Study Title:

DREAM: A **D**ouble-blind, Crossove**R**, placebo-controlled Study to compare the **E**ffects of Nighttime **A**dministration of suvorexant in Patients with **M**ultiple Sclerosis fatigue and insomnia

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SCHEDULE OF EVENTS

Parameter	Screening Clinic Visit 1	Baseline Clinic Visit 2	Phone Visit 1	Phone Visit 2	Phone Visit 3	Phone Visit 4	Phone Visit 5	Unscheduled Visits
	Week # 0	Week # 1-2		Week #3-4	Week #5-6		Week #7-8	
Medical History	X							
Informed consent	X							
Physical Examination/ Visit with MD	X	~~Ŧ~~						X
Vital Signs	X							
Urine pregnancy test for females *	X							
Laboratory testing **	X							
Beck Depression Inventory II	X			X			X	
BDI - Q9			X			X		
Current Medication	X	X	X	X	X	X	X	
EDSS	X							
Randomization		X						
Drug dispensing		X						
Fatigue Severity Scale	X							
MFIS		X		X			X	
Insomnia Severity Index		X		X			X	
Fatigue VAS		X		X			X	
Sleep diary		X		X			X	
Wearable sleep monitor review		X		X			X	
Step count		X		X			X	
Global impression		X		X			X	
Adverse Event assessment		X	X	X	X	X	X	X
Study drug pill counts							X	

~~Ŧ~~ Optional, indicated for any safety issues that arise

* As indicated by fertility status

** Laboratory testing: CBC, CMP

4. LIST OF ABBREVIATIONS

AE	Adverse event
AHI	Apnea - Hypopnea Index
BDI	Beck Depression Inventory
BDI- Q9	Beck Depression Inventory, question 9 (suicidality)
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Edition 5
EDSS	Expanded Disability Status Scale
EDSS	Expanded Disability Status Scale
FDA	Food & Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
ICF	Informed Consent Form
IRB	Institutional Review Board
ISI	Insomnia Severity Index
MFIS	Modified Fatigue Impact Scale
MS	Multiple sclerosis
OSA	Obstructive Sleep Apnea
PFT	Pulmonary Function Test
PI	Principal Investigator
PSG	Polysomnography
sQUAL	Subjective Quality of Sleep
sFRESH	Subjective Refreshed Feeling on Waking
SAE	Serious adverse event
VAS	Visual Analogue Scale
VAS-F	Fatigue Visual Analogue Scale
WSM	Wearable Sleep Monitor

5. Introduction and Rationale

Over 400,000 Americans have multiple sclerosis (MS), a chronic neurological disease characterized by demyelination and axonal degeneration. Despite their high prevalence in general adult populations, recently published studies provide compelling data that the prevalence of sleep disorders is further increased in individuals with MS (Merlino et al. 2009). Up to 40 % of MS patients may be at risk of having chronic insomnia disorder (Brass, Li, Auerbach 2014). MS-related symptoms including neurogenic bladder, pain, depression and spasticity should be viewed as potential triggers for insomnia and appropriately treated. Multiple medications frequently used by patients with MS, including stimulants, serotonin reuptake inhibitors and

beta-interferon may also contribute to insomnia. (Hurwitz et al. 2008) Recent studies suggest that daytime sleepiness and nocturnal sleep disturbances contribute to physical and cognitive fatigue in MS (Braley, Bondreau 2016, Stanton, Barnes, Silber 2006, Beran, Ainley 2005, Attarian et al. 2004). Timely diagnosis and treatment of sleep problems in MS offer a new opportunity to ameliorate some of the daytime fatigue experienced by patients with MS.

In the mid-1980s, fatigue came to light as an important MS symptom.(Kraft, Freal, Coryell 1986, 1984). Subsequent studies have found fatigue prevalence rates of 78% or more amongst MS patients (Bakshi et al. 2000, Krupp et al. 1988). For people with MS, fatigue is defined as "a sense of physical tiredness and lack of energy, distinct from sadness or weakness." (Krupp 2004) Fatigue may be brought on by exertion or be non-exertional. Because it is often the limiting factor for activity, it has been termed the single most frequent and often most disabling symptom of the disease (Bergamaschi et al. 1997, Fisk et al. 1994).

Non-medical treatments of fatigue include exercise, napping, energy conservation and cooling through application or consumption of cold substances. Fatigue is frequent in MS and yet there are no FDA-approved treatments for this indication. Therefore, drugs that have FDA approval for other indications are frequently used off-label. The following pharmacological agents are commonly used or have been used off-label in MS: modafinil, armodafinil, amantadine and methylphenidate. There is no convincing evidence of efficacy of any drug for MS fatigue and none of these drugs have been sufficiently tested in the population of MS patients (Stankoff et al. 2005, Rammohan et al. 2002, Zifko et al. 2002, Wingerchuk et al. 2005, Canadian MS Research Group 1987, Cohen, Fisher 1989, Tomassini et al. 2004, Gillson et al. 2002, Lebrun et al. 2006).

Sleep disturbances have been strongly associated with MS fatigue [Veauthier 2011]. One study found that poorer sleep was associated with worse perceived cognitive dysfunction and that this relationship was partially mediated by fatigue [Hughes 2016]. Assessment and treatment of sleep disorders is an important component of MS fatigue management [Tur 2016Braley 2016]. Two studies have demonstrated that treatment of sleep disorders in general or sleep apnea in particular improved symptoms of fatigue in individuals with MS [Veauthier 2013, Cote 2013]. Only one study could be found that included an intervention for insomnia in multiple sclerosis. Baron et al used a telephone-based psychotherapy approach to reduce the rate of insomnia in depressed MS patients [Baron 2011]

Suvorexant (MK-4305, Belsomra®) which is approved by the FDA for the treatment of insomnia characterized by difficulties with sleep onset and sleep maintenance, is a selective antagonist for orexin receptors (OX1R and OX2R). Suvorexant has been shown to improve sleep efficiency in healthy, non-elderly adults with primary insomnia (Herring et al. 2012, Sun et al. 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, Bray, Neville 2014).

Suvorexant may have other advantages that are of benefit specifically in the MS population. Suvorexant appears not to adversely affect next-day balance in healthy non-elderly subjects. In addition, suvorexant appears not to affect memory as measured by word recall. MS patients often have ataxia and cognitive impairment as a result of their disease. Orexins are considered to be involved in arousal and maintenance of the waking state. As such, suvorexant may provide unique clinical benefit as a treatment of MS fatigue with co-morbid insomnia.

This project proposes to study objective and clinical measures of insomnia, daytime sleepiness and fatigue in patients with MS fatigue and co-morbid insomnia while treated short-term with suvorexant 10-20mg versus placebo. Those qualifying will receive suvorexant and placebo for each of 14 nights in a cross over design with 7 nights of washout between treatments. There will be an optional titration to suvorexant 20mg (or matching placebo) after 5-7 days of each active treatment period. Primary outcome to be measured will be change in ISI on both conditions (Suvorexant 10/20mg versus placebo).

The primary outcome to be measured will be change from baseline for the two conditions (suvorexant 10/20 mg and placebo) on the Insomnia Severity Index.

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

6. Study Objectives

6.1 Primary Objective

1. To assess the efficacy of suvorexant in treating insomnia in Multiple Sclerosis patients with fatigue

6.2 Secondary Objective

2. To assess the effect of suvorexant on fatigue and daytime sleepiness in this population

7. Methodology and Timeline

7.1 Methodology:

- Multi-center (Evergreen as principal site)
- N= 50. Confirmed MS diagnosis, age 18-75, inclusive.
- Double-blind, cross-over trial

- Four clinic visits: Screening, baseline, cross-over, termination
- Timeline:
    - 1) Screening
    - 2) Treatment 1 (baseline)
        - Subjects who meet eligibility criteria will be randomized to receive 2 weeks of treatment (treatment period 1) with either suvorexant 10 mg or matching placebo (1:1) with optional titration (see 7.2). Drug will be dispensed by the independent research pharmacist, keeping both study staff and the subject blinded. 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 addition to a small monetary reimbursement per visit.
    - 3) Washout (14 days post baseline)
        - At the end of treatment period 1 (2 weeks), subjects will undergo efficacy assessment with repeated clinical scales. Subjects will then go through a 1-week open-label off-drug washout period. 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.
    - 4) Treatment 2 (7 days post washout, 21 days post baseline)
        - Treatment period 2 will also be 2 weeks long, with crossover from Period 1 - either suvorexant 10mg or matching placebo, with optional titration (see 7.2). At the end of this, subjects will undergo final assessment with clinical scales.

7.2 Interventions:

Study medication, to include 10-mg suvorexant and matching placebo, will be provided by Merck. The active medication will be suvorexant 10 mg every bedtime. The research pharmacist at EvergreenHealth will randomize the subject and the subject is provided active and placebo, in separate containers labeled for proper order of consumption based on study assignment. Study medication will be dispensed at randomization (Visit 2, start of Treatment Period 1) with separate pill bottles marked “Period 1, use this bottle first” and “Period 2, use this bottle after the break.” An extra 6-day supply of medication will be provided for each study period to allow a window for scheduling of appointments.

Optional Drug Titration: There will be an optional titration to two pills at night (changes to suvorexant 20mg or matching placebo) after 5-7 days of each active treatment period. This will be based on a phone interview entailing answering questions about drug tolerance and whether the participant would like to escalate the dose of drug.

8. Study Population:

8.1 Inclusion criteria

- Diagnosis of MS made at least 3 months prior based on McDonald criteria.
- Age 18-75 inclusive
- Expanded Disability Status Scale (EDSS) 0- 7.5.
- Clinical stability defined as no MS exacerbation or change in disease modifying therapy for 60 days prior to screening.
- Screening Fatigue Severity Scale score of ≥4.0.
- 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.
- 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.
- Signed and dated IRB-approved informed consent form before any protocol-specific screening procedures have been performed.

8.2 Exclusion criteria

- Use of potential MS-associated fatigue drugs within 3 days of screening until study completion, including modafinil, armodafinil, amantadine, methylphenidate, products with amphetamine or dextroamphetamine.
- Use of any of any prohibited medication (see below) from 3 days prior to screening to termination visit.
- Female 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).
- History of narcolepsy.

- Has a diagnosis of severe chronic obstructive pulmonary disease (COPD), defined by FEV1 < 50% of predicted on most recent available pulmonary function test (PFT). PFT is not required if the subject has never been diagnosed with COPD.
- Has a history of severe obstructive sleep apnea (OSA), with severe OSA defined as having an apnea-hypopnea index (AHI) > 30 on prior polysomnograph (PSG). PSG is not required if there is no history suggesting severe OSA.
- Is concurrently using other central nervous system(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. Medical marijuana is allowed if consumed at the patient's usual dose at least 2 hours prior to or 8 hours after taking the study drug. Recreational marijuana is not allowed from screening until end of study.
- Has evidence at screening of severe hepatic impairment as defined by a Child-Pugh score > 10.
- Cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent.
- Suicidality or severe depression as measured by screening Beck Depression Inventory II (BDI) score > 28 or score of >1 on BDI Q9 (suicidality screen) at any time during the study.
- Any other serious and/or unstable medical condition.

9. Prohibited Medications

The following medications are not permitted to be used from 3 days prior to screening through the duration of the subject's participation in the study:

- Fatigue Medications
    - Modafinil
    - Armodafinil
    - Amantadine
    - Methylphenidate
    - Products with amphetamine or dextroamphetamine
- 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 Wart

10. Visit Schedules and Assessments

10.1 Enrollment

Subjects who may qualify for this study will be identified in the context of clinical care at the participating site. 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 educational opportunities, referrals from other area neurologists, sleep medicine physicians, the National MS Center website, and the website of EvergreenHealth or other site. Patients may contact a participating site after reading a notice about the study on the Institute's website or other online postings. Subjects who are not established patients at a participating site 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.

10.2 Screening Clinic 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. A history of the patient's MS diagnosis, past medical history and sleep symptoms will be reviewed. Diagnosis of MS will be confirmed based on revised McDonald Criteria (Polman et al. 2011). Diagnosis of insomnia will be confirmed following DSM-5 criteria. Rating of MS fatigue will be based on the Fatigue Severity Scale. Beck depression index (BDI) will be performed. Current medication list will be reviewed. Eligible subjects will have a stable MS medication regimen for 60 days 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 3 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 and a neurological examination. Neurological exam will include disability rating by expanded disability status scale (EDSS) (Kurtzke 1983). Laboratory testing will include complete blood count (CBC), complete metabolic panel (CMP), with calculation of the Child-Pugh score for any subjects with liver dysfunction. Pre-menopausal women without surgical sterilization will have urine human chorionic gonadotropin (hCG) measured.

The wearable activity/sleep monitor will be dispensed at this visit to all subjects who meet eligibility criteria. This will be a FitBit™ device worn by the subjects throughout the remainder of the study. The research coordinator will oversee patient education around FitBit use. The FitBit is easy for subjects to put on and requires minimal user programming to upload data. Recorded outcomes are described below (see outcome measures). Subjects will be encouraged to wear the monitor 24-hours per day. Patients will be instructed to complete a sleep diary for seven days prior to next visit (see 11. Outcome measures).

10.3 Baseline Clinic Visit 2

Clinic Visit 2 will occur within 7-14 days after the screening visit. In addition to screening for eligibility, medications will be reviewed again to ensure stability of the MS medication regimen and absence of any prohibited medications.

Following confirmation of eligibility, an eligible patient will complete the baseline assessments of the insomnia severity index (ISI), modified fatigue impact scale (MFIS), Fatigue visual analogue scale (VAS-F), Global impression. The following measures will be provided for the participants to take home for use at the time of Phone Visit 2 and Phone Visit 5: Study scales (ISI, MFIS, VAS-F, BDI, Global impression). Sleep diaries will be provided for use after Phone Visit 1 and Phone Visit 3.

Following confirmation of eligibility, 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 and research coordinator 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 2 pill bottles, each containing identical appearing active or placebo study medication tablets, with identification known only to the research pharmacist. See Section 7.2 regarding study medication preparation and distribution.

The patient will be provided with pre-stamped and pre-addressed envelopes for return of unused study medication and study diaries at end of study.

10.4 Phone visit 1

Phone Visit 1 will occur 5-7 days after Clinic Visit 2 to review safety and tolerability through questioning about adverse events. BDI Q9 (suicidality risk) will be administered. Subjects with answer of 2 or 3 will be asked to discontinue study medication immediately and unscheduled visit or emergency referral will be arranged. Subjects with BDI Q9 score 0 or 1 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 20 mg po QHS (or matched placebo) using a titration decision algorhythm. At this visit, subject will be reminded to wear sleep monitors and to start recording sleep diaries every morning.

10.5 Cross-over Phone Visit 2 (14 days post treatment)

Phone Visit 2 will occur at the completion of the first treatment period (day 14 following baseline). Medications will be reviewed again to ensure absence of any prohibited medications. Any possible adverse events (AE) will be assessed.

Study scales (ISI, MFIS, VAS-F, BDI, Global impression) will be self-administered by the participant with study staff oversight, as needed. Data from the wearable activity / sleep monitor will be collected. Completion of the 7-days sleep diary and scales (sQUAL and sFRESH) will be verified remotely.

Subjects will be instructed to take no study medication for one week, then to start taking the study medication (active or placebo) for Period 2.

10.6 Phone Visit 3 : Start of Treatment Period 2

Phone Visit 3 will occur 1 week after Phone Visit 2 (day 21 after baseline) and will mark the beginning of treatment period 2. Medications will be reviewed again to ensure stability of the MS medication regimen and absence of any prohibited medications. Any possible adverse events (AEs) will be assessed.

Subjects will be instructed to begin taking drug from the bottle marked “Period 2.”. All subjects who received active medication in treatment period 1 will take placebo, and all subjects who received placebo in treatment period 1 will take active medication (10mg) while double blind.

10.7 Phone Visit 4

Phone Visit 4 will occur 5-7 days after Phone Visit 3 to review safety and tolerability through questioning about adverse events. BDI Q9 (suicidality risk) will be administered. Subjects with answer of 2 or 3 will be asked to discontinue study medication immediately and unscheduled visit or emergency referral will be arranged. Subjects with BDI Q9 score 0 or 1 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 20 mg po QHS (or matched placebo) using a titration decision algorhythm. At this visit, subjects will be reminded to wear sleep monitors and to start recording sleep diaries.

10.8 Termination Phone Visit 5

Phone Visit 5 (final visit) will occur 2 weeks after Phone Visit 3 (day 35 after baseline). Medications will be reviewed again. Any possible AE will be assessed.

Study scales (ISI, MFIS, VAS-F, BDI, Global impression) will be self-administered by the participant with study staff oversight, as needed. Data from the wearable activity / sleep monitor will be collected. Completion of the 7-days sleep diary and scales (sQUAL and sFRESH) will be verified remotely. Patients will be instructed to stop taking study medication and place all unused study medication from Period 1 and Period 2 in the mailing envelope. They will be asked to include all study materials (surveys and diaries) in the envelope and to mail it as soon as possible.

10.9 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.

11. Outcome Measures

All outcome measures will be based on end of treatment period compared to baseline visit.

11.1 Primary Efficacy Measure:

- **Insomnia Severity Index (ISI)**

The ISI is a 7-question survey assessing symptoms of insomnia over the past week. Maximum score is 28, with higher scores indicating greater severity. The ISI has been validated for use in insomnia research (Bastien, Vallieres, Morin 2001).

11.2 Secondary Efficacy Measures:

- **sQUAL (Subjective Quality of Sleep)**
  This is a single question, "How would you describe the quality of your sleep last night?" There are 4 choices to answer:
  Choices: 1= poor, 2 = fair, 3= good, 4= excellent

- **sFRESH (Subjective refreshed feeling on waking)**
  This is a single question, "How refreshed do you feel this morning?" There are 5 choices to answer:
  Choices: 1= not at all refreshed, 2 = a little refreshed, 3= moderately refreshed, 4= quite a bit refreshed, 5= extremely refreshed

- **Change in Modified Fatigue Index Scale (MFIS) Score at 2 weeks vs baseline.**
  The MFIS is a well-validated fatigue measure in MS (Tellez et al. 2005). The MFIS has a Cronbach's alpha of 0.81 (National MS Society). In MS, it has been found to have intratest reliability, no ceiling or floor effects and greater sensitivity to change than the FSS (Kos et al. 2003). The test has 21 items with physical, cognitive and psychosocial subscales. Subjects will complete the MFIS as the first test conducted on the day of visit. Their ratings on the 21-item questionnaire will be based on their fatigue experience over the previous 1 week. The total MFIS score will be used for primary efficacy measure.

- **Fatigue Visual Analogue Scale (VAS-F)**
  The VAS-F is a 10-cm line that asks subjects to rate fatigue on a scale of 0 (no fatigue) to 100 (fatigue "as bad as it can be") by marking their fatigue level on the line (See appendix). The VAS-F has been validated as a measure of response to therapy in MS fatigue populations (Rammohan et al.2002, Weinshenker et al. 1992). Ratings will be based on their fatigue experience over the previous 1 week.

- **Wearable Sleep Monitor (WSM)**
  A Fitbit device will be worn throughout the study. A 7-night average for screening period will be compared with the final 7-night average for both treatment periods. Outcome measures based on the wearable sleep monitor will include:
  - Total minutes asleep
  - Minutes awake during time in bed
  - Number of awakenings
  - Time in bed

- **Subjective Global Impression of Change**

  This is a single question: “How would you rate change in your level of physical and mental function, during the study?” Response ranging from "Extremely improved", "Much improved", "Slightly improved", "No change", "Slightly worse", "Much worse", and "Extremely worse".

11.3 Exploratory Efficacy Measures:

- **Daily step count**

  Data obtained from wearable activity monitor will be recorded. The average of 7 days will be calculated.

- **Beck Depression Inventory**

Note on sleep diary content

During screening and each treatment period, patients will complete a 7-day sleep diary. They will be asked to record each morning the following:

1. The time they went to bed
2. Approximate time they went to sleep
3. Number of awakenings
4. Approximate time they awoke for the last time (in the morning)
5. Time they got out of bed in the morning
6. sFRESH
7. sQUAL

Note on the Use of the Wearable Sleep Monitor and activity monitor

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

12. Safety Monitoring

12.1 Safety measures:

Laboratory testing: All subjects: CBC, CMP. As-indicated: urinary pregnancy testing
Safety will be monitored by adverse event (AE) reporting, physical examination, laboratory evaluation.

Monitoring for suicidality: The BDI is being performed due to suvorexant being a central nervous system depressant, which could cause suicidal ideation and behavior. This test is performed at screening, baseline and final visit. At phone visits 2 and 5, the BDI is administered and at phone

visit 1 and 4, question 9 of the BDI is administered to ascertain suicidal thoughts or wishes. A score of 2 or 3 on BDI question 9 indicates that the patient would be at significant suicide risk. A high score on the BDI or BDI question 9 at any point would result in immediate discontinuation of the study medication and unscheduled visit or emergency room referral, as indicated.

12.2 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. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events.

An 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:

- Unrelated: 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.

12.3 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 because the entire study will be conducted over 2 months. 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.

12.4 Serious Adverse Events Reporting

The Food and Drug Administration (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) in the case of reportable death or life-threatening events.
- 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, Admission H&P, Discharge Summary, Consultative reports, etc. could be very helpful. In the case of a fatal event, provide an autopsy report, when it becomes available.

13. Data Management and Statistical Analysis

Sample Size Considerations

This is a prospective, double-blinded, randomized controlled pilot study. The purpose is to test a hypothesis in a preliminary fashion in this population with a specific neurological disease. In our initial statistical plan, the study was underpowered, based on an enrollment target of 30 subjects. We later increased the enrollment to 50 subjects to adequately power the study. We assume that no more than 10% of subjects will withdraw, be lost to follow-up or be dropped for protocol violations, leaving 45 subjects for final analysis. Power calculation is based on a cross-over design. We assume that the true difference in mean Insomnia Severity Index (ISI) between the treatments will be 1.75 units based on the findings of a cross-over trial by Herring et al for treatment effect of suvorexant on ISI in patients with primary insomnia. (Herring et al, 2012) We assume that our cohort with MS with adjustable dose titration (10mg and 20mg) will yield a slightly lower treatment response than that of the Herring cohort at 20mg (-2.0 units). We assume a normal distribution with standard deviation of the difference in the ISI is 4.1, based on normative data from Bastien, et al, who conducted the primary validation study. (Bastien et al, 2001) With these assumptions, the probability (power) is 81 percent that the study will detect a treatment difference at a two-sided 5.000 percent significance level. (PS Power and Sample Size Calculations, version 1.7.15, http://hedwig.mgh.harvard.edu/sample_size/size.html#cross)

Statistical Analysis

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

Generally, the mean over the week prior to visit 2 (baseline) will be compared to the mean over the final week of Treatment Period 1 and the mean over the final week of Treatment Period 2 for treatment effects. This will be done by treatment arm. Level of significance will be $p < 0.05$. Minimum drug adherence for per-protocol criteria will be 75%. We plan to do both intention to treat and per-protocol analyses.

14. Study Management

14.1 Patient stipend

The subjects will be allowed to keep the wearable sleep monitor given at screening. They will also receive a small monetary stipend per completed in-office and phone visit.

14.2 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 Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

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