NN110

Statistical Analysis Plan

A Dose Selection Trial of Light Therapy for Impaired Sleep in Parkinson's Disease

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ABBREVIATIONS

ABBREVIATION	DEFINITION
ADR	Adverse Device Reaction
AE	Adverse Event
AERS	Adverse Event Reporting System
BWLT	Bright White Light Therapy
cIRB	Central Institutional Review Board
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DRLT	Dim-Red Light Therapy
ESS	Epworth Sleepiness Scale
FDA	United States Food and Drug Administration
FSR	Final Study Report
GDS-15	Geriatric Depression Scale
IMM	Independent Medical Monitor
LT	Light Therapy
MCID	Minimum Clinically Important Difference
MDS-UPDRS	Movement Disorder Society-Unified Parkinson Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
mRGC	Melanopsin-containing Retinal Ganglia Cells
NINDS	National Institute of Neurological Disorders and Stroke
NMSS	Non-Motor Symptoms Scale
PD	Parkinson's Disease
PDSS-2	Parkinson's Disease Sleep Scale - 2
PDQ-39	Parkinson's Disease Questionnaire - 39
PFS-16	Parkinson’s Disease Fatigue Scale
PP	Per-Protocol
PPI	Protocol Principal Investigator
SAD	Seasonal Affective Disorder
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCN	Suprachiasmatic Nucleus
SOC	System Organ Class
TST	Total Sleep Time
UV	Ultraviolet Light
WASO	Wake After Sleep Onset

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PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses for the NeuroNEXT NN110 (ENLITE PD) study [National Institute of Neurological Disorders and Stroke (NINDS) grant # U01NS114001; ClinicalTrials.gov ID: NCT04291014]. The intent of the planned analyses identified in this SAP is to support the completion of the final study report (FSR) and may be used to inform regulatory submissions or included in future manuscripts. All final, planned analyses identified in this SAP will be performed by the Data Coordinating Center (DCC) only after the last randomized study participant has completed the study. Once all data have been cleaned and verified, a "locked" version of the data will be used for reporting the final study results. Key statistics and study results will be made available to the Protocol Principal Investigator (PPI) following database lock and prior to completion of the final FSR. This SAP was finalized under protocol version 7.0.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting over one million people in the United States (Dorsey et al, 2005; Alves et al, 2008). Sleep disturbances are one of the most common and disabling non-motor manifestations of PD, affecting as many as 90% of patients (Lees et al, 1988; Factor et al, 1990; Tandberg et al, 1998). Disrupted sleep-wake cycles contribute to poor quality of life, impaired mood, poor cognitive performance, and increased risk for accidents, leading to increased morbidity and mortality in the PD population (Comella et al, 1993; Schenck et al, 1996; Frucht et al, 1999; Karlsen et al, 1999; Frucht et al, 2000; Ondo et al, 2001; Dhawan et al, 2006). Similarly, fatigue affects as much as 70% of patients with PD (Stocchi et al, 2014). Current treatment options for impaired sleep and fatigue are limited and associated with undesirable adverse effects. There is therefore a great need to develop new treatment modalities.

The exact pathophysiology of sleep/wake disturbances and fatigue in PD remains largely unknown, but the etiology is likely to be multifactorial, including impact of motor symptoms on sleep, adverse effects of antiparkinsonian medications, and neurodegeneration of central sleep regulatory areas (Linazasoro et al, 1993; Rye et al, 2000; Fabbrini et al, 2002; Fabbrini et al, 2003; Rye, 2003; Stack and Ashburn, 2006; Fronczek et al, 2007). Sleep disturbances may precede motor symptoms of PD, reflecting the degeneration of areas such as the raphe nucleus and locus coeruleus that constitute pre-clinical stages 1 and 2 of the pathological staging proposed by Braak (Braak et al, 2003; Abbott et al, 2005; Braak and Tredici, 2008). Dopaminergic dysfunction and neuronal degeneration of these areas may destabilize the "on-off-switch" pattern of regulation of the sleep-wake cycle (Saper et al, 2001; Lu et al, 20006). The input from the suprachiasmatic nucleus (SCN) of the hypothalamus, the central pacemaker of the circadian system, has a major influence on sleep stage switching (Saper et al, 2001; Achermann & Borbely, 2003). Circadian rhythms are physiological and behavioral cycles with a periodicity of approximately 24 hours, generated by the SCN (Ralph et al, 1990; Weaver, 19998; Dijk & Lockley, 2002). These rhythms influence most physiological processes, including the sleep-wake cycle (Scammell et al, 2017). A growing body of evidence suggests significant alterations of the circadian system in PD (Breen et al, 2014; Videnovic et al, 2014b; Videnovic and Willis, 2016). Videnovic et al (2014a) recently demonstrated blunting of the circadian melatonin rhythms in participants with PD, which may be indicative of a weakened circadian signal in PD.

Circadian rhythms are synchronized with the solar day by "zeitgebers" (German for "time-giver"), of which light is the most important and potent stimulus (Czeisler et al, 1986; Klerman et al, 1998). This synchronization ensures that behavioral, physiologic, and genetic rhythms are timed appropriately with daily changes in the environment and with each other. Supplementary exposure to bright light has shown beneficial effects on sleep quality and daytime vigilance of health elderly as well as patients with dementia, and has been increasingly applied in a variety of sleep and neuropsychiatric conditions (Kohsaka et al, 1998; Kobayashi et al, 1999; Iskra-Golec et al, 2001; Ancoli-Israel et al, 2003; Fetveit et al, 2003; Dowling et al, 2005). Stimulation of the SCN has been hypothesized as one of the mechanisms of bright environmental light effects on mood, sleep, and circadian rhythms (McEnany & Lee, 2005; Caiochen, 2007; Figueiro et al, 2007; Riemersma-van

der Lek et al, 2008; Hubbard et al, 2013). Light therapy (LT) has been demonstrated to be beneficial for fatigue as well. Supplemental light exposure among cancer patients treated with chemotherapy is associated with reduced fatigue and improved circulation activity rhythm synchronization compared with patients who did not receive LT (Ancol-Isreal et al, 2012; Liu et al, 2013).

While there has been limited exploration of the effects of supplemental light exposure on sleep in pre-clinical models of PD, there is substantial evidence that light signaling affects dopaminergic function. Electrophysiological studies in rodents have demonstrated that dopaminergic neurons respond to light (Dommett et al, 2005). Dopamine is a likely mediator of light signaling to the retinal circulation clock; the retino-hypothalamic tract provides direct input from the retina to the SCN (Witkovsky, 2004). Exposure to light facilitates recovery of motor function in a chronic experimental model of PD (Harrell & Balagura, 1974). Another potential, yet not systematically studied, mechanism of light exposure in PD is the neuroplastic remodeling of brain circuits. Neuroplastic changes, defined as adjustment through neuronal re-organization, have been shown in the dopaminergic system following chronic regimens of explore to, or deprivation from, light (Tsai et al, 2011).

A recent study using chemogenetic activation of intrinsically photosensitive melanopsin-containing retinal ganglia cells (mRGCs) in dark-housed mice, which simulates the excitatory effects of bright light, has indicated that the non-visual effects of light are selectively mediated by mRGCs (Milosavljevic et al, 2016). Circadian phase resetting, mood, and vigilance state modulation are among these light-modulated physiological effects (Milosavljevic et al, 2016; Fifel, 2019). In line with the anatomy of mRGCs, the study also showed that mRGCs mediate the activation of several brain structures involved in the regulation of widespread aspects of physiology and behavior which are also dysfunctional in PD. Another area related to this study and PD is research with amphetamines, as these agents interact with the production of dopamine. In a study that used light as a stimulus, light improved mobility, suggesting that LT may have a beneficial effect on the dopaminergic motor system (Kallman & Isaac, 1975).

Research of LT in the PD population is at an early stage. Several studies demonstrated significant improvements in sleep, sleepiness, mood, and tremor (Paus et al, 2007; Willis & Turner, 2007; Willis et al, 2012). The side effect profile for LT studies in PD is consistent with other LT studies (Terman & Terman, 1999; Terman & Terman, 2005). While these outcomes of LT are encouraging, LT parameters require further study, including optimal frequency, duration, intensity, and spectral properties of the light. This study will investigate frequency of LT, which represents one of the central aspects of dosing that will influence adherence and tolerability of this treatment modality in the PD population.

2. STUDY METHODS

2.1 Study Design

This is a 16-week, randomized, phase II, parallel-group, placebo-controlled, dose-selection clinical trial of LT in participants with PD and co-existing sleep disruption using a comparative selection trial design.

Selection trials are an early-stage design used to select a subset of treatments for further testing in a subsequent trial (Levin, 2012). Selection trials traditionally include only active comparators, and selection is based on numerical superiority of average treatment responses rather than formal inferential testing and control of type I error rates below the conventional 5% level. A comparative selection trial includes one or more placebo comparators and expands the criterion for selection of active treatments to also necessitate that at least one of the active treatments is demonstrably superior to the placebo comparators (Levy et al, 2006). In the present study, the primary objectives are to (i) determine whether daily bright-white light therapy (BWLT) improves sleep in PD sufficiently to carry forward in a phase III efficacy trial relative to two control LT conditions and, if so, (ii) to select the superior dose frequency to carry forward.

This trial is designed for selection of both efficacy and control LT treatments. Selection of the optimal efficacy dose frequency of daily BWLT will be based on 8-week change from baseline in Parkinson's Disease Sleep Scale 2nd Version (PDSS-2) score, on the relative burden of alternative dosages of daily BWLT, and on confirmation of adequate safety of the preferred dose frequency. Selection of the control LT condition will similarly be based on 8-week change from baseline in the PDSS-2 score, on the relative burden of alternative dosages of LT, and on confirmation of adequate safety of the preferred control LT condition. The trial is not designed to demonstrate statistical superiority of any dose frequency of LT but rather to have high probability of selecting the superior dose frequency based on a set of selection rules that combine information on change in PDSS-2, participant burden, and safety.

Participants will be consented and screened at 25 clinical sites that are part of the NeuroNEXT Clinical Trial Network. After screening, eligible participants will enter a 4-week lead-in period. They will be educated about principles of sleep hygiene. Specifically, participants will watch two video modules and receive a monograph developed by the Parkinson's Foundation (Videnovic, 2018). This monograph outlines principles of sleep hygiene and sleep issues associated with PD. Participants will wear a wrist activity monitor (Actiwatch Spectrum Plus: Phillips Respironics, Bend, OR) to collect wrist activity (for latter rest-activity cycle calculations) and light exposure. Light levels recorded by the monitor will be used to verify LT exposure times and spectrum, and to evaluate off-study exposure. Participants will also keep a daily sleep log in which bedtime, wake-up time, estimated total sleep time (TST), sleep latency, wake after sleep onset (WASO), naps, and sleep quality are recorded. The 4-week lead-in period will allow for proper characterization of baseline sleep and other motor and non-motor outcomes and will ensure that participant's sleep dysfunction cannot be remedied by sleep education using established training tools. Participants will be asked if and how they utilized the information from the monograph at the end of the lead-in period.

After completing their 4-week lead-in period, all participants will have a baseline visit. The investigator or designee will again review the study inclusion/exclusion criteria, participant medical history, concomitant medications, and record response on the Sleep Question of the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part I to confirm ongoing eligibility for study. Thereafter, up to 158 participants will be randomized 1:1:1:1 into four groups without stratification:

1) BWLT twice daily (morning and evening)
2) BWLT once daily (evening only)
3) BWLT once weekly (evening only)
4) Dim-red light therapy (DRLT) twice daily (morning and evening).

Participants randomized to the once-weekly BWLT and twice-daily DRLT groups will serve as controls of dose frequency and of wavelength and illuminance, respectively. DRLT will serve as a control condition as it has been widely accepted as control in clinical investigations of LT. All studies that employ DRLT as a control condition face the challenge of study participants being aware of their treatment assignment. Similarly, study personnel may easily be unblinded to the treatment assignment. Study participants will be informed that an important aspect of the study is to assess effects of different wavelengths of light on sleep and will be reminded not to disclose their assignment to the blinded evaluator.

Participants randomized to BWLT will receive one hour of full-spectrum white light (10,000 lux) in direction of gaze, in the morning and evening (twice daily) or in the evening only, daily, or weekly, for eight weeks. Participants randomized to DRLT will receive one hour of filtered red light (300 lux) in direction of gaze, in the morning and evening (twice daily), for eight weeks. To limit day-to-day variation in light exposure timing, yet to provide some individual flexibility, participants will be asked to select convenience fixed one-hour time-windows and, for the weekly condition, to select a convenient day for LT. The morning session will occur between 3 and 5 hours after habitual wake-up time. The evening session will occur between 3 and 5 hours before habitual sleep time. This schedule will minimize chances of LT causing phase advances or delays of the circadian clock. Participants will record light exposure duration and timing daily or weekly using an LT log, will wear

a wrist activity and light exposure monitor, and will complete a daily sleep log for the eight weeks of LT.

Four weeks after their baseline visit, all participants will have a Week 4 mid-treatment assessment. Eight weeks after their baseline visit, participants will discontinue LT. For the 4 weeks after completing their Week 8 visit, participants will continue to complete daily sleep logs and to wear a wrist activity monitor to assess carry-over effects of LT. At the week 8 or early termination visit, participants will be asked to complete a credibility question to evaluate their acceptance of their randomized intervention as a useful treatment for sleep dysfunction related to Parkinson's disease (Devilly & Borkovec, 2000).

We propose once-weekly BWLT as a control LT condition and not an alternative efficacy dose frequency because we believe that a true physiologic effect of once-weekly BWLT on sleep dynamics is implausible. If true or placebogenic effects of once-weekly BWLT are not less than those of twice-daily DRLT, then the lower burden of once-weekly BWLT makes it preferable. Nevertheless, regardless of whether any observed improvement in PDSS-2 score among participants exposed to once-weekly BWLT is due to true or placebogenic effects, we would judge daily BWLT as worthy of carrying forward to a phase III trial only if the benefit of daily BWLT is substantially greater than any benefit from once-weekly BWLT. Further trials testing low-frequency dosing of BWLT prior to initiating a phase III trial could be explored if neither daily BWLT treatment exceeds our prespecified comparison thresholds of mean 8-week change in PDSS-2 score, but once-weekly BWLT exceeds a prespecified threshold when compared to twice-daily DRLT.

2.2 SunRay Light Boxes

SunRay light boxes (The SunBox Co., Gaithersburg, MD) will be used for LT administration. The SunRay light box is a table-top, personal light therapy device. It is designed for use on a table, desk, or counter in a home, office, or clinical setting. The device consists of a light panel that contains light bulbs, diffuser, and on/off switch. It resembles a flat panel computer monitor. There are two metal stands that attach to two lateral sides of the light box. The power supply connects to standard household power (100 – 240 VAC). The power supply is shipped separately and is plugged into the back of the light panel. Dimensions of the box are 15.5" (H) x 23" (W) x 3.25" (D). SunRay light boxes will be equipped with a spectrally transparent prismatic diffuser or red filter, both of which block ultraviolet light.

> ***Bright White Light Box:*** In the light boxes used for BWLT, light emission comes from four light bulbs and diffusor to direct the light towards the user. This creates a soft, even treatment field.
>
> ***Dim Red Light Box:*** In the light boxes used for DRLT, light emission comes from four light bulbs and diffusor covered by a red filter.

The light boxes used for BWLT and DRLT are both non-invasive. The only physical interaction of the participant with the device is in turning the device on and off.

2.3 Enrollment & Randomization

Up to 158 participants will be randomized in a 1:1:1:1 ratio into four groups without stratification: (i) BWLT twice daily (morning and evening), (ii) BWLT once daily (evening only), (iii) BWLT once weekly (evening only), and (iv) DRLT twice daily (morning and evening). Randomization will be implemented using an interactive web response system. The randomization schedule will be constructed using permuted blocks to ensure balanced treatment allocation over time. Online randomization will follow confirmation of eligibility and completion of all required baseline procedures. Following randomization, participants will be given a light box with instructions to implement light therapy sessions twice daily, once daily, or once weekly.

2.4 Bias Mitigation Measures

Each investigation team will utilize an evaluator who will be responsible for collecting all of the primary, secondary, and exploratory endpoint data. These evaluators will be masked (blinded) to treatment arm assignment. Steps will be taken to maintain the masking throughout the

investigation. The evaluators will be certified to conduct the standard evaluations. During each study visit, the study coordinator will remind the participant of the importance of not discussing their device to prevent accidental breaking of the mask. The participants will be informed that one of the major goals of the project is to determine best frequency and spectral properties of LT.

It would be almost impossible to control for other sources of light, as the protocol is done in "real world" conditions not in a controlled experimental environment. The goals of this trial are to select an appropriate dosage of supplemental light for a future trial of effectiveness. A future trial will be carried forward only if supplemental BWLT improves sleep. Results from the pilot trial in which participants were similarly exposed to ambient light suggest that it will improve sleep. Estimates of person-to-person variation from the pilot trial, incorporating variable exposure to ambient light, were included in the basis of our power calculations. Nevertheless, a possible finding from this work may be that neither once- nor twice-daily BWLT adequately improves sleep, potentially due to exposure to ambient light. While one could more cleanly evaluate effects of BWLT in a controlled experimental environment, the relevant context for evaluating the proposed LT includes variable exposure to ambient light. Exploration of the effects of ambient light is included in planned exploratory analyses. The randomization should (in theory) lead to approximately equal light exposure from other sources across the four stud groups. In order to minimize effects of other light sources during LT sessions, participants will be advised to position the LT box away from direct light sources, such as windows with significant outside light exposure.

2.5 Participant Compliance

Study participants will be instructed on proper use of the light therapy device at the screening/baseline visits. Participants will be instructed to expose themselves to the light therapy device according to the investigator's instructions and to record exposure in their LT logs. Participants will complete LT logs and record time and duration of each LT session. Study staff will educate study participants on the relevance of completing sleep and LT logs fully and in a timely manner. During the study visits, staff will check on completeness of sleep and LT logs and reinforce the importance of having complete logs.

2.6 COVID-19 Design Modifications

As a result of the COVID-19 outbreak, several changes to the protocol were allowed ***only*** if a visit would otherwise be missed due to institutional guidance limiting in-person visits as a result of the outbreak, if site staff or participant are concerned with performing an in-person visit due to the outbreak, or if a study participant is unwilling to attend an in-person visit due to COVID-19.

2.6.1 Remote Study Visits

The following study visits may be performed remotely, via teleconference, if an in-person visit is not possible because of COVID-19:

- Visit 3 (Week 4): Mid-Treatment Assessment
- Visit 4 (Week 8): End of Intervention Assessment
- Visit 5 (Week 12): Final Study Visit / Washout Assessment

However, the week 8 (end of intervention assessment) should be conducted in-person unless site specific institutional guidance requires remote visits. In advance of the scheduled visits coordinators will request the Actiwatch to be shipped to their site. This will allow the Actiwatch to arrive at the site, be checked by the site, and sent on to the participant in time for their scheduled visit date. Along with the Actiwatch, new Sleep Logs and Light Therapy Logs (not required for Visit 5), the following items will need to be sent to participants in a sealed envelope to be opened during the video conference:

- PDSS-2
- Parkinson's Disease Fatigue Scale (PFS-16)
- Epworth Sleepiness Scale (ESS)

- Parkinson's Disease Questionnaire – 39 (PDQ-39)
- Geriatric Depression Scale (GDS-15)
- Visuospatial/Executive Section of the Montreal Cognitive Assessment (MoCA) only
    - Connect the Dots
    - Copy the Cube
    - Draw the Clock
- Patient Questionnaire of the MDS-UPDRS (Parts 1B and 2)
- Credibility Questionnaire (Visit 4 only)

A prepaid return FedEX envelope should be included for the participant to return the Actiwatch from their previous visit, completed Sleep Logs, completed Light Therapy Logs, and completed assessments from the current visit.

Both a site coordinator and a blinded evaluator must be available to meet with participants on the same day. As described above, study materials will be mailed by the site coordinator to the participant in advance of the visit in a sealed envelope. Participants will be instructed to open the sealed envelope during the videoconference. A return envelope will be provided to the participant to send back completed study materials to the site coordinator.

Due to the limitations of remote visits, the following items from the MDS-UPDRS Part III: Motor Examination will not be examined:

- 3.3 Rigidity
- 3.12 Postural Stability

For all remote visits, video conferencing software should be compliant with sites' institutional guidance for information security.

2.6.2 Limited In-Person Evaluation Visits

If an in-person evaluation visit at weeks 4, 8, and 12 is possible, then all assessments should be performed. If institutional guidance mandates a limited in-person visit, then the following procedures should have the highest priority:

- MDS-UPDRS
- MoCA
- Collect Actiwatch and Sleep Logs
- Dispense Actiwatch, Sleep Logs, and Light Therapy Logs

All other assessments may be performed remotely as soon as possible after the in-person visit, including the primary outcome of PDSS-2.

2.6.3 Visit 3 (Week 4) Mid-Treatment Assessment

If a participant's mid-treatment assessment needs to be performed remotely, the investigator should assess any adverse events (AEs) and determine if it is safe for the participant to continue light therapy for the next 4 weeks. This visit should mirror a full in-person week 4 visit with all assessments to be performed with the exception of the MDS-UPDRS Part III: Motor Examination as outlined in section 2.6.1.

2.6.4 Visit 4 (Week 8) End of Intervention Assessment

Every effort should be made to complete the end of intervention assessment visit in person. If due to a site's local COVID-19 guidance the visit must be completed remotely, the visit should mirror a full in-person week 8 visit, excluding the MDS-UPDRS Part III: Motor Examination as outlined in section 2.6.1. Additionally, arrangements should be made at the site to collect the light box from the participant via an approved in-person drop off.

2.6.5 Visit 5 (Week 12) Final Study Visit / Washout Assessment

If a participant's final study visit needs to be performed remotely, the visit should mirror a full in-person week 12 visit with all assessments to be performed, with the exception of the MDS-UPDRS Part III: Motor Examination as outlined in section 2.6.1.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives of this trial are:

i. To determine whether once- or twice-daily BWLT improves sleep in PD sufficiently to carry forward in a phase III efficacy trial.
ii. If the first objective is met, to select the optimal dose frequency to carry forward to the subsequent phase III efficacy trial.

These aims will be evaluated based on the 8-week change in the PDSS-2 score from baseline to the end of intervention and on the burden and safety of alternative dosing frequencies and wavelengths of LT using a comparative selection trial design. Only dose frequencies judged to be safe will be considered for selection. This type of trial is not designed to demonstrate statistical superiority of any dose frequency of LT but to have high probability of selecting the optimal dose frequency based on a set of selection rules that combine information on change in PDSS-2, participant burden, and safety.

3.1.2 Key Secondary Objective

The key secondary objective is to determine whether once-weekly BWLT is a non-inferior control condition relative to twice-daily DRLT. This aim will be evaluated based on the 8-week change in PDSS-2 score from baseline to end of study intervention and on the relative burden and safety of once-weekly vs. twice-daily LT.

3.1.3 Additional Secondary Objectives

Additional secondary objectives include the following:

i. To estimate the effect of daily BWLT on fatigue in PD as measured by 8-week change in the PFS-16 score from baseline to end of study intervention.
ii. To determine whether patients adhere to LT as assessed by the proportion of days with adherence to the prescribed dose frequency (weekly, once daily, or twice daily).

3.1.4 Safety Objectives

Safety will be evaluated by the occurrence of AEs classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Counts will be simultaneously compared among all four LT treatment groups to evaluate safety in regard to whether levels are statistically equivalent over time. While no serious safety outcomes are anticipated, we will track the proportion of participants in each treatment group who discontinue LT due to AEs and compare the rates of reportable safety events, e.g., serious or unanticipated adverse device effects. If any LT treatment is determined to be unsafe, then it will not be considered for a future trial as either an active or control condition.

3.2 Primary Endpoint

The primary efficacy endpoint will be the mean 8-week change from baseline in the PDSS-2 obtained from a linear contrast of least-square means estimated from the primary analysis model. The PDSS-2 is a 15-question instrument designed to simultaneously capture the multidimensional aspects of sleep-related problems and changes in sleep quality (Trenkwalder et al, 2011a). The Movement Disorders Society Task Force on Rating Scales has endorsed the PDSS-2 as an appropriate instrument for assessment of sleep in the PD population. Each question is scored from

0 to 4, with total scores ranging from 0 to 60 where higher scores indicate greater impairment. A total score cannot be computed if any component is missing. If two or fewer questions on an assessment are missing, missing items will be imputed using the mean over the observed item scores within the same visit. An imputed total score will be calculated based on the imputed item values, and then rounded to the nearest whole number. If more than two questions on the assessment are missing, the PDSS-2 total score will be considered missing for that assessment.

The PDSS-2 will be administered to study participants at baseline, and weeks 4, 8, 12, and early termination visits when applicable (visits 2, 3, 4, 5). The scale was derived from its first version, the PDSS, in order to encompass previously unmet needs in evaluation of specific sleep disturbances in PD, such as akinesia, pain and nocturnal restless leg syndrome. An important advantage of the PDSS-2 is its capacity to capture treatment effects better than the original PDSS. The minimal clinically important difference (MCID) for PDSS-2 has been recently reported and is 3.44 (Horvath et al, 2015). Since its publication in 2011, multiple studies have utilized the PDSS-2 to evaluate changes in sleep in the PD population (Trenkwalder et al, 2011b; Zibetti et al, 2013; Kovacs et al, 2014; Deli et al, 2015).

3.3 Key Secondary Endpoint

The key secondary objective of this study is to determine whether once-weekly BWLT is a non-inferior control condition relative to twice-daily DRLT. The PDSS-2 described above will be used again to select the preferred control LT condition.

3.4 Additional Secondary Endpoints

Additional secondary outcomes include mean 8-week change from baseline using the PFS-16 and the proportion of days with adherence to the prescribed dosage of LT.

3.4.1 Parkinson's Disease Fatigue Scale (PFS-16)

The secondary objective to capture the effect on fatigue will be assessed using the PFS-16, a patient-rated scale that measures fatigue (Brown et al, 2005). The scale allows the measurements of the presence of fatigue (seven items) and its impact on daily function (nine items). Seven items evaluate the presence or absence of the subjective experience of fatigue, with an emphasis on the physical effects of fatigue, e.g., "I feel totally drained." Nine items address the impact of fatigue on daily functioning and activities, including socialization and work, but not exercise specifically. Ratings are based on feelings and experiences over the prior 2 weeks. The item response options range from 1 ("strongly disagree) to 5 ("strongly agree"). A score of 1-5 is assigned to each response, with a maximum score of 80, where a higher score indicates a higher level of fatigue. A total score cannot be computed if any component is missing. If two or fewer questions on an assessment are missing, missing items will be imputed using the mean over the observed item scores within the same visits. An imputed total score will be calculated based on the imputed item values, and rounded to the nearest whole number. If more than two questions on the assessment are missing, the PDSS-2 total score will be considered missing for that assessment. The PFS-16 will be administered to study participants at baseline, and weeks 4, 8, 12, and early termination visits when applicable (visits 2, 3, 4, 5).

3.4.2 Adherence

The secondary objective of adherence will center on frequency of use, which is a major LT dosing question as it may influence effectiveness of LT and adherence to this form of therapy. Participants will record light exposure duration and timing daily or weekly using a LT log. LT logs will be dispensed/collected from study participants at baseline, and weeks 4 and 8, and early termination visits when applicable (visits 2, 3, 4).

For each prescribed dose frequency (weekly, once-daily, twice-daily), a binary measure of adherence will be recorded for each day (week). Each day (or week for those assigned to the once-weekly treatment group) from randomization to the earlier of the week 8 PDSS-2 collection date, return date for the light box, or early termination decision date will be assigned a binary indicator value based on whether the participant adhered to their prescribed dose frequency. If a

participant used LT in a manner that was more frequent or less frequent than their prescribed dose frequency, then they will be flagged as nonadherent for that day or week. The percent adherence of each participant will be calculated as the average of the daily or weekly binary indicator variable. A summary measure of adherence by treatment group will be calculated as the average of each participant's percent adherence within that group. Logs that indicated the participant had missed the session, by not providing a start and end time, will not be considered as a completed log.

3.5 Safety Endpoints

The number of AEs and serious adverse events (SAEs) will be tracked over time as described in section 4. While no serious safety outcomes are anticipated, we will track the proportion of participants in each treatment group who discontinue LT due to AEs and compare the rates of reportable safety events, e.g., serious, or unanticipated adverse device effects. Regardless of the selection based on the PDSS-2 for both primary and secondary outcomes, any safety concerns will take precedence.

4. SAFETY MONITORING

4.1 Adverse Event Reporting

The AE definitions and reporting procedures for this study comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization guidelines. The Site Investigator will carefully monitor each participant throughout the study for AEs. All AEs will be documented on case report forms (CRFs) designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational device being studied, whether serious or non-serious.

FDA, Office of Human Research Protection, and NeuroNEXT Central Institutional Review Board (cIRB) requirements for reporting AEs will be followed. Participants will be monitored for AEs from the time they provide informed consent until 30 days following their completion of the study (including early termination). At that point, all ongoing AEs will be followed to resolution.

Each Site Investigator and research team are responsible for identifying AEs and reporting them through the DCC Online Adverse Event Reporting System (AERS). Investigators are also responsible for complying with NeuroNEXT CIRB reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

All clinical AEs are recorded on the AE CRF and kept in the participant's study binder. The site should fill out the AE CRF and enter the AE information into the Online AERS within five working days of the site learning of a new AE or receiving an update on an existing AE. Entries on the AE CRF (and into the Online AERS) will include the following" type of event, data of onset, date of resolution, severity of event, relationship to the investigational device, action taken, and primary outcome of the event.

If discernible at the time of completing the AE form, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE CRF. However, if an observed or reported sign, symptom, or clinically significant (CS) laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE CRF. CS laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

4.2 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is any unfavorable and unintended sign (including a CS abnormal laboratory finding, for example), symptom, or disease in a study participant who utilized the study device, whether or not it is considered related to the study device.

Examples of AEs include new conditions, worsening of pre-existing conditions, CS abnormal physical examination signs (e.g., skin rash, peripheral edema, etc.), or CS abnormal test results

(i.e., lab values or vital signs). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered AEs. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity would be considered as worsened and therefore would be recorded as AEs.

AEs are detected in two ways:

- Clinical – Symptoms reported by the participant or signs detected on examination.
- Ancillary Tests – Abnormalities of vital signs, laboratory tests, and other diagnostic procedures.

The severity of all AEs will be graded according to common terminology criteria for adverse events (CTCAE), version 5.0. AEs reported using CTCAE will be recoded into MedDRA terms by the DCC.

The relationship of the AE to the investigational device should be specified by the Site Investigator, using the following definitions:

- **Unrelated:** Concomitant illness, accident, or event with no reasonable association with treatment.
- **Unlikely to be Related:** The reaction has little or no temporal sequence from administration of the investigational device, and/or a more likely alternative etiology exists.
- **Possibly Related:** The reaction follows a temporal sequence from administration of the investigational device and follows a known response pattern to the suspected investigational device; the reaction could have been produced by the investigational device or could have been produced by the study participant's clinical state or by other modes of therapy administered to the participant. [Suspected treatment related AE or adverse device reaction (ADR)
- **Probably Related:** The reaction follows a temporal sequence from administration of investigational device; is confirmed by discontinuation of the investigational device or by re-challenge; and cannot be reasonably explained by the known characteristics of the study participant's clinical state. (Suspected treatment-related AE or ADR)
- **Definitely Related:** The reaction follows a reasonable temporal sequence from administration of investigational device; that follows a known or expected response pattern to the investigational device; and that is confirmed by improvement on stopping or reducing the dosage of the investigational device, and reappearance of the reaction on repeated exposure (Suspected treatment-related AE or ADR)

An unexpected AE is any AE for which the specificity or severity of which is not consistent with the risks described in the protocol. An unexpected, suspected ADR is any unexpected AE in which, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational device caused the event.

4.3 Serious Adverse Events

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life threatening (i.e., poses an immediate risk of death to the study participant as the event occurred). This serious criterion applies if the study participant, in the view of the Site Investigator or Independent Medical Monitor (IMM), is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.

- Results in persistent or significant disability or incapacity. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the participant’s ability to conduct normal life functions.
- Results in congenital anomaly or birth defect in the offspring of the participant (whether the participant is male or female).
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgement, may jeopardize the participant, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for "seriousness" but is not an adverse experience and will therefore not be considered an SAE. An example of this would include a social admission (study participant admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

SAEs must be reported to the NeuroNEXT DCC within 24 hours of the site learning of the SAE. When an SAE is entered by a site investigator, the DCC will notify the IMM. The IMM will review the SAE report and may request further information if necessary.

4.4 Risk Assessment of Light Therapy

LT is a well-established treatment modality in sleep medicine and psychiatry. It is widely utilized in circadian rhythm disorders, seasonal affective disorder (SAD), depression, bipolar disorder, and Alzheimer’s disease (Eastman et al, 1992; Kohsaka et al, 1998; Dowling et al, 2005; Riemersma-van der Lek et al, 2008). LT devices have been studied and marketed internationally for 25 years. Numerous products have been used during this time frame, and the long-term effects of LT have been documented. To date, only benign and no long-term side effects have been reported with LT. In addition, studies of ocular safety of BWLT have shown daily BWLT to be safe and long-term ophthalmological reviews after up to 6 years of use have shown no ocular changes (Gallin et al, 1995). The majority of these devices have been intended for the treatment of SAD. No LT devices for the treatment of the symptoms of PD have been marketed to date. Though the indications are different, LT for SAD and PD are comparable, and the safety experience of LT for SAD is relevant to this clinical trial.

Safety-related events experienced during LT are generally benign and are resolved within the first two weeks of treatment. The most common side effects are headaches, eye strain, blurred vision, nausea, and jitteriness. Sleep problems have been reported but remit with proper timing of LT. For example, if LT is administered too late in the night, it may provoke hyperactivation of inability to initiate sleep. LT used too early in the morning may cause premature waking. Mood swings and agitation have been reported mainly in patients with bipolar disorder. Clinical reviews recommend such patients be on an effective mood stabilizer before initiating LT. Suicidality with LT is extremely rare. Over the past 30 years, three cases of an increase in suicidal ideation have been associated with LT (Praschak-Rieder et al, 1997). Two of these were in patients with bipolar I disorder, and one was from a patient with recurrent major depression. In an extensive follow-up analysis of 191 SAD cases, LT showed an improvement in HAM-D scores, suggesting that LT relieved rather than worsened suicidality on average (Lam et al, 2000).

An assessment of photobiological ocular safety of LT devices is necessary as participants are chronically exposed to light that is much brighter than indoor light, but orders of magnitude lower than outdoor light even at dawn. There are not any naturally accompanying or associated treatments of LT. The literature has not shown any interactions with concurrent treatments including standard dopamine replacement therapies. It is not anticipated that there will be any such interactions during the conduct of this study. Certain drugs are photosensitizing. The warning labels for these drugs caution against exposure to sunlight, particularly because they are activated by UV light, but some have been shown to react with longer wavelengths. It is therefore

recommended to avoid using LT while taking any photosensitizing medication. Although lightboxes used in this study do not emit any UV light, participants using photosensitizing medication are excluded from the study.

Due to the benign nature of AEs reported in prior clinical investigations of LT, the history of LT being well-tolerated by PD participants, and the non-significant nature of risks associated with the investigational LT device itself, potential benefits of the proposed intervention in this clinical trial outweigh risks associated with its use. Residual risks associated with the discontinuation of the LT are anticipated to be limited to the gradual deterioration of symptoms to pre-light therapy treatment levels.

4.5 Independent Medical Monitor

An IMM will be appointed to oversee this study and operate in a manner similar to that of a Data and Safety Monitoring Board. The IMM will be independent of the study and have no real or apparent conflict of interest. The DCC will prepare aggregate reports of all AEs (serious/not serious, expected/unexpected and relationship to study device) for the IMM on a quarterly basis or as requested. Safety Monitoring will include contemporaneous assessment of Grade III AEs and SAEs.

In addition, the DCC will prepare reports at specified monitoring intervals for the IMM to review ongoing study activities with emphasis on data integrity, protocol adherence, and safety issues. The IMM will report on his/her review to the NINDS and the PPI raising any concerns, issues, and recommendations while protecting the confidentiality of the trial data and results of monitoring.

5. ANALYSIS POPULATIONS

5.1 As-Assigned Population

Primary, secondary, and safety outcomes will be compared across LT groups using an analysis of participants classified according to their prescribed treatment. The prescribed treatment may differ from the participant's randomized treatment if the instructions to implement light therapy sessions were not aligned with the randomization assignment due to errors by the site at the time of randomization. By analyzing all participants who were prescribed treatment, results from this trial will best guide the design of a future trial whose aim is to assess the effectiveness of daily BWLT. Effectiveness, which does not depend on compliance with the intervention, most accurately estimates the expected benefit of daily BWLT when actually used by patients with PD. To permit accurate estimates of effectiveness, all participants who were prescribed LT should be followed equivalently and included in analyses, without regard to their compliance with LT, to best estimate the effectiveness of daily BWLT.

5.2 Per Protocol (PP) Population

To assess the sensitivity of the results, and to better understand the potential effects when the protocol was strictly adhered to, we will also replicate all primary efficacy objectives using a per protocol population. Depending on results of the primary analyses, we may consider repeating all secondary analyses using the PP population. The PP population includes the subset of all participants assigned treatment who satisfy all of the following conditions:

- Did not withdraw from the light therapy early or withdrew from LT early but at least one post-baseline PDSS-2 assessment was completed prior to withdrawal. For the latter, endpoint data will be included through the early withdrawal decision date.
- Had a summary adherence measure indicating adherence to at least 50% of expected LT use as prescribed.
- Was prescribed the treatment to which the participant was randomly assigned.
- Have no major protocol deviations due to "protocol compliance" (defined as any deviation from the protocol that impacts safety, welfare, or rights of a study participant, or impacts the primary objective of the study. Examples include inclusion/exclusion violations, missed

assessments affecting primary endpoints, or LT administration that affects a study endpoint of the participant's welfare.).

6. ANALYSES

6.1 Primary Analysis

Key Primary Objective (i): *Determine whether once- or twice-daily bright-white light therapy (BWLT) improves sleep in PD sufficiently to carry forward in a phase III efficacy trial.*

Key Primary Objective (ii): *If the first objective is met, then select the superior dose frequency to carry forward to the phase III efficacy trial. Only dose frequencies judged to be safe will be considered for selection*.

6.1.1 Primary Analysis Selection Criteria

The primary objectives of this trial will be accomplished using a comparative selection trial design, which is not designed to demonstrate statistical superiority of any dose frequency of LT, but rather to have high probability of selecting the optimal dose frequency based on a set of selection rules that combine information on change in PDSS-2, participant burden, and safety.

The following criteria will be used (i) to determine whether either daily BWLT improves sleep in PD sufficiently to carry forward in a phase III efficacy trial and, if so, (ii) to select the superior dose frequency to carry forward.

Selection Criterion 1a: Daily BWLT will be judged worthy to carry forward in a phase III efficacy trial if the estimated mean 8-week change from baseline in PDSS-2 score of either once- or twice-daily BWLT is larger than the estimated mean 8-week change from baseline in PDSS-2 score of both one-weekly and twice-daily DRLT by at least 1.7 units.

Selection Criterion 1b: If selection criterion 1a is met, then twice-daily BWLT will be selected to carry forward in a phase III efficacy trial if its mean 8-week change from baseline in PDSS-2 score is larger than that of once-daily BWLT by at least 1.0 units (30% of the MCID), or if the mean 8-week change from baseline in PDSS-2 score for once-daily BWLT is not larger than that of both once-weekly BWLT and twice-daily DRLT by at least 1.7 units. Otherwise, once-daily BWLT will be selected to carry forward in a phase III efficacy trial.

Selection Criterion 1c: Regardless of criteria 1a and 1b, safety will be assessed in a variety of ways and any safety concerns for any arm would take precedence over either of the prior selection criterion.

6.1.2 Analysis Model of Primary Endpoint: PDSS-2

Treatment-dependent estimates of 8-week change from baseline in PDSS-2 score will be analyzed in a mixed model repeated measures analysis with a shared baseline. The model will include terms for fixed effects of visit and treatment by post-baseline visit interaction and unstructured participant-level covariance among repeated measures.

The primary analysis will treat each visit as a discrete measure. Data from all visits (baseline, week 4, week 8, and week 12) will be included as outcome measures, accounting for within-person covariance with an unstructured covariance matrix. This increases precision of our estimate of residual variance. Any primary outcome measures collected at an early termination visit will be included based on the collection date. Visits that were performed outside of an expected scheduled visit will be categorized into the next expected scheduled visit. The use of a shared baseline in combination with the unstructured covariance induces an adjustment for baseline levels equivalent to analysis of covariance increasing the precision of treatment effect estimates (Liang & Zeger, 2000). From this discrete-time, shared-baseline, repeated-measures model, treatment-specific change from baseline to week 8 and treatment-dependent differences in change from baseline to week 8 using one degree of freedom contrasts of the least-square mean estimates will be estimated.

For this analysis, assuming non-linear change over time, the linear mixed model can be written in the following manner:

$$y_{ij} = \alpha + \beta_1 * x_{1i} * t_4 + \beta_2 * x_{1i} * t_8 + \beta_3 * x_{1i} * t_{12} + \beta_4 * x_{2i} * t_4 + \beta_5 * x_{2i} * t_8 + \beta_6 * x_{2i} * t_{12} + \beta_7 * x_{3i} * t_4 + \beta_8 * x_{3i} * t_8 + \beta_9 * x_{3i} * t_{12} + \beta_{10} * x_{4i} * t_4 + \beta_{11} * x_{4i} * t_8 + \beta_{12} * x_{4i} * t_{12} + \varepsilon_{ij}$$

$$\boldsymbol{\varepsilon_i} \sim \boldsymbol{N_4}\left(\begin{pmatrix}0\\0\\0\\0\end{pmatrix}, \begin{pmatrix}\sigma_0^2 & \sigma_{01} & \sigma_{02} & \sigma_{03}\\ \sigma_{01} & \sigma_1^2 & \sigma_{12} & \sigma_{13}\\ \sigma_{02} & \sigma_{12} & \sigma_2^2 & \sigma_{23}\\ \sigma_{03} & \sigma_{13} & \sigma_{23} & \sigma_3^2\end{pmatrix}\right)$$

where:

- y_{ij} is the PDSS-2 response for the i^{th} participant at the j^{th} observation week
- x_{1i} is 1 if the i^{th} participant is in the twice daily BWLT group; 0 otherwise
- x_{2i} is 1 if the i^{th} participant is in the once daily BWLT group; 0 otherwise
- x_{3i} is 1 if the i^{th} participant is in the once weekly BWLT group; 0 otherwise
- x_{4i} is 1 if the i^{th} participant is in the twice daily RDLT group; 0 otherwise
- t_4 denotes the Week 4 timepoint
- t_8 denotes the Week 8 timepoint
- t_{12} denotes the Week 12 timepoint
- α is the common intercept parameter
- ε_{ij} is error for the i^{th} participant at the j^{th} observation week.

We will determine whether either daily BWLT improves sleep in PD sufficiently to carry forward in a phase III efficacy trial and, if so, which to select the optimal dose frequency to carry forward will be based on mean 8-week change from baseline in PDSS-2 scores estimated from the primary analysis. In selecting between once- and twice-daily BWLT, this measure of efficacy will be balanced against the relative burden of each dose frequency. In addition, only dose frequencies judged to be safe will be considered for selection.

Based on selection criterion 1a, daily BWLT will be judged worthy to carry forward in a phase III efficacy trial if the estimated mean 8-week improvement from baseline in PDSS-2 score of either once- or twice-daily BWLT is larger than the estimated mean 8-week change from baseline in PDSS-2 score of both once-weekly BWLT and twice-daily DRLT by at least 1.7 units. The following differences (along with corresponding 95% CIs) will be estimated to evaluate this criterion:

- Twice-daily BWLT vs Once-weekly BWLT: β_2 - β_8
- Twice-daily BWLT vs Twice-daily DRLT: β_2 - β_{11}
- Once-daily BWLT vs Once-weekly BWLT: β_5 - β_8
- Once-daily BWLT vs Twice-daily DRLT: $\beta_5 - \beta_{11}$

Since a lower PDSS-2 score indicates improvement, we would indicate greater improvement in PDSS-2 scores for once-daily or twice-daily BWLT relative to the controls and move forward to selection criterion 1b if:

$$(\beta_2 - \beta_8) \leq -1.7 \text{ and } (\beta_2 - \beta_{11}) \leq -1.7$$

OR

$(\beta_5 - \beta_8) \leq -1.7$ and $(\beta_5 - \beta_{11}) \leq -1.7$.

If selection criterion 1a is met, then twice-daily BWLT will be selected to carry forward in a phase III efficacy trial if its mean 8-week improvement from baseline in PDSS-2 score is larger than that of once-daily BWLT by at least 1.0 units (30% of the MCID), or if the mean 8-week change from baseline in PDSS-2 score for once-daily BWLT is not larger than that of both once-weekly BWLT and twice-daily DRLT by at least 1.7 units. Otherwise, once-daily BWLT will be selected to carry forward in a phase III efficacy trial. The following differences will be estimated to evaluate this criterion:

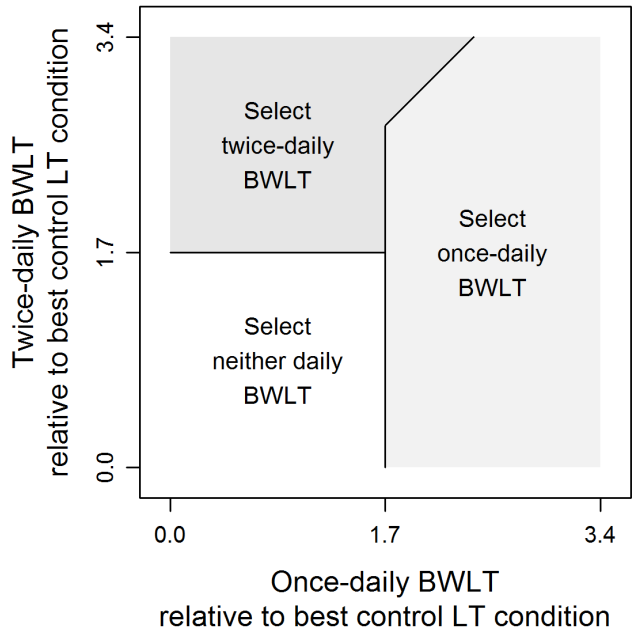
- Twice-daily BWLT vs Once-daily BWLT: $\beta_2 - \beta_5$

Assuming both once-daily and twice-daily BWLT satisfy selection criterion 1a, twice-daily BWLT will be selected to carry forward over once-daily BWLT if:

$$\beta_2 - \beta_5 \leq -1.0$$

Figure 1 displays the conditions for selecting twice-daily BWLT, once-daily BWLT, or neither daily BWLT based on selection criteria 1a and 1b.

Figure 1. Selection criteria 1a and 1b.



Regardless of criteria 1a and 1b, safety will be assessed in a variety of ways and any safety concerns would take precedence over either of the prior selection criterion. The safety analyses are detailed in Section 6.5.

Treatment-group specific and pairwise comparisons between the four LT groups will also be performed and reported to provide further information to aid in understanding the effect of LT use on sleep quality and to guide future planning. If retention rates are lower than expected, an additional pattern-mixture model may be fit stratifying the primary model by duration of follow-up. The results of these analyses will provide essential information regarding the sensitivity of the findings to missing data and will be critical in assessing the full value of the study results.

6.2 Missing Data

The primary analysis will include all randomized participants analyzed in the treatment group to which they were prescribed. As such, it will be critically important to minimize the occurrence of missing data. Obviously, the optimal strategy for dealing with missing data is to make every effort

to obtain complete data during the conduct of the study. Our team of data managers and protocol coordinators will work diligently and use a variety of methods in order to minimize the percentage of missing data in this trial. Nevertheless, there is likely to be a small percentage of missing data. We will employ strategies to mitigate and then assess the impact of missing data in our study.

To further assess the potential dependence of the results of the primary analysis to these missing values, a series of sensitivity analyses will be conducted. For participants that do not provide complete data, we will analyze the data using the following strategies:

- ***Using Only Observed Endpoint Data (No Imputation).*** While the primary analysis will impute missing PDSS-2 scores for participants with two or fewer questions missing at a given assessment, a sensitivity analysis will be performed excluding any observations with any missing data in these assessments (i.e., not imputing missing values for any items on PDSS-2 assessments).
- ***Worst-Case Scenario:*** Assume no change in PDSS-2 score from baseline to Week 8 for a given participant with missing data.
- ***Pattern-Mixture Model:*** We will fit a pattern-mixture model with placebo-based imputation. Under this model, participants with missing data in all treatment groups will be assumed to follow the same trajectory as participants in the DRLT group. Imputation will be implemented using the full conditional specification regression method.

6.3 Key Secondary Analysis

Key Secondary Objective: *Determine whether once-weekly BWLT is a non-inferior control condition relative to twice-daily DRLT.*

The secondary objective will be evaluated based on the 8-week change in PDSS-2 score from baseline to end of study intervention and on the relative burden and safety of once-weekly vs. twice-daily DRLT. The difference in the mean change in PDSS-2 from baseline to week 8 between once-weekly BWLT and twice-daily DRLT will be estimated using the same shared baseline, repeated measures primary analysis mixed model as described in section 6.1.2.

> ***Selection Criterion 2a:*** Once-weekly BWLT will be considered non-inferior to twice-daily DRLT as a control LT condition if the mean 8-week change from baseline in PDSS-2 score of once-weekly BWLT is not smaller than the mean 8-week change from baseline in PDSS-2 score of twice-daily DRLT by more than 1.7 units. This criterion reflects our assessment of the added burden of twice-daily DRLT.

Using the model specified in section 6.1.2, the following difference (along with corresponding 95% CI) will be estimated to evaluate this criterion:

- Once-weekly BWLT vs Twice-daily DRLT: β_8 - β_{11}

In order for once-weekly BWLT to be considered a non-inferior control, we must observe that:

$$(\beta_8 - \beta_{11}) \leq 1.7.$$

Otherwise, twice-daily DRLT would be deemed to optimal control arm.

> ***Selection Criterion 2b:*** Regardless of criteria 2a, safety will be assessed in a variety of ways and any safety concerns for either control arm would take precedence over the prior selection criterion.

6.4 Additional Secondary Analyses

6.4.1 PFS-16

The effects of once- and twice-daily BWLT on fatigue as measured by change in PFS-16 score from baseline to week 8 will be modeled with a shared-baseline, repeated-measures mixed model equivalent to that described in Section 6.1.2, with the exception that the outcome variable will differ accordingly.

Unlike the primary analysis for PDSS-2 that is based on selection criteria, results for this secondary endpoint will be assessed and reported primarily through hypothesis testing. The main focus of this secondary objective is to formally assess the effectiveness of daily BWLT for the trial and, if met, to compare the two active arms. To achieve that goal, a series of stepwise analyses will be implemented at the 0.05 level.

First, we will compare the efficacy of daily BWLT for the full trial by comparing the joint efficacy of daily BWLT to the standard accepted control condition of twice-daily DRLT:

- (Once-daily + Twice-daily BWLT) vs. Twice-daily DRLT:

$$H_0: (\beta_2 + \beta_5)/2 - \beta_{11} = 0 \text{ vs } H_A: (\beta_2 + \beta_5)/2 - \beta_{11} \neq 0$$

Since a lower PFS-16 score indicates improvement, an estimated difference that is less than zero will suggest that the first compared treatment group showed more improvement (or less decline) than the second comparison group. A 95% confidence interval that excludes estimates of zero suggests that the test of superiority is statistically significant at the 0.05 level.

Conditional on achieving statistical significance at the 0.05 level, we will formally compare twice-daily BWLT vs. one-daily BWLT:

$$\beta_2 - \beta_5 = 0 \text{ vs } H_A: \beta_2 - \beta_5 \neq 0$$

A series of remaining comparisons will also be assessed by the following hypothesis tests:

- (Once-daily BWLT + Twice-daily BWLT) vs Once-weekly BWLT:

$$H_0: (\beta_2 + \beta_5)/2 - \beta_8 = 0 \text{ vs } H_A: (\beta_2 + \beta_5)/2 - \beta_8 \neq 0$$

- Once-weekly BWLT vs Twice-daily DRLT:

$$H_0: \beta_8 - \beta_{11} = 0 \text{ vs } H_A: \beta_8 - \beta_{11} \neq 0$$

No formal adjustment for multiple comparisons will be implemented for these assessments. We will just report the nominal p-values.

6.4.2 Adherence

Participant adherence to LT, defined as the proportion of days with adherence to the prescribed dose frequency (weekly, once daily, or twice daily), will be analyzed from daily light exposure logs as described in section 3.4.2 and summarized as percentage of planned exposures completed for all treatment groups.

The percentage of days with adherence will be further compared between the two daily BWLT treatments to provide more information on the treatment group that is potentially selected to carry forward in a phase III efficacy trial. The percentage of adherent days will be compared between the two groups.

For comparing adherence between once-daily BWLT and twice-daily BWLT, we will implement a generalized linear mixed model of the log-odds of daily adherence with each day of each participant flagged as adherent or not-adherent according to the intended dosage (1x or 2x daily) as prescribed with a fixed term for prescribed treatment group and random participant-specific intercepts and reporting of the estimated proportion adherent by treatment group and the treatment-dependent odds ratio. To do this, the following repeated-measures logistic regression model will be used to model the log odds of adherence. The model can be written as:

$$logit(Y_{ij}) = \beta_0 + \beta_1 * x_i + b_{0i} + \epsilon_{ij}$$

where:

- Y_{ij} is 1 if the i^{th} participant adhered to the assigned daily frequency on the j^{th} day; 0 otherwise
- x_i is 1 if the i^{th} participant was randomized to twice-daily BWLT treatment group; 0 if randomized to the once-daily BWLT treatment group

- b_{0i} is a random participant-specific intercept, assumed to be normally distributed
- ε_{ij} is error for the i^{th} participant at the j^{th} observation day, assumed to have a normal distribution with non-zero variance.

In the defined model, once-daily BWLT is the reference group and is represented by $x_i = 0$. To determine if the percent of participants that adhered to the assigned treatment differs across treatment groups, we will test the following hypothesis:

$$H_0: \beta_1 = 0 \; vs. \; H_A: \beta_1 \neq 0$$

The estimate of the odds of adherence for a participant in the twice-daily BWLT versus a participant in the once-daily BWLT group will be computed by exp(β_1), and reported with a corresponding 95% CI.

The estimated proportion adherence will be calculated for each treatment group using the following equation, where $\hat{\pi}_i$ represents the estimated proportion adherent for an individual with b_{0i} = 0:

$$\hat{\pi}_i = \exp(\beta_0 + \beta_1 * x_i) \; / \; [1 + \exp(\beta_0 + \beta_1 * x_i)]$$

6.5 Safety Analysis

Safety will be evaluated by the occurrence of AEs and other safety outcomes. While no serious safety outcomes are anticipated, we will track the proportion of participants in each treatment group who discontinue LT due to AEs and compare the rates of reportable safety events, e.g., serious or unanticipated adverse device effects. If any LT treatment is determined to be unsafe, then it will not be considered for a future trial as either an active or control condition.

To determine whether a particular LT treatment is unsafe, first the percentage of participants who experience any AE in each treatment group will be compared using the following logistic regression model:

$$logit(Y_i) = \beta_0 + \beta_1 * x_{1i} + \beta_2 * x_{2i} + \beta_3 * x_{3i} + \varepsilon_i$$

where:

- Y_i is 1 if the i^{th} participant had at least one AE; 0 otherwise
- x_{i1} is 1 if i^{th} participant was randomized to twice-daily BWLT treatment group; 0 otherwise
- x_{i2} is 1 if i^{th} participant was randomized to once-daily BWLT treatment group; 0 otherwise
- x_{i3} is 1 if i^{th} participant was randomized to once-weekly BWLT treatment group; 0 otherwise
- ε_i is the random error for the i^{th} participant.

In the defined model, twice-daily DRLT is the reference group and is represented by x_{1i}=0, x_{2i}=0, and x_{3i}=0. Thus β_0 is the log odds of at least one AE for twice-daily DRLT. To determine if the percentage of participants who experience any AE in each group differ across treatment groups, we will test the following hypothesis:

$$H_0: \beta_1 = \beta_2 = \beta_3 = 0 \; vs. \; H_A: \text{At least one } \beta_i \text{ is not equal to zero}$$

Contrasts will be used to report treatment group comparisons. Analyses will be repeated to compare the percentage of participants having at least one AE within each MedDRA system organ class (SOC). If there are significant differences between groups within any specific SOC, then additional tests will compare differences across groups for specific MedDRA preferred terms in order to further explore the cause of the observed differences.

In addition to the comparison of percentage of participants who experience any AE described above, the rate of AEs in each treatment group will be compared using the following Poisson regression model:

$$log\left(\frac{Y_i}{T_i}\right) = \beta_0 + \beta_1 * x_{1i} + \beta_2 * x_{2i} + \beta_3 * x_{3i} + \varepsilon_i$$

where:

- Y_i is the number of AE's experienced by the i^{th} participant
- T_i is the number of months between the date of randomization and the date of last follow-up for the i^{th} participant
- x_{i1} is 1 if i^{th} participant was randomized to twice-daily BWLT treatment group; 0 otherwise
- x_{i2} is 1 if i^{th} participant was randomized to once-daily BWLT treatment group; 0 otherwise
- x_{i3} is 1 if i^{th} participant was randomized to once-weekly BWLT treatment group; 0 otherwise
- ε_i is normally distributed zero mean random error for the i^{th} participant

In the defined model, twice-daily DRLT is the reference group and is represented by x_{1i}=0, x_{2i}=0, and x_{3i}=0. To determine if the rate of AEs differs across treatment groups, we will test the following global hypothesis:

$$H_0: \beta_1 = \beta_2 = \beta_3 = 0 \; vs. H_A: at\ least\ one\ \beta_i\ is\ not\ equal\ to\ zero$$

Contrasts will be used to report treatment group comparisons between the coefficients.

SAEs will be analyzed in the same manner described above. Additional safety analyses may assess treatment-related AEs, treatment-related SAEs & unanticipated SAEs in a similar manner.

6.6 Exploratory Analyses

Additional exploratory analyses are also planned but will not be included as part of the FSR. Exploratory analyses for this study will include, but are not limited to, the following:

- Credibility as assessed by the credibility questionnaire
- Overall PD symptom severity as measured by the MDS-UPDRS total score
- Non-motor symptoms in PD as measured by the Non-Motor Symptoms Scale (NMSS) score
- Motor symptoms in PD as measured by the MDS-UPDRS Part III score
- Objective measures of sleep as measured by actigraphy. The following key standard actigraphy measures will be generated on each day's data: sleep onset, sleep offset, sleep latency, Time in Bed, TST, WASO, sleep efficiency, sleep FI, and naps – as calculated using the software analysis program (Actiware, Phillips Respironics, Bend, OR) by an analyst blinded to treatment assignment with sleep timing being reconciled with daily sleep log timing values and the Actiware software rerun with new sleep timing if required
- Self-reported measures of sleep and wake as measured by sleep log
- Daytime sleepiness as assessed by the ESS
- Quality of life as measured by the PDQ-39
- Mood as assessed by the GDS-15
- Cognition as assessed by the MoCA

7. SAMPLE SIZE JUSTIFICATION

Planned enrollment is at least 144 participants randomized to achieve 120 participants completing follow-up while accommodating up to 15% loss to follow-up. We may enroll up to 158 participants to compensate for participants lost to follow-up. The feasibility survey submitted by 29 study sites interested to participate in this trial supports the optimism that the capacity of the Network is adequate for timely and complete recruitment of the study cohort. The initial feasibility survey for this trial documented an estimated 4016 PD patients who meet inclusion/exclusion criteria for the trial. The Network sites estimated that among this pool of patients, 321 can be enrolled in one year.

The minimum planned sample size is based on variance estimates from our pilot LT trial in PD. In a repeated-measures analysis, the standard error for comparing 4-week change from baseline of PDSS scores between twice-daily BWLT and twice-daily DRLT in our pilot trial was 3.23 units. Scaling from the PDSS (range 0 to 150) to the PDSS-2 (range 0 to 60), extrapolating from a 4-week change to an 8-week change while assuming equal contributions from residual variance and random slopes in the 4-week estimate, and given 31 participants split 15:16 in the pilot trial, the effective standard deviation for our planned comparison is { 3.23 x 60 / 150 x 0.5 x (1 + 2) } / sqrt(1/15 + 1/16) = 5.4 units.

The proposed trial has a comparative selection trial design. The criterion that the mean 8-week change in PDSS-2 score with daily BWLT exceeds that of both control LT conditions by at least 1.7 units reflects our desire to move forward to a phase III trial only with preliminary evidence of efficacy. The cut-off of 1.7 units was selected to yield desired type 1 and type 2 error rates. In particular, for the primary aim, the cut-off of 1.7 units provides greater than 80% power if the true efficacy of the superior daily BWLT dose frequency is superior to the inferior daily BWLT dose frequency and control LT conditions by 3.4 units (100% of the MCID), and less than a 1% probability to select the inferior BWLT dose frequency. With 144 participants randomized 1:1:1:1 to twice-daily BWLT, once-daily BWLT, once-weekly BWLT, or twice-daily DRLT, and assuming up to 15% loss to follow-up, the study would have an 80% probability of selecting once-daily or twice-daily BWLT treatment if the true efficacy of either once-daily or twice-daily BWLT is at least 3.4 units (100% of the MCID) better than the best of once-weekly BWLT and twice-daily DRLT.

The criterion that the mean 8-week change in PDSS-2 score of twice-daily BWLT exceeds that of once-daily BWLT by at least 1.0 units reflects the belief that the added burden of twice-daily BWLT is only justified if the added benefit of twice-daily BWLT is adequate. The cut-off of 1.0 units yields a 68% probability of selecting the once-daily bright-white light therapy if both once- and twice-daily dosing are better than both controls by the MCID and equally effective. The cut-off of 1.0 units yields a 66% probability of selecting the twice-daily bright-white light therapy if twice-daily dosing is better than both controls by the MCID and once-daily bright-white light therapy is only better than both control by 50% of the MCID. The chosen thresholds yield favorable probabilities for carrying daily BWLT forward in a phase III efficacy trial, and for selecting the superior dose frequency. If the efficacy of both daily BWLT dose frequencies is superior to both control LT conditions by 3.4 units (100% of the MCID), then the study has a 68% probability of selecting once-daily BWLT and a 25% probability of selecting twice-daily BWLT. If the efficacy of once-daily and twice-daily BWLT follow a linear dose response with a 3.4-unit benefit from twice-daily BWLT, then the study would have a 62% probability of selecting twice-daily BWLT and an 18% probability of selecting once-daily BWLT.

Given the minimum planned sample size, drop-out, and variance estimates, if the true efficacy of neither daily BWLT treatment is better than both once-weekly BWLT and twice-daily DRLT, then this criterion holds probability of falsely identifying daily BWLT treatment as sufficiently efficacious to carry forward to a phase III trial (expected false positive rate) is less than 7%. Finally, based on the chosen non-inferiority bound of 1.7 units (50% of the MCID), if the true efficacy (or inefficacy) of once-weekly BWLT and twice-daily DRLT are equal, then the study would have a 78% probability of judging once-weekly BWLT non-inferior to twice-daily DRLT.

Stated probabilities were calculated by integration of the multivariate normal distribution by Mathematica (Wolfram Research Inc, 2020) and confirmed by simulation using $1x10^5$ multivariate normal random variates generated using the mvtnorm package in R (R Core Team, 2019) with means and homoscedastic variance as noted, and no covariance of treatment group means.

8. TABULATIONS

8.1 Study Tabulations

All study participants who provide informed consent will be accounted for in this study. The number of randomized participants and their study disposition will be reported overall, and by prescribed treatment group. The number of study participants who prematurely discontinued from the trial and

the reason for discontinuation will be presented based on the categories on the CRF. A CONSORT diagram summarizing screening, prescribed treatment, and the final status of all study participants will be provided. Additional summary reports will describe:

- Number of study participants consented, eligible, and randomized by site
- Reasons for ineligibility
- Completeness of study visits and CRFs
- Protocol deviations
- Early treatment withdrawals
- Early study terminations

Baseline demographics and clinical characteristics will also be summarized by prescribed treatment group and overall, with respect to important demographic characteristics, baseline PD characteristics, and baseline clinical characteristics. Categorical variables will be tabulated by proportions or percentages. Continuous variables will be summarized as mean, median, standard deviation, minimum, and maximum. Variables that will be summarized include:

- Demographic Characteristics
    - Sex
    - Race
    - Ethnicity
    - Age
- Baseline PD Characteristics
    - Age at Symptom Onset
    - Years Since Symptom Onset
    - Age at Diagnosis
    - Years Since Diagnosis
    - Hoehn & Yahr Stage
    - Use of Antiparkinsonian Medications
        - Levodopa
        - Dopamine Agonists
        - MAO-B Inhibitors
        - Amantadine
        - Anticholinergics
        - Levodopa-Equivalent Daily Dosage
    - Years Since First Use of Levodopa
- Baseline Clinical Characteristics
    - PDSS-2 Score
    - PFS-16 Score
    - MDS-UPDRS Part III Score
    - NMSS Score
    - ESS Score
    - PDQ-39 Score
    - GDS-15 Score
    - MoCA Score

8.2 COVID-19 Tabulations

Additional tabulations will summarize potential impacts of COVID-19 on the NN110 trial that might impact the interpretation of trial results. The following tabulations will be provided overall and by treatment group:

- Number of primary assessments completed remotely
- Listing of the protocol deviations related to COVID-19 by major and minor designation
- Number of out of window visits

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