#1740 Lipoic Acid for Treatment of Progressive Multiple Sclerosis

Funding Agencies: Rehabilitation Research & Development, National Multiple Sclerosis Society, MS Society of Canada

Principal Investigator/Study Chair: Rebecca Spain

Version 8.0: 18 February 2021

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NCT# 03161028

INVESTIGATOR AGREEMENT

Protocol Version 8.0

Lipoic Acid for Treatment of Progressive Multiple Sclerosis

By signing, the Investigator agrees to have read the foregoing protocol and agrees to conduct the study as described herein.

The Investigator agrees to keep all study documents stored appropriately to ensure their confidentiality. The Investigator should not disclose study information to others without authorization, except to the extent necessary to conduct the study.

_____
Investigator Name (Print)

_____ _____
Investigator Signature Date

Synopsis

Study Investigator/Sponsor: Rebecca Spain, MD, MSPH

Funding Sources: VA Merit review (RX002682-01, RR&D) National MS Society (R-1705-27628), MS Society of Canada

Investigational product: Lipoic acid (previous names alpha lipoic acid, thiotic acid). Investigational drug provided by Pure Encapsulations®

IND#: 110132

Title: Lipoic acid for treatment of progressive multiple sclerosis.

Study Centers: VA and non-VA MS Centers (United States), Ottawa, Ontario (Canada)

Study Sites: VA Portland Health Care System (VAPORHCS), VA Puget Sound Health Care System, Washington DC VA Medical Center, VA Salt Lake City Health Care System, Dallas VA Medical Center, Ottawa Hospital Research Institute, Swedish Medical Center, University of Alabama at Birmingham, University of Utah, University of Vermont, and University of Colorado.

Duration of Study: Approximately 2 years **Phase of Development:** Phase 2

Study Objectives:

Primary objective:

- Determine if lipoic acid (LA) is superior to placebo at 2 years in maintaining a clinically meaningful outcome, mobility, as measured by the primary outcome of change in completion time of the Timed 25 Foot Walk (T25FW). Two Minute Timed Walk (2MTW) and fall count will be evaluated to confirm the primary outcome results.

Secondary objectives:

- Determine if LA is superior to placebo at 2 years in slowing whole brain atrophy with an estimated 40-50%% effect size. Additional secondary outcome measures will include neurological disability, cognition, mood, and quality of life.
- Monitor safety and tolerability of LA via laboratory testing and adverse event reporting.

Study Design: Participants with primary progressive and secondary progressive multiple sclerosis (MS) will be randomized on a 1:1 basis to LA or placebo. Subjects will

complete 7 study visits over 2 years. Walking tests and secondary outcome measures will be performed at every visit. MRIs will be completed at baseline and study end. Safety laboratory measures will be collected at every study visit. The sample size of 59 per arm will allow for a 25% drop-out rate.

List of Abbreviations

ACR, albumin to creatinine ratio
AE, Adverse Event
AIRC, Advanced Imaging Research Center
ALP, alkaline phosphatase
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BBB, blood brain barrier
BDP, Biostatistics & Design Program
BND, Biorepository for Neurological Diseases
CCC, Clinical Coordinating Center
CDA, Career Development Award
CFR, Code of Federal Regulations
CNS, central nervous system
DCC, Data Coordinating Center
DMT, disease-modifying therapies
DSMB, Data Safety and Monitoring Board
EAE, experimental autoimmune encephalomyelitis
EDSS, Expanded Disability Status Scale
eGFR, estimated glomerular filtration rate using MDRD calculation
FESI, Falls Efficacy Scale-International
FDA, Food & Drug Administration
GGT, gamma-glutamyl transferase
GI, gastrointestinal
GLTEQ, Godin Leisure-Time Exercise Questionnaire, modified
ICF, informed consent form
IND, Investigational New Drug
IRB, Institutional Review Board
LA, lipoic acid
LSI, local site investigator
M, month
MDRD, Modification of Diet in Renal Disease
MedDRA, Medical Dictionary for Regulatory Activities
MPRAGE, Magnetization Prepared Rapid Acquisition Gradient Echo
MS, multiple sclerosis

NMSS, National Multiple Sclerosis Society
OCTRI, Oregon Clinical & Translational Research Institute
OHSU, Oregon Health & Science University
PCBV, percent change brain volume
PCP, Primary Care Provider
PD, Protocol Deviation
PHI, protected health information
PMS, progressive multiple sclerosis
QC, quality control
RCT, randomized controlled trial
RIC, Recruitment Innovation Center
RRMS, relapsing-remitting multiple sclerosis
SAE, serious adverse events
SBQ-R, Suicide Behaviors Questionnaire-Revised
SC, Subcutaneous
SCC, Statistical Coordinating Center
SDMT, Symbol Digit Modalities Test
SIENA, Structural Image Evaluation using Normalization of Atrophy
SPMS, secondary progressive multiple sclerosis
T, Tesla
T25FW, Timed 25 Foot Walk
UP, Unanticipated Problem

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1.0 Key Study Personnel/Study Centers

A current personnel list is provided with the manual of operations

Principal Investigator/Study Chair:
Rebecca Spain, MD, MSPH
VA Portland Health Care System
L226, 3181 SW Sam Jackson Park Road
Portland, OR, 97239
Ph: (503) 346-0768
Fax: (503) 346-6921
spainr@ohsu.edu (preferred); Rebecca.Spain@va.gov

Project Manager:
Carin Waslo, MPH
VA Portland Health Care System
waslo@ohsu.edu (preferred); Carin.Waslo@va.gov

Clinical Coordinating Center (Rebecca Spain)
VA Portland Health Care System

Data Coordinating Center
Oregon Clinical & Translational Research Institute (OCTRI)
Oregon Health & Sciences University (OHSU)
Portland, OR

Statistical Coordinating Center
OHSU Biostatistics & Design Program (BDP)
Portland, OR

Central MRI Reading Site
OHSU Advanced Imaging Research Center
Portland, OR

2.0 Introduction

Scientific Rationale and Significance

Multiple sclerosis (MS) is a chronic progressive autoimmune disease of the central nervous system (CNS), and the most common neurologic disease of young adults including Veterans. More than 2.5 million people worldwide and around 500,000 people in the U.S live with MS. At any time, nearly half have a progressive MS (PMS) phenotype characterized by clinical worsening in the absence of exacerbations associated with CNS inflammation (1). Mobility deficits are a hallmark of MS with approximately half of all patients requiring a walking aid by 15 years after diagnosis. MS is divided into subtypes according to its course. About 85% people present with a relapsing-remitting MS (RRMS) subtype, then transition into a secondary progressive subtype (SPMS) after 10-20 years. The remaining 10-15% present with unremitting progression from onset called primary progressive MS (PPMS) (2). Taken together, PPMS and SPMS are termed progressive MS (PMS). Patients with PMS, including veterans, use a disproportionate quantity of social and medical services, and report a lower quality of life than RRMS (3).

MS is traditionally considered an inflammatory disorder characterized by episodic CNS demyelination but current understanding is that neurodegeneration accompanies progression from disease onset. Neurodegeneration causes generalized atrophy throughout the CNS including the brain, spinal cord, and optic nerves (4-6). Atrophy of both the brain and spinal cord can be observed on MRI using now standard post-processing techniques (7). Targeting specific mechanisms of neurodegeneration is a rational strategy for development and validation of therapeutic interventions for PMS.

Lipoic acid (LA) is an endogenously-produced eight carbon sulfur-containing fatty acid that is synthesized de novo in plants and animals. Endogenous LA is bound to proteins and is involved in acyl transfer reactions (8). It can also be absorbed from natural food sources and nutritional supplements. LA and its reduced form dihydrolipoic acid (DHLA) form a redox couple serves as a cofactor for at least five enzymes. LA in addition has antioxidant functions including free-radical scavenging, metallic ion chelation, regeneration of intracellular glutathione, and repair of oxidative damage to macromolecules (9). In mitochondria, the LA/DHLA redox couple serves as a key co-factor for the pyruvate dehydrogenase complex of oxidative respiration, and aids synthesis of nucleic acids (10). LA is involved in modulation of signal transduction including the PKB/Akt signaling pathway important for vascular endothelial integrity, redox-sensitive transcription factors including Nrf2, and acts as an insulin mimetic to reduce insulin resistance (11, 12). LA is available as an inexpensive dietary

supplement, and the most common synthetic formulation of LA is the racemic mixture of its R and S enantiomers.

Our center and others have shown that LA reduces impairment in a dose-dependent fashion in the murine model of MS, experimental autoimmune encephalomyelitis (EAE) (13, 14). Our center has also shown that LA is safe and tolerated in people with MS, and conducted dose-finding pharmacokinetic (PK) studies. Oral administration of LA at 1200 mg/day produces easily detectable blood levels in people with MS and achieves levels comparable to therapeutic blood levels in mice with EAE (15). The same dose of LA has been used in trials for diabetic polyneuropathy and shown to be well-tolerated in two year trials for this indication (16). The most common adverse reactions in LA trials are gastrointestinal intolerance, headache, malodourous urine, and rash (16, 17). One participant in our Center's prior clinical trial of LA in secondary progressive MS and one in the currently ongoing study developed biopsy-proven membranous glomerulonephritis (18). Both participants developed urine protein and limb edema leading to the diagnosis. At 6 months follow-up from study exit, the participant no longer had abnormal labs, edema, or required nephrologist care. This participant is under ongoing care monitoring.

We discovered that LA significantly reduced brain atrophy in people with SPMS compared to placebo in our pilot randomized controlled trial (RCT, see Preliminary studies) (18)**.** The natural antioxidant, LA, produced a significant reduction in brain atrophy assessed by MRI in people with secondary progressive MS (SPMS). Additionally, the LA cohort had a trend toward improvement in walking tests and a reduction in falls. Importantly, LA was safe, well tolerated, and had very high compliance.

Significance: The impressive results of the pilot LA in SPMS trial make LA an attractive, safe, natural, and tolerated DMT candidate for people who suffer from PMS. The goal of this larger, multi-site, Phase 2 RCT of LA in a broader PMS population is to confirm the effects on brain atrophy rate reduction and to establish the clinical benefits of LA.

<u>Preliminary Studies</u>

LA suppresses EAE, the animal model of MS, in a dose-dependent fashion. In a study of EAE mice treated with LA before disease onset, LA in doses of 100 mg/kg/day, 50 mg/kg/day, and 20 mg/kg/day were all effective in

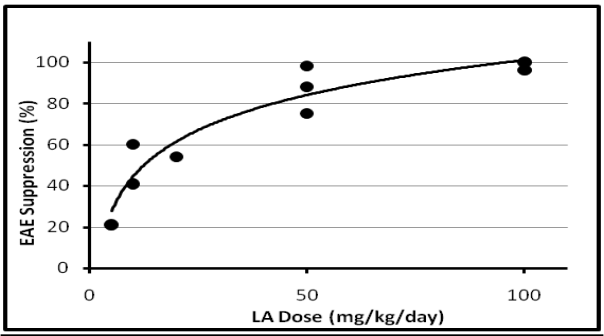

Fig. 1. Dose-response curve of EAE suppression in LA-treated mice.

suppressing EAE (19). An LA dose of 20 mg/kg/day suppressed EAE development by almost 50% (according to Cumulative Disease Scores scores), a dose of 50 mg/kg/day suppressed EAE by ~80%, and a dose of 100 mg/kg/day suppressed EAE by 100% over 10 days (Fig.1).

PK studies in EAE and humans have determined the human equivalent dose to the therapeutically effective dose in EAE. Two PK studies of LA in people with MS were conducted at OHSU and determined that doses of 1200mg taken with food were easily detectable LA levels in the serum and had reasonable gastrointestinal tolerability (15, 17). A formulation from the PK studies was used in the pilot LA in SPMS trial and will be used again in the current trial of LA in PMS.

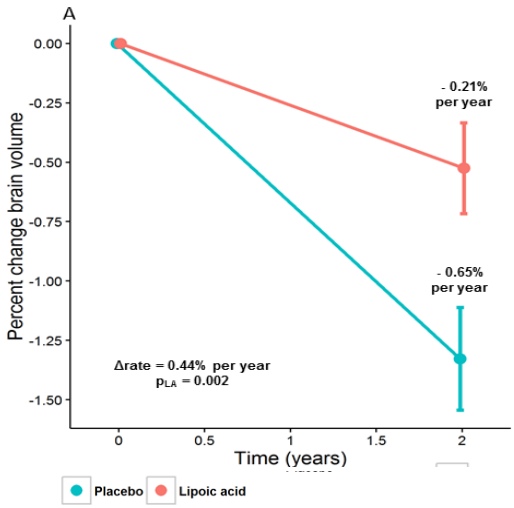

Figure 4. LA reduces brain atrophy in SPMS participants using intention-to-treat analysis.

Spain *et al* conducted a single-center, 2-year randomized, double-blind, placebo-controlled phase 2 trial (n=51) of daily oral LA in SPMS (18). The LA cohort demonstrated a 68% reduction in the annualized rate of whole brain atrophy (0.21% vs -0.65%, p = 0.002, Fig 4). Although not powered to detect clinical outcomes, the LA cohort had a trend toward improvement in walking speed in the T25FW (-0.54 SD 0.36 vs 0.14 SD 0.25, p = 0.06). Overall LA was safe and well tolerated with high compliance and at the time, no unexpected deleterious adverse events (AE) were attributed to LA. A later review of AE's in light of safety data emerging from the present study indicate that the serious adverse event of biopsy-proven glomerulonephritis and a second case of proteinuria in subjects in the LA cohort was related to lipoic acid (see above). To date, all three cases resolved within a 3-12 month period. Gastrointestinal (GI) upset was significantly greater in the LA cohort compared to placebo (17% v 3% p = 0.004). Unexpectedly, the LA cohort had a significantly lower number of falls than the placebo cohort (15% v 38%, p = 0.03). The results of this study formed the basis of the current research trial.

3.0 Objectives

Hypothesis: The purpose of this study is to determine if the oral antioxidant LA provides clinical benefits and reduces brain atrophy in PMS. The hypothesis is that daily LA will both maintain mobility and reduce whole brain atrophy, thus paving the way for

consideration of LA as a disease-modifying therapy for PMS. The specific aims of this multi-center RCT of 1200mg oral daily LA versus placebo in PMS are:

Specific Aim 1. Determine if LA is superior to placebo in maintaining mobility as measured by the primary outcome of change in completion time of the Timed 25 Foot Walk (T25FW). Secondary outcomes are changes in the 2 Minute Timed Walk (2MTW) and fall count for consistency of the effects of LA on mobility.

Specific Aim 2. Determine if LA is superior to placebo in slowing whole brain atrophy with an estimated 40-50%% effect size. Additional secondary outcome measures are changes in neurological disability, cognition, mood, and quality of life.

Specific Aim 3. Monitor safety and tolerability via laboratory testing and adverse event reporting.

4.0 Resources and Personnel

The research study will be conducted at both VA and non-VA study sites. VA Portland Health Care System (VAPORHCS) is the lead study site and serves as the Clinical Coordinating Center (CCC). The Oregon Clinical & Translational Research Institute (OCTRI) within Oregon Health & Science University (OHSU, Portland, OR) will serve as the Data Coordinating Center (DCC). The Statistical Coordinating Center (SCC) is housed in the OHSU Biostatistics & Design Program (BDP). The OHSU Advanced Imaging Research Center will act as the Central MRI Reading Site.

Rebecca Spain is the Grant PI and the Sponsor-Investigator for this IND study. Dr. Spain is responsible for the overall conduct of the study. She has access to PHI from all study subjects. She is permitted to be the LSI and treating neurologist at VAPORHCS.

Local Site Investigators (LSI): Each study site has a LSI that is responsible for the overall conduct of the study at their site including regulatory oversight. The LSI has access to PHI for subjects from their site only.

Site treating neurologist: The treating neurologist is responsible for reviewing the inclusion/exclusion criteria, conducting the screening medical history and exam, reviewing safety laboratory results, adverse event recording and reporting, and conducting unscheduled visits as needed for adverse event evaluation. The site treating neurologist has access to PHI for subjects from their site only. The treating neurologist may also hold the role of LSI.

Project Manager (PM): This person at principal study site (Portland) will assist the study PI in all aspects of study management and coordination. The PM will not collect primary data from subjects. The PM will work closely with all study team members to attain initial IRB approval, ensure the accurate and timely collection and recording of study data, monitor recruitment, assist with site IRB submissions and revisions, improve study logistics, conduct conference calls, tabulate data for the DSMB, and assist in any other aspects of study required for successful completion. The PM will serve as the study monitor. The PM has access to PHI for all study subjects.

Site blinded EDSS examiners: EDSS examiners must have training in the neurological exam and experience conducting EDSS exams. The blinded EDSS examiner should not be the usual treating neurologist of the subject in order to maintain the blind. The blinded EDSS examiners may have access to PHI for subjects from their site only.

Central Research Pharmacy: Portland VA Research Pharmacy will act as the Central Research Pharmacy for the entire study. They will receive bulk study drug from the product donor and redistribute it to US study site Research Pharmacies who then prepare study drug for individual subjects. The Central Research Pharmacy works with the SCC to maintain the randomization lists for each study site. The Central Research Pharmacy has access to PHI for all study subjects.

Site research pharmacies: The US site research pharmacies will receive study drug from the Central Research Pharmacy and package it for individual subjects according to the randomization schedule. They will also provide medication reconciliation reports. The Canadian site research pharmacy will receive study drug directly from the product donor and then perform the same functions as the US site pharmacies. The site research pharmacies have access to PHI for subjects from their site only.

Clinical Coordinating Center (CCC): VAPORHCS will serve as the CCC. The CCC will serve as the primary communication hub between study sites, study centers, and monitoring bodies.

Data Coordinating Center (DCC): The DCC and the PM will work closely to set up and maintain the study database, create policies and procedures for the study, monitor data quality and accuracy, and help create DSMB reports. The DCC will receive reports from all study sites regarding adverse events (AE), serious adverse events (SAE), unexpected problems (UP), and protocol deviations (PD) and ensure proper reporting to IRBs per reporting requirements.

Statistical Coordinating Center (SCC): The SCC will conduct all data analyses, assist in DSMB reports, and create all final reports, figures, and statistical analysis sections of manuscripts that result from this study. The SCC will have access to PHI from all subjects.

Central MRI Reading Site: The Central MRI Reading Site will receive MRI images from all study sites, perform QC monitoring of images and facilities, provide feedback on image quality issues, conduct all study related image analyses, and enter the analysis results into the study database. The Central MRI Reading Site will have access to PHI from all study subjects.

Data Safety and Monitoring Board (DSMB): The DSMB will develop the DSMB charter and will meet at least yearly to review aggregate safety data and study progress. The DSMB will provide a report to the PI with recommendations regarding ongoing conduct of the study. As a member of the DSMB, Dr. Mary Samuels will be the Medical Monitor for this study. Dr. Rupali Avasare, a nephrologist at OHSU, will monitor any abnormal kidney function at the time of entry of during the course of treatment. The DSMB will have access to PHI from all study subjects.

5.0 Study Procedures

5.1 Study Design

5.1a. Design and specific aims: This is a phase 2, double-blind, multi-center RCT to compare the daily administration of 1200 mg oral LA to a placebo, as a disease-modifying treatment in PMS. A total of 118 subjects with PMS will be randomized 1:1 to LA or placebo. None of the study procedures involve usual care. All study procedures will be covered by study funding.

5.1b. Study population: A convenience sample of adults with PMS will be recruited from the study sites. The multi-site design of the trial is intended to promote generalizability of the study results.

5.1c. Study timeline and visit scheduling. The anticipated study recruitment period is for the first 18 months once the study is approved at the first study site or until enrolment is completed, whichever occurs first. The study will end when the last participant exits the study. There should be no more than 60 days inclusive between the screen and baseline visits. Subsequent study visits will occur at 3 months, 6 months, and every 6 months thereafter, each visit within +/- 2 weeks from the ideal visit based on the baseline/month zero (M0) visit. The MRI can take place up to 2 weeks prior to the baseline and final visits. Should the final MRI be postponed for any reason until after the

final visit, the subjects should continue taking study drug until the MRI has been done. Reasons for conducting visits outside the scheduling window are recorded.

Performance on clinical measures may be subject to variation due to the day-to-day fluctuations characteristic of PMS. Effects of fluctuations on study outcomes will be minimized by encouraging subjects to maintain their usual sleep, eating, and medication intake patterns on study days. Study visits will be scheduled at the same time-period each visit (morning versus afternoon). Study visits may be postponed for concurrent non-MS related illness affecting neurological performance on the discretion of the treating neurologist.

5.1d. Unscheduled visits for relapse evaluation and adverse events (AE): Unscheduled visits will occur in the event of MS clinical relapses or investigations of AE of at least moderate severity *considered directly related to the study drug or study procedures*. The unscheduled visit for AE is for the purpose of evaluation by the treating neurologist, documentation, and reporting according to IRB guidelines. If sufficient medical documentation by other health providers for the symptoms of the AE exist, or if the symptoms had resolved by the time of reporting, the treating neurologist may use the medical documentation or telephone interview in lieu of an unscheduled visit. Asymptomatic elevations or depression in laboratory values considered related to the investigational drug do not require an unscheduled visit but instead follow the monitoring procedure (5.1m. Protection from risks). If AEs warranting an unscheduled visit are noted during a scheduled study visit, procedures for both the unscheduled visit for AE and the scheduled study visit are completed. An unscheduled visit for AE evaluation includes collection of case report forms for:

AE evaluation documentation including event history

General medical exam

Vital signs

Concomitant medications

Safety laboratory measures (per treating neurologist discretion)

Adverse events monitoring

SBQ-R

A protocol-defined MS clinical relapse is defined as new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, which is

followed by a period of stability or improvement. In addition, a protocol-defined relapse requires an increase in the EDSS Functional System corresponding to the symptom(s) of the relapse, or an increase in the overall EDSS secondary to a functional change related to symptoms(s) of the relapse. A relapse is not considered an adverse event. MS clinical relapses can occur in PMS and may be treated by the usual treating neurologist with standard courses of intravenous methylprednisolone or oral steroids of less than 2 weeks duration.

An unscheduled visit should be conducted within 1 week of a reported MS clinical relapse. The unscheduled visit for MS clinical relapse evaluation includes:

MS clinical relapse evaluation documentation including

General medical exam

Vital signs

Concomitant medications

EDSS examination (blinded)

Safety laboratory measures (per treating neurologist discretion)

Adverse events monitoring

SBQ-R

Subjects who have discontinued the investigational drug for adverse events including laboratory monitoring (see section 5.1m.) do not require unscheduled visits for subsequent MS clinical relapses.

Scheduled study visits involving MRIs will be delayed for at least 30 days following high dose oral or intravenous corticosteroid treatment given for any indication. MS clinical relapses not treated with corticosteroids do not affect study visit scheduling. Ongoing MS clinical relapses noted during a scheduled study visit have procedures for both the unscheduled visit for MS clinical relapse and the scheduled study visit completed.

Subjects who withdraw early from the study follow the procedures outlined in Withdrawal of Subjects (sec 5.7).

5.1e. Source of investigational drug. Pure Encapsulations®, which follows Good Manufacturing Procedures in their production of LA, will provide gelatin capsules

containing 600 mg of LA and the encapsulated placebo rendered to appear similar to LA (Letter of support, Appendix A).

5.1f. Investigational New Drug (IND). Dr. Spain holds an IND for testing LA in PMS (#110132). The current proposed study has been added as an amendment to the current IND. Reporting requirements to the FDA will be followed.

5.1g. Labeling: The investigational product will have a label that will be visible on the pertinent storage containers. The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

5.1h. Blinding. Blinding of the investigational drug will be implemented by the site research pharmacies using identical containers, and instructions. The Central Research Pharmacy will maintain a master record of subject assignment. Subjects and all personnel involved in conducting the trial will remain blinded to treatment assignment and undergo a blinding questionnaire at study end.

5.1i. Duration of treatment: Treatment with study drug will be for 2 years. Treatment will extend beyond 2 years if the final study visit is postponed. See section 5.7 for reasons for early termination of treatment.

5.1j. Randomization. The assignment of subjects to the treatment arms will be based on permuted block randomization defined by study site. The Central Research Pharmacy and SCC will oversee the randomization schedule. The Central Research Pharmacy will also maintain a master list of all study subjects in order to ship appropriate amounts of bulk study drug to the US site pharmacies for individual subject packaging and shipping.

5.1k. Compliance and medication reconciliation: Compliance with taking the investigational drug will be encouraged at each visit and between visits by telephone calls. Unused pills will be collected at each study visit and if necessary, by mail between visits. The study site research pharmacies will conduct medication reconciliation with returned pills and provide feedback to research staff to monitor if compliance is less than 75% or more than 125% of prescribed doses to encourage proper compliance.

5.1l. Risks: Risks of the investigational drug, study procedures, and potential loss of confidentiality are reviewed with potential subjects during the informed consent process. Risks, reporting, responses to risks, and methods to minimize risks are further outlined in section 6.0, Reporting and 7.0, Privacy and Confidentiality. Briefly, risks of the

investigational drug are minimized by adverse event reporting safety and safety laboratory studies. Risks of study procedures are minimized by careful screening procedures and trained study personnel. Risks of loss of confidentiality are minimized by limiting collection of PHI, limiting access of PHI to the minimum necessary study staff, and use of secure data transfer methods.

Risks of LA: Oral LA can cause physical side effects including gastrointestinal (GI) intolerance, nausea and vomiting and rash. LA may cause liver, renal and urinary disorders. There is a possibility of developing proteinuria and/or membranous glomerulonephritis due to study drug. It is not known how LA could affect a fetus. LA may increase the risk of hypoglycemia in diabetics. The risks of LA taken with DMTs or with alcohol are unknown.

Risks of study procedures and loss of confidentiality: There is a risk of falls and injury during gait testing. The MRI magnet can cause metal in the body to move, heat, and cause injury. The MRI space is small, so those with claustrophobia are at risk of discomfort during the study. There is a risk of psychological harm from incidental findings unrelated to the study found on MRI such as brain tumors, stroke, other. The risks of blood draws include discomfort, vasovagal syncope, bleeding, bruising, and infection. The risks of clinical testing and patient-reported outcome measures include psychological discomfort from discovering or reporting deficits due to MS. There is a risk of loss of confidentiality of the study data.

5.1m. Protection from risks: The informed consent process will inform potential subjects of the risks of participation. The study will be conducted with IRB oversight. Procedures in this study were specifically designed to minimize risks to the subjects. The investigators will adhere to the Data and Safety Monitoring Plan (sec. 6.2). Trained study personnel will perform all data collection, and information will be coded with a subject identifier to protect subject confidentiality. Findings that could affect the subjects' health or welfare will be reported to the appropriate authorities (e.g. IRB) and communicated to the subjects and appropriate medical service(s) which could include the primary care physician.

Risks to subjects from LA will be minimized by excluding unsuitable patients from enrollment, reviewing medical histories and medications at each study visit for potential interactions with the investigational drug, reviewing AEs for relation to investigational drug, and requiring unscheduled visits for AE evaluation and management.

To minimize the possible GI side effects of oral LA, we recommend subjects take the investigational drug with food, or if necessary, to divide the daily dose, or the dose

reduced by 50% at the discretion of the treating neurologist. Serum renal panels and urinalyses will monitor for kidney damage at every visit.

Trained phlebotomists will perform blood draws to minimize the associated risks of blood draws. Safety monitoring laboratory panels will monitor for liver, kidney, and hematological problems, pregnancy for women of childbearing potential and changes in HbA1c.

a. Proteinuria monitoring: Subjects must have urine protein ***monitored every 3 months*** for the duration of the study. Subjects must pause study drug if they skip or miss a visit until draw can occur.

   Subjects with baseline (screening) negative or trace proteinuria may participate in the study. Subjects with baseline 1+ or higher proteinuria are further tested for albumin to creatinine ratio (ACR): 1) ACR ≤ 300mg/g may participate, 2) ACR >300mg/g are excluded and receive referral to PCP. No repeat screening for proteinuria in subjects who have ACR >300mg/g will be done.

   Subjects who experience 1+ or higher proteinuria during the study are further tested for ACR: 1) ACR ≤ 300mg/g may continue participation, 2) ACR >300mg/g permanently stop study drug and receive referral to PCP or nephrologist along with notification of the Medical Monitor. A referral to Nephrology is recommended if ACR>1000mg/g. A kidney biopsy is recommended if proteinuria >300 does not resolve within 6 weeks of drug cessation.

b. Renal function monitoring: Subjects with baseline eGFR ≥ 60 may participate in the study. Subjects with baseline eGFR<50 are excluded. Subjects with baseline eGFR 50-59.9 are retested: 1) eGFR ≥ 60 may participate in the study, 2) eGFR<60 are excluded.

   Subjects who experience eGFR 50-59.9 during the study are retested within 1 month: 1) eGFR ≥ 60 may continue participation in the study, 2) eGFR<60 permanently stop study drug and are referred to PCP. Subjects who experience eGFR<50 during the study permanently stop study drug and referred to PCP. Regardless of the eGFR, if the eGFR decreases by 25% or more compared to the baseline eGFR, the Medical Monitor should be notified and should review the information to determine the next course of action.

c. Liver function monitoring: Abnormal liver laboratory results are graded according to the Common Terminology Criteria for Adverse Events v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Subjects who have stable and asymptomatic baseline Grade 1 abnormal laboratory liver values may, at the discretion of the site treating neurologists, participate in the study. Subjects who experience laboratory abnormalities of Grade 1 during the study will be permitted to continue at the full dose of study drug unless advised otherwise by the DSMB or other monitoring entities.

Abnormal laboratory tests may be repeated immediately if laboratory testing error is suspected. Laboratory tests should be repeated within 1 month for any liver values reaching a Grade 2 or greater.

If laboratory liver value(s) are still Grade 2 or greater by 1 month, the investigational drug will be reduced by 50% and levels checked again within 1 month. The rationale is that liver-related abnormalities are often dose-dependent. If laboratory liver value(s) improve to Grade 1 or less, the study drug dose is then increased to the full dose. If the same subsequent laboratory value(s) worsen again at the full dose, the subject may continue for the study duration at the 50% dose as long as subsequent laboratory values do not meet Grade 2 or greater levels. If subjects on a 50% dose demonstrate continued Grade 2 value(s) at a maximum of 1 month, subjects should stop the investigational drug. Those subjects for whom laboratory values do not improve to Grade 1 or better levels after 2 months off study drug permanently stop study drug. Only two investigational drug cessations are allowed for each subject. Any subject who experiences a third Grade 2 or higher laboratory test must permanently discontinue the investigational drug. If in question, permanent study drug discontinuations can be discussed with the Medical Monitor to establish the relationship of the laboratory result to the investigational drug. Subjects continue study procedures following the study flowsheet until study end during any investigational drug dose reductions and temporary cessations (see 5.1d for special handling of MS clinical relapse evaluations).

Safety laboratory results will be reviewed by site treating neurologists within 3 business days to determine if dose adjustments or safety reporting is required along with documentation and reporting as required (section 6.0 Reporting).

Sexually active female subjects capable of becoming pregnant and female partners of sexually active male subjects will be asked to use effective birth control during the study. If a female participant or partner of a male participant becomes pregnant during the research study, study personnel must be notified immediately. Subjects will be advised not to breastfeed while taking this investigational drug. Screening for pregnancy in female subjects of child-bearing potential will be conducted via pregnancy tests at study visits.

Because LA may increase the risk of hypoglycemia in diabetics, otherwise eligible subjects who are diabetics must have their diabetes controlled on non-insulin medications. Safety monitoring labs at every visit for all subjects includes non-fasting blood glucose levels, and HbA1c levels.

Because the risks of LA taken with DMTs are unknown, safety laboratory monitoring will screen for interactions affecting target organs. Subjects will be advised not to drink alcohol while taking the investigational drug and to store it out of reach of children.

The risk of falls during gait testing will be minimized by having trained research staff present at all times during gait testing, and a gait belt will be utilized as needed. Gait testing will be aborted if there is concern for safety or falls by either the participant or research staff.

Risks of MRI will be minimized by careful attention to MRI exclusion criteria at the screening visit including those who require non-oral sedatives during the scan. Any incidental findings unrelated to the study found on MRI such as brain tumors, stroke, etc., will be reviewed by the site treating neurologist who will consider referral to the appropriate medical service, determine ongoing safety for the subject's continued participation in the study, and to fulfil any reporting requirements necessary. Site treating neurologists will counsel subjects with unexpected findings on MRI to minimize any psychological trauma incurred by the discovery.

Overall, the risks of LA are considered minimal and are outweighed by the potential benefits to be gained by the study.

5.1n. Data banking: MRI and images and analyses results along with subject demographics and medical histories will be banked in the VAPORHCS Biorepository for Neurological Diseases (BND #2916). The only PHI included in the data repository is the date of study visit. These dates are necessary for the proper identification of images and data in subjects with multiple data entry points. The banking of the images is described in the Informed Consent Form (ICF).

5.1o. Optional biorepository participation: All subjects who have consented to the LAPMS study will be asked if they would like to contribute their blood to the Biorepository for Neurological Diseases (BND) #2916 (Rebecca Spain, director, Portland, OR). If the subject consents to the blood donation, approximately 10ml (2 teaspoons) of the blood collected at each study visit requiring a routine lab draw will be saved for storage in the BND indefinitely for future research. A coded data set including study ID, date of specimen collection, study visit, sex, age at time of blood draw, education, diagnosis, disease duration, study arm, and comorbid health conditions is

also stored indefinitely with the donated blood. Subjects are allowed to start or stop participation in the biorepository at any time, however, per the consent for the BND, blood samples already provided to recipient IRB-approved studies cannot be extracted after donation.

Subjects who consented to the LAPMS trial, prior to the addition of blood donation to the BND, will be asked to sign an updated consent indicating if they do or do not consent to adding their blood to the BND. Only subjects who sign an updated ICF indicating agreement will have their blood included in the biorepository.

5.2 Recruitment Methods

5.2a. Recruitment goal: A total of 118 subjects will be recruited for the study which includes an expected 25% will-drop rate out after enrolment. More potential subjects will be screened than enrolled as it is expected that some will not meet eligibility requirements despite screening methods. The PM and DCC will monitor recruitment across study sites and provide feedback on when enrolment is complete in order to stop recruitment (see Communication Plan 8.0). Recruitment data and reasons for failing to enroll in the study will be collected periodically from all study sites for the purpose of encouraging enrolment and identifying barriers to participation.

5.2b. Subject Identification/Recruitment: Potential subjects for the study will be recruited by the site study staff from MS clinics and from the general public by methods approved by the study site's local Institutional Review Board (IRB) and/or a Central IRB. Sample advertisements recruitment flyers (Appendix B), recruitment letters to local MS practitioners (Appendix C), and telephone scripts for interested Veterans and non-veterans (Appendix D) are provided to each site. Email blasts to potential subjects will be sent from the National MS Society using the approved language contained in the recruitment flyers and letters (Appendix E). The NMSS promotes the study by hosting a webpage including a study summary, site locations, and study coordinator contact information. A short URL (Appendix X), linking to the NMSS webpage, may be distributed during media interviews, and added to promotion materials (Appendix Y) during MS related events, such as but not limited to, MS Walks, MS races, and MS support groups. ResearchMatch.org will be used as one of the recruitment tools for this research study/protocol. ResearchMatch Volunteers will be contacted through ResearchMatch.org using the approved language contained in the recruitment message (Appendix W). A release of information will be obtained as needed to request medical records for eligibility review prior to scheduling screening visits. Participants enrolled in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry for Multiple Sclerosis will receive an approved study flyer in the mail. As with other recruitment tools, a release of information will be obtained as needed to request medical

records for eligibility review prior to scheduling screening visits. We will make use of the contact information in Dr. Rebecca Spain's MS Research Repository (IRB#18541). This repository contains names and contact information of people interested in research participation. All subjects included in the repository have consented to being contacted for opportunities for participation in research. Initial contact with potential participants will be made by the research coordinator. The CCC will also work with the Recruitment Innovation Center (RIC) at Vanderbilt University to implement a 4-week, multicity, social media ad campaign in partnership with a marketing agency, Red Deluxe. Red Deluxe, a recruitment tool, will have 3rd party administrative access to a study Facebook page, managed by the CCC, in order to monitor and push Facebook ads to a targeted audience based on eligibility criteria and interest in MS. Examples and text of the components within the social media ad campaign include the Facebook page (Appendix Z), the Facebook Ads (Appendix AA), and the study webpage (Appendix BB) and content (Appendix CC), adhering to the VA Graphic Standards Guide.

5.2c. Recruitment of specific subpopulations. MS has a predilection for affecting women in a 3-4:1 ratio. Therefore we expect women to be adequately represented in this current study using a convenience sample. Minorities will not be preferentially recruited as there is no data to suggest a differential effect of LA on specific minority populations and/or with particular genetic characteristics. MS is rare in children, and progressive forms of MS rare within this small population. Therefore no children will be enrolled.

5.2d. Recruitment of Veterans: The pilot trial of LA recruited 21 Veterans from the total 51 subjects. The current proposed study has more restrictive inclusion criteria than the pilot study, requiring that subjects are ambulatory. Recruitment of non-Veterans and use of VA and non-VA study sites is necessary to fulfil the enrolment timeline.

5.2e. Sources of materials: Sources from human subjects will include blood and urine samples and data in the form of clinical tests (e.g. gait, neurologic exam), patient-reported outcomes, and radiographic information (MRI). Medical records will be reviewed prior to the screening visit to assess for eligibility and confirm MS diagnosis. Data will be collected solely for research purposes.

5.2f. Benefits: Subjects may or may not benefit directly from the study. The benefits to society may be the discovery of a safe and low-cost oral therapy to treat PMS.

5.2g. Costs to subjects: There will be no cost to subjects to participate in this study. The study drug and investigations will be covered by the study budget.

5.2h. Subject compensation: Subjects will receive $50 per visit including unscheduled visits and $25 for extra laboratory visits if needed and cannot be performed locally. In addition, subjects are compensated for travel with $0.50/mile over 30 miles up to a maximum of $100 per visit. The payments will be in the form approved by each local study site, and will cover the costs of transportation and meals during the study visits. The compensation is included in the ICF. Subjects will be provided compensation after each visit regardless if all procedures are completed.

5.3 Informed Consent Procedures

Subjects will be required to sign IRB- approved ICFs in accordance with FDA Code of Federal Regulations (21 CFR 50). The ICF will be presented to all potential subjects at the screening visit by study personnel who are trained in human subjects protection as required by the site IRBs. Briefly, the ICF describes the purpose of the study, procedures and participant involvement, potential risks, protection against risks, alternatives to participation, costs and compensation, confidentiality, right to withdraw, potential benefits, relevant contact personnel, and new information regarding the Health Insurance Portability and Accountability Act of 1996. Potential subjects will have ample time to read and ask questions, and, when satisfied, will document their consent to participate by signing the ICF. A copy of the ICF is given to the participant and the other retained for study records. All subjects must be able to provide informed consent in English. Potential subjects with impaired decision making ability will not be included in the study as they may not be able to adhere to study procedures per the eligibility requirements.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria:

i. Age ≥ 18 years.
ii. Previous diagnosis of RRMS or PPMS by 2010 revised McDonald criteria.(20)
iii. Current SPMS or PPMS.
iv. Progression of MS in the previous 2 years defined by medical record or reliable historical interview as:
    a. Non relapse-related MS decline resulting in a 0.5 step change in EDSS, decline in T25FW, or other clinically documented decline (can be assigned retrospectively) if not on a DMT, OR
    b. If currently on a DMT, non-relapse-related MS decline resulting in a 0.5 step change in EDSS, decline in T25FW, or other clinically documented decline (can be assigned retrospectively) while on the current DMT taken continuously for at least 1 year prior to enrolment.

v. Able to give informed consent and to adhere to study procedures.
vi. EDSS 3.0 to 6.5.

Exclusion criteria:

i. A self-reported medical or neurological problem other than MS that is a cause of progressive or fluctuating gait dysfunction (e.g. worsening neuropathy, uncontrolled lower extremity arthritis, uncontrolled cardiopulmonary disease). Fixed and/or stable conditions of greater than 1 year that affect their gait are permitted (e.g. joint replacement, stable lumbar stenosis, remote alcoholism, remote stroke, etc.).
ii. MRI constraints (metal implants including pacemaker, devices with electrodes, or shrapnel, excessive weight per site MRI requirements, need for sedation with non-oral agents due to claustrophobia or muscle spasticity).
iii. MS clinical relapse in the 1 year prior to enrolment.
iv. Unable to follow directions in English as standardized scales are not all validated in other languages.
v. Current major disease or disorder other than MS (e.g., cancer, renal disease, end-stage cardiopulmonary disease, post-traumatic stress disorder, etc.) that may interfere with study procedures. Stable abnormal laboratory values of no more than Grade 1 determined to not be of clinical significance to the primary treating physician for that condition may be permitted per LSI discretion and comply with specific renal and liver testing requirements described in section 5.1m.
vi. Pregnant or breast-feeding.
vii. Insulin-dependent diabetes or diabetes not controlled on oral diabetes medications.
viii. Scheduled (every 3 months or more frequently) IV or oral steroids in the year prior to enrolment.
ix. IV or oral steroids in the 60 days prior to enrolment.
x. Use of LA in the prior 2 years exceeding the equivalent of 1200mg daily for 3 months.
xi. Participation in the pilot LA in SPMS trial.

5.5 Study Evaluations

5.5a. Study flowsheet

Procedure		Screen	Baseline M 0	M 3	M 6 M 12 M 18	M 24
Consent		X				
Medical history		X				
General medical exam		X				
Inclusion/Exclusion review		X	X			
Safety labs[ab]		X	X[c]	X	X[h]	X
Randomization			X[g]			
Vital signs		X	X	X	X	X
Concomitant Medications		X	X	X	X	X
T25FW		X	X		X	X
9 HPT		X	X		X	X
2MTW		X	X		X	X
EDSS		X	X		X	X
Cognitive tests	SDMT		X		M12 only	X
	CVLT-2ed		X		M12 only	X
	BVMT-R		X		M12 only	X
Patient reported outcome measures	PROMIS – pain intensity		X		X	X
	PROMIS – pain interference		X		X	X
	PROMIS- participation in social roles		X		X	X
	PHQ-9		X		X	X

	SS-MOS		X		X	X
	MFIS		X		X	X
	FESI		X		M12 only	X
	GLTEQ		X		X	X
Fall count				X		X
MRI			X[e]			X[e]
SBQ-R		X	X	X	X	X
Adverse event monitoring & compliance review[d]			X	X	X	X
Investigational drug dispensing			X	X	X	
Subject/provider blinding questionnaire						X
Subject compensation		X	X	X	X	X
Subject disposition[f]						X
Length of visit (hours)		3	4	1	3	4

BVMT-R, Brief Visuospatial Memory Test- Revised; CVLT-2ed, California Verbal Learning Test- Second Edition; EDSS, Expanded Disability Status Scale; FESI, Fall Efficacy Scale-International; GLTEQ, Godin Leisure-Time Exercise Questionnaire, modified; MRI, magnetic resonance imaging; MFIS, Modified Fatigue impact Scale; 9 HPT, 9 Hole Peg Test; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient Reported Outcome Measures Information Systems; SBQ-R, Suicide Behaviors Questionnaire-Revised; SDMT, Symbol Digit Modalities Test; SS-MOS, Sleep Scale from the Medical Outcomes Study; T25FW, Timed 25 Foot Walk; 2MTW, 2 Minute Timed Walk

[a]Includes pregnancy test for female subjects of childbearing potential only

[b] Optional Biorepository #2916 participation

[c]Only pregnancy test for female subjects of childbearing potential.

[d]Occurs at study visits and approximately halfway between each visit after baseline by telephone calls

[e]MRIs scheduled up to 14 days prior to M0 and up to 14 days prior to M24 visits. MRIs can be same day as M0 and M24 visits.

[f]Occurs at visit M24, at final visit for early termination, and when a subject is determined lost to follow-up.
[g]May occur prior to M0 visit day, when appropriate for logistical purposes, to avoid excessive M0 study visit times.
[h]Urine protein additionally tested M9, M15, M21.

5.5b. Consent, medical history, general medical exam: The ICF will be presented by the PI, LSI, or designated study staff. After consent has been obtained, the rest of the study procedures can occur. The medical history and general medical exam is conducted by the treating neurologist for the purpose of eligibility.

5.5c. Vital signs: Resting blood pressure, pulse, and weight are collected by trained study staff at every study visit for the purpose of initial eligibility and ongoing health monitoring. Consistent methods of obtaining data (e.g. same resting period prior to blood pressure and pulse assessments, etc.) is encouraged across study visits. Height is assessed at the screening visit only.

5.5d. Concomitant medication review: Current use of prescribed scheduled and as needed medications as well as over the counter medications and supplements is recorded by the study staff and reviewed at the screen visit by the treating neurologist for study eligibility. Concomitant medications are reviewed at each subsequent visit by study staff and changes reviewed by the treating neurologist. Any start, stop, or change to MS disease-modifying therapies will be noted and dated for data analysis purposes. Supplements will be reviewed by research staff in case they contain lipoic acid or other potential confounders to the study results.

5.5e. Safety laboratory analyses: Laboratory studies will be collected from all subjects at the screening visit if not available within the prior 3 months for establishing eligibility. Additional laboratory analyses occur at visits M3, M6, M12, M18 and M24 to monitor blood cell count, renal function, liver function, urine protein, non-fasting blood glucose levels, HbA1c, and (for women of child-bearing potential) pregnancy testing. Subjects must have urine protein monitored every 3 months for the duration of the study. Pregnancy testing is additionally conducted at the baseline visit for women of child-bearing potential. This involves taking approximately 15-25 mL (3 to 5 teaspoons) of blood at each draw for a total of 90-150mL (2/3 cup) over the course of the study. Laboratory draws will be performed by trained phlebotomists using universal precautions.

5.5f. Inclusion/Exclusion review: Eligibility criteria are reviewed by the treating neurologist during the screening visit. Once all criteria are met and confirmed at the baseline visit, the study staff will use REDCap to assign a randomization code and then

request study drug using the blinded randomization code. For logistical purposes, this may occur prior to M0 visit day to avoid excessive M0 study visit times. Each site pharmacy will then dispense the drug according to the assigned treatment on the randomization schedule, which will be located at each site pharmacy. Subject screens who do not meet inclusion/exclusion requirements will be accounted for in the recruitment monitoring process (See 5.2 Recruitment Methods).

5.5g. Walking tests. The T25FW and 2MTW will be collected at the screening and baseline visits, and every 6 months during the study (21, 22). For the T25FW, subjects are instructed to walk 25 feet marked on the ground "quickly but safely" (Appendix F). The measure is immediately repeated and the two results averaged. Assistive walking devices including canes and walkers are permitted. The 2MTW determines the distance a participant walks in 2 minutes. Dalfampridine is an FDA-approved symptomatic treatment for improving walking speed in MS. Subjects will be asked to maintain their usual dose of dalfampridine at all study visits. Subjects will be strongly encouraged to use the same assistive devices (insoles, orthotics, canes, walkers, etc.) if used at the study start throughout the remainder of the study as safely possible. Subjects who become unable to complete the mobility testing during the course of the study due to worsening MS will continue the study and be analyzed as having worsening mobility according to the data analysis plan. Subjects who are unable to complete mobility testing for non-MS related reasons will not have data recorded for that study visit. Because gait testing is the primary outcome measure, subjects should be tested as early as possible during each study visit. Testing conditions should be as uniform as possible from visit to visit (see 5.1 Study Design, Study timeline and visit scheduling).

5.5h. EDSS: The EDSS is an eight functional system scale to assess overall MS disability including motor, sensory, cerebellar, brain stem, visual, mental, sphincteric, and other systems (24). Each functional system is graded from 0 (no disability) to 5 or 6 (maximal disability). An integrated score between 0 (normal examination) and 10 (death from MS) is formed based on the score in each functional system. The EDSS exam will be performed by a blinded and trained EDSS examiner who is not the subject's usual treating neurologist (Appendix G).

5.5i. 9HPT: The 9 Hole Peg Test (9HPT) is a timed test of upper extremity arm and hand function. Subjects place pegs into a platform with hole and then take them out again (Appendix F). The 9HPT and T25FW will be administered in accordance with the instructions for the Multiple Sclerosis Functional Composite (21).

5.5j. Cognitive tests: Cognitive testing will utilize the Brief International Cognitive Assessment for MS (BICAMS (25) which includes the Symbol Digit Modalities Test (26) (Appendix H), the California Verbal Learning Test- Second Edition (27) (Appendix I),

and the Brief Visuospatial Memory Test- Revised (28) (Appendix J). These measures will be assessed at baseline, M12 and M24.

5.5k. Patient-reported outcome measures: The Patient Reported Outcome Measures Information Systems (PROMIS) will pain intensity (Appendix K), pain interference (Appendix L), and ability to participate in social roles (Appendix M) (29). Additional measures of depression (Patient Health Questionnaire-9, Appendix N), sleep the previous 4 weeks (Sleep Scale from the Medical Outcomes Study, Appendix O), exercise (Godin Leisure-Time Exercise Questionnaire, modified, Appendix V), and the Modified Fatigue impact Scale (Appendix P) will be administered at baseline and every 6 months thereafter (30, 31). The Fall Efficacy Scale-International (FESI) (Appendix T) is administered annually.

5.5l. Fall count: Fall count will be kept by a daily Fall Count Diary (Appendix Q). Each calendar page will cover 1 month and will include space to count falls and fall-related injuries each day. Each page will include the definition of a fall as “any unexpected event that results in you ending up on the ground, floor, or any lower surface” (23). At the baseline visit, subjects will be given calendars to cover the first 3 months. Subjects will be called once at the between visit telephone call to encourage falls calendar reporting and have the opportunity to answer any fall counting related questions. A final 3 month supply of falls calendars will be mailed before the end of the study with a target start date on the calendar corresponding to 3 months prior to the final study visit. Subjects will again be called once to encourage compliance and answer any related questions.

5.5m. MRI procedures.

a. MRI acquisition protocol: A 3T MRI will be utilized to acquire the following series of the brain. 1. A high resolution Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) for high resolution structural (T1-weighted) information, as the basis for brain atrophy measures. Partitions will be 1.0 mm; voxels 1 mm^3. 2. Conventional brain imaging with T2-weighted, and FLAIR series; 2mm (non-gapped) slice acquisition, with in plane resolution $1mm^2$. Intravascular MR contrast will not be administered. 3. The American College of Radiology phantom scan will be utilized as necessary for quality control. The imaging procedure will require 60 minutes with approximately 30 minutes participant scan acquisition time, 10 minute phantom scan acquisition time (when needed), and the remaining 20 minutes for positioning and questions. Careful screening of subjects prior to MRI will be done to reduce the chance of injury due to MRI-contraindicated conditions.
b. MRI clinical readings. MRIs will receive a clinical read from site clinical radiology staff and results reviewed by site treating neurologists for concerning findings

(tumor, stroke, etc.) which, if found, will be communicated to the appropriate clinical service for optimal management including treatment of MS exacerbations.

c. MRI volumetric analyses: MRI analyses used for study outcomes will be analyzed by the Central MRI Reading Site at OHSU. MRI images are sent to the Reading Site via secure methods. Prior to analyses, AIRC staff will ensure that only the study ID and PHI element of date of study visit are visible to the analysts to reduce any bias. Brain volume measures will be based on SIENAX software and brain atrophy measures on SIENNA tools in the FSL software library produced by the Oxford Centre for Functional MRI of the Brain (32). Total brain T2-hyperintense lesions will be determined using in-house software. In-house and FSL software will be used to explore differential gray versus white matter atrophy as an exploratory MRI outcome measure. Study MRIs will be reviewed for quality within 2 weeks of receipt in order to rescan a subject (1 rescan per subject per MRI visit permitted) if needed within an acceptable time-frame.
d. MRI quality control (QC): In order to ensure high quality and comparable images across study sites, the Central MRI Reading Site will coordinate QC by having each site perform test scans prior to study start and after every scanner upgrade during the study to review for image quality. In addition, each site will conduct standard phantom scan according to protocols set by the American College of Radiology. Feedback from the Central MRI Reading Site staff to the study sites regarding test, phantom QC, and study MRIs will occur in a timely manner so that errors can be fixed promptly.

5.5n. Suicidality monitoring: Monitoring suicidality is a requirement by the Food and Drug Administration for all neurology studies involving an IND. Monitoring using the with the Suicide Behaviors Questionnaire-Revised (SBQ-R) occurs at the screen to establish a baseline and every subsequent study visit to evaluate for the development of new suicidality (Appendix R).

5.5o. Adverse event (AE) monitoring: This occurs at baseline, every subsequent visit, at between visit telephone calls, and *ad hoc*. Unscheduled visits will occur to evaluate AE per the protocol guidelines (sec. 5.1d). AE are coded by the DCC according to MedDRA and reported per the reporting guidelines (sec. 6.0).

Subjects will be encouraged to remain in the study through study completion if they start, stop, or switch a DMT, if their disability progresses due to MS to an EDSS of more than 6.5, or if they have an MS relapse. Subjects who develop MRI contraindications may continue through the study end without further MRIs. Study staff will review eligibility at study visits and during regularly scheduled meetings.

5.5p. Investigational drug dispensing: Drug dispensing occurs at baseline and every study visit according to dispensing schedules by the site research pharmacies.

5.5q. Subject/provider blinding questionnaire: All blinded study staff and subjects take a blinding questionnaire at M24 to evaluate the blind (Appendix S).

5.5r. Subject disposition form: Final disposition of each subject is recorded on this form at the M24, early termination visit, or when determined that the subject is unable to attend an early termination visit.

5.6 Data Analysis

5.6a. Sample size: The sample size and power analysis were based on the pilot LA in SPMS trial in which LA had improved time to complete the T25FW (-0.54 seconds SD 0.36 vs 0.14 SD 0.25, p = 0.06). A sample size of 44 per group will have 80% power to detect a difference between the LA group with a coefficient, β_1 regression slope of -0.50 seconds and the placebo group coefficient, β_2 slope of -1.00, assuming that the standard deviation of the difference between the groups is 2.20 and the standard deviation of the residuals (repeated measures within each participant) is 1.80 with a 0.05 two-sided significance level and the correlation of 0.85 between the measurements over time, which if lower increases the power. The delta of improvement is a reduction in the rate of walking slowing of 0.5 seconds per unit of time. This translates into 2 seconds on the average timed walk over 2 years. A sample size of 59 per arm will allow for a 25% drop-out rate. The pilot study had a 10% drop out rate however 25% is more realistic for a multi-site trial in an era with more therapeutic options for MS. Screen visit failures are likely to be minimal (<10% of all screen visits) as most eligibility requirements can be made prior to the screening visit using the methods described in 5.2 Recruitment Methods.

As a check on these calculations we compared the estimates, Altmann et al.'s estimates of sample size when using SIENA as the method of determining whole brain atrophy rate, the current sample of 44 per group will achieve 80% power at significance level 0.05 assuming a 40-50% effect size (33).

5.6b. Data analysis plan: Data is analyzed by the SCC at study completion or at any point requested by the DSMB. Only subjects that complete the baseline evaluation and take at least one dose of study drug will be included in the data analysis.

The SCC will use the mixed model approach to compare, between the treatment groups, mean rates of change from baseline in the times to complete the T25FW. The SCC will use the transformation 25/T25FW, which is the walking speed in feet per

second. In constructing these models for the T25FW walking speed outcome, baseline disability will be incorporated as a predictor. The primary outcomes is whether there is a difference between the treatment groups in the T25FW rate changes. Given evidence of interaction, comparisons of both 12 and 24 month change between the treatment groups will be made, using a Bonferroni multiple comparison adjustment for two time points of interest. Additional models will include as covariates, baseline measures of disease duration and use of MS medications if significantly related to the response when added to the original model or result in a 10% change or greater in the estimated overall treatment effect. Secondarily, the SCC will compare with a t-test or nonparametric tests the proportion of participants who demonstrate clinically significant worsening in gait defined by a 20% improvement in the T25FW and/or 2MTW and/or requires greater assistance to walk (e.g. newly require a cane, transition from cane to walker, etc.). A sensitivity analyses will be performed using an intention to treat analysis with the cross-over with and without participants who have a change in their disease-modifying therapy during the course of the study. Compliance information will be added as determined by pill-counts to the mixed model.

The impact of LA on falls frequency will be assessed by comparing changes in fall frequency from the first to the last 3 months. A principal intention-to-treat analysis using linear Poisson mixed models to evaluate the association between time period, fall frequency, and group allocation will test the hypothesis that fall frequency is reduced more by LA than placebo. Mixed models will be used to correct for autocorrelation of within-subject repeated measures and allow for missing data, and include covariates associated with falling such as age, level of disability, and use of a walking aid. As exploratory secondary outcome measure, the SCC will investigate the disconjugate composite endpoint based on sustained change in EDSS, clinically significant worsening in gait as defined above, or 20% increase in 9HPT.

The mixed model approach will compare the mean rates of change from baseline in brain as measured by SIENA. Age, sex, and disease duration will be used as covariates along with disability.

Adverse and serious adverse events will be tabulated and compare the differences in the occurrence and the frequencies between the two groups. The frequency of side effects will be compared using χ^2 tests or Fisher's exact test as appropriate depending on the number of adverse events seen. For evaluation of patient safety, laboratory test results at baseline and changes from baseline will be summarized and compared using t-tests for continuous measures and Fisher's exact test for proportions.

5.7 Withdrawal of Subjects

Subjects can withdraw from the study at any time. Reason for withdrawal will be recorded. Subjects may also be withdrawn from the study by LSIs and in agreement with the study PI for any of the following reasons: 1. New or worsening medical conditions (e.g., cancer, renal disease, end-stage cardiopulmonary disease, post-traumatic stress disorder, uncontrolled diabetes, etc.) that may interfere with study procedures or otherwise pose concern for subject health or safety, 2. New pregnancy, 3. Inability of subjects to comply with study procedures, 4. Other reasons deemed important to subject safety or data quality raised by the DSMB, IRB, FDA, or any other regulatory body that has the authority to do so. If subjects are deemed no longer safe to take the investigational drug but otherwise are able to participate in the study outcomes for the remainder of the study, they are encouraged to do so.

Female study subjects of childbearing potential will be encouraged to use effective birth control methods during the study. Pregnancy testing in female subjects of childbearing potential will be conducted as part of safety laboratory studies at each study visit according to the study flowsheet. Should pregnancies occur during the study, those female subjects will be withdrawn from the study. Information will be collected as to the pregnancy course, outcome and health of the newborn infant. Because LA is available as an over the counter supplement, male subjects whose female partners become pregnant will continue in the study, however pregnancy and birth outcomes of the female partners will be recorded and presented to the DSMB.

If a subject wants to withdraw from the study, the subject will contact the site study staff using the contact information and procedures on the ICF and request withdrawal. If a subject withdraws or is removed from the study for any reason and is unable or unsuitable to continue the study procedures off investigational drug, the reason and date of discontinuation of the investigational drug is recorded. At the time of study discontinuation, every effort will be made to schedule the subject for an early termination visit following the procedures for M24 without the MRI or Fall Count Diary if termination is within 6 months of the baseline visit, and M24 procedures with MRI but without fall count if termination is greater than 6 months of the baseline visit. Subjects withdrawn due to reportable adverse events and subjects with adverse events thought related to the study that are ongoing at the final study visit are followed for 30 days or until resolved, whichever is first, or longer per request of the Medical Monitor.

6.0 **Reporting:** All SAE, UAP, and PD are reported to the IRB within defined timelines.

6.1 Adverse event reporting

Adverse event (AE) information will be monitored in detail throughout the course of the study. AEs are defined as and will be graded as to their expectedness and attribution (unrelated, possibly, probably, or definitely related to the protocol). Dr. Mary Samuels will act as the medical monitor to determine relationship of AEs to the study intervention if uncertain. AEs will be reviewed by site treating neurologists, graded, and reported to the DCC. The DCC will code the events using MedDRA and will assist the CCC with IRB reporting per reporting guidelines.

6.2 Limited collection of non-serious AE

Some AEs are expected, so a limited set of AEs will be collected for this trial. Upper respiratory and urinary tract infections will not be tracked or reported, unless they reach an intensity of *severe*. Gastrointestinal distress is a known side effect of LA. Therefore only GI distress related and probably related to study of any intensity is tracked and reported. All other AEs are collected and stored at the study sites.

6.3 Limited reporting of AE

Not all AE captured at sites are reported to the DCC. The limited set of AE reported to the DCC via the REDCap database is according to guidelines in 6.3a below. Serious AE (SAE) and select UP and PD are reported under expedited guidelines according to IRB and other monitoring entity requirements.

6.3a Limited reporting of AE, UP, and PD to the DCC. Bold items require expedited reporting to the DCC via REDCap.

AE Intensity*	AE **related** to study	AE **probably related** to study	AE **possibly related** to study	AE **unrelated** to study
Mild	REDCap	AE Log only	AE log only	AE log only
Moderate	REDCap	REDCap	AE log only	AE log only
Severe	REDCap	REDCap	REDCap	REDCap
SAE	**REDCap**	**REDCap**	**REDCap**	**REDCap**
UP with risk to subjects or others	**REDCap**	**REDCap**	AE log only	AE log only
Severe PD: REDCap	Moderate PD: REDCap.		Mild PD: AE log only	

* Increases after Screen in CTCAEv5 grades (ALT, AST), new ACR >300mg/g, and new eGFR<60 are always reported in REDCap regardless of intensity or relationship to study. GI distress related and probably related to study of any intensity is reported in REDCap.

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ACR, Albumin to creatinine ratio

6.4 Adverse event (AE) definition: Any untoward or undesirable, although not necessarily unexpected, event experienced by a human subject that may be a result of:

- The interventions and interactions used in the research.
- The collection of identifiable private information in the research.
- An underlying disease, disorder, or condition of the subject.
- Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

6.5 Serious Adverse Event (SAE) definition: Any AE that:

- Is fatal.
- Is life-threatening.
- Is persistent or significantly disabling or incapacitating.
- Results in inpatient hospitalization or prolongation of hospitalization.
- Results in psychological or emotional harm requiring treatment.
- Creates a persistent or significant disability.
- Causes a congenital anomaly or birth defect.
- Results in a significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

6.6 Unanticipated problem (UP) definition:

- Any event that is not expected given within the context of the study.
- Any event that places subjects or others at a greater risk of harm or discomfort relative to what was previously known.
- No harm to a subject needs to occur for an event to be an unanticipated problem.

6.7 Protocol Deviation (PD): The term “protocol deviation” is not defined by either the HHS human subjects regulations (45 CFR 46) or the FDA human subjects regulations (21 CFR 50). All PD are graded by the treating neurologist and entered into REDCap. Severe PD have expedited reporting to the DCC via REDCap. Moderate PD are entered into REDCap according to the usual timelines. Mild PD are recorded on the site AE log only.

6.7a. <u>Mild PD:</u>

- The deviation resulted in no harm or risk of harm to research participants; or
- The deviation did not result in or require any substantive action to be taken or result in a substantive change to the subject’s condition or status (i.e., did not

affect the subject's participation in a substantive way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)
- The deviation had no substantive effect on the value of the data collected (i.e., the deviation does not confound the scientific analysis of the results);
- The deviation did not result from willful or knowing misconduct on the part of the investigator(s);
- The deviation is easily corrected (e.g., consenting a subject with an old version of an ICF, recording data on an expired/incorrect form, forgetting to record data that may be acceptably recorded at the next visit, etc.)

6.7b. Moderate PD:
- The deviation resulted in a harm or risk of harm that is not significant; or
- The deviation resulted in the need for minimal risk interventions, such as those defined in 45CFR46.110 and 21CFR56.110;
- The deviation resulted in the loss or improper collection or recording of some data for one or more subjects, but did not invalidate the entire data set for the study;
- The deviation resulted in a regulatory violation that can be acceptably resolved;
- Repeated minor protocol deviations from the same laboratory, site or research team; or
- There has been a failure to follow action ordered to correct minor or moderate protocol deviations**.**

6.7c. Severe PD:
- The deviation resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status;
- The deviation has significantly harmed or posed a risk of significant harm to research participants;
- The deviation has substantially damaged the scientific integrity of the data collected for the entire study;
- The deviation is evidence of willful or knowing misconduct on the part of the investigator(s);
- The deviation involves serious or continuing noncompliance with federal, state, or local research regulations;
- There have been repeated minor and/or moderate protocol deviations from the same laboratory, site or research team;
- There has been a failure to follow action ordered to correct minor and/or moderate protocol deviations;

- There has been a failure to follow action ordered in accordance with the emergency action provision of this policy.

6.8 Data and Safety Monitoring Plan

Data and safety monitoring will involve AE reporting by site study staff, and review of AE, SAE, UP, protocol deviations (PD), dropouts, complaints, or breaches of confidentiality by the DCC. Subjects will be encouraged to report any study-related and/or health problems at any time to the study site staff. AEs reported to the DCC and other data and safety issues found during site visit audits will be subject to additional reporting (IRB, FDA) per reporting policies.

A Data Safety Monitoring Board (DSMB) will be assembled for subject safety. This board will consist of members who have expertise in any of the following: neurology, multiple sclerosis, clinical trials, and medical safety. The board members will document their lack of conflict of interest and approve a DSMB Charter prior to study start. All members of the DSMB will review and approve study protocol and informed consent forms for all study sites prior to enrollment.

The DSMB Chair or DSMB member designee reviews SAE in real time according to reporting timetables (6.0). The DSMB receives quarterly reports, developed by the DCC and SCC, which includes aggregate reports of AE, SAE, UP, and PD, including the safety lab data according to Limited Reporting of AE (6.3) presented grouped by study arm and study site (as necessary). The board will meet every six months, as necessary, to review quarterly reports, enrollment/screening progress, data collection problems, and missing data. No non-safety related study outcome analyses will be performed until study completion, unless the committee determines there is a compelling reason to do so related to patient safety concerns. The DSMB also meets when the last subject completes participation. The DSMB will provide a written summary of each meeting to the PI with a statement about appropriateness of continuation of the study. DSMB reports are communicated at least annually to the Central IRB and non-VA IRBs.

7.0 Privacy and Confidentiality

7.1. Protected health information (PHI)

Study subjects will be given a unique study ID that will be linked to the name and contact information by a key. The key will be held by the LSIs for their site subjects, and for all subjects by the PI. Local sites may collect PHI elements including name, address, email address, telephone numbers, dates of birth, social security numbers, and medical record numbers for the purpose of recruitment, screening potential subjects, scheduling,

and creating site medical charts. These identifiers are necessary to avoid duplication of recruitment and screening efforts and to ensure that the correct study procedures such as laboratory assessments and MRIs are performed at the local sites. Dates of study visit will be the only PHI element recorded in the REDCap study database, the only PHI viewed by the SCC, and the only PHI retained in the data repository (BND #2916). PHI will be transmitted on MRIs to the Central MRI Reading Site in order to properly identify the scans. The PHI elements may include dates of study visits, names, dates of birth, social security numbers, and medical record numbers. Prior to analyses and to ensure blinding, staff at the Central MRI Reading Site will ensure that only the subject ID along with the PHI element of date of study visit are visible to the MRI analysts. This is outlined on the ICF. All other PHI including names, addresses, contact information and medical records will be managed according to the procedures below.

7.2 Privacy and Confidentiality

Privacy of subjects will be maintained by obtaining and storing the minimum necessary PHI for the purposes of screening, enrolling, and maintaining subject participation. Study data will be seen only by study staff authorized to do so.

7.3 Information and specimen management

Subject data, initially identifiable when obtained, will be coded and dated according to the date of study visit. The key to the code will be maintained by each LSI and available to the study PI. Hard copies of study data will be stored in on-site locked cabinets, and electronic data stored on secure servers according to the privacy regulations of each study site.

Trained and designated study staff will enter study data, from each site and the Central MRI Reading Site, into a web-based REDCap database. OCTRI's REDCap software is a highly secure and robust web-based research data collection and management system, which is physically housed on servers located in the OHSU’s Advanced Computing Center. The servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.

REDCap is a robust multi-level security system that will enable the PM and study PI to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. The only PHI entered into REDCap will be the dates of study visits. Study sites will maintain up-to-date study staff personnel lists so that REDCap access is limited to approved study staff. User activities are logged to enable auditing of all data access. REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's

Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups.

Hard copies of study data containing PHI will be sent, when necessary, through secure methods. For VA to VA transmission, this can include email using PKI or RMS encryption. Otherwise, transmission is via secure fax or secure mail such as FedEx/UPS with tracking. MRI images will be sent to the Central MRI Reading Site by secure electronic methods as allowed by OHSU and the sending institution such as an sftp account, or on compact disks by secure mail such as FedEx/UPS with tracking.

Study data management is under the oversight of the DCC. Members of the DCC will have REDCap access to view, enter and edit data, and update the REDCap database throughout the study for the purposes of quality control. The DCC will work with the PM and site study staff to resolve data discrepancies in an ongoing fashion throughout the study.

Blood samples for subjects participating in the optional BND are shipped to the VA Portland Health Care System via secure mail, such as FedEx/UPS with tracking. The only PHI on the specimen label is the date of specimen collection. An electronic copy of coded data that does not contain protected health information, except for the date of specimen collection, will be transferred to the BND for storage via methods allowed by the VA and the sending institution, such as an sftp account, or on compact disks by secure mail.

The BND is located at the VA Portland Health Care System in Portland, Oregon, in VA Building 101, Room 434 which is secured by card access only. An electronic copy of coded data is stored on secure VA networks located behind VA firewalls. Dr. Rebecca Spain, director of the biorepository, makes the decisions regarding how the blood samples and data are used in the future under IRB-approved protocols. Samples from the biorepository released to other investigators may include the date of specimen collection.

The ICF and HIPAA authorization provide information about how specimens will be transferred, how long they will be kept, and who will view/use the specimens. Subjects who consented to the LAPMS study prior to the addition of the option of donating blood to the biorepository will re-consent with the version that includes the blood donation to the BND either at the next study visit, or if necessary, via an approved phone script.

The ICF will describe that the HIPAA identifier, date of study visit, will be included on all stored study data including in the REDCap database on MRI images sent to the Central MRI Reading Site, and on specimens within the BND.. The ICF also describes that

additional PHI including name, date of birth, social security number and medical record number may be sent to the Central MRI Reading Site if those elements are unable to be removed by the local sites prior to sending. Only study staff at each site, the Central MRI Reading Site study staff, the DCC, and members of the DSMB will have access to the study data that includes PHI. Once the study has concluded, study records will be maintained at each site for the duration of time required by each site regulations.

8.0 Communication Plan

8.1 Multi-site study coordination plan

The Principal Study site will be responsible for initial submission and ongoing reporting to the VA Central IRB. The PI and PM will provide notification to study site Directors when VA Central IRB approval has been obtained. The Principal Study site will provide support to both VA and non-VA study sites for obtaining local IRB approval. The Principal Study site will be responsible for reconciling protocol-changing differences between IRBs. In addition, the Principal Study site will provide Standard Operating Procedures, a Manual of Operations & Procedures, and data collection forms to each site. An Investigator Meeting will familiarize the LSIs with the study prior to study start. As necessary, the study monitor (PM) will hold 1 training visit with study staff at each site to review the protocol, study documents, review data collection techniques, review communication plans, demonstrate and certify use of the REDCap database, inspect facilities and study materials, and verify site readiness to participate in the study prior to enrolment of subjects at the site. Investigators are required to store all source documents per study site requirements.

8.2 Ongoing communication

Local site investigators will participate in regular LSI Research Teleconferences led by Dr. Spain and the PM to discuss study-related matters including but not limited to IRB issues, training, study preparation, subject recruitment, data collection, REDCap database entry, adverse events, budgets, and publications. The PM with conduct regular (e.g. monthly) teleconferences with site study staff for data collection and related issues. LSIs are expected to hold regular meetings with their site research staff in order to review study progress, review adverse events, and other study matters. Email will also be utilized as a primary method of communicating information about changes to the protocol, informed consent, and HIPAA authorization. Communication about AEs, SAEs, unanticipated problems, or DSMB reports will also be conducted by email, phone, or the LSI teleconferences as appropriate to the level of urgency of information

transmitted. This information will be relayed to the appropriate IRBs under the direction of the DCC according to the DSMP (sec. 6.8).

Initial and ongoing IRB approval documents will be provided by each study site to the PI to ensure that no study activities occur without IRB approval. Acknowledgment of these notifications will be maintained as documentation of understanding from each study site.

Study sites will be notified when enrolment targets are reached, when sites have completed their final study visits, and when the entire study has completed. Acknowledgment of these notifications will be maintained as documentation of understanding from each study site. Study LSIs will have the opportunity to participate in manuscript preparation with authorship order related to recruitment achieved and/or level of participation in manuscript editing.

8.3 Study monitoring

Yearly on-site study monitoring visits and study closing visits by the PM will be performed to assess critical study procedures including study data endpoints, subject safety, protocol compliance, and regulatory compliance. The monitoring may include the following: Audit data listings to source documentation, ensure subject eligibility, verify reporting of adverse events, assess compliance with protocol, audit regulatory files, and ensure adequate site personnel training. The Central Research Pharmacy may request site pharmacy investigational drug accountability review during these visits. Centralized monitoring processes at the DCC occur at regular intervals and will include data quality checks, site performance checks, and safety reporting monitoring. Regular feedback and data queries will be issued to each site by the DCC, and resolution of queries managed by the PM and DCC.

9.0 References

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Appendix – Supporting Documents List

A. Letter of Support, Pure Encaps
B. Recruitment Flyer
C. Recruitment Letter to MS Practitioners
D. Recruitment Telephone Script
E. Recruitment Email Blast
F. Timed 25 Foot Walk & 9 Hole Peg Test
G. Expanded Disability Status Scale
H. Symbol Digit Modalities Test
I. California Verbal Learning Test- 2nd edition
J. Brief Visuospatial Memory Test – Revised
K. PROMIS - Pain Intensity
L. PROMIS - Pain Interference
M. PROMIS - Ability Partic in Soc Roles and Activities
N. Patient Health Questionnaire-9
O. Sleep Scale from the Medical Outcomes Study
P. Modified Fatigue Impact Scale
Q. Fall Count Diary
R. Suicide Behaviors Questionnaire-Revised
S. Subject Blinding Questionnaire
T. Falls Efficacy Scale-International
U. Study Drug Instructions
V. Godin Leisure-Time Exercise Questionnaire, modified
W. ResearchMatch Message
X. Short URL
Y. LAPMS sticker
Z. LAPMS Facebook page
AA. LAPMS Facebook ad
BB. LAPMS webpage
CC. LAPMS Webpage Content