A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Suvorexant for Insomnia in Parkinson Disease

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List of Abbreviations

AE	Adverse Event
AHI	Apnea-Hypopnea Index
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory – II
CBC	Complete Blood Count
CGI-C	Clinician's Global Impression of Change
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A	Cytochrome P450, 3A
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ENI	EvergreenHealth Neuroscience Institute
ESS	Epworth Sleepiness Scale
FDA	United States Food and Drug Administration
FEV1	Forced Expiratory Volume, 1 second
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose, Throat
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
ISI	Insomnia Severity Index
LEDD	Levodopa Equivalent Daily Dose
LPS	Latency to Persistent Sleep
MDS	Movement Disorder Society

MDS-UPDRS	MDS Unified Parkinson Disease Rating Scale
mHY	Modified Hoehn & Yahr Scale
MoCA	Montreal Cognitive Assessment
OSA	Obstructive Sleep Apnea
PD	Parkinson Disease
PFT	Pulmonary Function Test
PO	Per os (by mouth)
PRN	Pro re nata (as needed)
PSG	Polysomnogram
QHS	Quaque hora somni (every night at bedtime)
RBD	REM Sleep Behavior Disorder
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SGI-C	Subject's Global Impression of Change
UKBB	United Kingdom Parkinson Disease Society Brain Bank
WASO	Wakefulness After Sleep Onset
WPDR	Washington State Parkinson Disease Registry
WSM	Wearable Sleep Monitor

1. SYNOPSIS

1.1 Study Title

A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Suvorexant for Insomnia in Parkinson Disease

1.2 Study Drug

Suvorexant 10-15 mg PO QHS

1.3 Study Subjects

20 subjects with Parkinson disease (PD) and insomnia

1.4 Study Design

Multiple-dose, randomized, placebo-controlled prospective, single-site, investigator-initiated trial.

1.5 Study Overview

The proposed study is a randomized, double-blind, placebo-controlled, cross-over trial to assess the safety, tolerability, and efficacy of suvorexant specifically in a cohort of 20 PD patients between the ages of 30 and 80 (inclusive) who have a complaint of insomnia. After informed consent is given, potential subjects will be screened to ensure they meet eligibility criteria. This will include an overnight polysomnogram (PSG), which will serve both as a baseline and a screening PSG. Active drug will be suvorexant 10 mg po QHS with an optional up-titration to 15 mg po QHS after 2 weeks. The first treatment period will be 4 weeks long, in which subjects will be randomized 1:1 to receive active drug or matching placebo. At the end of treatment period 1, subjects will undergo efficacy assessment with repeat PSG and clinical scales. This will be followed by a 2-week washout period with placebo; this period only will be single-blinded, as subjects only will be blinded to treatment. Subjects will then be crossed over into the alternate treatment group, which will once again be double-blinded; those on active treatment for period 1 will be switched to placebo, and those on placebo in period 1 will be switched to active treatment. Treatment period 2 will also be 4 weeks long, and at the end of this, subjects will undergo final assessment with PSG and clinical scales.

All subjects, whether in placebo or active arm, will receive a wearable sleep monitor to be worn continuously throughout the study. The subjects will be allowed to keep the wearable sleep monitor in lieu of a monetary reimbursement for Office Visit 1; subjects will receive a small monetary reimbursement per visit for each office visit after Office Visit 1.

1.6 Study Hypothesis

1.6.1 Primary hypothesis

Suvorexant will provide greater improvement in sleep, as measured by polysomnographic parameters and symptom rating scales, compared to placebo, with no clinically significant increase in adverse events.

1.6.2 Secondary Hypotheses

- On nights of PSG, total hours of sleep and WASO as measured by a wearable sleep monitor will not be significantly different from those values as measured by PSG.
- Suvorexant will not worsen motor symptoms or non-motor symptoms of PD compared to placebo; motor signs and motor and non-motor symptoms will be assessed by the Movement Disorder Society's Unified Parkinson Disease Rating Scale; specific non-motor symptoms will be assessed by the Beck Depression Inventory, the Beck Anxiety Inventory, and Montreal Cognitive Assessment; REM behavior disorder will be assessed by muscle tonicity during PSG.

1.7 Study Timeline

Each subject's participation in this study will last 11-15 weeks. This includes a 1- to 5-week screening period (depending on the scheduling of the initial PSG), two 4-week treatment periods, and a 2-week washout period between the treatment periods.

1.8 Treatment Regimen

1.8.1 Treatment Period 1

Group A will receive suvorexant 10 mg to be taken by mouth every night, at most 30 minutes before the intended bedtime and at least 7 hours before the intended time of awakening. At Phone Visit 2, those who are eligible to up-titrate will be instructed to begin taking an additional 5-mg tablet, for a total of suvorexant 15 mg by mouth every night.

Group B will receive placebo that matches suvorexant 10 mg with the same instructions. At Phone Visit 2, those who are eligible to up-titrate will be instructed to begin taking an additional placebo matching the suvorexant 5 mg tablet.

1.8.2 Treatment Period 2

The regimen will be the same as in treatment period 1 but the groups will be reversed.

1.9 Inclusion and Exclusion Criteria

1.9.1 Inclusion Criteria

An eligible patient:

- Has signed and dated an IRB-approved informed consent form before any protocol-specific screening procedures are performed;
- Has a diagnosis of Parkinson disease according to the United Kingdom Parkinson Disease Society Brain Bank Criteria (UKBB);

- Has a modified Hoehn and Yahr (mHY) Stage of 1-3, inclusive;
- Is aged 30-80 years old, inclusive;
- Has had no change in PD medications during the 4 weeks preceding screening, with no dose changes during the study, except that PRN (as needed) doses of carbidopa/levodopa will be allowed to address periodic worsening of parkinsonian symptoms;
- Is willing and able to complete PSG;
- Is willing and able to abstain from alcohol, caffeine, and marijuana for 6 hours prior to and during each study-related PSG;
- Is willing and able to abstain from products containing nicotine during each study-related PSG;
- Has Insomnia Disorder defined by diagnostic criteria published in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); namely, subject report of all of the following:
    - One of the following: difficulty initiating sleep; difficulty maintaining sleep; or early morning waking;
    - Sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning;
    - Sleep difficulty has occurred on 3 or more nights per week;
    - Sleep difficulty has been present for at least the past 3 months;
    - Sleep difficulty occurs despite adequate opportunity for sleep;
    - Insomnia is not explained by another sleep disorder;
    - Insomnia is not attributable to physiological effects of a consumed substance;
- On screening PSG, has a latency to persistent sleep $\geq$ 20 minutes OR total wakefulness after sleep onset $\geq$ 45 minutes;
- May use other medications that could influence sleep, other than those specifically prohibited, as long as the dose is stable for 4 weeks preceding screening, with no dose changes during the study; and
- Has valid health insurance coverage at the time of study enrollment and expects this coverage to remain valid for the duration of the study period.

1.9.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following:

- Is a woman who is breast-feeding, pregnant, or has the potential to become pregnant during the course of the study (fertile and unwilling/unable to use effective contraceptive measures);
- Has an implanted deep brain stimulator;
- Has a history of narcolepsy;
- Has a diagnosis of severe COPD, defined by FEV1 < 50% of predicted on most recent available pulmonary function test (PFT) (a PFT is not required if the subject has never been diagnosed with COPD);

- Has a history of severe obstructive sleep apnea (OSA) or evidence of severe OSA on screening PSG, with severe OSA defined as having an apnea-hypopnea index (AHI) > 30;
- Is concurrently using other CNS depressants, including alcohol, except that one alcoholic drink per day will be allowed for those with normal hepatic function provided the drink is consumed at least 2 hours prior to or 8 hours after taking the study drug, and no alcohol will be permitted for 6 hours before PSG visits;
- Is concurrently using digoxin;
- Is concurrently using any moderate or strong inhibitor of CYP3A;
- Is concurrently using any strong inducer of CYP3A;
- Has evidence at screening of severe hepatic impairment as defined by a Child-Pugh score > 10;
- Has evidence at screening of severe cognitive impairment as defined by a MoCA score < 15, or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent.
- Has evidence at screening of suicidal ideation in the past 6 months as defined by a positive response to any one of Questions 2-5 on the Columbia Suicide Severity Rating Scale (C-SSRS); or of a lifetime history of suicidal behavior as defined by any positive response to the suicidal behavior section of the C-SSRS.

1.9.3 Note on the Use of the Wearable Sleep Monitor

Of note, inability or unwillingness to use the WSM is specifically *not* an exclusion criterion. Those subjects who are unable or unwilling to use the WSM correctly will be allowed in the study (provided all eligibility criteria are otherwise met), and the observations from their WSM variables will be treated as missing data.

1.10 Efficacy Assessment

1.10.1 Primary Outcome Measure

The primary outcome measure will be sleep efficiency as measured by PSG, defined as (total sleep time / total time in bed) * 100%

1.10.2 Secondary Outcome Measures based on PSG

Secondary outcome measures based on PSG will include:

- Wake after sleep onset
- Latency to persistent sleep
- Muscle tonicity (as measure of REM Behavior Disorder)

1.10.3 Secondary Outcome Measures based on Clinical Rating Scales

The following clinical rating scales will be administered as secondary outcomes measures:

- Insomnia Severity Index
- Epworth Sleepiness Scale
- Subject's Global Impression of Change
- Clinician's Global Impression of Change.
- Montreal Cognitive Assessment
- Beck Depression Inventory
- Beck Anxiety Inventory
- MDS-UPDRS Total Score
- MDS-UPDRS Part 1 (Non-Motor) Score
- MDS-UPDRS Question 1.7 (Sleep Problems) Score
- MDS-UPDRS Question 1.8 (Daytime Sleepiness) Score

1.10.4 Secondary Outcome Measure based on Wearable Sleep Monitor

The secondary outcome measure based on the wearable sleep monitor (WSM) will include:

- Total hours of sleep per night, mean over final 7 nights of treatment period compared to mean over final 7 nights of screening period
- Wakefulness after sleep onset (WASO), mean over final 7 nights of treatment period compared to mean over final 7 nights of screening period

1.11 Statistical Methods

Analysis of primary and secondary outcome measures will include:

- Summary statistics (n, mean, standard deviation, median, minimum and maximum) at baseline, Office Visit 3 and Office Visit 5 by treatment.
- For clinical rating scales, summary of % change from baseline to Office Visit 3, from baseline to Office Visit 5, and from Office Visit 4 to Office Visit 5, by treatment
- For PSG variables, summary of % change from PSG 1 to PSG 2 and from PSG 1 to PSG 3, by treatment
- For wearable sleep monitor, summary of % change in total hours of sleep and WASO. Mean over the week prior to Office Visit 2 (baseline) will be compared to the mean over the final week of Treatment Period 1 and to the mean over the final week of Treatment Period 2. Mean over the week prior to Office Visit 4 (during washout) will be compared to the mean over the final week of Treatment Period 2. This will be done by treatment arm.
- Significance testing

The following characteristics will be summarized descriptively for placebo and drug groups:

- Demographics (age, gender, race)
- Parkinson disease characteristics at baseline (disease duration, date of onset, initial symptom, modified Hoehn and Yahr stage in the ON state, and MDS-UPDRS part 3 score in the ON state)

- Levodopa-equivalent daily dose (LEDD), calculated according to published formulae (Tomlinson 2010, Rytary Prescribing Information, Duopa Prescribing Information).

Outcome measures will be compared between groups using analysis of covariance (ANCOVA) or other method as deemed appropriate by the consulting statistician. Demonstration of superiority will depend on achieving statistical significance for the primary endpoint. Level of significance will be defined as $p = 0.05$. All statistical tests will be two-sided.

The study population will include all patients who pass screening and undergo randomization. Data will be analyzed in an intent-to-treat fashion.

This is an exploratory study. Therefore, a small sample size is appropriate. Any treatment effect could be used to power a future larger study.

Statistical analysis will be performed by a consulting statistician contracted with EvergreenHealth and whose services we have used on recent studies in PD.

1.12 Safety

Female subjects will undergo urine pregnancy testing if they are deemed to have any risk of being pregnant or becoming pregnant during the study. Baseline assessment of CBC, CMP, albumin, and INR will be conducted to address exclusion criteria.

Subjects will be monitored for adverse events throughout the trial in phone visits and office visits, both scheduled and unscheduled as needed. The occurrence of adverse events will be ascertained by observation, telephone monitoring if subjects call in, and by questioning by the investigator. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy). Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse events include adverse drug reactions, illness with onset during the study, exacerbations of pre-existing conditions or clinically significant changes in physical examination or significantly abnormal objective test findings. All adverse events will be recorded and graded as mild, moderate or severe by the principal investigator in accordance with general guidelines of clinical research. The principal investigator will also determine the relatedness of each adverse event to the study drug in accordance with general guidelines of clinical research.

A serious adverse event is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening, 2. requires or prolongs hospitalization, 3. results in persistent or significant disability/incapacity, 4. constitutes a congenital anomaly or a birth defect, 5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. If any serious adverse events occur, the treatment status of the subject(s) may be revealed, as clinically indicated. Subjects who discontinue medication use will be followed for adverse events until reaching the termination of adverse

events. The frequency of adverse events (AE) will be under continuous scrutiny during the observation with comparison to AE rates that have been recorded in published PD drug trials.

1.13 Schedule of Events

Please refer to the attached Schedule of Assessments for timing of procedures.

1.14 Expected Study Timeline

Study duration is estimated at 17 months (start-up period of 2 months and enrollment period of 15 months), with an additional 2 months for data analysis and manuscript preparation.

2. BACKGROUND AND RATIONALE

2.1 Insomnia in PD

Parkinson disease (PD) is the second most common neurodegenerative disease behind Alzheimer disease. Prevalence is estimated to be 0.3% of the general population and 1% of the population over the age of 60 (de Lau 2006). It is estimated that there were over 4 million cases worldwide in 2005, and that number is expected to more than double by 2030, to 8.7 million (Dorsey 2007). Prevalence in the United States is expected to nearly double over the same time period, with a projected 610,000 cases in the US by 2030 (Dorsey 2007).

Sleep disorders are common in PD. In one community-based survey (Tandberg 1998), disrupted sleep had an estimated prevalence of 60% among PD patients, compared to 33% in the healthy elderly population. Nearly 32% of the PD patients in this study reported trouble falling asleep, 39% reported frequent awakening, and 23% reported early awakening. More than 40% reported taking a medication to help them sleep. This corresponds with findings of a more recent survey, in which nearly half of respondents scored 8 or greater on the Insomnia Severity Index (Chung 2013).

The reasons for the prevalence of insomnia in Parkinson disease are not entirely clear, but have been attributed to physical symptoms, depression, and direct effects of PD on the neural control of sleep onset and maintenance (Tandberg 1998). Since some currently used insomnia medications may adversely affect mood and PD symptoms, it is important in studies of insomnia in PD to measure the severity of motor and non-motor symptoms, especially mood.

Despite the high prevalence of insomnia in PD, there are relatively few studies specifically in PD of medications to improve insomnia. Doxepin has shown benefit (Rios Romenets 2013) and dopamine agonists may increase somnolence generally but have not been shown to specifically improve insomnia in published reports. Melatonin has shown improvement in subjective sleep quality in 2 small studies in PD but not other measures of sleep disturbance (Dowling 2005, Medeiros 2007). Clonazepam is frequently used when REM behavior disorder is present (Gagnon 2006). Other soporifics are used on the basis of standard clinical practice rather than evidence from randomized clinical trials in Parkinson disease patients.

2.2 Suvorexant for insomnia

Suvorexant (MK-4305, Belsomra®) is a recently FDA-approved medication for the treatment of insomnia in the general population. Suvorexant has a novel mechanism of action. The first orexin-receptor antagonist on the market, suvorexant has been shown to improve sleep efficiency in healthy, non-elderly adults with primary insomnia (Herring 2012, Sun 2013). It is believed that suvorexant does not pose a risk of physical dependence or rebound insomnia as do the benzodiazepines and non-benzodiazepine soporifics (Bennett 2014).

Suvorexant may have other advantages that are of benefit specifically in the PD population. Suvorexant appears not to have a deleterious effect on next-day balance in healthy non-elderly subjects. This could be a significant advantage for suvorexant in patients with PD, who already have impaired balance and for whom, therefore, benzodiazepines may not be safe. In addition, suvorexant appears not to affect memory as measured by word recall. Again, this may be a distinct benefit in people with PD, who often have cognitive impairment as a result of their disease.

In addition to insomnia itself, people with PD have high rates of other conditions that may be improved by more efficient sleep, including depression and anxiety. REM behavior disorder (RBD), also experienced at high rates by people with PD, has limited treatment options. The effects of suvorexant in these ancillary conditions in PD are unknown and warrant study.

Suvorexant is approved at doses up to 20 mg daily (Prescribing Information, Merck 2015). Although this dose has been found to be safe in a healthy geriatric population, people with PD may be more sensitive to the therapeutic and adverse effects of suvorexant. It is also likely that subjects in a PD trial will be on other medications that may increase daytime somnolence. For these reasons, we are proposing a study of the 10-mg and 15-mg doses only. If suvorexant is found to be well-tolerated at a dose of 10 or 15 mg daily, future studies can explore the safety and efficacy of 20 mg daily in a PD population.

2.3 Wearable Sleep Monitors in Insomnia

The use of wearable sleep monitors has become increasingly common in the general population. However, the role these devices may play in diagnosing or monitoring insomnia and other sleep disorders is unknown. For this study, the FitBit Charge will be used. This device was chosen for its practicality and affordability, which makes it a device consumers are already using. Understanding how the feedback from this commonly used device relates to data from PSG and clinical ratings will be important in informing discussions with patients in the future.

3. STUDY OBJECTIVES & HYPOTHESES

3.1 Primary Objective

To assess the safety and efficacy of suvorexant in treating insomnia in Parkinson disease

3.2 Secondary Objectives

1. To assess the precision of a wearable sleep monitor in measuring total hours of sleep and WASO as compared to nocturnal polysomnogram (PSG).
2. To assess the effect of suvorexant on motor and non-motor symptoms of PD, including REM behavior disorder (RBD).

3.3 Primary Hypothesis

Suvorexant will provide greater improvement in sleep, as measured by polysomnographic parameters and symptom rating scales, compared to placebo, with no clinically significant increase in adverse events.

3.4 Secondary Hypotheses

1. On nights of PSG, total hours of sleep and WASO as measured by a wearable sleep monitor will not be significantly different from those values as measured by PSG.

2. Suvorexant will not worsen motor symptoms or non-motor symptoms of PD compared to placebo.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This study is a randomized, double-blind, placebo-controlled 15-week study of suvorexant for the treatment of insomnia in a cohort of 20 PD subjects between the ages of 30 and 80. Active drug will be suvorexant 10 mg at bedtime with an optional up-titration to 15 mg at bedtime after 2 weeks. Subjects will be enrolled based on a clinical history of insomnia as defined by the DSM-5 and on results of a screening PSG. The primary outcome measure will be change in sleep efficiency as measured on PSG. Participants will also receive a wearable sleep monitor to assess sleep efficiency over a longer period of time.

The study is composed of 5 office visits, 3 overnight sleep studies (PSGs), and up to 6 phone visits over the course of 11-15 weeks.

4.2 Enrollment

Subjects who may qualify for this study will be identified in the context of clinical care at the EvergreenHealth Neuroscience Institute or the EvergreenHealth Sleep Disorders Center. Such eligible patients may receive a copy of the informed consent form (ICF) at the time of their clinic visit. Recruitment may also occur through local promotional opportunities, referrals from other area neurologists, sleep medicine physicians, and the Washington State Parkinson Disease Registry. Patients may contact the EvergreenHealth Neuroscience Institute without clinic visitation after reading a notice about the study on the Institute's website or other online postings. Subjects who are not established patients at EvergreenHealth will be offered the chance to undergo a telephone screening using an institutional review board (IRB) approved telephone screening text. Subjects will be requested to send pertinent outside medical records for chart review by the principal investigator and be scheduled for a screening visit.

4.3 Screening

4.3.1 Office Visit 1

Office Visit 1 is the screening visit. At this clinic visit, subjects will provide written, informed consent. Once consent is provided, a unique identification number will be assigned. This will be the only identification number assigned to the subject for the duration of the study. After consent is obtained, subjects will be assessed for eligibility (excluding those eligibility criteria requiring completion of a PSG). A history of the patient's PD symptoms and sleep symptoms will be taken, and the patient's past medical history will be reviewed. Diagnosis of PD will be confirmed based on UK PD Society Brain Bank criteria (Hughes 1992). Current medication list will be reviewed, and a levodopa-equivalent daily dose will be calculated based on the patient's current PD medication list and on published conversion factors (Tomlinson 2010, Rytary Prescribing Information, Duopa Prescribing Information). Eligible subjects will have a stable PD medication regimen for 4 weeks prior to the screening visit and remain on a stable regimen for the duration

of the study. Eligible patients will also not be concomitantly taking any of the prohibited medications for at least 14 days prior to the screening visit. The patient's history of medication allergies will be reviewed.

Physical examination will be performed, both a general medical examination including vital signs (blood pressure, heart rate, and respiratory rate) and a neurological examination. Neurological exam will include a general neurological exam as well as MDS-UPDRS part 3 evaluation and modified Hoehn and Yahr (HY) staging of PD (Goetz 2004). Laboratory testing will include CBC, CMP, albumin, and INR, with calculation of the Child-Pugh score for any subjects with liver failure. Pre-menopausal women will have urine hCG measured. MoCA and the C-SSRS will be performed.

The wearable sleep monitor will be dispensed at Office Visit 1 to all subjects who meet non-PSG eligibility criteria. This will be worn by the subjects throughout the study and will record sleep efficiency on every night of the study. The wearable monitor will be the FitBit Charge, which is easy for subjects to put on and use, and provides automatic detection of sleep, calculating sleep duration and sleep efficiency. The FitBit Charge will be kept by the subjects as an honorarium for their time.

4.3.2 PSG 1

For all subjects who meet non-PSG eligibility criteria, the screening/baseline PSG will be completed within 3 weeks (0-21 days) after Office Visit 1. This will be performed at EvergreenHealth's Sleep Disorders Center according to their standard clinical protocol. At a minimum, PSG interpretation will report latency to persistent sleep (LPS), wakefulness after sleep onset (WASO), sleep efficiency, and apnea-hypopnea index (AHI). In addition to screening for eligibility, the screening PSG will provide baseline values for the PSG variables of interest. Eligibility will be confirmed based on the results of the PSG according to the eligibility criteria listed in section 5.1.

4.4 Treatment Period 1

4.4.1 Office Visit 2

For those who satisfy all eligibility criteria, Office Visit 2 will occur within 7-14 days after the screening PSG. Medications will be reviewed again to ensure stability of the PD medication regimen and absence of any prohibited medications.

Following confirmation of eligibility, an eligible patient will complete the baseline assessments of the MDS-UPDRS (only parts 1, 2, and 4; the data from part 3 that was collected at Office Visit 1 as a part of the screening will serve as the baseline for this measure), ISI, ESS, BDI, and BAI during Office Visit 2. Data from the wearable sleep monitor will be collected.

An eligible patient will be randomized in a 1:1 randomization scheme to receive suvorexant 10 mg qhs or placebo. Randomization will occur at the research pharmacy of EvergreenHealth using

a computer-generated randomization list. The pharmacist will maintain a codebook indicating the treatment allocation of each subject. Study medication will be delivered by the research pharmacist to the research study staff from the research pharmacy (a separate locked room containing only research medications). The investigating physicians, research coordinator(s), and study subjects will be blinded as to treatment arm until the code is broken. The randomization code may be broken by the investigator only in a medical emergency. The reasons for such an emergency will be documented carefully. The subjects will receive identical appearing active or placebo study medication tablets, with identification known only to the research pharmacist.

4.4.2 Phone Visit 1

Phone Visit 1 will occur 3-4 days after Office Visit 2 to review safety and tolerability through questioning about adverse events.

4.4.3 Phone Visit 2: Titration in Treatment Period 1

Phone Visit 2 will occur 2 weeks (12-15 days) after Office Visit 2 to review safety and tolerability through questioning about adverse events. The SGIC and C-SSRS will also be administered over the phone. Those subjects who report no AEs on suvorexant 10 mg po QHS (or matched placebo) and who report a persistent sleep disturbance will be titrated to suvorexant 15 mg po QHS (or matched placebo).

4.4.4 Phone Visit 3

Only for those subjects who are titrated to 15 mg, Phone Visit 3 will occur 3-4 days after Phone Visit 2 to review safety and tolerability through questioning about adverse events. For those who remain on 10 mg, Phone Visit 3 will not be conducted.

4.4.5 PSG 2

Overnight PSG 2 will occur after 4 weeks (25-32 days) after Office Visit 2 and will mark the last night of Treatment Period 1. Subjects will continue to take the study medication on the night of PSG 2. This will be performed at EvergreenHealth's sleep lab according to their standard clinical protocol. At a minimum, PSG interpretation will report latency to persistent sleep (LPS), wakefulness after sleep onset (WASO), and sleep efficiency.

4.5 Washout Period (Office Visit 3)

Office Visit 3 will occur within 7 days after PSG 2. In addition to PSG review, medications will be reviewed again to ensure stability of the PD medication regimen and absence of any prohibited medications. Any possible adverse events (AEs) will be assessed. General physical exam will be performed, including vital signs (blood pressure, heart rate, and respiratory rate).

PD symptoms and signs will be assessed with the complete MDS-UPDRS. Study scales (MoCA, ISI, ESS, BDI, BAI, CGI-C, SGI-C, C-SSRS) will be administered. Data from the wearable

sleep monitor will be collected. Laboratory testing will be performed as deemed appropriate by the investigator.

A new supply of study pills will be dispensed. For the washout period, all subjects will be given the placebo matching the dose being administered most recently (i.e. in the second half of treatment period 1).

4.6 Treatment Period 2

4.6.1 Office Visit 4

Office Visit 4 will occur 2 weeks (11-18 days) after Office Visit 3 and will mark the beginning of treatment period 2. Medications will be reviewed again to ensure stability of the PD medication regimen and absence of any prohibited medications. Any possible adverse events (AEs) will be assessed.

To serve as baseline scores for treatment period 2, PD symptoms and signs will be assessed with the complete MDS-UPDRS and study scales (MoCA, ISI, ESS, BDI, BAI, CGI-C, SGI-C) will be administered. Data from the wearable sleep monitor will be collected. Laboratory testing, including urine hCG, will be performed as deemed appropriate by the investigator.

A new supply of study pills will be dispensed in a crossover fashion. All subjects who received study drug in treatment period 1 will be given placebo in treatment period 2, and all subjects who received placebo in treatment period 1 will be given study drug in treatment period 2. For treatment period 2, double-blinding will be resumed. Initial dose for all subjects will be 10 mg qhs.

4.6.2 Phone Visit 4

Phone Visit 4 will occur 3-4 days after Office Visit 4 to review safety and tolerability through questioning about adverse events.

4.6.3 Phone Visit 5: Titration in Treatment Period 2

Phone Visit 5 will occur 2 weeks (12-15 days) after Office Visit 4 to review safety and tolerability through questioning about adverse events. The SGIC and C-SSRS will also be administered over the phone. Those subjects who report no AEs on suvorexant 10 mg po QHS (or matched placebo) and who report a persistent sleep disturbance will be titrated to suvorexant 15 mg po QHS (or matched placebo).

4.6.4 Phone Visit 6

Only for those subjects who are titrated to 15 mg, Phone Visit 6 will occur 3-4 days after Phone Visit 5 to review safety and tolerability through questioning about adverse events. For those who remain on 10 mg, Phone Visit 6 will not be conducted.

4.6.5 PSG 3

PSG 3 will occur 4 weeks (25-32 days) after Office Visit 4 and will mark the last night of Treatment Period 2. Subjects will continue to take the study medication on the night of PSG 3. This will be performed at EvergreenHealth's sleep lab according to their standard clinical protocol. At a minimum, PSG interpretation will report latency to persistent sleep (LPS), wakefulness after sleep onset (WASO), and sleep efficiency.

4.7 Final Visit (Office Visit 5)

Office Visit 5 will occur within 7 days after PSG 3. Medications will be reviewed again to ensure stability of the PD medication regimen and absence of any prohibited medications. Any possible adverse events (AEs) will be assessed. General physical exam will be performed, including vital signs (blood pressure, heart rate, and respiratory rate).

PD symptoms and signs will be assessed with the MDS-UPDRS and study scales (MoCA, ISI, ESS, BDI, BAI, CGI-C, SGI-C, C-SSRS) will be administered. Data from the wearable sleep monitor will be collected. Laboratory studies will be performed (CBC, CMP). Pregnancy testing with urine hCG will be performed if deemed appropriate by the investigator.

4.8 Unscheduled Visits

Subjects may return to the clinic for safety evaluation or to receive additional study medication as needed. Unscheduled visits will include a review of concomitant medications and any adverse effects, and, if needed in the estimation of the study physician, physical examination in whole or in part.

5. STUDY POPULATION

The population for this study is PD patients aged 30-80 years old (inclusive) with symptoms of insomnia who meet all of the inclusion criteria (section 5.1) and who do not meet any of the exclusion criteria (section 5.2).

5.1 Inclusion Criteria

An eligible subject:

- Has signed and dated an IRB-approved informed consent form before any protocol-specific screening procedures are performed;
- Has a diagnosis of Parkinson disease according to the United Kingdom Parkinson Disease Society Brain Bank Criteria (UKBB);
- Has a modified Hoehn and Yahr (mHY) Stage of 1-3, inclusive;
- Is aged 30-80 years old, inclusive;
- Has had no change in PD medications during the 4 weeks preceding screening, with no dose changes during the study, except that PRN (as needed) doses of carbidopa/levodopa will be allowed to address periodic worsening of parkinsonian symptoms;
- Is willing and able to complete PSG;
- Is willing and able to abstain from alcohol, caffeine, and marijuana for 6 hours prior to and during each study-related PSG;
- Is willing and able to abstain from products containing nicotine during each study-related PSG;
- Has Insomnia Disorder defined by diagnostic criteria published in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); namely, subject report of all of the following:
    - One of the following: difficulty initiating sleep; difficulty maintaining sleep; or early morning waking;
    - Sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning;
    - Sleep difficulty has occurred on 3 or more nights per week;
    - Sleep difficulty has been present for at least the past 3 months;
    - Sleep difficulty occurs despite adequate opportunity for sleep;
    - Insomnia is not explained by another sleep disorder;
    - Insomnia is not attributable to physiological effects of a consumed substance;
- On screening PSG, has a latency to persistent sleep $\geq$ 20 minutes OR total wakefulness after sleep onset $\geq$ 45 minutes;
- May use other medications that could influence sleep, other than those specifically prohibited, as long as the dose is stable for 4 weeks preceding screening, with no dose changes during the study; and

- Has valid health insurance coverage at the time of study enrollment and expects this coverage to remain valid for the duration of the study period.

5.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following:

- Is a woman who is breast-feeding, pregnant, or has the potential to become pregnant during the course of the study (fertile and unwilling/unable to use effective contraceptive measures);
- Has an implanted deep brain stimulator;
- Has a history of narcolepsy;
- Has a diagnosis of severe COPD, defined by FEV1 < 50% of predicted on most recent available pulmonary function test (PFT) (a PFT is not required if the subject has never been diagnosed with COPD);
- Has a history of severe obstructive sleep apnea (OSA) or evidence of severe OSA on screening PSG, with severe OSA defined as having an apnea-hypopnea index (AHI) > 30;
- Is concurrently using other CNS depressants, including alcohol, except that one alcoholic drink per day will be allowed for those with normal hepatic function provided the drink is consumed at least 2 hours prior to or 8 hours after taking the study drug, and no alcohol will be permitted for 6 hours before PSG visits;
- Is concurrently using digoxin;
- Is concurrently using any moderate or strong inhibitor of CYP3A;
- Is concurrently using any strong inducer of CYP3A;
- Has evidence at screening of severe hepatic impairment as defined by a Child-Pugh score > 10;
- Has evidence at screening of severe cognitive impairment as defined by a MoCA score < 15, or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent.
- Has evidence at screening of suicidal ideation in the past 6 months as defined by a positive response to any one of Questions 2-5 on the Columbia Suicide Severity Rating Scale (C-SSRS); or of a lifetime history of suicidal behavior as defined by any positive response to the suicidal behavior section of the C-SSRS.

5.2.1 Note on the Use of the Wearable Sleep Monitor

Of note, inability or unwillingness to use the WSM is specifically *not* an exclusion criterion. Those subjects who are unable or unwilling to use the WSM correctly will be allowed in the study (provided all eligibility criteria are otherwise met), and the observations from their WSM variables will be treated as missing data.

5.3 Prohibited Medications

The following medications are not permitted to be used within 14 days prior to screening nor for the duration of the subject's participation in the study:

- Digoxin;
- CNS depressants such as:
    - Benzodiazepines
        - Alprazolam
        - Chlorazepate
        - Chlordiazepoxide
        - Clonazepam
        - Diazepam
        - Estazolam
        - Flurazepam
        - Halazepam
        - Lorazepam
        - Midazolam
        - Oxazepam
        - Prazepam
        - Temazepam
        - Triazolam
    - Barbiturates
        - Amobarbital
        - Mephobarbital
        - Pentobarbital
        - Phenobarbital
        - Primidone
        - Secobarbital
        - Sodium thiopental
    - Opiates
        - Codeine
        - Hydrocodone
        - Hydromorphone
        - Methadone
        - Morphine
        - Oxycodone
    - Zolpidem
    - Zaleplon
    - Eszopiclone
- Moderate or strong inhibitors of CYP3A, such as:
    - Aprepitant
    - Atazanavir
    - Bromocriptine

  - Chloramphenicol
  - Ciprofloxacin
  - Clarithromycin
  - Cobicistat
  - Conivaptan
  - Darunavir
  - Desipramine
  - Diltiazem
  - Dronedarone
  - Erythromycin
  - Felodipine
  - Fluconazole
  - Fluvoxamine
  - Fosamprenavir
  - Grapefruit Juice
  - Imatinib
  - Indinavir
  - Itraconazole
  - Ketoconazole
  - Lopinavir
  - Nefazadone
  - Nelfinavir
  - Nicardipine
  - Posaconazole
  - Quinidine
  - Quinupristin
  - Ritonavir
  - Saquinavir
  - Telaprivir
  - Telithromycin
  - Verapamil
  - Voriconazole
- Strong inducers of CYP3A, such as:
  - Carbamazepine
  - Dexamethasone
  - Phenobarbital
  - Primidone
  - Phenytoin
  - Rifampin
  - St. John’s Wort

5.4 Removal of Patients from Study

A patient will be considered to have completed the study when he or she has completed all study visits through the final visit. Every patient has the right to discontinue study participation at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Criteria for early termination include, but are not limited to, poor adherence to study medication (less than 70% of study medication consumed), loss of health insurance coverage, and safety issues related to study-related or non-study related adverse events.

If a patient has a clinical necessity to alter their standard PD medications, the patient will be withdrawn from the trial so that changes may be made, except that occasional additional doses of carbidopa/levodopa will be allowed if needed to address periodic worsening of parkinsonian symptoms. If a patient is withdrawn due to an adverse event, the event will be followed, when possible, until resolution. Patients who withdraw from the study may be replaced, but withdrawn patients will not be re-entered into the study.

All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

5.5 Screen Failures & Re-screening

Subjects who fail screening because they do not meet inclusion criteria or because of certain exclusions, e.g. concurrent use of a prohibited medication, may be re-screened after 4 weeks at the discretion of the investigator.

6. TREATMENTS

6.1 Investigational Drug

Study medication, to include 5-mg and 10-mg suvorexant and matching placebo, will be provided by Merck. The active medication will be suvorexant 10-15 mg qhs. The research pharmacist at EvergreenHealth will be responsible for packaging and labeling individual bottles, which will be done in a standard prescription bottle with child-proof cap. The pharmacist will dispense the active or placebo medication at randomization (Office Visit 2, start of Treatment Period 1) and again Office Visit 4 (start of Treatment Period 2). This will include a 4-week supply of 10 mg tablets (suvorexant or matching placebo) and a 2-week supply of 5 mg tablets (suvorexant or matching placebo). The subject will use the 5-mg tablets only if instructed to do so at Phone Visit 2 or Phone Visit 5. In this case, the 5-mg tablets will be taken concurrently with the 10-mg tablets to achieve the titration dose of 15 mg QHS. To prevent confusion, the bottle of 5-mg tablets will be packaged in a sealed bag with a label stating, "Open only if instructed to do so on _____." In the blank, the coordinator will write in the date of Phone Visit 2 or 5, as appropriate. In addition, a pictorial depiction of the titration schedule will be provided to the subject.

At Office Visit 3 (start of washout period), placebo will be dispensed that matches what the subject was taking at the end of Treatment Period 1. For example, if the subject titrated to 15 mg at Phone Visit 2, both a 10-mg and 5-mg placebo will be dispensed at Office Visit 3. If the subject remained on 10 mg for the duration of Treatment Period 1, only a 10-mg placebo will be dispensed.

An extra 7-day supply of medication will be provided for each study period to allow a window for scheduling of appointments.

6.2 Randomization and Blinding

Following confirmation of eligibility, an eligible patient will be randomized in a 1:1 randomization scheme to receive suvorexant or placebo. Randomization will occur at the research pharmacy of EvergreenHealth using a computer-generated randomization list. The pharmacist will maintain a codebook indicating the treatment allocation of each subject. Study medication will be delivered by the research pharmacist to the research study staff from the research pharmacy (a separate locked room containing only research medications). The investigating physicians, nurse, research coordinator, and study subjects will be blinded as to treatment arm until the code is broken. The randomization code may be broken by the investigator only in a medical emergency. In the event of a medical emergency, the reasons for breaking the code will be documented carefully. The subjects will receive identical appearing active or placebo study medication tablets, with identification known only to the research pharmacist.

6.3 Concomitant Therapy

All concomitant therapy will be documented. Concurrent (defined as "within 14 days of screening") use of medications listed in section 5.3 will be prohibited. Medications that are likely to influence sleep or sleepiness may not be initiated between screening and study completion. They may be continued with no dose changes during the study.

6.4 Treatment Compliance

Patients will be asked to return all unused medication and all medication bottles, including empty bottles, at each visit and at the end of the study. The quantity of medication dispensed and returned will be documented.

7. DESCRIPTION OF ASSESSMENTS

7.1 Safety Monitoring

Safety will be monitored by physical examination, vital signs, laboratory evaluation, and adverse event (AE) reporting with particular inquiry on falls and next-day drowsiness.

7.1.1 Physical Examination

A general physical examination will be performed at Office Visit 1 (Screening Visit), Office Visit 3 (Start of Washout Period) and Office Visit 5 (Final Visit). This exam will include, at minimum, HEENT, heart, lungs, abdomen, musculoskeletal, and neurologic systems. Subjects with a range of health conditions that may put the patient at risk for adverse outcomes will be excluded, as listed under Section 5.2, Exclusion Criteria.

7.1.2 Laboratory Evaluations

All subjects will undergo baseline testing with CBC, CMP, albumin, and INR. Child-Pugh score will be calculated if there is a history of liver failure or if AST or ALT are elevated. Those subjects with a Child-Pugh score > 10 will be excluded. CBC and CMP will be assessed at Office Visit 3 (start of washout period) and Office Visit 5 (final visit) to ensure stability.

7.1.3 Pregnancy Status

All pre-menopausal women will have pregnancy screening with urine hCG at all Office Visits (1-5). A positive urine hCG at screening will result in exclusion from the study; a positive urine hCG at any other office visit will result in discontinuation of the study drug and withdrawal of the subject from the study.

7.1.4 Adverse Events

Subjects will be monitored for adverse events throughout the trial. The occurrence of adverse events will be ascertained by observation, telephone monitoring and questioning by the investigator or coordinator. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events. Falls and next-day drowsiness will be specifically queried.

An adverse event (AE) is any symptom, physical sign, or medical condition that emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause. Adverse events include adverse drug reactions, illness with onset during the study, exacerbations of pre-existing conditions or clinically significant changes in physical examination or significantly abnormal objective test findings. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study

treatment. All adverse events will be recorded and graded as mild, moderate or severe by the principal investigator in accordance with general guidelines of clinical research, outlined here:

- **MILD**: An event that causes transient or minimal symptoms and that does not interfere with daily activities.
- **MODERATE**: An event that causes symptoms sufficient to interfere with but not prevent daily activities.
- **SEVERE**: An event that prevents normal, everyday activities.

Adverse events will also be classified by their relationship to the study medication by the principal investigator in accordance with general guidelines of clinical research, outlined here:

- **Definitely Unrelated**: The AE is definitely not related to the drug. This designation is reserved for those events that do not follow a reasonable temporal sequence following drug administration (e.g. occur prior to study treatment) or for those events that cannot be even remotely related to study participation.
- **Unlikely related**: There is no reasonable association between the study treatment and the suspected event and the event could have been produced by the patient's clinical state or other therapy administered to the patient.
- **Possibly related**: The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the patient's clinical state or other therapy administered to the patient.
- **Probably related**: The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state or other treatments.
- **Definitely related**: The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and, if appropriate, resumes upon re-introduction of the treatment. Additionally, the suspected AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other treatments.

The principal investigator and all other research staff except the research pharmacist will be blinded towards randomization of active drug versus placebo until after completion of study.

7.1.5 Serious Adverse Events

A serious adverse event (SAE) is any AE that meets one of more of the following criteria:

- Is fatal or life-threatening
- Requires hospitalization or prolongs a current hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
- Requires medical or surgical intervention to prevent one of the above outcomes

If any SAE occurs, the treatment status of the subject(s) may be revealed, as clinically indicated. If a patient discontinues medication use due to an AE, the event will be followed, when possible, until resolution. No interim analysis of safety data is planned. However, the frequency of AEs will be under continuous scrutiny during the trial with comparison to AE rates that have been recorded in published PD drug trials.

7.1.5.1 Serious Adverse Events Reporting

The FDA will be informed of SAEs as soon as possible or within 15 calendar days. In addition, the Investigator will notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible, or within 7 calendar days, by telephone or facsimile. When the principal investigator has determined that an SAE requires reporting to the FDA (unexpected and possibly related to study drug), the following actions will be taken:

- Telephone the FDA immediately (day of awareness) if the case involves a reportable death or a life-threatening event.
- Complete FDA Form 3500.
- Send the completed Form 3500 to the FDA (preferably by fax at 1-800-FDA-0178) within the timelines mentioned above.
- Attach the photocopy of all examinations, medical notes and records related to the SAE and document the dates these were made. For laboratory results, include the laboratory normal ranges. For hospitalizations, include Admission H&P, Discharge Summary, Consultative reports, and other similar notes. In the case of a fatal event, if an autopsy is performed, a copy of the autopsy report will be provided when it becomes available.

7.1.6 Special Note on Suicidality as an Adverse Event

In the event that the administration of the C-SSRS at follow-up visits (Phone Visits 2 or 5 or Office Visits 3 or 5) reveals worsening suicidal ideation relative to baseline or any suicidal behavior since the last administration, the subject will be withdrawn from the study. Intervention will be initiated as deemed appropriate in the clinical judgment of the investigator and may include referral to the subject's primary care provider, referral to the in-house psychology group at EvergreenHealth Neuroscience Institute, emergency referral to the EvergreenHealth Emergency Department, or activation of Emergency Medical Services by dialing 9-1-1. Suicidal ideation requiring hospitalization will be considered an SAE, and any suicidal behavior will be considered an SAE, with reporting requirements as per section 7.1.5.1.

7.2 Efficacy Assessment Based on Polysomnogram

7.2.1 Sleep Efficiency

The primary outcome measure will be sleep efficiency as measured by PSG, defined as (total sleep time / total time in bed) * 100%.

7.2.2 Wake After Sleep Onset

WASO is defined as total time spent awake after first epoch of sleep and before final awakening. This will be a secondary outcome measure.

7.2.3 Latency to Persistent Sleep

LPS is defined as total time between lights out and first epoch of sleep. This will be a secondary outcome measure.

7.2.4 Muscle Tonicity

Muscle activity during REM sleep will be recorded as a measure of REM Behavior Disorder.

7.3 Efficacy Assessment Based on Clinical Rating Scales

7.3.1 Insomnia Severity Index

The ISI is a 7-question survey assessing symptoms of insomnia. Maximum score is 28, with higher scores indicating greater severity. The ISI has been validated for use in insomnia research (Bastien 2001). This will be performed at Office Visits 2, 3, 4, and 5, and will be a secondary outcome measure.

7.3.2 Epworth Sleepiness Scale

The ESS is an 8-question survey assessing symptoms of sleepiness. Maximum score is 24, with higher scores indicating greater severity. The ESS has been validated for use in the general population (Johns 1991) and in PD (Hagell 2007). This will be performed at Office Visits 2, 3, 4, and 5, and will be a secondary outcome measure.

7.3.3 Subject's Global Impression of Change

The SGIC will be assessed by asking a single question at Phone Visits 2 and 5 and Office Visits 3, 4, and 5: "Since baseline (when first starting this study), how have your sleep symptoms changed?" Answers will be on a 7-point scale: 1 = much improved; 2 = somewhat improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = somewhat worse; and 7 = much worse. This will be performed at Phone Visits 2 and 5 and at Office Visits 3, 4, and 5, and will be a secondary outcome measure.

7.3.4 Clinician's Global Impression of Change

The CGIC will be assessed by the investigator at Office Visits 3, 4, and 5 using a similar question: "Since baseline (when first starting this study), how have the subject's sleep symptoms changed?" Answers will be on a 7-point scale: 1 = much improved; 2 = somewhat improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = somewhat worse; and 7 = much

worse. This will be performed at Office Visits 3, 4, and 5, and will be a secondary outcome measure.

7.3.5 Montreal Cognitive Assessment

The MoCA is an assessment of global cognition using a 30-point scale and investigating performance in visuospatial ability, executive function, naming, attention, language, abstraction, delayed recall, and orientation. It will be performed at Office Visits 1, 3, 4, and 5, and will be used as a secondary outcome measure to assess the effect of suvorexant on cognition in PD.

7.3.6 Beck Depression Inventory-II

The BDI is a 21-question assessment of symptoms of depression, with higher scores indicating more severe depression, to a maximum score of 63. This scale has been validated for use in assessing depression in Parkinson disease (Leentjens 2000). It will be performed at Office Visits 2, 3, 4, and 5, and will be used as a secondary outcome measure to assess the effect of suvorexant on depression in PD.

7.3.7 Beck Anxiety Inventory

The BAI is a 21-question assessment of symptoms of anxiety, with higher scores indicating more severe depression, to a maximum score of 63. This scale has been validated for use in assessing depression in Parkinson disease (Leentjens 2011). It will be performed at Office Visits 2, 3, 4, and 5, and will be used as a secondary outcome measure to assess the effect of suvorexant on anxiety in PD.

7.3.8 Movement Disorder Society's Unified Parkinson Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a widely used and validated (Goetz 2008) rating scale in PD, assessing non-motor symptoms of PD (part I), motor symptoms of PD (part II), motor signs of PD on physical exam (part III), and symptoms of motor complications in PD (part IV). Part I includes two questions about sleep symptoms: question 1.7 (sleep problems) and question 1.8 (daytime sleepiness). All questions are rated on a 5-point scale (0-4), with higher scores indicating greater severity. The maximum score on part I is 52, on part II it is 52, on part III it is 132, and on part IV it is 24. Total score, the score on part I, the score on question 1.7, and the score on question 1.8 will be secondary outcome measures. The scores on parts II, III, and IV will be used as safety measures to ensure no worsening of motor symptoms, motor signs, or motor complications. Part III will be performed at Office Visit 1; Parts I, II, and IV will be performed at Office Visit 2; and the full scale (parts I-IV) will be performed at Office Visits 3, 4, and 5.

7.3.9 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale is a widely used and validated assessment of suicidal ideation and suicidal behavior (Posner 2011). It provides a structured interview to assess, over both lifetime and the past 6-months, several types of suicidal ideation and behavior,

stratified by risk for suicide completion. This will be used to assess suicide risk at screening and to monitor for an adverse event of increasing suicidality throughout the study. It will be administered at Office Visits 1, 3, and 5, and at Phone Visits 2 and 5.

7.4 Efficacy Assessment Based on Wearable Sleep Monitor

The secondary outcome measure based on the wearable sleep monitor (WSM) will include:

- Total hours of sleep per night, mean over final 7 nights of treatment period compared to mean over final 7 nights of screening period
- Wakefulness after sleep onset (WASO), mean over final 7 nights of treatment period compared to mean over final 7 nights of screening period

8. Statistical Methods

8.1 Statistical Analysis

Statistical analysis will be performed by a consulting statistician contracted with EvergreenHealth and whose services we have used on recent studies in PD. All data will remain blinded throughout the data analysis and will be unblinded only in the event of a medical emergency.

8.2 Sample Size Considerations

This is a prospective, double-blinded, randomized controlled pilot study. The purpose is to test a hypothesis in a preliminary fashion and to assess for safety in this population with a specific neurological disease. As such, a power calculation may be irrelevant. However, a small number of subjects (e.g. less than 10) may cause significant sampling error to miss a treatment effect or common safety issue. Some entities that establish criteria for level of evidence consider a sample size of 20 subjects in each arm to be a minimum representative population to be considered for Class III or better classification of Level of Evidence. This will be achieved by having 20 subjects complete both treatment and placebo arms using a crossover study design. Therefore, a sample size of 20 subjects is a reasonable number for a pilot study of this nature.

8.3 Study Population

The study population will include all patients who pass screening and undergo randomization. Data will be analyzed in an intent-to-treat fashion.

8.4 Baseline and Demographic Characteristics

The following characteristics will be summarized descriptively for placebo and drug groups:

- Demographics (age, gender, race)
- Parkinson disease characteristics at baseline (disease duration, date of onset, initial symptom, modified Hoehn and Yahr stage in the ON state, and MDS-UPDRS part 3 score in the ON state)
- Levodopa-equivalent daily dose (LEDD), calculated according to published formulae (Tomlinson 2010, Rytary Prescribing Information, Duopa Prescribing Information).

8.5 Efficacy Analysis

Analysis of primary and secondary outcome measures will include:

- Summary statistics (n, mean, standard deviation, median, minimum and maximum) at baseline, Office Visit 3 and Office Visit 5 by treatment.
- For clinical rating scales, summary of % change from baseline to Office Visit 3, from baseline to Office Visit 5, and from Office Visit 4 to Office Visit 5, by treatment
- For PSG variables, summary of % change from PSG 1 to PSG 2 and from PSG 1 to PSG 3, by treatment

- For wearable sleep monitor, summary of % change in total hours of sleep and WASO. Mean over the week prior to Office Visit 2 (baseline) will be compared to the mean over the final week of Treatment Period 1 and to the mean over the final week of Treatment Period 2. Mean over the week prior to Office Visit 4 (during washout) will be compared to the mean over the final week of Treatment Period 2. This will be done by treatment arm.
- Significance testing

Outcome measures will be compared between groups using analysis of covariance (ANCOVA) or other method as deemed appropriate by the consulting statistician. Demonstration of superiority will depend on achieving statistical significance for the primary endpoint. Level of significance will be defined as $p = 0.05$. All statistical tests will be two-sided.

9. STUDY MANAGEMENT

9.1 Ethics and Good Clinical Practice

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)], the declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written approval from the appropriate Institutional Review Board or Independent Ethics Committee.

9.2 Informed Consent

For each trial patient, written informed consent will be obtained before any study-related activity is commenced. Both the informed consent form (ICF) and an oral explanation that occurs as part of the informed consent process will include information about the study objective, the nature and duration of the study, the action of the study drug, potential risks, inconveniences, adverse effects, and alternatives. The patient will be informed that he or she is free to withdraw from the study at any time without consequence.

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11. APPENDIX

11.1 Schedule of Assessments

Appendix 11.1: Schedule of Assessments

	Visit 1: Screening	PSG 1	Visit 2: Start Treatment Period 1	Phone Visit 1	Phone Visit 2	Phone Visit 3	PSG 2	Visit 3: Start Washout Period	Visit 4: Start Treatment Period 2	Phone Visit 4	Phone Visit 5	Phone Visit 6	PSG 3	Visit 5: Final
Timing	Week 0	Week 3 (0-21 days post Visit 1)	Week 5 (7-14 days post PSG 1)	Week 5.5 (3-4 days post Visit 2)	Week 7 (12-15 days post Visit 2)	Week 7.5 (3-4 days post Phone Visit 2)	Week 9 (25-32 days post Visit 2)	Week 9 (0-7 days after PSG 2)	Week 11 (11-18 days post Visit 3)	Week 11.5 (3-4 days post Visit 4)	Week 13 (12-15 days post Visit 4)	Week 13.5 (3-4 days post Phone Visit 5)	Week 15 (25-32 days post Visit 4)	Week 15 (0-7 days after PSG 3)
Informed Consent	X													
Study Eligibility (inclusion/exclusion)	X		X											
Medical History	X													
Sleep History	X													
PD History	X													
Concomitant Medication and Allergy Review	X		X					X	X					X
Levodopa-equivalent daily dose calculation	X													
AE Assessment				X	X	*		X	X	X	X	*		X
Physical Exam	X							X						X
MDS-UPDRS, Part 3 (Motor Exam)	X													
MDS-UPDRS, Parts 1, 2, & 4			X											
MDS-UPDRS, full assessment								X	X					X
UK Brain Bank Criteria review	X													
Hoehn and Yahr Staging for Parkinson's	X													
Laboratory Testing (CBC, CMP, albumin, INR)	X							X (CBC, CMP)	*					X (CBC, CMP)
Assessment of Child-Pugh Score	X													
Pregnancy Testing (urine hCG)	**		**					**	**					**
Overnight Polysomnogram (Sleep Study), including analysis by sleep specialist		X					X						X	
Calculation of Sleep Efficiency		X					X						X	
Calculation of Waking after Sleep Onset (WASO)		X					X						X	
Calculation of Latency to Persistent Sleep		X					X						X	
Insomnia Severity Index			X					X	X					X
Epworth Sleepiness Scale			X					X	X					X
Montreal Cognitive Assessment (MoCA)	X							X	X					X
Beck Depression Inventory			X					X	X					X
Beck Anxiety Inventory			X					X	X					X
Columbia Suicide Severity Rating Scale	X				X			X			X			X
Clinician's Global Impression of Change of disease symptoms								X	X					X
Subject's Global Impression of Change of disease symptoms					X			X	X		X			X
Dispense wearable sleep monitor	X													
Upload data from wearable sleep monitor			X					X	X					X
Randomization			X											
Drug Dispensing			X					X (placebo)	X					

*As indicated

**Urine hCG will be performed for all pre-menopausal women.