STUDY TITLE:	Evaluating the Potential Role of Melatonin in Subjects with Relapsing Multiple Sclerosis (MS)
PRINCIPAL INVESTIGATOR:	Kyle Smoot, MD Providence Neurological Specialties West Providence Health and Services
SUB-INVESTIGATORS:	Stanley Cohan, MD, PhD Elisabeth Lucassen, MD Justine Brink, MD Leah Gaedeke, MSN, FNP-BC
INSTITUTION:	Providence Brain and Spine Institute Providence Health & Services
PROTOCOL VERSION & DATE:	Version 3.0 09JUN2020

NCT#: NCT03498131

A. Background/specific aims:

Multiple sclerosis is an immune mediated disorder with no clear cause determined. Likely, the combination of genetics and environmental factors trigger this disorder[1]. The disease is driven possibly by pro-inflammatory cells, Th17 and Th1 cells. There is also a decrease in number and function of regulatory T cells (RegT) and B cells (RegB). This inflammation is responsible for clinical relapses and radiographic changes. However, if the disease is left untreated, the majority of patients transition to the progressive phase. The exact cause for this transition is unclear; however, mitochondrial injury and loss of axonal homeostasis due to demyelination may contribute to this degeneration[2]. This mitochondrial injury may be secondary to oxidative stress driven by chronic inflammation[3].

Melatonin is primarily produced in the pineal gland, helps regulate the sleep-wake cycle, and a reduction in melatonin contributes to insomnia[4, 5]. However, melatonin also can be produced by mitochondria which can help optimize cell function[6]. In addition, melatonin can modulate the immune system by acting as both an anti-oxidant and an anti-inflammatory agent by scavenging toxic free radicals, reducing the up-regulation of pro-inflammatory cytokines, and reducing transendothelial migration[7].

Melatonin levels are higher in fall and winter as production is stimulated by darkness. Interestingly, MS disease activity is higher in spring and summer when melatonin production is lower[8, 9]. In a study of 139 relapsing MS patients, there was a 32% reduction in the number of relapses in the fall and winter[10]. In the same study, Farez and colleagues were able to demonstrate a reduction in clinical symptoms in the Experimental Autoimmune Encephalitis (EAE) model when mice were give melatonin. Also, in this study, they detected a decrease in pro-inflammatory cells, Th17, and an increase in IL-10 which has anti-inflammatory properties.

Fatigue is one of the most disabling symptoms in patients with multiple sclerosis, affecting approximately 90% of patients with MS[11]. There are multiple reasons for this fatigue, but poor sleep is a contributing factor. Treatment naïve MS patients have demonstrated a reduction in 24 hour urinary 6-sulfatoxymelatonin (6-SMT) [12]. In the same study, the levels increased when interferon-β treatment was added with a trend in improving fatigue.

B. Research Strategy:

To date, there are no published data on the role of melatonin supplementation or the appropriate dose for patients with multiple sclerosis. Because of the potential benefits of melatonin, this pilot study will be an exploratory investigation to evaluate the effect of supplementing melatonin in subjects with multiple sclerosis who are taking an oral disease modifying therapy (DMT) for 6 months or longer. It is our intent that the results of this study will support the rationale and be a prelude to a larger trial which can focus on clinical efficacy of melatonin therapy outcomes.

C. Research Objectives

1. The primary objective of this study is to evaluate the change in 24 hour urinary 6-SMT collected for 24 hours in two twelve hour sessions.

2. The secondary objectives are to evaluate the change in serum morning melatonin level. In addition, quality of life (QOL) measures will be assessed including the Modified Fatigue Impact

Scale (MFIS)[13], Multiple Sclerosis Impact Scale (MSIS-29)[14], and the Pittsburgh Sleep Quality Index (PSQI)[15]. Clinical objectives include the number of relapses during the trial and a change in the Patient Determined Disease Steps & Performance Scales (PDDS-PS).[16-19]

D. Study Design

The proposed pilot study is a one-year randomized, rater- and dose-blinded trial evaluating the potential role of melatonin in subjects with relapsing multiple sclerosis who have been taking a stable dose of an oral DMT for at least 6 months. The oral DMTs include dimethyl fumarate, fingolimod, teriflunomide, diroximel fumarate, siponimod, and ozanimod. Thirty subjects with relapsing forms of multiple sclerosis who meet all of the eligibility criteria will be enrolled at Providence Neurological Specialties in Portland, Oregon. The subjects will be consented by the investigator or delegated research personnel before undergoing any study procedures. Subjects will be randomized to melatonin 3 mg, or melatonin 5 mg. There will be 15 subjects in each group. As this is a pilot study, we do not include a sample size calculation.

Urinary and serum melatonin testing will be conducted at baseline, month 3, month 6, month 12, and any early termination or unscheduled visits. Subject reported measures for the assessment of fatigue, QoL, sleep, and MS severity (MFIS, MSIS-29, PSQI, and PDDS-PS) will be administered at baseline, month 3, month 6, month 12, and any early termination or unscheduled visits. Relapses during the study will be documented and recorded. If the subject does have a relapse, they will be treated per our clinical protocol which consists of Solu-Medrol 1 gram IV once a day for 3 to 5 days depending on the severity of symptoms.

If discontinuation of oral DMT and/or melatonin occurs, the subject may continue in the trial for observational purposes. An unscheduled (UNS) visit will be completed within 7 days after the last dose of oral DMT and/or melatonin (date of whichever is stopped first, if both discontinued). They will complete all applicable visits items moving forward (urinary 6-SMT reminder, urinary 6-SMT collection, dispense 24- hour urine collection materials, serum melatonin collection, dispense subject dosing diary, dispense study drug, study medication compliance/accountability, and potentially oral DMT compliance assessment will no longer be relevant/required). If oral DMT and/or melatonin is discontinued and the subject is unwilling to stay on the study for observational purposes, an early termination visit must be performed within 7 days after the last dose date of whichever is stopped first.

Melatonin will be provided by the study. However, oral DMT will be provided by the subject's specialty pharmacy and paid by the subject or the subject's insurance.

E. Outcome Measures

1. Primary Outcome

    i. Change in urinary 6-SMT in 24 hours urine

2. Secondary Outcomes:

    i. Change in Serum morning Melatonin level

    ii. Change in MFIS

iii. Change in MSIS-29

iv. Change in PSQI

v. Number of Relapses during enrollment

vi. Change in PDDS-PS

F. Methods

1. Subject Selection

a. Inclusion Criteria

i. Male and female subjects with relapsing forms of MS who have been on a stable dose of dimethyl fumarate, fingolimod, teriflunomide, diroximel fumarate, siponimod, or ozanimod for 6 months or longer

ii. Confirmed diagnosis of Relapsing MS

iii. Ages 18 to 65 who are able to provide informed consent

iv. Women of childbearing potential must employ proven methods to prevent pregnancy during the course of the trial; the acceptable method will be left to the judgment of the investigator

v. Not pregnant or lactating

vi. No evidence of significant cognitive or psychiatric disorder

vii. Able to understand the purpose and risks of the study

viii. Must be willing to sign an informed consent and follow the protocol requirements

b. Exclusion Criteria

i. Use of melatonin within 30 days of enrollment

ii. The addition of any sleep aide or change in dose within 30 days of enrollment or during the trial

iii. The addition or change in dose of Vitamin D within 30 days of enrollment or during the trial

iv. Change in DMT during the trial

v. Steroid therapy within 30 days of enrollment

vi. Use of anticoagulation at the time of enrollment and during the trial

vii. The addition of an antidepressant is not allowed during the study period; if on an antidepressant at screening, the dose must be stable 30 days prior to enrollment and dose changes are prohibited during the study

viii. The addition or change in dose of any stimulants, including but not limited to, amantadine, armodafinil, methylphenidate, or modafinil within 30 days of enrollment or during the trial

2. Discontinuation of Subjects from the Study

i. Subjects may voluntarily withdraw consent and discontinue their participation in the study at any time

ii. If a subject has a relapse during the study, the study doctor may discontinue melatonin and/or oral DMT

a. A relapse is defined as a new symptom, or worsening of pre-existing neurologic symptoms, of at least 24 hours duration, in subjects who had been clinically stable for the prior 30 days, in the absence of fever, sleep deprivation or severe emotional stress.

iii. Subject has an adverse event that presents unacceptable risk, per investigator discretion

iv. Subject has inadequate adherence to the protocol, per investigator discretion

v. Subject is lost to follow-up

vi. Subject becomes pregnant

3. Method of Treatment Assignment

The randomization sequence will be generated using R statistical software and will be stratified by age group and gender with a 1:1 allocation using a fixed block size of four. The following four strata will be used: 1) younger females, 2) older females, 3) younger males, and 4) older males. As subjects enter the study, they will be designated to a stratum and will be assigned either a 3 mg or 5 mg melatonin dose based on the pre-generated randomization scheme within that stratum. A master list containing drug kit numbers and drug assignment will be kept in a password-protected computer file in the research pharmacy. The investigator, study coordinator and subjects will remain blinded until study completion. The blind will only be violated if, in the judgment of the treating investigator, unblinding is necessary for subject safety.

4. Study Treatment

i. All subjects will continue their oral DMT and start the study drug on Day 1 (Baseline Visit).

ii. Oral DMT will be taken per standard of care dosing and paid for by the subject/subject insurance.

iii. Subjects randomized to melatonin will take either 3mg once a day or 5mg once a day. Melatonin will be supplied by Thorne Pharmaceuticals. The study drug will be taken at 21:00 each day ±2 hours.

5. Concomitant and Excluded Therapy

The addition of a sleep aide is not allowed during the study period. If subjects were on a sleep aide prior to the trial, no change in this medication is allowed and the dose must be stable 30 days prior to enrollment.

No change in Vitamin D supplementation will be allowed during the study and the dose must be stable 30 days prior to enrollment.

The addition of an antidepressant is not allowed during the study period. If on an antidepressant at screening, the dose must be stable 30 days prior to enrollment and dose changes are prohibited during the study.

Stimulants, amantadine, armodafinil, methylphenidate or modafinil cannot be added during the study period. If subjects were on any of these listed medications prior to the trial, no change in this medication is allowed and the dose must be stable 30 days prior to enrollment.

The enrolling investigator is to review prior and concomitant medications at screening to ensure concomitant and excluded therapy requirements are met.

6. Study Assessments

The investigator or designated research staff will obtain informed consent from each subject after explaining the purpose of the study and the potential risks and benefits known or can be reasonable expected. The IRB approved informed consent will be signed by the subject before any screening assessments or procedures are performed.

The serum melatonin level will be drawn in the morning (09:00±2 hours).

i. Assessments During Treatment

a. Visit 1 or Screening Visit (1-30 days prior to baseline)

i. Informed consent

ii. Inclusion/exclusion criteria review

iii. Demographic Information

iv. Vital signs (including height and weight at screening)

v. Review of concomitant medications

vi. Review of all prior medications taken within last 30 days

vii. Medical history

viii. MS history

ix. Childbearing potential review

x. Physical exam [If a subject had a physical exam during the screening window (1-30 days prior to baseline) with a trial investigator but it was completed

prior to consent as part of standard of care, the data from this exam may be used for the screening visit physical exam requirement. This is allowed only if all elements of the required exam were completed.]

xi. Neurological exam [If a subject had a neurological exam during the screening window (1-30 days prior to baseline) with a trial investigator but it was completed prior to consent as part of standard of care, the data from this exam may be used for the screening visit neurological exam requirement. This is allowed only if all elements of the required exam were completed.]

xii. Oral DMT compliance assessment

xiii. Vitamin D laboratory level (the most recent vitamin D laboratory level that was collected as part of standard of care, not to be ordered specifically for trial)

xiv. Dispense lab collection materials/instructions for Urinary 6-sulfatoxymelatonin collection (24-hr urine collection), specimen to be collected within -3 days of visit 2 and returned to clinic at visit 2

xv. Adverse event assessment (starting after informed consent obtained)

xvi. Telephone contact-remind subject to complete 24 hour collection within -3 days of visit 2 (to be completed within -5 days of visit 2, not applicable/required if screening and baseline are 1 day apart)

b. Visit 2 or Baseline Visit (Day 1)

i. Urine collection (within -3 days of visit 2)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Dispense Subject Dosing Diary

vi. Adverse event assessment

vii. Relapse assessment

viii. MFIS

ix. MSIS-29

x. PSQI

xi. PDDS-PS

xii. Oral DMT compliance assessment

xiii. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care, not to be ordered specifically for trial)Inclusion/exclusion criteria review

xiv. Randomization

xv. Dispense study drug-first dose at 21:00 ±2 hours on Day 1

xvi. Dispense lab collection materials/instructions for Urinary 6-sulfatoxymelatonin collection (24-hr urine collection), specimen to be collected within -3 days of visit 3 and returned to clinic at visit 3

xvii. Telephone contact-study medication compliance, verify study drug first dose date/time (within +3 days of visit 2)

xviii. Telephone contact-remind subject to complete 24 hour collection within -3 days of visit 3 (to be completed within -5 days of visit 3)

c. Visit 3 (3 months +/- 14 days from baseline)

i. Urine collection (within -3 days of visit 3)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Adverse event assessment

vi. Relapse assessment

vii. MFIS

viii. MSIS-29

ix. PSQI

x. PDDS-PS

xi. Physical exam

xii. Neurological exam

xiii. Study medication compliance and accountability assessment

xiv. Collect study medication and dispense new study medication

xv. Oral DMT compliance assessment

xvi. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care, not to be ordered specifically for trial)Collect and dispense new Subject Dosing Diary

xvii. Dispense lab collection materials/instructions for Urinary 6-sulfatoxymelatonin collection (24-hr urine collection), specimen to be collected within -3 days of visit 4 and returned to clinic at visit 4

xviii. Telephone contact-remind subject to complete 24 hour collection within -3 days of visit 4 (to be completed within -5 days of visit 4)

d. Visit 4 (6 months +/- 14 days from baseline)

i. Urine collection (within -3 days of visit 4)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Adverse event assessment

vi. Relapse assessment

vii. MFIS

viii. MSIS-29

ix. PSQI

x. PDDS-PS

xi. Physical exam

xii. Neurological exam

xiii. Study medication compliance and accountability assessment

xiv. Collect study medication and dispense new study medication

xv. Oral DMT compliance assessment

xvi. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care, not to be ordered specifically for trial)Collect and dispense new Subject Dosing Diary

xvii. Dispense lab collection materials/instructions for Urinary 6-sulfatoxymelatonin collection (24-hr urine collection), specimen to be collected within -3 days of visit 5 and returned to clinic at visit 5

xviii. Telephone contact-remind subject to complete 24 hour collection within -3 days of visit 5 (to be completed within -5 days of visit 5)

e. Visit 5 (12 months +/- 14 days from baseline)

i. Urine collection (within -3 days of visit 5)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Adverse event assessment

vi. Relapse assessment

vii. MFIS

viii. MSIS-29

ix. PSQI

x. PDDS-PS

xi. Physical exam

xii. Neurological exam

xiii. Study medication compliance and accountability assessment

xiv. Collect study medication

xv. Oral DMT compliance assessment

xvi. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care, not to be ordered specifically for trial)Collect Subject Dosing Diary

f. Early Termination Visit (ET)

If discontinuation of oral DMT and/or melatonin occurs and the subject is unwilling to continue in the trial for observation, an ET visit must be performed within 7 days after the last dose of oral DMT and/or melatonin (date of whichever is stopped first, if both discontinued).

i. Urine collection (±3 days of visit ET)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Adverse event assessment

vi. Relapse assessment

vii. MFIS

viii. MSIS-20

ix. PSQI

x. PDDS-PS

xi. Physical exam (only required if subject was last examined more than 6 months ago or per treating physician's discretion)

xii. Neurological exam (only required if patient was last examined more than 6 months ago or per treating physician's discretion)

xiii. Study medication compliance and accountability assessment

xiv. Collect study medication

xv. Oral DMT compliance assessment

xvi. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care, not to be ordered specifically for trial)Collect Subject Dosing Diary

g. Unscheduled Visits(UNS)

Subjects will be instructed to contact their treating investigator in the event of a relapse and may be asked to return for an UNS visit. Additionally, an UNS visit will be completed within 7 days after the last dose of oral DMT and/or melatonin (date of whichever is stopped first, if both discontinued) if stopped between visits and the subject is willing to continue in the trial for observation.

i. Urine collection (±3 days of visit UNS)

1. Urinary 6-SMT collection will begin and continue for 24 hours

ii. Vital signs

iii. Serum melatonin level collection (09:00±2 hours)

iv. Review of concomitant medications

v. Adverse event assessment

vi. Relapse assessment

vii. MFIS

viii. MSIS-29

ix. PSQI

x. PDDS-PS

xi. Physical exam (only required if a relapse is suspected or per treating physician's discretion)

xii. Neurological exam (only required if a relapse is suspected or per treating physician's discretion)

xiii. Study medication compliance and accountability assessment

xiv. Oral DMT compliance assessment

xv. Vitamin D laboratory level (if collected since the last trial visit as part of standard of care)

xvi. Collect and dispense new Subject Dosing Diary

h. Discontinuation of study drug

i. If the subject becomes pregnant

ii. At the discretion of the investigator for medical or ethical reasons

iii. If the subject withdrawals consent

iv. If the subject is unwilling or unable to comply with the protocol, per investigator discretion

G. Statistical Methods

Subject characteristics for each arm will be reported for continuous variables (mean, standard deviation, median, and range) and categorical variables (counts and percentages). All analyses will use two-sided tests at the 0.05 significance level. This study is based on an intention to treat model, in which all subjects receiving at least one dose of melatonin will be included.

a. Primary Analysis

Longitudinal analyses using a linear mixed models for repeated measures will be used to compare changes in 24-hour urinary 6-sulfatoxymelatonin and serum morning Melatonin over time between arms. Each outcome will be treated as continuous and identify link functions will be used. Overall trajectories as well as the mean change from baseline to 3, 6, and 12 months for each arm will be reported and compared.

b. Secondary Analysis

Changes in the MFIS, MSIS-29, PSQI, & PDDS-PS from baseline to 3, 6, and 12 months will be reported and tested using a paired t or Wilcoxon signed-rank test for related samples. Two-sample t or Mann-Whitney tests will be used to compare change between arms at each time point. The mean number of relapses during enrollment for each arm will be reported and compared using a Poisson analysis. Kaplan-Meier survival analysis methodology will be used to estimate the proportion of subjects relapse-free at months 3, 6, and 12 and log rank tests will be used to compare arms.

To examine agreement between 24-hour urinary 6-sulfatoxymelatonin and serum morning melatonin level, the measurements will be plotted and compared using prediction intervals from regression analysis as outlined in 2003 paper by J. M. Bland and D. G. Altman[20].

H. Regulatory

a. Regulatory Requirements

The study will be performed in accordance with ICH GCP Guidelines and the Code of Federal Regulations for clinical research. Any amendments to the study protocol must be approved by Providence Health and Services Institutional Review Board before implementation. AEs and protocol violations or deviations must be reported according to the guidelines of Providence Health and Services Institutional Review Board.

b. Safety Assessments

Full physical and neurological exams will be performed at months 3, 6 and 12 visits. Any worsening or new abnormality that is clinically significant is to be recorded as AE and will be analyzed as such. MS relapse symptoms are not to be reported as AE unless, in the opinion of the investigator, the symptoms are unusually serious and relevant.

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease that is experienced by a subject who has received an investigational drug, whether or not there is a causal relationship with the investigational drug. At the signing of the informed consent form, each subject will be given the names and telephone numbers of investigational site personnel for reporting adverse events and medical emergencies. The investigator must conduct thorough assessment to determine the severity of the AE and the relationship to the study drug. Any clinically significant AE of severity moderate or higher, requires follow up until resolution or stabilization.

I. Reporting Adverse Events

a. Per International Conference of Harmonization (ICH) guidelines, an AE for this trial will be any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment and AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a product, whether or not considered related to the medicinal product. Pre-existing conditions which worsened during his stay are to be reported as adverse events. All adverse events fitting this description will be captured and recorded on the case report forms.

b. In the event that the subject is withdrawn from the study because of an adverse event, it must be recorded on the case report form as such.

c. Serious Adverse Events

i. Death

ii. Life-threatening experience which places his subject at immediate risk of death from the event as it occurred.

iii. Full inpatient hospitalization or prolongation of hospitalization

iv. Persistent or significant disability/incapacity

v. Congenital anomaly or birth defect

d. All adverse events (including pre-dosing and treatment-emergent) should be recorded in the subject's Adverse Event CRF regardless of severity or relationship to study drug. This includes abnormal, clinically significant laboratories being drawn as standard of care for routine monitoring with oral DMT. The investigator must review the laboratory findings and sign and date the laboratory report either electronically in the EMR, or as a paper source copy for significance review. All SAEs must be reported by the investigator to the regulatory associate and study manager by email to suzanne.balleisen@providence.org and tiffany.gervasi-follmar@providence.rog or fax to 503-215-6547 and 503-216-1039 within 24 hours of the investigator's knowledge of the event. All SAEs must be recorded on the Medwatch 3500A form and be reported, whether or not the event is considered by the investigator to be related to study drug.

e. Severity

The intensity of severity of an AE will be graded as follows:

Mild	Symptoms(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms(s) but may be given because of personality of subject
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with investigational drug; treatment for symptom(s) may be given and/or subject hospitalized.

f. Relationship to Study Drug

The relationship or association of the AE to a study drug will be characterized as follows:

Not related	Any event that does not follow a reasonable temporal sequence from administration of investigational drug AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Unlikely Any event that does not follow a reasonable temporal sequence from administration of investigational drug *OR* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly Any reaction that follows a reasonable temporal sequence from administration of investigational drug *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Related Any reaction that follows a reasonable temporal sequence from administration of investigational drug *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

Investigator Reporting Responsibilities for Safety and Monitoring

- Monitor and record all adverse events
- Determine the seriousness, causality, and severity of each adverse event
- Form a Data Safety Monitoring Board (DSMB) and conduct regular meetings to review safety findings
- Report all serious adverse events to the FDA according to the code of federal regulations
- Actively and persistently pursue follow-up of serious adverse events
- Submit annual reports to study sponsor

J. Estimated Duration of the Study and Critical Timeline Elements

a. IRB Approval – April 26th, 2018
b. Study Start Date– May 9th, 2018
c. Enrollment Completion Date, Estimated – November 9th, 2020
d. Study Completion Date, Estimated – November 9th, 2021

Table 1: Schedule of Events

Visit Number	Visit 1	TC	Visit 2[A]	TC	TC	Visit 3	TC	Visit 4	TC	Visit 5	Visit ET	Visit UNS
Visit Schedule	**Screening** 1-30 Days prior to Baseline	Within -5 days of Visit 2	**Baseline** Day 1	Within +3 days of Visit 2	Within -5 days of Visit 3	**Month 3**[K] ±14 days	Within -5 days of Visit 4	**Month 6**[K] ±14 days	Within -5 days of Visit 5	**Month 12**[K] ±14 days		
Informed Consent	X											
Inclusion/Exclusion Review	X		X									
Demographic Information	X											
Vitals[B]	X		X			X		X		X	X	X
Height and Weight	X											
Prior Medication Review	X											
Concomitant Medication Review	X		X			X		X		X	X	X
Adverse Event Assessment	X[M]		X			X		X		X	X	X
Medical History	X											
MS History	X											
Childbearing Potential Review[C]	X											
Physical Exam	X[Q]					X		X		X	X[N]	X[O]
Neurological Exam	X[R]					X		X		X	X[N]	X[O]
Urinary 6-SMT reminder		X[L]			X		X		X			
Urinary 6-SMT Collection[D]			X			X		X		X	X	X
Dispense 24hr Urine Collection Materials	X		X			X		X				
Serum Melatonin Collection[E]			X			X		X		X	X	X
Standard of Care Vitamin D Level[P]	X		X			X		X		X	X	X
Collect/Dispense Subject Dosing Diary[J]			X			X		X		X	X	X
Relapse Assessment			X			X		X		X	X	X
MFIS			X			X		X		X	X	X
MSIS-29			X			X		X		X	X	X
PSQI			X			X		X		X	X	X
PDDS-PS			X			X		X		X	X	X
Randomization			X									
Collect/Dispense Study Drug			X[G]			X		X		X[H]	X[H]	X[F]
Study Medication Compliance				X[I]		X		X		X	X	X
Study Medication Accountability						X		X		X	X	X
Oral DMT Compliance Assessment	X		X			X		X		X	X	X

A: Screening and baseline may occur one day apart if all screening procedures are completed/reviewed at time of baseline. Urine and serum melatonin labs must be collected prior to dosing on Day 1. These visits cannot be completed on the same day due to the required 24 hour urinary 6-sulfatoxymelatonin collection to be initiated after consent.

B: Vitals to include blood pressure, respiration rate, pulse, and oral temperature after being seated at rest for 5 minutes.

C: Adequate contraception method for female subjects of childbearing potential will be left to the discretion of the treating investigator.

D: Urinary 6-sulfatoxymelatonin collection for 24 hours in two twelve hour sessions. See local laboratory manual for reference ranges and collection specifications. To be collected within -3 days of indicated visit date, with the exception of ET and UNS visits-to be collected within ±3 days of visit.

E: Serum melatonin be collected at 0900 ±2 hours. See local laboratory manual for reference ranges and collection specifications.

F: Collect study drug only if reason for UNS visit is stopping DMT and/or study medication. None to be dispensed in this case

G: Dispense study drug only, none to be collected.

H: Collect study drug only, none to be dispensed.

I: Phone contact to be completed within +3 days of baseline visit to verify study drug first dose date and time.

J: Dispense Subject Dosing Diary at baseline. Collect and dispense new diary at each subsequent visit. Collect diary at visit 5 or ET and do not dispense new diary.
K: One month is equal to 30 days.
L: Not applicable/required if screening and baseline are 1 day apart.
M: Adverse events to be reviewed during screening period after informed consent is obtained (i.e., at end of screening visit).
N: only if requested by the treating physician or if subject was examined more than 6 months ago
O: only if requested by the treating physician or if a relapse is suspected
P: At screening, the most recent vitamin D level collected as part of standard of care for the subject will be reported in the trial. At all additional visits, if a vitamin D level was collected since the last trial visit as part of standard of care, it will be reported in the trial. Not to be ordered specifically for the trial.
Q: If a subject had a physical exam during the screening window (1-30 days prior to baseline) with a trial investigator but it was completed prior to consent as part of standard of care, the data from this exam may be used for the screening visit physical exam requirement. This is allowed only if all elements of the required exam were completed.
R: If a subject had a neurological exam during the screening window (1-30 days prior to baseline) with a trial investigator but it was completed prior to consent as part of standard of care, the data from this exam may be used for the screening visit neurological exam requirement. This is allowed only if all elements of the required exam were completed.

Scientific References:

1. Hauser SL eta al. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 2006; 52:61-76.

2. Lassmann H, Van Horseen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurol 2012; 37:175-84.

3. Campbell GR, Ohno N, Turnbull DM, Mahad DJ. Mitochondrial changes within axons in multiple sclerosis: an update. Curr Opin Neurol. 2012; 25(3):221-30.

4. Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of melatonin system in the control of sleep: therapeutic implications. CBS Drugs 2007; 21:995-1018.

5. Brzezinski A. Melatonin in humans. NEJM 1997; 336:185-96.

6. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin – a pleiotrophic, orchestrating regulator molecule. Pro Neurobiol. 2011; 93:350-84.

7. Escribano B, Colin-Gonzalez A, Santamaria A, and Tunez I. The Role of Melatonin in Multiple Sclerosis, Huntington's Disease and Cerebral Ischemia. CNS & Neurological Disorders. Drug Travets. 2014; 13: 1096-1119.

8. Jin Y, de Pedro-Custa J, Soderstrom M, Stawiarz L, Link H. Seasonal patterns in optic neuritis and multiple sclerosis: a meta-analysis. Journal of the Neurological Sciences. 2000; 191:56-64.

9. Spelman T, Gray O, Trihano M, Petersen T, Izquierdo G, Lugaresi A, Huppers R, Bergamaschi R, Duquette P, Grammond P, et al. Seasonal variation of relapse rate in multiple sclerosis is latitude dependent. Ann Neurol. 2014; 76(6):880-90.

10. Farez M, Mascanfroni I, Mendez-Huergo, S, Correale J, et al. Cell 2015; 162(6):1338-1352.

11. Compston A, Ebers F, McDOnald I, Mattews B, Wekjerie H. Symptoms and signs of Multiple Sclerosis. McAlpine's Multiple Sclerosis. Third Ed. London: Churchill Livingstome; 1998: 154-5.

12. Melamud L, Golan D, Luboshitzky R, Lavi I, Miller A. Journal of Neurologic Sciences; 314: 37-40.

13. Multiple Sclerosis Council. Fatigue and multiple sclerosis- clinical practice guideline. Washington DC, USA:Paralyzed Veteran of America, 1998.

14. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain : a journal of neurology 2001;124:962-973.

15. Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research 28:193-213, 1989.

16. Hohol MJ, Orav EJ, Weiner HL. Disease Steps in multiple sclerosis: A simple approach to evaluate disease progression. Neurology 1995; 45: 251–55.

17. Hohol MJ, Orav EJ, Weiner HL. Disease Steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. Multiple Sclerosis 1999; 5: 349–54.

18. Marrie RA and Goldman M. Validity of performance scales for disability assessment in multiple sclerosis. Multiple Sclerosis 2007; 13: 1176-1182.

19. Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of patient determined disease step scale scores in persons with multiple sclerosis. BMC Neurology 2013; 13: 37

20. Bland, J. M., & Altman, D. G. (2003). Applying the right statistics: analyses of measurement studies. Ultrasound In Obstetrics & Gynecology: The Official Journal Of The International Society Of Ultrasound In Obstetrics And Gynecology, 22(1), 85-93.