration of medications that disrupt normal sleep architecture.[7] Although these postoperative sleep disruptions could increase risk for postoperative delirium,[8] physical debility,[9] and cognitive dysfunction,[10] we seldom utilize FDA-approved medications that restore normal sleep architecture and prevent sleep deprivation in hospitalized older surgical patients because there are few studies testing effective sleep aids in this setting. Further, commonly used pharmacologic sleep aids such as benzodiazepines actually disrupt normal sleep architecture and promote complications such as falls and delirium. Thus, there is an urgent need to test therapies that normalize sleep in older surgical patients such as suvorexant to determine whether suvorexant improves postoperative sleep and decreases the incidence of postoperative delirium.

Postoperative delirium is a fluctuating disturbance in attention and consciousness that occurs in up to the 40% of the >19 million older Americans who undergo surgery each year. Although postoperative delirium is associated with longer hospitalization, decreased quality of life,[11] increased risk for Alzheimer's disease,[12, 13] and increased 1-year mortality, there are few, if any, FDA-approved medications to prevent and/or treat delirium.[14] To help find interventions to reduce postoperative delirium, our group is investigating the role of sleep disruptions in the development of postoperative delirium. We have generally found that ~25% of older adults develop postoperative delirium after non-cardiac, non-neurologic surgery (Figure 1). In our recently completed study: **S**leep **A**pnea, **N**euroinflammation, & cognitive **D**ysfunction **M**anifesting **A**fter **N**on-cardiac surgery (SANDMAN) we investigated the role of neuro-inflammation and disrupted sleep (due to sleep apnea) in postoperative delirium. Although we found that sleep apnea was not associated with postoperative delirium, preoperative excessive daytime sleepiness is associated with increased postoperative delirium severity (Figure 2), suggesting that perioperative sleep dysfunction contributes to postoperative delirium. Our next step is to measure perioperative sleep disruptions and test interventions to improve postoperative sleep, because few studies have determined whether improving postoperative sleep actually decreases delirium incidence and severity. Since delirium

is associated with higher hospitalization costs and mortality, there is a critical need to find an FDA-approved therapeutic to decrease delirium incidence and severity.

There is also an unmet need for safe and effective sleep pharmacotherapy for older hospitalized patients. Commonly used hypnotic sleep aids such as benzodiazepines and non-benzodiazepines (z-drugs) are increasingly avoided in hospitalized patients because they increase delirium, but this leaves older hospitalized patients with few, if any, options for safe pharmacologic sleep aids. Medications that improve circadian alignment, such as ramelteon and melatonin are increasingly used but have mild, if any, effects on overall sleep time or delirium in hospitalized patients.[15] In contrast, suvorexant is an effective sleep aid that can be used to treat insomnia and increase total sleep time in older dementia patients,[16] suggesting that suvorexant has potential as an effective and safe in-hospital pharmacologic sleep aid in older hospitalized patients. Instead of increasing risk for falls and delirium like benzodiazepines and other sleep aids,[17] suvorexant might *decrease* delirium (as described above), since it has been found to decrease postoperative delirium in older surgical patients in randomized controlled trials in Japan.[18, 19] Thus, it is important that we study suvorexant in older American surgical patients, to determine if the Japanese findings are applicable to our population. Even if we find that suvorexant has no effect on postoperative delirium, our proposed study will be useful to demonstrate that suvorexant effectively improves postoperative sleep, in contrast to the benzodiazepines and non-benzodiazepines (z-drugs) that increase delirium and falls. These data could support the widespread use of suvorexant to improve postoperative sleep in older surgical patients.

Decreased preoperative sleep and circadian rhythm disruptions could increase risk for postoperative sleep disruptions and postoperative delirium, but few studies have thoroughly evaluated preoperative sleep and circadian rhythms. Wrist-watch actigraphy that measure movement using accelerometry can quantify sleep time and sleep onset time using well-studied algorithms, allowing for determination of total sleep time and circadian patterns. Sleep deprivation and excessive sleepiness is also associated with decreased fluctuations in resting pupil diameter. Thus, decreased fluctuation in resting pupil diameter could indicate sleep deficits and increased preoperative delirium risk but no studies have investigated this. Importantly, these preoperative sleep indicators could shed insight into patients who are most likely to benefit from interventions to improve postoperative sleep.

Here, we propose a double-blinded, randomized placebo-controlled trial to determine whether postoperative suvorexant administration improves objective and subjective measures of sleep and reduces postoperative delirium severity in older non-cardiac, non-neurologic surgery patients.

1.2 Investigational Agent

Belsomra tablets contain suvorexant, an orexin receptor antagonist. Suvorexant is used in older adults with insomnia characterized by difficulties with sleep onset and/or maintenance. Each film coated table contains 10 mg of suvorexant. Suvorexant is administered orally and exhibits similar pharmacokinetics and bioavailability in healthy

subjects and patients with insomnia. Suvorexant is primarily metabolized by CYP3A, and thus dosage is recommended to be lower in patients receiving moderate CYP3A4 inhibitors and is not recommended for use with strong CYP3A4 inhibitors.

Each Belsomra tablet contains, suvorexant is a white powder that is insoluble in water in addition to the inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polyvinylpyrrolidone/vinyl acetate copolymer (copovidone). In addition, the film coating contains the following inactive ingredients: hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The film coating for the 10 mg tablets also contains FD&C Blue #1/Brilliant Blue FCF Aluminum Lake and iron oxide yellow.

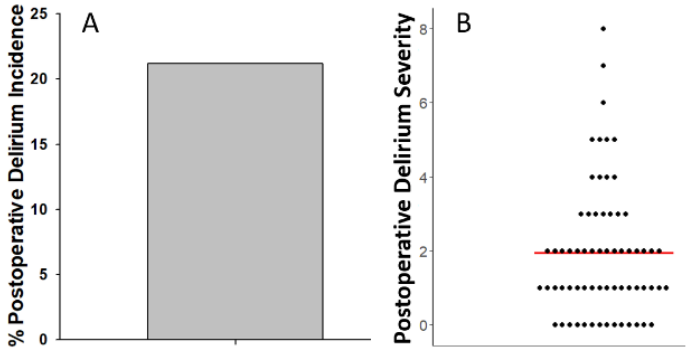
1.3 Clinical Data to Date

Suvorexant has been previously studied in older adults with mild to moderate Alzheimer's disease for the treatment of insomnia symptoms and was found to significantly increase total sleep time and decrease wake after sleep onset time compared to those treated with placebo.[16] The FDA approved for this data to be included in its label packaging insert.

In a small randomized controlled trial in Japan,[18] suvorexant significantly improved subjective sleep quality and decreased postoperative delirium incidence, suggesting that proactive treatment of common postoperative sleep problems in older surgical patients could reduce the incidence of delirium.

In our previous studies, we found that delirium occurs in ~20% of older (age≥65) non-cardiac, non-neurologic surgery patients (Figure 1A) and has a wide range of severity (Figure 1B). We have also found that increased preoperative daytime sleepiness was associated with increased postoperative delirium severity (Figure 2), suggesting that poor sleep could contribute to delirium pathogenesis.

Figure 1: Delirium incidence and severity



A. Delirium incidence in older adults after non-cardiac, non-neurologic surgery. B. Postoperative delirium severity distribution amongst these same patients.

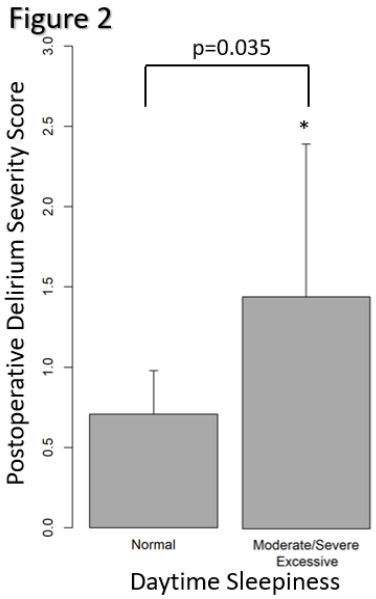


Figure 2. Older surgical patients with preoperative excessive daytime sleepiness (Epworth Sleepiness Scale score ≥13) experienced increased postoperative delirium severity (adjusted odds ratio 3.95, p= 0.035).

1.4 Dose Rationale and Risk/Benefits

We choose to administer 20 mg suvorexant by mouth each night for the first 3 nights postoperatively because 1) this dosage has the greatest effect on increasing total sleep time in previous clinical trials,[20] 2) it is unlikely that lower doses of suvorexant would be effective in keeping patients asleep because sleep is frequently disrupted in hospital settings, and 3) this dosage is being studied to improve postoperative sleep in a separate study of older cardiac surgery patients.[21] Using the same dose will allow for future combined analyses comparing its potential effects across surgical groups on postoperative sleep that has potential to help clinicians decide what postoperative pharmacologic sleep aid to use. Patients will receive nightly (between 9 and 10PM) oral suvorexant, which is the standard administration route and typical time of suvorexant administration. Patients will receive suvorexant for up to three nights, starting with the night of postoperative day 0, because sleep is most disrupted in this immediate postoperative period.[22] Patients will not receive any study medication after discharge from the hospital because sleep disruptions are less frequent at home.

Known potential risks of suvorexant:

Most common side effects of suvorexant include:

1. Headache (7%)
2. Diarrhea (2%)
3. Xerostomia (2%)
4. Cough (2%)
5. Abnormal dreams (2%)
6. Dizziness (3%)
7. Drowsiness (3%)

8. Daytime tiredness (4%)

Less common side effects of suvorexant include
1. Sleep paralysis
2. Sleep-walking
3. Itchiness
4. Nausea
5. Vomiting
6. Palpitations
7. Daytime sedation
8. Worsening of depression and suicidal Ideation

Known potential benefits of suvorexant:
There are currently no known benefits of suvorexant administration in older adults after surgery. Since suvorexant has been shown to decrease time to sleep onset and improve sleep maintenance in outpatients with insomnia, suvorexant has the potential to improve postoperative sleep, which could improve patient satisfaction and postoperative cognition as well as prevent the development of postoperative delirium.

2 Study Objectives

Primary Objective:
- To determine the effect of the postoperative administration of oral suvorexant (20 mg) on electrographic total sleep time on the first night after surgery that patient received study drug.

Secondary Objectives:
- To determine the effect of the nightly administration of postoperative suvorexant or placebo on peak postoperative delirium severity scores up through postoperative day 5 or discharge, whichever occurs first.

Exploratory Objectives:
Objective sleep measures
- To determine the impact of the daily administration of postoperative suvorexant or placebo on 3-day average electrographic total sleep time over nights of postoperative day 0, 1, and 2.

Subjective sleep measures:
- To determine the effect of the daily administration of postoperative suvorexant or placebo on average postoperative Richards-Campbell subjective sleep quality scores over postoperative day 1, 2,3, 4 and 5.

Other endpoints:
- Additional study endpoints that will be compared between suvorexant and placebo groups include: 1. postoperative length of stay 2. postoperative pupil diameter fluctuations 3. average response latency on postoperative psychomotor vigilance testing.

Potential effect modifiers:

- In exploratory analyses, we will determine if the effect of suvorexant on sleep characteristics and peak delirium severity is modified by specific patient baseline characteristics including: 1. Actigraphically measured long vs. short preoperative sleep duration 2. High vs. low resting preoperative pupil diameter fluctuations; and 3. Preoperative average response latency on psychomotor vigilance testing. 4. Insomnia severity index scores ≤7 vs ≥8.

3 Study Design

3.1 General Design

This randomized, double-blind, placebo-controlled phase II trial will be conducted at Duke University Medical Center. A total of 130 subjects, age ≥ 65 undergoing non-cardiac, non-intracranial surgery with planned inpatient stay ≥ 24 hours will be randomized 1:1 to receive nightly oral suvorexant 20 mg vs. placebo on the nights of postoperative day 0, 1, and 2.

Prior to surgery, participants will be assessed with structured sleep questionnaires, pupillometry, and a sustained attention test known as the psychomotor vigilance task (PVT). When there is enough time prior to surgery, wrist-watch actigraphy to measure sleep patterns and duration will be attempted for ≥ 3 nights prior to surgery, up to 6 weeks prior to surgery. Study drug (placebo vs suvorexant 20 mg) will be administered once nightly between 21:00 and 22:00 (+- 30 min) on postoperative day 0, 1, and 2 or until hospital discharge, whichever occurs first. Postoperative sleep will be measured with electroencephalography (EEG) collected with the easy-to-wear Dreem headband 3 on postoperative nights 0, 1, and 2 or until hospital discharge, whichever occurs first. Delirium will be assessed twice daily with the 3D-CAM (or CAM-ICU if non-verbal) up until postoperative day 5 or discharge, whichever occurs first. Subjects will be contacted for an adverse event assessment at 4 weeks (+/-2 weeks) after surgery.

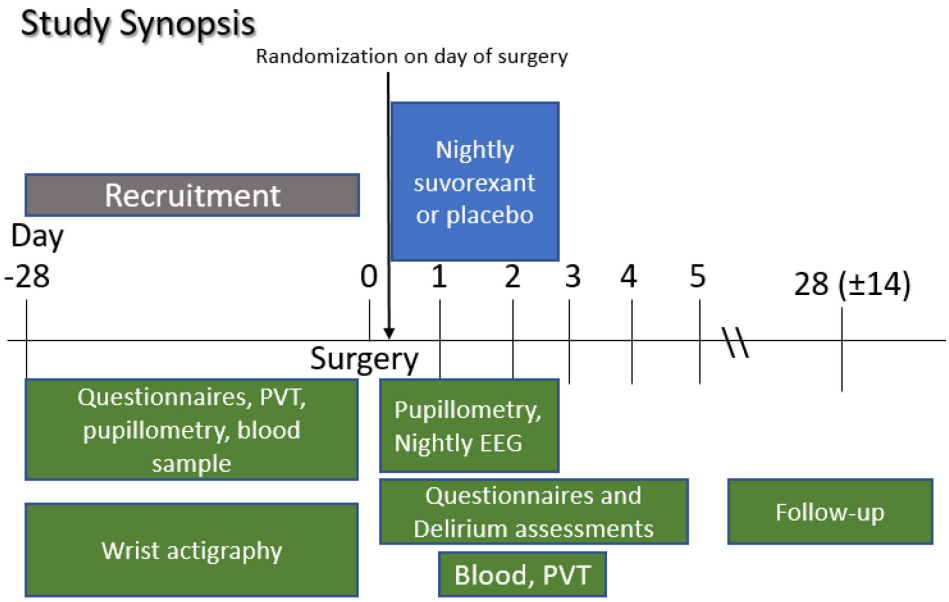


Table 1: Study Synopsis

3.2 Primary Study Endpoints

Total sleep time (TST) on the first postoperative night that study medication is received, as measured by electroencephalography (EEG) with the Dreem 3 headband. Total sleep time includes amount of time in sleep during the lights out period (defined between 21:00 and 06:00).

3.3Secondary Study Endpoints

Peak 3D-CAM postoperative delirium severity scores up through postoperative day 5 or discharge, whichever occurs first, in patients receiving suvorexant vs placebo

3.4 Exploratory endpoints

Objective sleep measures

- Average total sleep time over nights of postoperative day 0, 1, and 2 as measured by EEG in patients receiving suvorexant vs placebo.

Subjective sleep measures:

- Average postoperative Richards-Campbell subjective sleep quality scores over postoperative days 1,2,3,4 and 5 in patients receiving suvorexant vs placebo

Other endpoints:

1. Overall postoperative length of stay in patients receiving suvorexant vs. placebo.
2. Average postoperative resting pupil diameter fluctuations in patients receiving suvorexant vs. placebo.
3. Average response latency on psychomotor vigilance testing postoperatively in patients receiving suvorexant vs. placebo

Potential effect modifiers:

1. Long (>8 hours average) vs. short (< 6 hours average) sleep preoperative sleep duration as measured with wrist-watch actigraphy for at least 3 nights and up to 6 weeks before surgery
2. High (upper quartile) vs. low (lower quartile) preoperative resting pupil diameter fluctuations as measured with pupillometer before surgery
3. High (upper quartile) vs. low (lower quartile) average response latency on psychomotor vigilance testing preoperatively
4. Low (≤7) vs. high (≥8) insominia severity index scores measured before surgery

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Age 65 and older
2. Undergoing non-cardiac, non-intracranial surgery, any surgical procedure not involving the skull, brain, cerebrovascular structures
3. Scheduled postoperative inpatient overnight stay
4. Able to give informed consent or has legally authorized representative able to give informed consent on their behalf
5. English-speaking

4.2 Exclusion Criteria

1. Inmate of correctional facility
2. Body mass index> 40
3. Legal blindness
4. Unable to perform study related questionnaires and assessments
5. Use of outpatient sedating sleep aids > 2 times per any week in 1 month preceding day of surgery. Sedating sleep aids, listed in section 5.5.
6. History of psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform or brief psychotic disorder.
7. History of liver failure with documented international normalized ratio (INR) of >1.2 or with history of hepatic encephalopathy
8. History of severe sleep apnea or obesity hypoventilation syndrome requiring home bilevel positive airway pressure therapy or home ventilator or other forms of noninvasive ventilation
9. Chronic lung disease requiring home oxygen therapy
10. History of narcolepsy
11. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inhibitors within 1 week prior to surgery, listed in section 5.5.
12. Current or planned administration of digoxin, or is currently experiencing digoxin toxicity
13. Undergoing surgery that will result in inability to take medications by mouth including laryngectomy, tracheostomy, and oral resection/reconstructive surgery
14. Undergoing surgery that will require postoperative strict bowel rest, including gastrectomy, esophagectomy, and pancreaticoduodenectomy

15. Undergoing surgery in an area that will make it unsafe to wear a headband, such as scalp or forehead procedures.
16. Inappropriate for study inclusion based on the judgement of the principal investigator.

4.3 Subject Recruitment and Screening

Potentially eligible patients will be identified in the electronic medical record by a report, and those patients will be sent an automated message through Duke's MyChart application briefly describing the study and including a link to contact the study team if they are interested in participating. Patients will be consented before study activities begin.

If the surgical patient is admitted prior to surgery, the patient or their LAR will be approached and ask whether they are interested in hearing about the study. If the patient is not admitted before surgery, the patient or LAR will be approached in one of the preoperative screening clinics, or approached via a phone call by a member of the study team using an IRB approved phone script. If the subject or LAR is interested in participating in the study, a study team member will explain the purpose, procedures, and intent of the study to each potential study subjects or LAR. Written informed consent must be obtained before the subject can begin any screening procedures that are not considered standard patient care

We will enroll participants of both sexes and all ethnicities and racial groups.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

At any time, a subject may be withdrawn from the study at the discretion of the PI.

In the case that study drug is discontinued for any reason after randomization, participants will still be encouraged to remain in the study to continue the other study-related assessments

If the patient withdraws consent to participate in the study, the subject will be withdrawn from the study. Consent to obtain data from the electronic medical record will be attempted per section 4.4.3.

4.4.2 When to Withhold Study Drug

The study drug will be withheld in the following circumstances:

1. If the subject has received a strong CYP3A inhibitor (see Section 5.5 for a complete list of CYP3A) within 12 hours prior to scheduled study drug administration time.
2. If the subject is scheduled to receive digoxin within 24 hours after administration of study drug or is currently experiencing digoxin toxicity.

3. If the subject is receiving 8 liters or greater of oxygen via nasal cannula at the time of study drug administration.
4. The subject cannot receive medications by mouth or enteric feeding tube at the time of study drug administration.
5. If at any time during the dose period, participant safety is considered at risk due to study drug-related adverse events per the judgement of the PI

Study drug will be administered at half dose in patients who have received a moderate CYP3A inhibitor within the past 12 hours from study drug administration.

In the case that study drug is withheld for any reason on any given day after randomization, participants will be assessed for study drug eligibility on subsequent administration times and will continue the other study-related assessments, pending the discretion of the study PI.

4.4.3 Data Collection and Follow-up for Withdrawn Subjects

If study drug is discontinued after randomization, the subject will be asked for permission to record data and other study-related assessment until the end of the follow-up period, because important information about sleep and study outcomes can be ascertained from study-related assessments. These assessments include the nightly EEG, twice daily delirium assessments, psychomotor vigilance task, pupillometry, and questionnaires. Additionally, if a subject no longer wishes to participate in particular study activities, those activities will not be performed, but the subject will be asked permission to continue other study-related assessments until the end of the follow-up period, because important information about sleep and study outcomes can be ascertained from study-related assessments.

The study subject can opt out of any assessments at their discretion and remain in the study. Additionally, early withdrawal could be related to the study drug and it is important to understand factors related to withdrawal from the study and study drug administration. If the subject wishes to opt entirely out of the study, the subject will be asked permission to record data from the electronic medical record so that hospitalization and recovery factors related to study drug administration can be ascertained.

5 Study Drug

5.1 Description

Suvorexant 10 mg green tablets and matching placebo will supplied by Merck. The medication will be stored at 20-25 degrees Celsius. Dosing labels will be attached to each study drug dose and include pre-printed fields with

- Protocol number
- Personal ID number
- Participant initials
- Date
- Time

5.2 Treatment Regimen

Eligibility to receive study drug will be determined by clinical research staff based on study inclusion and exclusion criteria. Study drug (i.e., 2 tablets of suvorexant 10 mg vs two tablets of placebo) will be given via mouth or via feeding tube nightly between 21:00 and 22:00 (±30 min) for the first 3 postoperative nights or until hospital discharge, whichever occurs first. In the case that participants are not able to take medications by mouth due to difficulty swallowing, the medication can be administered via an indwelling nasogastric or gastrostomy tube, if one is already present and is usable. In the case that the patient cannot receive enteric medications (i.e., strict NPO) by study drug administration time, then the study drug will not be administered.

- If the patient has received a moderate CYP3A inhibitor within the last 12 hours, the study drug dose will be halved by the investigational drug services (i.e., one tablet of suvorexant 10 mg vs. placebo will be provided and administered).

- If the patient has received a strong CYP3A inhibitor within 12 hours prior to study drug administration, the study drug will not be given to the subject.

5.3 Method for Assigning Subjects to Treatment Groups

Stratified permuted block randomization 1:1 to suvorexant vs placebo will be performed to assign patients to blinded treatment groups. The randomization will be stratified by age and sex. The randomization to study drug will be performed by our investigational pharmacy using age by sex strata tables provided by our study statistician, and the study team will be blinded to treatment allocation. Randomization will occur on the day of surgery.

5.4 Subject Compliance Monitoring

The patient care nurse will administer the study drug and document the time of administration in the electronic medical record.

Compliance with nightly EEG will be monitored daily via interrogation of the Dreem Headband 3 data.

5.5 Prior Therapy

Prior Therapy:
Preoperative medication use will be gathered from the electronic medical record. Prior to consent, potential subjects will be asked whether they are taking any of the strong or moderate CYP3A inhibitors, digoxin or CYP3A inducers. If they are currently taking these medications, then they are not eligible for the study. Additionally, patients will be asked whether they are taking medications to help them sleep, and how often that they take that medicine. If they have required any sedating sleep medicines greater than 2 times per week within the last month, they are not eligible for the study.

Moderate CYP3A inhibitors: Amprenavir, Aprepitant, Atazanavir, Ciprofloxacin, Diltiazem, Erythromycin, Fluconazole, Fosamprenavir, Imatinib, Verapamil.

Strong CYP3A inhibitors: Ketoconazole, Itraconazole, Posaconazole, Clarithromycin, Ritonavir, Saquinavir, Nelfinavir, Indinavir, Boceprevir, Telprevir, Telithromycin, Conivaptan

Moderate/Strong CYP3A inhibitors: Apalutamide, Carbamazepine, Enzalutamide, Ivosidenib, lumacaftor, Mitotane, Phenytoin, Rifampin, St. John's wort, Bosentan, Cenobamate, Dabrafenib, Efavirenz, Etravirine, Lorlatinib, Pexidartinib, Phenobarbital, Primidone, Sotorasib.

Sedating sleep aids: Mirtazapine, Trazodone, Flurazepam, Temazepam, Triazolam, Estazolam, Quazepam, Clonazepam, Lorazepam, Midazolam, Alprazolam, Diazepam, Zolpidem, Zaleplon, Eszopiclone, Diphenhydramine, Doxylamine, Hydroxyzine, Suvorexant, Doxepin

Concomitant Therapy:
For enrolled subjects, the primary clinical team (anesthesia and surgical teams) will be instructed to avoid administration of moderate or strong CYP3A4 inhibitors unless there is no equivalent alternative therapy. During the study period, the electronic medical record will be checked in the evening up to 4 hours prior to release of the study drug to assess whether the patient had received any moderate or strong CYP3A inhibitors within 12 hours prior to study drug administration time.

- If the patient has received a moderate CYP3A inhibitor within the last 12 hours, the study drug dose will be halved by the investigational drug services.

- If the patient has received a strong CYP3A inhibitor within 12 hours prior to study drug administration, the study drug will not be given to the subject.

The subject will still be eligible to receive future drug doses on subsequent postoperative nights until postoperative night 3, as long as they meet criteria listed above (e.g., no strong CYP3A inhibitor within last 12 hours from study drug administration time).

Non-sedating concomitant pharmacologic sleep aids such as melatonin and ramelteon are permitted at any time during the study. Sedating sleep aids are not permitted postoperatively during nights that study drug will be administered unless the patient exhibits sleeplessness and is requesting additional pharmacologic sleep aids. In this case, additional sleep aid is permitted starting 1 hour after the study drug has been delivered up until midnight. After midnight, no further administration of sedating sleep aids (for sleeplessness) are permitted. Administration of sedating sleep aids for other medical indications are permitted at any time (e.g., administration of midazolam for seizures, diphenhydramine for itching, etc.).

5.6 Packaging

Suvorexant 10 mg tablets and matching placebo will supplied by Merck in bottles. The bottles will be labeled with a unique ID.

5.7 Blinding of Study Drug

Dosing labels will be attached to each study drug dose and include pre-printed fields with

- Protocol number
- Personal ID number
- Participant initials
- Date
- Time

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Upon receipt of the study drug from Merck, an inventory will be performed by Investigational Drug Services (IDS) Pharmacy and a drug receipt log will be completed and signed by the personnel receiving the shipment. The counts of placebo and suvorexant tablets will be recorded. Damaged and unusable study drug in a given shipment will be documented in study files. Merck will be notified of any damaged or unusable study treatments that were supplied.

5.8.2 Storage

The study drug will be stored in IDS pharmacy at controlled room temperature between 20°C to 25°C in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access. Temperature excursions permitted to 15°C to 30°C, in the original package until use to protect from light and moisture. There are no special handling requirements.

5.8.3 Dispensing of Study Drug

IDS pharmacy will maintain a Study Drug Dispensing Log. The following information will be recorded:

- Total amount of study drug dispensed (quantity of tablets dispensed)
- Identification (study number and initials) of the patient to whom the study drug was dispensed;
- Initials of the person who dispensed the study drug;
- Initials of the person who received the study drug for administration to the patient

5.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated,

resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

Table 2: Schedule of Events:

	Consent	Preop	Postop day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5	Postop week 4
	Visit 1	Visit 2[2]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Enrollment									
Informed Consent	X								
Demographics & History	X								
Confirm Inclusion/Exclusion	X	X[3]							
Questionnaires									
Montreal Cognitive Assessment (MOCA)		X[3]							
Pittsburgh Sleep Quality Index (PSQI)	X								
Insomnia Severity Risk Index	X								
Epworth Sleepiness Scale	X								
Delirium Assessment	X		X[4]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	
Modified Richards-Campbell Sleep Quality				X[4]	X[4]	X[4]	X[4]	X[4]	
Medications									
Suvorexant vs. placebo			X[4]	X[4]	X[4]				
Randomization		X							
Procedures									
Nightly EEG			X[4]	X[4]	X[4]				
Wrist actigraphy	X[1,2]								
Psychomotor vigilance task (PVT)		X[3]		X[4]	X[4]				
Pupillometry		X[3]	X[4]	X[4]	X[4]				
Blood sampling		X[3]		X[4]	X[4]				
Other									
Adverse Event review		X	X	X	X	X	X	X	X[6]
Medication Review	X	X[3]	X	X	X	X	X	X	
Notes									

[1]Will be performed if adequate time before surgery
[2]Visit 1 and 2 activities may be performed at same time
[3]These activities may be performed during visit 1 or anytime between visit 1 and surgery start.
[4]These activities will not be performed after hospital discharge
[5]Performed twice daily
[6]To occur 4 weeks ± 2 weeks after surgery via phone call

Questionnaires:

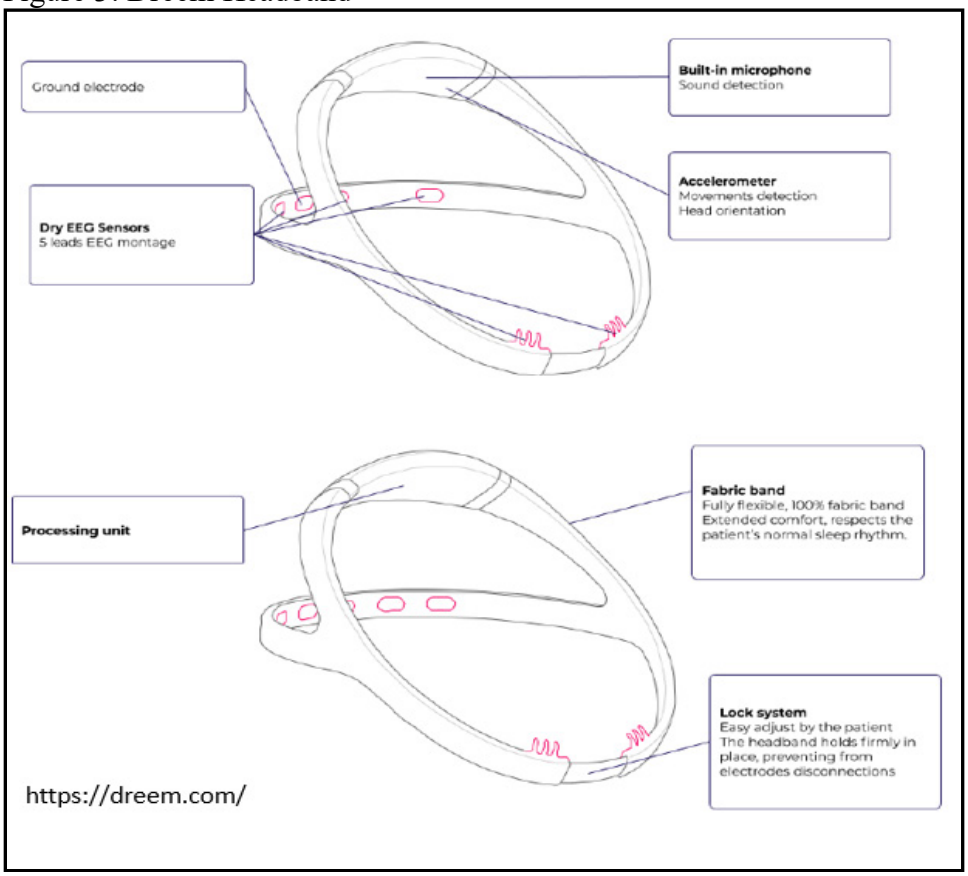
1) Montreal Cognitive Assessment (MOCA): used to measure baseline cognitive performance and screen for cognitive impairment. If this assessment is unable to be done in a study visit or over web-conferencing, then the MOCA questionnaire will be at later time after consent prior to surgery, such as on the day of surgery in preoperative holding.
2) Pittsburgh Sleep Quality Index (PSQI): a questionnaire that assesses sleep quality and disturbances over a 1-month time interval, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction
3) Insomnia Severity Index (ISI): Assesses the nature, severity, and impact of insomnia
4) Epworth Sleepiness Scale: a questionnaire that assesses excessive daytime sleepiness
5) Delirium will be assessed with the 3-minute diagnostic interview for confusion assessment method (3D-CAM) in patients who are able to communicate verbally. In non-verbal or intubated patients, the confusion assessment method for the intensive care unit (CAM-ICU) will be used in place of the 3D-CAM instrument. Delirium will be assessed between once daily prior to 21:00 starting on postoperative day#0 and will continue twice daily in the morning (prior to noon) and then in the afternoon sometime before 21:00 until the end of postoperative day #5, or hospital discharge, whichever occurs first.
6) Modified Richards-Campbell sleep quality: self-report questionnaire that assesses perceived sleep depth, sleep latency, number of awakenings, sleep efficiency, quality in addition to the number of hours of daytime napping the day prior. This questionnaire will be administered until the end of postoperative day #5, or hospital discharge, whichever occurs first.

Relevant tests listed above may be recorded using a digital voice recorder for quality assurance purposes. Quality assurance activities will include reviewing of testing audio files, generating performance review documents, and providing feedback on accuracy and completeness. There is no risk to the trial participants since participant identifiers will not be provided. Trial participants will not be identified by name on the recording. Only the trial number, test date, and initials of the tester will be provided on the digital file label. The link between trial number and participant identifiers will be maintained. These files will be stored on locked computers within locked offices to which only authorized research personnel will have access.

Nightly EEG:

After surgery, nightly EEG will be collected using the Dreem Headband 3 (Figure 3) approximately between 9PM-6AM on the nights of postoperative day 0, 1, and 2, or until hospital discharge, whichever occurs first. The Dreem headband 3 includes dry frontal and occipital EEG electrodes in addition to head accelerometry to determine sleep stage and total sleep time. These devices will be cleaned with isopropyl alcohol between assessments.

Figure 3: Dreem Headband



Wrist Actigraphy:
When there is enough time prior to surgery, wrist-watch actigraphy with the Actigraph wGT3X-BT will be attempted for ≥ 3 nights prior to surgery up to 6 weeks prior to surgery to measure sleep patterns and duration. By measuring motion with the actigraph (wrist-watch accelerometer), patterns of inactivity that reflect periods of sleep are quantified. This enables quantification of sleep during any period throughout the day/night, permitting a comprehensive understanding of sleep timing and patterns (i.e., circadian rhythms). The device will be collected when the patient presents for their surgery. Preoperative actigraphy will be performed for up to 6 weeks prior to surgery to provide information on preoperative total sleep duration. If the participant is unwilling, or the equipment is unavailable, the wrist actigraphy will not be performed.

Psychomotor Vigilance Task (PVT):
The 5-minute psychomotor vigilance task (PVT) is a measure of alertness and sustained attention that will be obtained using an electronic device that displays a stimulus image at random times, such as a shape on the screen. The participant is instructed to press a button as soon as they see the stimulus (i.e., shape on screen). Reaction times to the stimulus, lapses (missed stimuli), and errors are recorded electronically throughout the 5-minute test, which will be performed in a quiet room without interruptions. The data recordings will be recorded in a file that is labeled with the patient study number and date but no identifying information on the electronic tablet

computer, and the file will be transferred to a secure server after the test. The PVT will be performed in the morning sometime before 12:00. If the participant is unwilling, or the equipment are unavailable, the psychomotor vigilance task will not be performed.

Pupillometry:
Pupillometry measurements will also be obtained at the preoperative study visit or alternatively on day of surgery, if the equipment is available. Pupil measurements will be performed using the NeuroLight infrared pupillometer sold by IDMed. This device is 510K exempt by the FDA and is already being commercialized in the United States for pupil measurements in the intensive care unit setting. Up to three measurements of pupil diameter fluctuations at ambient light will be performed in each eye during each measurement. Subsequently, pupillary constriction to light will be assessed with the device. We expect these measurements to take about 5 minutes on average and no longer than 10 minutes. Patients who are blind or cannot tolerate pupil measurements will be excluded from these assessments but not from the study. Inability to undergo pupil measurements will not prohibit the subject from participating in any other study-related activity. If the participant is unwilling, or the equipment is unavailable, pupillometry will not be performed.

Blood Sampling:
Blood samples will be used for metabolic/inflammatory marker assays. Whole-blood (10mls at each time point) will be collected on the day of surgery before incision, and on the mornings of postoperative day 1 and 2, between 8AM and noon. A total of 30mls of blood will be collected for this study. Blood samples will be collected either from an arterial or IV catheter, or from sterile venipuncture, into a purple top EDTA tube. After collection, the sample will be placed on ice, and then spun in a centrifuge at 4°C at 3500 RPM for 15 minutes. Samples will be aliquoted intro cryovials and placed into -80°C freezer. All assay measurements will be performed at DUMC or in the accredited laboratory of a collaborator. All blood samples will be held in freezers in the Department of Anesthesiology and/or DUMC research facilities.

6.1 Visit 1 – Consent

During this visit, the study will be explained in detail to the patient, or a legally authorized representative, and informed consent will be obtained. This visit can occur in person, via secure video web conferencing, or over the telephone.

- Verify eligibility based on inclusion/exclusion criteria
- Obtain voluntarily given, written informed consent from subject or LAR
- Record demographics, medical history, and current medication list
- MOCA
- PSQI
- Insomnia Severity Index
- Epworth Sleepiness Scale
- Delirium assessment
- Wrist actigraphy if sufficient time prior to surgery
- Psychomotor vigilance task

- Pupillometry
- Medication review

6.2 Visit 2 – Preoperative

- Confirm inclusion/exclusion criteria
- MOCA, if not completed at consent visit
- Randomization
- Psychomotor vigilance task, if not completed at consent visit
- Pupillometry, if not completed at consent visit
- Blood sampling
- Adverse event review
- Medication review

6.3 Visit 3 – Postoperative Day of Surgery

- Delirium assessment
- Confirm eligibility to receive study drug
- Study drug administration (between 21:00-22:00 ± 30 min)
- Nightly EEG
- Pupillometry
- Adverse event review
- Medication review

  If the patient is discharged at this time, the study drug will not be administered and no further assessments will be completed until the 4-week visit.

6.4 Visit 4 and 5 Postoperative days 1-2

- Delirium assessment (twice daily)
- Richards-Campbell Subjective Sleep Quality assessment (in morning)
- Confirm eligibility to receive study drug
- Study drug administration (between 21:00-22:00 ± 30 min)
- Nightly EEG
- Psychomotor vigilance task
- Pupillometry
- Blood sampling
- Adverse event review
- Medication review

If the patient is discharged at this time, the study drug will not be administered and no further assessments will be completed until the 4-week visit.

6.5 Visit 6 Postoperative day 3

- Delirium assessment (twice daily)
- Richards-Campbell Subjective Sleep Quality assessment (in morning)
- Blood sampling

- Psychomotor vigilance task
- Pupillometry
- Adverse event review
- Medication review

If the patient is discharged at the time of assessment, no further assessments will be completed until the 4-week visit.

6.6 Visit 7 and 8 – Postoperative Days 4 and 5

- Delirium assessment (twice daily)
- Richards-Campbell Subjective Sleep Quality assessment (in morning)
- Adverse event review
- Medication review

If the patient is discharged at the time of assessment, no further assessments will be completed until the 4-week visit.

6.7 Visit 9 – 4-week (+/- 2 week) telephone call

Study patients will be contacted over the phone to assess for adverse events since discharge from the hospital.

7 Statistical Plan

7.1 Sample Size Determination

Based on American Academy of Sleep Medicine insomnia clinical practice guidelines, we will consider a 20 minute difference in TST a clinically meaningful difference.[25] Given a standard deviation (SD) of approximately 35 min for TST in healthy adults,[26] a sample size of 58 subjects per group will provide 86% power to detect a 20 minute difference in TST between treatment groups using a two-sample t-test with a two-sided alpha= 0.05. Although few older surgical patients have dementia (<5% in our prior studies), it is still possible that the TST SD will be greater than 35 min in our older cohort. Even if our measured TST SD approaches 57 min, approximating the SD of TST found in dementia patients,[16] we would have 80% power to detect a 30 min difference in TST in our study. A 30 min difference in TST is a clinically meaningful effect, as it was recently shown in a study of older dementia patients treated with suvorexant.[16]

7.2 Statistical Methods

Our primary analysis of sleep will be conducted on a modified intent to treat basis using data collected on the first postoperative night that the participant received a dose of study drug. The total sleep time and the peak postoperative delirium severity score will be compared between suvorexant and placebo groups using a two-sample t-test, and subsequent multivariable linear regression. Sensitivity analyses will be performed on the full intent-to-treat population, on the per-protocol cohort, and restricted to those who did

not receive any additional pharmacologic sleep aid and/or sedatives during the first 3 postoperative nights.

Covariates chosen for the multivariable modeling will explore potential effect modifiers and include insomnia severity index score as the main variable of interest. Further precision variables including preoperative performance on the MOCA, excessive daytime sleepiness measured with Epworth sleepiness scale, and poor preoperative sleep habits measured with the Pittsburgh sleep quality index will also be considered.

Exploratory analysis of the effect of suvorexant administration on postoperative delirium incidence will be performed by chi-squared tests and logistic regression. Mixed model regression analyses will be used to explore the effect of suvorexant administration on 1) subjective sleep quality as measured with average postoperative Richards-Campbell sleep quality scores 2) postoperative pupil diameter fluctuations 3) average response latency on postoperative psychomotor vigilance testing and 4) total average electrographic sleep time over nights of postoperative day 0, 1, and 2.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

AE Classification The following definitions were based on guidelines provided by the Office for Human Research Protections (OHRP). The following URL provides useful examples to help clarify classification of adverse events https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

An AE is deemed an unanticipated problem if it is not expected given (a) the known or foreseeable risk of the study procedures that are described in the informed consent document or study protocol, (b) the characteristics of the population being studied, (c) related or possibly related to participation in the study, and (d) suggests the research places subjects are greater risk of harm than previously known.

The following adverse events are expected in this study population: nausea, vomiting, increased incisional pain, wound hernia, wound dehiscence, abscess formation, pressure sores, muscular pain, sore throat, endobronchial aspiration, hoarseness, teeth trauma, ulceration of lips/mouth/pharynx, vocal cord paralysis, trauma to lips/mouth/pharynx, dry mouth, eye trauma, corneal abrasion, blood loss anemia, wound infection, acute respiratory failure requiring prolonged mechanical ventilation, sepsis, fever, septic shock, perforation of intra-abdominal viscus, peritonitis, diarrhea, nerve injury, ileus, mechanical bowel obstruction, dysphagia, deep vein thrombosis, pulmonary embolism, pneumonia, respiratory depression, acute hypercapnic respiratory failure, acute hypoxic respiratory failure pulmonary atelectasis, urinary retention, urinary tract infection, sleeplessness, allergic reaction to medication, lower extremity edema, hypotension, supraventricular tachycardia, ventricular tachycardia, myocardial infarction, acute renal failure, stroke, acute confusion, delirium, somnolence, agitation, and malnutrition due to protein-calorie intake deficiency.

Adverse reactions potentially associated with suvorexant use include:

- worsening of suicidal ideation
- complex sleep behaviors including sleep-walking
- sleep paralysis and cataplexy-like symptoms
- central nervous system depression and daytime impairment

Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 4 weeks (+/- 2 weeks) following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management, e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to Merck within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the Merck within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by facsimile to: 215-661-6229 or toll-free fax 1-800-547-5552. Merck will confirm receipt of the report within one business day.

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 IRB Notification by Investigator

Reports of serious adverse events that are unexpected and related to study drug must be submitted to the IRB and Sponsor within 24 hours. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA of any unexpected fatal or life-threatening experience causally associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information. Other serious, unexpected adverse events associated with the use of study drug shall be reported to the FDA no later than 15 calendar days from the sponsors' original receipt of the information. SAEs that are expected and/or unrelated to study drug will be reported annually.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

In the case that three unexpected, related SAEs are reported in this study, the enrollment of new participants will be halted and the unblinded staff statistician can perform analyses to determine whether these related SAEs are associated with suvorexant vs. placebo. This information then can be used by the medical monitor to decide whether to continue the study or halt it.

8.5 Stopping Rules

There are no predetermined stopping rules for efficacy. A staff statistician that will not perform analyses related to this study will be unblinded to treatment assignment. Additionally, a staff pharmacist at the investigational drug pharmacy will be unblinded to treatment assignment. None of these staff members will participate in study-related assessments or analyses. We will monitor closely for SAEs. In the case that three unexpected, related SAEs are reported in this study, the unblinded staff statistician will perform analyses to determine whether these related SAEs are associated with suvorexant vs. placebo. This information then will then be used by the medical monitor to decide whether to continue the study.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious

adverse events. A medical monitor will be designated to review unexpected severe adverse events to determine if they are related or unrelated to the study drug. This study will be subject to Duke Clinical Quality Management (CQM) policy and will have designated review.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a authorization signed by subject informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, electronic medical record, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the Duke Clinical Quality Management Plan (CQMP). The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before

commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through an investigator-initiated grant from Merck. Merck will provide Suvorexant to subjects free of charge.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the University conflict of interest policy.

13 Publication Plan

The intent is to publish our data in per-reviewed scientific literature. Affiliations and inclusion of study support will be transparent. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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